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Matthew Macaluso
Sheldon H. Preskorn *Editors*

Antidepressants

From Biogenic Amines to New Mechanisms of Action

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From MM and SHP: To our patients, for whom we do this work with the hope that we can improve lives and alleviate suffering.

From MM: To Katie, Matty, and William, thank you for your love and support. I love you.

From SHP: To Belinda, Erika, Lillianah, Viktor, Jack, and Goran for being so loving and supportive.

Preface

Major depressive disorder (MDD) costs society on the order of 100 billion dollars per year when taking both direct (i.e., cost of healthcare) and indirect (i.e., lost wages, lost tuition) costs into account. With a lifetime prevalence of 15–17%, the 100 billion dollars is an astounding figure that places MDD among the most common and disabling of all medical conditions. In addition, 15% of patients with MDD die by suicide, which is a tragic and potentially preventable outcome. Given the prevalence and seriousness of MDD, it is not surprising that antidepressants are among the most widely used of all medications. Despite their widespread use, currently marketed drugs (i.e., antidepressant treatments or ADT) are limited in their effectiveness. For example, after four adequate trials of ADT, the STAR∗D study suggested that up to 40% of patients with MDD remain symptomatic. This lack of efficacy may be in part explained by the fact that currently marketed ADT do not target the underlying physiology of MDD. In addition, they all share the same limited mechanisms of action (i.e., work on biogenic amine neurotransmitters). While currently marketed ADT are relatively well tolerated, particularly when compared to their predecessors, they do not act rapidly and take 6 or more weeks to demonstrate an effect or lack thereof. This results in a large portion of the population of depressed patients being poorly treated, which leaves room for more effective medications that work more rapidly than their contemporary counterparts and target the underlying physiology of the disease.

While great strides have been made to increase the safety, tolerability, and effectiveness of antidepressants, more is needed and being done. After more than 50 years of antidepressant drugs that worked almost exclusively on biogenic amine neurotransmitters, the field is currently focused on two major areas of study: (1) novel mechanism of action drugs including glutamatergic drugs and (2) the relationship between glutamate, inflammation, and depression. These two areas of research, which are reviewed in this book by Drs. Farber and Felger, may result in novel treatments or the repurposing of existing treatments from other therapeutic areas (e.g., ketamine and COX-2 inhibitors). Unlike drugs targeting biogenic amine neurotransmitters, these new or repurposed therapies may more closely target the underlying physiology of MDD which is still unknown.

Along the lines of novel therapies that are potentially more efficacious, three drugs are currently being studied as antidepressants and have received "breakthrough" designations from the United States Food and Drug Administration (FDA). This means **their development will be** expedited because preliminary clinical evidence indicates the drugs may demonstrate substantial improvement over available therapies on clinically significant endpoints. All three (esketamine, rapastinel, and Sage-217) work on the NMDA receptor and affect glutamatergic transmission. Esketamine may promote synaptogenesis in the brain. Other treatments being studied that may be potentially more efficacious include brain stimulation techniques. This area is reviewed by Dr. Conway and includes treatments such as deep transcranial magnetic stimulation (dTMS), which expands upon the processes used in repetitive transcranial magnetic stimulation (rTMS) and may improve our ability to upregulate or downregulate specific areas of the brain and more effectively treat the symptoms of depression.

This book will not only review future directions of ADT but also review the current state of antidepressant treatment in clinical practice, providing an overview of antidepressants from antiquity to modern times. This includes a review of both first generation ADT (i.e., MAOIs and TCAs) and other established treatments. The goal of this discussion is to help the reader understand (1) how currently marketed drugs fit into the modern practice algorithm for treating depression, (2) how this algorithm may change in specific situations such as patients who have substance use disorders or bipolar disorder, and (3) how new developments may change these approaches. We start with Dr. Coryell's review of the neurobiology and phenomenology of MDD, which will provide an overview of the current thinking regarding the underlying physiology of MDD. It is difficult to understand how to treat a condition without understanding the clinical syndrome, presentation, phenomenology, and underlying neurobiology. Dr. Coryell's chapter summarizes the DSM-5 nosology regarding MDD, helps us understand the link between depression and suicide, and reminds us of classic information on biogenic amine neurotransmitters, which sets the stage for every chapter that follows on the treatment of MDD.

The book builds upon the foundational knowledge presented by Dr. Coryell on the diagnosis and neurobiology of MDD with an overview of older and established treatments. In reviewing the older drugs, Dr. Conway and colleagues help us understand how MAOIs and TCAs continue to have a role in current clinical practice, particularly for patients who do not respond to first-line treatments that are safer, but less effective despite working on the same neurotransmitters systems. Dr. Rush, who was the principal investigator for the largest study to date on the treatment of depression, summarizes the data from STAR∗D and the numerous papers (i.e., greater than 100) it yielded. The chapter on STAR∗D may be the single largest summary of the study data to date and helps us understand the treatment algorithm for MDD including how groups of patients responded at each level and the characteristics of patients that are associated with relapse and adverse events.

Following the discussion of the current state of practice in treating MDD, Dr. Trivedi and colleagues summarize the potential use of biological markers in depression, which is a common occurrence in modern research protocols where

biomarkers are used to confirm the diagnosis or demonstrate target engagement. In the future, the treatment of depression may involve neuroimaging to confirm clinical diagnostic opinions. Neuroimaging can demonstrate overactive or underactive areas of the brain such as the ventromedial prefrontal cortex, which influences autonomic and neuroendocrine responses and is involved in the underlying neurobiology of MDD. In addition, many researchers predict that in the near future a laboratory workup may be included in the initial assessment of MDD including the examination of inflammatory cytokine levels and genetic markers as they pertain to the disease and possibly to drug metabolism and target engagement. Along with neuroimaging, this information may lead to greater diagnostic certainty and personalized treatments for patients.

The book also reviews specific subpopulations of patients with depression including how comorbid conditions affect antidepressant treatment, how depression presents and is treated in elderly patients and in women, and how bipolar depression is different than unipolar depression. Dr. Beyer helps us understand the depressive phase of bipolar disorder and how it is treated differently than MDD. Bipolar depression may not be caused by the same physiologic process that leads to unipolar MDD, as evidenced by the fact that treatments for MDD do not have the same efficacy in treating bipolar depression. In addition ADT can destabilize patients with bipolar disorder by leading to manic switches. Dr. Carey helps us understand the treatment of patients with co-occurring depression and substance use disorders, which clinically can be difficult to diagnose and treat. In treating depression in patients with substance use disorders, clinicians struggle to understand if the substance use disorder caused the depression or if the patient has a primary depression and comorbid substance use disorder. Dr. Nelson helps us understand the treatment of depression in older adults, which is a population that often has other comorbid medical problems, is psychologically dealing with the type of loss and grief that is unique to late life, and may have comorbid neurocognitive disorders.

Given its broad overview of antidepressants from antiquity through present times including a discussion of current practice and future directions in the field, this textbook is ideal for those studying the basic science of depression, for clinical researchers and for academicians, residents, and practitioners who are actively involved in treating patients with major depressive disorder. We thank all of the contributors for their excellent contributions to the book. The chapter authors are among the leaders in the field of antidepressant treatment, and their work represents an authoritative source on the same.

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Impact, Diagnosis, Phenomenology, and Biology

William Coryell

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Abstract

This section provides summaries of the epidemiology, phenomenology, nosology, and the suspected biological substrates of the depressive disorders. It particularly emphasizes the historical evolution of the pertinent diagnostic constructs and the prognostic import both of the various diagnostic groupings and of the individual symptoms and symptom clusters.

Keywords

History · Melancholia · Neurotransmitter · Nosology · Phenomenology

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1 Section 1: Prevalence

According to the most definitive effort to estimate prevalence of specific mental disorders in the United States, the National Comorbidity Survey Replication, the 12-month prevalence rates for DSM-IV-TR major depressive disorder (MDD), dysthymia, and bipolar I/bipolar II disorders are 6.7%, 1.5%, and 2.6%, respectively (Kessler et al. 2003). Lifetime rates are 16.6%, 2.5%, and 3.9%, respectively. Twelve-month prevalence rates from an earlier, large-scale study that used nearly identical methods were somewhat higher for MDD (10.3%), but were similar for dysthymia (1.3%) and bipolar I/bipolar II (2.5%) (Kessler et al. 1994).

Notably, the lifetime prevalence of MDD was approximately twofold higher for individuals below the age of 60 than for older individuals. Among those with a lifetime MDD diagnosis, those aged 18–29 years had 12-month prevalence rates that were threefold higher than those 60 and over. Individuals with incomes below the poverty line were nearly four times as likely to be depressed than those with incomes significantly above the poverty line.

Three-quarters of those with a lifetime history of MDD met criteria for another DSM-IV-TR diagnosis which, in a large majority of cases, began before MDD. A meta-analysis of the prevalence of MDD episodes among primary care patients given structured interviews estimated a point prevalence of 17% (Mitchell et al. 2009). Comparisons against whether the provider considered depression to be present, as stated in the medical record, showed a higher rate of false positives than false negatives. Diagnostic accuracy improved with repeated examinations.

Important caveats apply to these numbers. An earlier prevalence study that canvased over one million individuals at five centers across the United States reported a 1-year prevalence rate for MDD of 3.0% and a lifetime rate of 5.2%. These figures are less than one-half and one-third, respectively, those from the NCS-R study. It seems unlikely that secular trends or differences in sampling methods would account for discrepancies of this magnitude. Rather much of the difference has been attributed to variables such as subtle as differences in the number of probe questions built into the structured interviews used in the two studies (Kessler et al. 1994).

The assessment of lifetime rates of MDD is prone to particular difficulties. An example is the observation that, in numerous cross-sectional studies of adults across international settings, older individuals were reported to have substantially lower lifetime rates of MDD than younger ones (Weissman et al. 1996; Cross-National Collaborative Group and Wittchen 1992). This leads to considerable speculation as to the reason for this finding. Yet, test-retest studies have shown that past MDD episodes are recalled with poor reliability and that individuals are more likely to underreport than overreport previously described major depressive episodes (Simon and VonKorff 1995; Giuffra and Risch 1994). Because younger adults are considerably more likely to be experiencing major depressive episodes in any given year than are older ones (Kessler et al. 2005), this “telescoping effect” is likely to be quite large.

Methodical differences preclude meaningful comparisons across separate studies undertaken in different countries. The Cross-National Collaborative Group report applied the same sampling and assessment methods across ten countries and found six-fold differences between countries with the lowest and highest 1-year prevalence rates of major depression (Weissman et al. 1996). No clear explanation for these differences emerged. Relative cross-national consistencies did exist, however, for higher female prevalence, for mean age of onset in the late 20s, and for the increased risk for MDD posed by comorbidity with substance abuse and with being separated or divorced.

2 Impact

2.1 Disability and Economic Impact

Depressive disorders are the fourth leading cause of disability worldwide and account for the most years with disability of all illnesses in the Americas (Ustun et al. 2004). The annual economic burden resulting from MDD in the United States was $210.5 billion in 2010 (Greenberg et al. 2015), approximately half of which results from the cost of treatment with the other half due to work place or other indirect costs. Moreover, the economic consequences of depressive disorders grew substantially between 2005 and 2010, due largely to increases in the size of the population and the cost of care.

MDD appears to carry substantial additional impairment and cost through its relationships with cardiovascular disease (Fiedorowicz et al. 2011a). According to an extensive literature, inflammatory markers are likely to be elevated in patients with depressive disorder (Munkholm et al. 2013; Howren et al. 2009), and this comprises a plausible link between depressive disorder and cardiovascular disease. It is notable, then, that treatment with antidepressants appears to decrease cytokine activity, an important marker for inflammatory activity (Hiles et al. 2012).

2.2 Suicide

Suicide is the leading cause of death worldwide, more so in western countries. According to results pooled from 27 psychological autopsy studies, nine of ten suicides had met criteria for a psychiatric disorder when they died, and mood disorders were the most common, followed by substance use disorders (Arsenault-Lapierre et al. 2004). In the longest prospective study of new disorders, 17.5% of 186 patients who have been hospitalized for unipolar depression committed suicide over a span of 40–44 years (Angst et al. 2005). Suicide rates are substantially lower among individuals who are outpatients at the beginning of follow-up (Bostwick and Pankratz 2000). Despite widespread efforts in the United States to improve screening and treatment access for individuals at risk for suicide,

age-adjusted rates for both males and females have increased steadily from 2000 to 2014 (Curtin et al. 2016).

Among the risk factors for completed suicide identified across many studies, a history of suicide attempts is the most consistently robust (Coryell and Young 2005). While the value of a suicide attempt history is a clinically useful risk factor, it is nevertheless quite modest in predictive power as can be deduced from prevalence rates of 50 to 1 for suicide attempts and suicides, respectively (Kessler et al. 2005). The relative frequency of suicide attempts, though, underscores the societal burden associated with attempt behaviors per se. One estimate of the medical costs associated with suicide attempts in 2013 in the United States was $1.5 billion (Shepard et al. 2016).

3 Diagnosis

3.1 History

Probably the earliest currently known descriptions of depressive illness appeared in the writings of Hippocrates in 1550 B.C. and he, as have most subsequent writers on the subject, used the term melancholia to label the condition.

Suppositions regarding the causes of melancholia have varied widely from an excess of black bile to religious, moral, and societal etiologies. In the early 1920s, psychoanalytic explanations centered on the experiences of loss. Across all of these periods writers consistently recognized that dominant features included a persistently low mood, lethargy and slowing, decreases in appetitive functions, fear and fretfulness, self-reproach, and, in more severe cases, delusions of sin or persecution.

Proposed sub-classifications have also been numerous. The separation of unipolar and bipolar depression, first proposed by Leonhard et al. (1962) and later by Angst (1966), Perris (1966), and Winokur et al. (1969), is now the most fundamental and widely accepted of these. Notably, these proposals were based principally on family history differences between unipolar and bipolar patients. Another subdivision, between reactive or endogenous depression and endogenous or melancholic depression, has had long-standing intuitive appeal (Shorter 2007).

3.2 Operational Definitions

The first widely used set of operational criteria for depressive disorders was published in 1972 (Feighner et al. 1972) along with criteria for other psychiatric disorders considered to have validity at the time. Dysphoria was a requisite symptom, and a minimum of five from a list of eight symptoms with a duration of 1 month was necessary for a diagnosis. The term "major depressive disorder" first appeared in the subsequently published Research Diagnostic Criteria (RDC) (Spitzer et al. 1978).

The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders III* adopted the operational criteria format as did the subsequent iterations of DSM-III-R, DSM-IV, and DSM-5. The RDC shortened the minimum duration to 2 weeks and added anhedonia to dysphoria as an option for the single required symptom. It also required four rather than five of the eight other symptoms. The DSM additions from DSM-III onward maintained these changes. Otherwise, the eight core symptoms of depressive disorder have remained essentially unchanged through all six of these diagnostic revisions.

Despite this definitional continuity, an active and far from settled debate continues between those who view depressive disorder as a unitary concept, in which cases fall along a severity continuum, and those who hold the disorder to be inclusive of two or more fundamentally different biological disorders (Shorter 2007). Currently many who take the later position assert that melancholia is a discrete illness characterized by biological abnormalities with well-established connections to severe depressive disorders such as hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis and reduced REM latency (Taylor and Fink 2008).

The DSM-5 work groups deliberated under an overarching and carefully enforced principle that the degree of empirical evidence required for major changes in the definition of a disorder increased in proportion to the length of time that the definition had been in wide use without undergoing major changes. The threshold for substantial changes in the definition of MDD was correspondingly quite high. The mood disorder work group was not convinced by published evidence that the distinction between melancholic and non-melancholic depressive disorders was more valid than the simple distinction based on severity alone.

The prevailing view that melancholia, or endogenous depression, is less a result of ongoing social stressors and more anchored in measurable biological abnormalities leads intuitively to the assumption that the former would be more amenable to antidepressant treatment and the later to psychotherapy. The results of several large-scale comparisons of specific psychotherapies and antidepressant treatment support this position (Brown 2007; Thase and Friedman 1999). These studies did not show, however, that the presence or absence of melancholia was a more effective predictor of such deferential treatment response than the cruder distinction between greater and lesser overall symptom severity. A more recent meta-analysis shows that melancholia does not predict deferential responses to antidepressant and psychotherapeutic treatments when baseline severity scores are included in the statistical model (Cuijpers et al. 2017).

The realization that DSM-5 would not evolve to incorporate biological measures into diagnostic criteria and that none of the many biologic abnormalities that had been demonstrated in psychiatric illness have, in fact, been shown to be adequately specific and sensitive to any given DSM disorder led the NIMH, in 2008, to propose the Research Domain Criteria (RDoC) for use in future funded research. This approach was designed to cut across diagnostic categories with the application of a matrix. Rows consist of domains or constructs such as negative valence systems and arousal/modulatory systems and columns consist of units of analysis. Among the seven specified units are genes, neuro-circuits, physiology, and behaviors. The

RDoC approach emphasizes continuation over categories to provide researchers with a wider range of measures and greater statistical power.

3.3 Subtypes

There is near universal recognition that criteria for major depressive disorder encompass conditions that vary markedly in phenomenology, severity, course of illness, family history, and response to treatment. Many subtypes have been proposed but, despite substantial efforts to validate many of them, none has gained an acceptance that is clearly greater than that for the others. However, some have accumulated enough evidence for validity that they warrant clinical recognition.

The only subdivision of unipolar depression included in the first of the operational criteria of psychiatric disorders (Feighner et al. 1972) was that of *primary and secondary depression*. Patients with secondary depression have experienced the onset of a list of certain other disorders antedating the first depressive episode. This grouping followed well-established precedence from the nosology of medical illnesses such as that for hypertension. Accordingly, a syndrome arising in the context of another might have some etiologic role and should be separated from the same syndrome that develops de novo. The course of the former, secondary, condition is likely to reflect the course of the underlying disorder and treatment should be selected that recognizes this. In the case of depressive disorders, examples include episodes that occur in the context of alcoholism that then resolve with detoxification, as well as those that develop in the context of anorexia nervosa that then clear with weight restoration. Continuing with the medical illness analogy, the course, treatment response, and family history of secondary depression are likely to differ according to which non-affective illness comprises the background condition. Thus, it is not surprising that efforts to validate the primary/secondary distinction in which the secondary depression group have varying primary diagnoses yield generally disappointing results.

A notable exception was a study of 146 patients hospitalized with primary depression who were compared to 42 patients with secondary depression based on responses to a 1 mg dexamethasone suppression test (DST). Rates of non-suppression, a response once thought to have specificity for melancholia or endogenous depressive disorder, were 45% and 0%, respectively (Schlesser et al. 1980).

Another study used course and family history to compare patients with episodes of primary depression that included panic attacks, but who had no prior panic attacks outside of depressive episodes, to patients who had panic attacks that clearly preceded the first depressive episode (secondary depression), and to depressed patients with no history of panic attacks (primary depression) (Coryell et al. 1992). Patients with primary depression complicated by panic attacks in comparison to those with primary depression without panic attacks suffered greater depressive symptom severity and more depressive morbidity during a 5-year follow-up. They did not, however, have a greater risk of panic disorder among their relatives and did not experience panic attacks outside of depressive episodes during follow-up. The

group with depression secondary to panic disorder, in contrast, did have significantly more panic disorder among their relatives and were more likely to experience freestanding panic attacks during follow-up.

Interest in the distinction between *psychotic and nonpsychotic depression* began with observations that patients with MDD who also had delusions and/or hallucinations were less likely to respond to tricyclic antidepressants (Glassman et al. 1975). An extensive literature has since accumulated to show that patients with psychotic features, in comparison to depressed patients without them, have greater symptom severity, particularly in regard to symptoms thought to comprise melancholic depression (Coryell et al. 1984, 1985). They also experience longer depressive episodes, shorter times to relapse, and more depressive morbidity over extended follow-up periods (Coryell et al. 1996). They are less likely to show placebo responses (Glassman and Roose 1981), and, probably because of this, patients with psychotic features are more likely to show a substantial response differential between real and sham electroconvulsive therapy (Buchan et al. 1992). Of greater relevance to the distinctiveness of psychotic depression, patients with this condition are significantly more likely to experience delusions or hallucinations in subsequent episodes (Coryell et al. 1992; Charney and Nelson 1981; Nelson et al. 2018) and to have increased risks for psychotic depression among their relatives (Leckman et al. 1984).

The separation between depression that develops in the context of adverse events and those that appear without apparent external cause has, perhaps, the most intuitive appeal of all of the subgroupings for major depressive episodes. The assumption underlying the separation of *situational and non-situational depression* would predict that the former would have fewer of the symptoms associated with melancholia, that they would have fewer episode recurrences, and that they would have a lower familial risk of MDD. They might also be expected to show smaller outcome differences between responses to antidepressants and placebo. Somewhat surprisingly, research has supported none of these predictions.

Findings from family and twin studies have particular import for the concept of reactive or situational depression. Contrary to expectations, a family study of patients with recurrently situational depressive episodes showed they had approximately twice the morbid risk for MDD among their first-degree relatives than did patients with recurrently non-situational depressive episodes (Coryell et al. 1994a). Results from twin studies give these findings more meaning because they provide clear evidence that those adverse life events that are, to some degree, under individual control are heritable (Kendler and Karkowski-Shuman 1997). The concordance for the presence of recent adverse life events at a random point in time was shown to be significantly greater in monozygotic than in dizygotic twin pairs. Thus, personality traits that foster adverse life events seem highly heritable. This is clear with such dimensions as neuroticism, as measured by the NEO (McCrae and Costa 1987), which has been shown to be both highly heritable and marked by an increased sensitivity to stressors (Kendler et al. 2004).

A special case of the nosological recognition of the role of stressors in the genesis of depressive symptoms is the *bereavement exclusion* that was part of the MDD

criteria in DSM-III, DSM-III-R, and DSM-IV, but not in DSM-5. In the earlier DSM iterations, depressive symptoms that developed following "the loss of a loved one" did not warrant the diagnosis of MDD unless symptoms had persisted longer than 2 months or were attended by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic features, or psychomotor retardation.

The DSM-5 mood disorders work group, however, determined that little evidence existed to separate depressive symptoms following the loss of loved ones from depressive symptoms that develop following other losses or those following significant stressors in general (Kendler et al. 2008). Thus, unless depressive symptoms that occur after any significant stressor are to be excluded as indications of an illness, retention of the bereavement exclusion criteria was untenable. This change was viewed in some quarters as a play by organized psychiatry to "pathologize" normal human reactions and to thus increase patient populations (New York Times). Others, though, put forward evidence that suspension of the bereavement criteria was likely to result in minimal increases in the numbers of individuals given diagnosis of MDD by providers (Zisook et al. 2013).

DSM-5 expanded the boundaries of *pregnancy-related mood disorder* from 1-month postpartum in DSM-IV to any onset during the pregnancy or during the 2 months following delivery. This change arose in large part from evidence that a large portion of women with a depressive syndrome during the postpartum period experienced onset during pregnancy (Gotlib et al. 1989). While much has been written concerning the risks for, and adverse effects of, depression during pregnancy, evidence that pregnancy is a high-risk period for depression onset is scant. A comparison of the risk for depressive episodes during pregnancy to the risk during the 9 months preceding pregnancy showed no significant difference in a large community sample (Vesga-Lopez et al. 2008) though episode frequency was significantly higher during the postpartum period. That pregnancy does not protect against depression is shown by observations that most euthymic women who discontinue an antidepressant when they discover their pregnancy eventually relapse during pregnancy (Cohen et al. 2006). Most postpartum onsets develop within 1 month of delivery, and psychotic, mixed, or manic episodes have particularly rapid postpartum onsets (Di Florio et al. 2013).

In addition to the clustering of onsets following parturition, family studies have provided evidence that mood disorder episodes with postpartum onset differ from those with onset at other times. At least three sib-pair studies (Forty et al. 2006; Jones and Craddock 2001; Murphy-Eberenz et al. 2006) and one twin study have shown that postpartum onset has a significant familial component.

DSM-5 criteria for a diagnosis of *catatonia* require at least 3 symptoms from a list of 12, of which mutism, stupor, and catalepsy are perhaps the most common (Krishna et al. 2011; Morrison 1973). This syndrome can complicate schizophrenia, mania or major depressive episodes, drug intoxication or withdrawal, or a wide variety of medical conditions. A substantial minority of cases do not appear to have an underlying medical or psychiatric diagnosis (Krishna et al. 2011; Barnes et al. 1986). Such cases may be highly recurrent with some consistency in the presence of

catatonic symptoms across episodes (Francis et al. 1997). Catatonia with or without other underlying illnesses also appears to be familial (Barnes et al. 1986).

A prompt response to benzodiazepine administration is widely accepted as diagnostic of catatonia. Because patients with catatonia are at increased risk for developing neuroleptic malignant syndrome (Berardi et al. 2002), it is prudent to treat a catatonic state with benzodiazepine before antipsychotics are introduced (Rasmussen et al. 2016). Maintenance treatment with benzodiazepines may prove necessary in some cases (Thamizh et al. 2016).

ICD and DSM iterations have long distinguished *single episode and recurrent MDD*. Many studies have shown that patients with a recurrent major depression have shorter times to relapse following recovery (Maj et al. 1992; Pintor et al. 2004; Keller et al. 1983a; Gonzales et al. 1985). The number of previous episodes is a stronger predictor of relapse risk than is the simple separation of single vs. one or more prior episodes. Others have found that patients with recurrent depression are more likely to have family histories that are positive for depressive disorders as well as earlier ages of onset (Hollon et al. 2006). Patients with multiple prior major depressive episodes are more likely to eventually switch to a bipolar diagnosis than are patients with fewer episodes (Angst et al. 2003).

According to DSM-5, "full remission has occurred when two months have passed with no significant signs or symptoms of the disturbance were present." Other groups have proposed more nuanced definitions to indicate the concepts of response, recovery, remission, relapse, and recurrence. The terms "response" or "remission" as applied to most antidepressant treatment trials require only that depressive symptoms over the preceding week fall beneath a specified severity threshold such as 7 or less on the 17-item Hamilton Depression Rating Scale (Nierenberg and DeCecco 2001). Definitions put forward by the American College of Neuropsychopharmacology incorporated minimum durations of severity levels such that remission required at least 3 weeks at a clearly defined sub-criteria level while recovery required 4 or more months (Rush et al. 2006). An increase in symptoms to the criteria level after remission, but before recovery, was termed a "relapse," while such a symptom increase after recovery was a recurrence.

It is now well established that even residual depressive symptoms well below the numbers needed to meet the criteria for a major depressive syndrome are powerfully predictive of impairment, as well as of risk for recurrence (Judd et al. 1998, 2000). Accordingly, Judd et al. (2016) have shown that a mere 1-month period of fully asymptomatic recovery was a more powerful predictor of subsequent time well than any of 18 other potential predictors.

Definitions of a *chronic major depressive episode* in the RBC, and in each of the DSM iterations from DSM-III through DSM-5, specify the persistence of depressive symptoms for 2 or more years. Other proposals have specified 1 year or 3 years. Origins of the 2-year threshold are obscure, and it probably was not empirically derived. The DSM-IV definition required the persistence of 2 or more years of a full major depressive syndrome for the diagnosis of chronic depressive disorder. Depressive symptoms that persisted for 2 or more years, but which fell beneath the symptom number threshold for major depression, were designated as dysthymic

disorder. The DSM-IV definition of dysthymia was inherently unreliable, however, in that it required the absence of any 2-week period in the first 2 years of the illness during which symptoms rose to the full number and persistence required for a major depressive episode. This is a distinction that often involved the presence or absence of only a few symptoms during a 2-week period over a span of 2 years that may have occurred many years previously. Moreover, direct comparisons with DSM chronic major depressive episodes and dysthymic disorder failed to find differences in demographic variables, symptom patterns, treatment response, or family history (McCullough et al. 2000, 2003; Klein et al. 2004; Yang and Dunner 2001; Blanco et al. 2010). This lead to the change in DSM-5 in which chronic major depressive disorder has been merged with dysthymic disorder under the new label of *persistent depressive disorder*.

Whether chronicity is captured under the older criteria for chronic major depressive episode or under that for dysthymic disorder, patients who are so identified, in comparison with patients who have non-chronic episodes, have earlier onsets (Gilmer et al. 2005), higher levels of depressive morbidity over long prospective follow-up periods (Keller et al. 1983a, b; Gonzales et al. 1985; Klein et al. 1988, 2000; Coryell et al. 1990; Rhebergen et al. 2009, 2010), greater familial loading for affective disorders (Klein et al. 1988), greater likelihood of a coexisting personality disorder (Klein et al. 1988), higher levels of neuroticism (Rhebergen et al. 2010), a higher likelihood of suicide behaviors (Gilmer et al. 2005; Garvey et al. 1986), and more early adversity (Barnhofer et al. 2014).

DSM definitions of chronic major depressive episodes, dysthymia, and persistent depressive disorder are confined to non-bipolar individuals. Historical reasons for this are unclear. Chronicity in bipolar illness does not appear to be less common than in unipolar illness (Benazzi 1999; Angst et al. 2009).

Anxiety symptoms are frequent concomitants to depressive disorders, and evidence for their prognostic importance has become increasingly well-established over the past several decades. Whether the co-occurrence of anxiety symptoms with major depressive episodes is expressed as categorical comorbidity, as the coexistence of an anxiety disorder diagnosis, or as a quantification of anxiety symptoms, individuals with both MDD and anxiety states have more depressive morbidity in the short and long term (Coryell et al. 1992, 2009; Otto et al. 2006). They also have poorer responses to antidepressants (Fava et al. 2008; Papakostas et al. 2008) and to psychotherapy (Feske et al. 1998), and are at greater risk for suicidal behaviors (Sareen et al. 2005; Goes et al. 2012). There also appears to be a continuous positive relationship between anxiety symptom severity and the persistence of depressive symptoms over time (Coryell et al. 2009, 2012). This is true across a variety of anxiety symptom types and is an effect that endures with little change over decades of prospective follow-up. The comorbidity of MDD with anxiety disorders is apparently also familial (Goes et al. 2012; Kendler 1995). Kraepelin devoted a chapter to *mixed states* in his book *Manic Depressive Illness and Paranoid States* (1921). In it he described six subtypes and concluded that "they often occur in the transition between the fundamental forms (mania or depression). It may, however, appear as an independent morbid attack and, when this occurs, there is a certain

probability that similar states will follow later. The course of those mixed states when occurring as independent attacks appears in general to be lingering."

DSM-III, DSM-III-R, and DSM-IV reserved the term "mixed states" for individuals who met full criteria for MDD and mania concurrently. Such individuals, by definition, had bipolar disorder. The nomenclature provided no means to describe those individuals who had no history of mania or hypomanic episodes but who had subthreshold manic symptoms embedded within a major depressive episode. It is clear, however, that such individuals exist in significant numbers (Zimmermann et al. 2009) and that they have, in comparison to those with MDD but without accompanying manic symptoms, longer episodes, more morbidity over extended periods (Zimmermann et al. 2009; Persons et al. 2017; Benazzi 2001), poorer responses to antidepressants (Koukopoulos et al. 2007), and a higher likelihood of suicidal behavior (Persons et al. 2017). Recent evidence shows that individuals with mixed episodes are at a higher risk for suicide attempts because they spend more time in depressive states than do patients with no history of mixed states (Persons et al. 2017).

Not surprisingly, patients who experience manic symptoms within an episode of major depressive disorder are more likely to eventually develop a separate episode of mania or hypomania (Fiedorowicz et al. 2011a). In accord with this, the presence of manic symptoms in an episode of major depressive disorder is associated with an earlier age of onset and with greater familial loading for bipolar disorder. The likelihood of a family history of bipolar illness appears to increase with the number of manic symptoms present (Zimmermann et al. 2009). A receiver operating curve analysis, however, shows that the presence of three manic symptoms is the most efficient predictor of an eventual diagnostic switch to bipolar disorder (Fiedorowicz et al. 2011a). This is the number necessary for DSM-5 designation of MDD with mixed features.

4 Measurement

Two broad categories of instruments are available to quantify the severity of depressive symptoms – self ratings and clinician ratings. Each type has certain advantages and disadvantages over the other, and therapeutic trials typically use both. Congruence between self and clinician ratings may be lower during the more severe phases of depressive illness (Prusoff et al. 1972).

4.1 Self-Rated Scales

The Beck Depression Inventory (BDI) (Beck et al. 1961), the Inventory for Depressive Symptomatology (IDS) (Rush et al. 1986), and the Patient Health Questionnaire (PHQ-9) (Kroenke et al. 2001) are among the most commonly used self-rating scales. In comparison to the IDS, the BDI is weighted toward cognitive symptoms and less so toward vegetative symptoms. The PHQ-9 simply quantifies each of the

DSM criteria symptoms for a major depressive episode by the persistence of that symptom over the preceding week.

4.2 Clinician-Rated Scales

The Hamilton Rating Scale for Depression (HRS-D) (Hamilton 1960) and the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979) are probably the most extensively used clinician rating scales. The HRS-D places more emphasis on somatic symptoms than does the MADRS. Neither the HRS-D nor the MADRS reflect hypersomnia or hyperphagia. The clinician-rated counterpart to the self-rated IDS, the clinician-rated IDS-C (Rush et al. 1996), do take these symptoms into account.

5 Phenomenology

Dysphoria is one of the two A criteria symptoms for DSM-5 major depression and thus must be present for a diagnosis to be made if anhedonia is absent. While depressed mood is initially specified in criteria A for a major depressive episode, subsequent text indicates that a sad affect as reported by informants can be used to infer dysphoria. In many cases, particularly in medical settings, neither a depressed mood nor a depressed affect is apparent in the individual who satisfies many of the other criteria of a depressive syndrome. Alexithymia, as a stable feature, increases with age and may indicate dysfunction in the right rostral anterior cingulate cortex (Paradiso et al. 2008). A failure to manifest dysphoria either subjectively or objectively is also more likely in individuals who present with a focus on somatic symptoms. Such a presentation has been termed "masked depression" (Fisch 1987, 1997). Thus, self-rating screening tools may be particularly helpful in outpatient medical settings.

Anhedonia is also considered a core depressive symptom (criteria A). Depressed individuals may lose interest in, or derive no pleasure from, their work, hobbies, interactions with friends or family members, music, or sex. The inability to enjoy all facets of life, pervasive anhedonia, is nearly always included among symptoms of melancholia or endogenous depression, however defined.

A recent meta-analysis showed that anhedonia is strongly correlated with suicide ideation even after control for the severity of other depressive symptoms (Ducasse et al. 2017). A persistence of anhedonia also appears to account for most of the lag between improvement in depressive symptoms and psychosocial functioning during treatment (Vinckier et al. 2017).

Either "significant" *loss of weight or appetite*, or *gain in weight or appetite*, satisfies one of the nine criteria for a major depressive episode. Gains in weight or appetite, together with hypersomnia, are considered "reverse vegetative" symptoms and are more common in bipolar I or bipolar II depressive episodes than in non-bipolar depressive episodes (Andreasen et al. 1988; Coryell et al. 1985). They

also comprise two of the five features used to define the DSM-5 specifier "with atypical features." This syndrome was originally based on symptoms that appeared to separate responders to monoamine oxidase inhibitors from responders to tricyclic antidepressants (McGrath et al. 1992). Strong evidence subsequently appeared that reverse vegetative symptoms are the most important components or the atypical feature cluster (Benazzi 2002; Kendler et al. 1996). Atypical depression defined as such is associated with obesity and has a significant genetic determinant (Kendler et al. 1996). The association between obesity and depressive illness in general may be etiologically bidirectional (Coryell et al. 2016), and individuals who overeat are substantially more likely to be obese between episodes (Murphy et al. 2009).

Complaints within the same individual of both *insomnia* and *hypersomnia* in a major depressive episode are particularly characteristic of those with a bipolar diagnosis (Geoffroy et al. 2018). Insomnia, more than most other depressive symptoms, is a relatively robust risk factor for completed suicide (Bernert et al. 2015). This aligns with observations that the most likely time for suicide to occur in the United States population is from 2:00 to 3:00 a.m. (Perlis et al. 2016).

Fatigue, or the subjectively perceived lack of energy, is among the most consistently reported symptom in major depressive episodes and has been identified as the one that most interferes with work functioning (Lam et al. 2012). It is also one of the most common residual symptoms following antidepressant treatment, and this persistence accounts for much of the impairment in functioning associated with incomplete remission from depressive episodes (Fava et al. 2014).

The DSM describes the criteria symptom of *self-reproach* as "feelings of worthlessness or inappropriate guilt." More than the other criteria symptoms for major depressive episodes, it is often difficult to identify the threshold above which self-criticism and remorse reaches the symptomatic level. The qualities of guilty feeling described by a patient deserve particularly careful attention in that the boundary between a painful preoccupation and a delusion can be a subtle one. As noted earlier, the distinction between delusional and non-delusional depression has important implications for treatment selection and for prognosis.

Moreover, relatively few studies have focused on this component of the depressive syndrome. Those that have showed that self-blaming emotions occur in the large majority of depressive patients and that they correlate closely with depressed mood, hopelessness, and with overall depressive symptom severity (Zahn et al. 2015). A study that tested the robustness with which individual criteria symptoms separated individuals with depressive disorders from comparison groups found guilt to be the most important discriminator, both from individuals with no illness and from those with generalized anxiety disorder (Breslau and Davis 1985). Individuals with past major depressive episodes appear more likely than those with chronic medical illness to have persistent feelings of guilt (Ghatavi et al. 2002).

In psychiatry the term *agitation* refers to non-purposeful hyperactivity that is often manifest as fidgetiness, hand wringing or pacing, and that is accompanied by feeling of inner tension. It should be distinguished from the hyperactivity that characterizes manic or hypomanic states in that the latter is purposeful, albeit marked by inconstancy and distractibility. It is regularly included among the features of

melancholia and is more prominent in depressed patients with psychotic features than in non-psychotically depressed patients (Coryell et al. 1985).

Individuals with psychomotor agitation are also much more likely to have a history of *psychomotor retardation* (Maj et al. 2006). Some have argued that agitation should be diagnostically linked to bipolar disorder and considered, together with subthreshold manic symptoms, as indicative of a mixed state (Benazzi et al. 2004). Evidence for this was not sufficient for the inclusion of psychomotor agitation in the DSM-5 criteria for the MDD mixed states specifier, however.

As noted, histories of psychomotor retardation and those of agitation are likely to coexist. Taken together, depressive syndromes marked by agitation or retardation have some stability across repeated episodes (Coryell et al. 1994b). Retardation is also notable because it shades into catatonia as severity increases. Psychomotor retardation, together with psychotic features, are the only symptoms found to distinguish responders to real ECT from responders to sham ECT (Crow et al. 1984).

Self-described *concentration difficulties* experienced by depressed patients have been shown to correlated strongly with health-related quality of life, independent of the severity of other depressive symptoms (Fattori et al. 2017). Subjectively rated problems with concentration also correlate with objectively measured cognitive deficits. Research into the implications of such objectively measured cognitive deficits for consequent impairment, course of illness, and both neuroanatomical and neurofunctional abnormalities is extensive. Notably, both subjectively and objectively measured deficits make contributions to disability ratings beyond the contribution of other depressive symptoms (Naismith et al. 2007). The search for treatments that specifically target cognitive deficits in depressive disorder is understandable in this light (Salagre et al. 2017).

Nearly all psychiatric disorders confer an increased risk for *suicidal behavior*. Largely because of its relatively high prevalence, the majority of individuals who die by suicide do so while in a depressive syndrome (Yoshimasu et al. 2008). Of the nine criteria symptoms for major depressive episodes, only thoughts of suicide or suicidal behaviors necessitate a careful estimate of near- and long-term risks for future suicide attempts or suicide completions. The most consistently identified risk factor for completed suicide is a history of suicide attempts, even attempts in the distant past (Coryell and Young 2005). Among attempters, those that employed violent means carry much higher risks for eventual suicide (Runeson et al. 2010), and risks for all individuals admitted for suicidal ideas or behaviors are highest in the weeks following discharge (Mortensen et al. 2000). For patients psychiatrically admitted because of suicidal ideation or behaviors, the subsequent denial of suicidal plans should, of its self, not justify discharge. The illness, and other factors, that gave rise to the suicide threats or behaviors should have demonstrably improved as well.

6 Diagnostic Boundaries

Personality disorders often accompany MDD in clinical settings (Corruble et al. 1996) and have considerable importance when they do. Depressed patients with personality disorders have earlier onsets of depression (Charney et al. 1981;

Pfohl et al. 1984; Black et al. 1988), are more likely to have histories of suicide attempts (Pfohl et al. 1984; Black et al. 1988), have fewer melancholic symptoms (Charney et al. 1981; Black et al. 1988), and have higher rates of psychosocial adversity (Pfohl et al. 1984). Prospective studies show that depressed patients with personality disorders experience more depressive morbidity over time (Pfohl et al. 1984; Zimmerman et al. 1986; Shea et al. 1990) and a poorer response to treatment, whether that be treatment with antidepressants (Charney et al. 1981; Pfohl et al. 1984), with ETC (Zimmerman et al. 1986), or with psychotherapy (Shea et al. 1990).

Among the personality disorders listed in DSM-5, borderline and antisocial personality disorders are perhaps the most thoroughly studied. Patients with ASPD often present with suicidal thoughts or behaviors in the context of depressive symptoms, and an ASPD diagnosis maybe missed unless it is considered in the differential. If it is present, the likelihood of concurrent substance abuse is substantially higher and maybe the more appropriate treatment target.

The recognition of comorbid borderline personality disorder is particularly important for treatment selection and patient counseling. First, though many controlled trials have shown that some widely used antidepressants are globally effective for the various facets of BPD, some, such as SNRIs or bupropion, have not been tested in this population (Mercer et al. 2009). Similarly, RCTs have supported the use of valproate, carbamazepine, and topiramate, but lithium has not been tested. Moreover, the time in which depressive symptom ratings for placebo and active treatment groups separate is typically later than is the case at uncomplicated MDD. It is important that both the treating physician and patient know this.

Second, patients with depressive symptoms and BPD often have a history of multiple unsuccessful antidepressant trails and, in addition, often report auditory hallucinations that may be construed as psychotic features. This picture thus may result in referral for ECT treatment. However, direct comparisons of patients with depression and borderline personality to those with other personality disorders showed that the former group had significantly poorer ECT outcomes than did those with other personality disorders whose outcomes were no different from depressed patients without personality disorders (Feske et al. 2004).

Third, there exists a substantial overlap between features of BPD and those of bipolar illness. This overlap includes sudden shifts in mood, periods of irritability and recklessness, and a predisposition to substance abuse. Not surprisingly there is now convincing evidence that borderline personality disorder is being widely misdiagnosed as bipolar disorder in the United States (Zimmerman et al. 2010). Such misdiagnoses are likely to have the unfortunate effect of shifting treatment focus to one that emphasizes polypharmacy and an external locus of control. Indeed, there is some evidence that patients with borderline personality disorder who have been misdiagnosed with bipolar disorder have poorer outcomes than patients who have never been given a diagnosis of bipolar disorder (Zimmerman et al. 2010).

Many patients given a firm diagnosis of *schizophrenia* have received other diagnosis previously, and a mood disorder diagnosis is frequently among these. Such diagnostic instability is particularly likely among patients who present with major depressive episodes and psychotic features. In a rigorously designed study,

43% of patients who began follow-up with a diagnosis of MDD with psychotic features had a consensus diagnosis of schizophrenia at 10 years (Bromet et al. 2011). Notably, diagnostic shifts in the opposite direction, from schizophrenia to MDD, occurred in only 2.4% of cases. Those who switched from MDD to schizophrenia were more likely to have had an insidious onset and to have had a family history of MDD. Baseline variables were otherwise of little value in predicting this shift (Ruggero et al. 2011). Taken together these results show the importance of reassessments over time. A diagnosis of major depressive disorder with psychotic features that is based on a single assessment should be considered a provisional one.

Much more research addresses the likelihood of, and risk factors for, transitions from MDD to *bipolar disorder*. The rates of such switches are quite variable across studies but are generally lower in prospective studies that have employed structured diagnostic interviews in the baseline assessment. Manic symptoms are among the most consistent predictors in both adult (Fiedorowicz et al. 2011b) and child/adolescent samples (Biederman et al. 2014), and the risks appear to increase in a stepwise fashion with the number of manic symptoms observed. Perspective studies have also repeatedly identified an early onset, and a family history of bipolar disorder as robust risk factors for diagnostic shifts to bipolar disorder (Zimmermann et al. 2009; Fiedorowicz et al. 2011b).

7 Biology

Of the many labels assigned to syndromes now encompassed as depressive disorders, the term melancholia has been the most enduring and was described by Hippocrates over 2,400 years ago (Lewis 1934). Later physicians in the classical period, such as Aretaeus of Cappadocia and Galen, also provided similar descriptions. They noted its episodic nature and the frequent alternations with manic states. Efforts to systematically describe and classify psychiatric disorders were superseded by church teachings in the Dark and Middle Ages, and conditions that would now be considered psychiatric were attributed to demonic possession, witchcraft, and other supernatural causes. With the Renaissance the observations of the ancient writers again became influential. The attributions to a humoral imbalance with an excess of phlegm and black bile persisted.

In the seventeenth to the eighteenth centuries, writers proposed many classifications schemes for mental disorders. These were generally inclusive of melancholia, but none achieved clear ascendancy over the others. Early in the twentieth century, Kraepelin proposed the fundamental distinction between manic depressive illness and dementia praecox. Psychoanalytic thinking then dominated from the 1940s to the 1960s, particularly in American psychiatry. Psychoanalytic formulations generally viewed depressive states as being reactive or psychotic depending on whether an identifying loss could be identified in a given case. If it could, then the problem was assumed to arise from inwardly directed anger triggered by loss reminiscent of unresolved childhood conflict or by an overactive superego.

Coincident with the advent of effective pharmacotherapy for mood disorders and the advent of a medical model or "neo-Kraepelinian" school of thought, emphasis shifted to the value of explicit and inherently reliable criteria for mood disorder diagnosis. This strongly influenced DSM-III and its subsequent iterations. The perceived need for diagnostic reliability influenced the decision to apply the label of major depressive disorder to conditions widely acknowledged to be heterogeneous. Some have proposed a solution in which major depression is replaced by a distinction between melancholia and non-melancholic mood disorders (Shorter 2007). Questions as to whether the observed differences between melancholic and non-melancholic depression can be attributed solely to the greater severity associated with melancholic depression remain unresolved, however.

With effective drug therapies for schizophrenia and mood disorders came investigations into the role of neurotransmitters in these illnesses. For depressive orders this interest grew initially from evidence for the antidepressant effects of monoamine oxidase inhibitors that emerged in the late 1950s (Schildkraut et al. 1965; Schildkraut 1967), as well as the pro-depressant effects of reserpine (Harris 1957). In its simplest form, the *catecholamine hypothesis* posited that depressive illness resulted from a relative deficiency of *norepinephrine* and that its relative excess promoted mania. Subsequent studies of norepinephrine or of norepinephrine metabolite concentrations, whether in urine, blood, or cerebrospinal fluid, yielded very inconsistent results, however.

Interest in the role of *serotonin*, an indolamine, developed soon after that for the catecholamines. Replicated observations showed a bimodal distribution of CSF 5-HIAA concentrations in which groups with the lower concentrations were comprised of individuals with more severe or endogenous depressive symptoms (Asberg et al. 1976; Gibbons and Davis 1986).

Additional evidence that norepinephrine and serotonin play important roles in depressive illness derives from precursor depletion studies. A low tryptophan diet followed by a tryptophan-free drink of amino acids results in abrupt lowering of serotonin synthesis. Alternatively, the addition of alpha-methyl-para-tyrosine to the diet blocks the production of L-dopa and thus depletes norepinephrine (Berman et al. 1999). These manipulations result in the rapid onset of depressive symptoms among individuals who have responded to SSRIs (Delgado et al. 1990) or to norepinephrine reuptake inhibitors (Miller et al. 1996), respectively. These maneuvers do not produce depression in well controls or in individuals who have responded to the alternative type of antidepressant.

Far fewer studies have targeted the possible role of *dopamine* functioning in depressive disorder. However, because anhedonia is often given prominence in criteria for depressive disorders and because it appears to be associated with much of the resulting disability (Vinckier et al. 2017), the fact that the dopamine system is integral to motivational arousal makes it also a likely candidate. Evidence for this includes lower dopamine metabolite concentrations in the CSF (Reddy et al. 1992) and lower dopamine transport binding (Sarchiapone et al. 2006). Some controlled trials of augmentation with dopamine agonists in major depressive episodes exist (Madhoo et al. 2014), but their efficacy may be greater in bipolar depression (Szmulewicz et al. 2017).

Other systems are clearly involved in pathogenesis of MDD, but none of the drugs approved for treatment in the United States target them. Probably the most extensively researched of these is the *hypothalamic-pituitary-adrenal (HPA) axis*. Early evidence suggested that the HPA is hyperactive, as manifest in a positive dexamethasone suppression test (DST), and that this hyperactivity might be specific for melancholia (Carroll et al. 1981), bipolar depression (Schlesser et al. 1980), or psychotic depression (Nelson and Davis 1997). Other findings pointed to the utility of the DST in the prediction of long-term outcome in schizoaffective depression (Coryell et al. 1992; Coryell and Zimmerman 1989). Subsequent failures to show consistent levels of diagnostic specificity, however, resulted in disillusionment over the DST (Hirschfeld et al. 1983). The test is, consequently, not now in wide use. The recent review of 48 studies on this topic, though, pointed to the problems inherent and the varied definitions used for melancholia or endogenous depression and noted that HPA hyperactivity distinguishes melancholic from atypical depression with notable consistency (Juruena et al. 2017). Also of note is that follow-up studies have found positive DST results to be a robust predictor of eventual completed suicide among patients hospitalized for depressive disorder (Mann and Currier 2007).

Inescapable stress, a reliable inducer of a depression model in rodents, impairs long-term potentiation in portions of the hippocampus (Shors et al. 1989), an area rich in *N-methyl-D-aspartate (NMDA)*. Such observations prompted a search for drugs that had antidepressant effects through their effects, direct or indirect, on NMDA receptors (Trullas and Skolnick 1990). While a number of glutamate or NMDA receptor modulators have shown preclinical antidepressant effects (Jaso et al. 2017), ketamine, an NMDA antagonist, has shown the most promise. The first controlled trial of ketamine infusion (Berman et al. 2000) has been followed by at least nine controlled trials (Kishimoto et al. 2016). The fact that the administration of ketamine produces antidepressant effects that peak at day 1 has created considerable notice, particularly because reductions in suicidal thinking appear to show an especially robust and rapid response, even after control for the effects of ketamine on other depressive symptoms (Ballard et al. 2014; Murrough et al. 2015; Grunebaum et al. 2018). Several open trials (aan het Rot et al. 2010; Ghasemi et al. 2014; Vande Voort et al. 2016) and at least one RTC (Singh et al. 2016) have demonstrated that repeated administration of ketamine can sustain the antidepressant effects. Only one of these reports followed patients more than a week after the final infusion, and this one described a high relapse rate within a month of the last treatment (aan het Rot et al. 2010). A substantial minority of depressed patients, however, show sustained response even after a single administration. The means to identify such individuals would be of obvious importance, and a positive family history for alcoholism is the most replicated of the potential predictors studied (Pennybaker et al. 2017). This is notable because individuals with family histories that are positive for alcoholism, even if they are not alcoholics themselves, react to alcohol differently from those that lack such a family history (Schuckit 1994) and the behavioral effects of alcohol on humans prominently involve NMDA receptors (Krystal et al. 2003).

Though research into the neuropathogenesis of depressive illness has focused on monoaminergic systems, a role for gamma-aminobutyric acid (GABA) deficits is also likely (Luscher et al. 2011). GABA-A receptor function comprises an integral link between stress and the HPA axis (Mody and Maguire 2011) and thus between stress, either in childhood or later in life, and depressive illness. Lower GABA levels in the brain have been shown in the CSF (Kasa et al. 1982; Gerner and Hare 1981) and in the brain through the use of magnetic resonance spectroscopy (Sanacora et al. 1999). There is some evidence that these deficits are associated with symptom severity or with the melancholic subtype (Sanacora et al. 2004).

GABA levels are increased by various antidepressant treatments (Luscher et al. 2011), and one study indicated that such increases can be induced acutely by an infusion of an SSRI in well individuals (Bhagwagar et al. 2004). This implies that 5-HT receptor changes associated with antidepressant response exist downstream from acute changes in GABA.

The GABA deficit hypothesis also indicates the potential of neuroactive steroids as antidepressants. Thus, such positive allosteric modulators of the $GABA_A$-R receptor as pregnanolone and allopregnanolone have been tested recently as treatments for depressive illness (Brown et al. 2014) and for postpartum depression in particular (Deligiannidis et al. 2016; Kanes et al. 2017). In contrast to conventional antidepressants, and akin to ketamine, the response to infusions of allopregnanolone occurs within the first 24 h.

Yet another pathogenic mechanism, that of inflammation, holds promise for new antidepressant approaches. The administration of pro-inflammatory agents in the treatment of autoimmune disorders regularly results in depressive syndromes (Capuron et al. 2001, 2002, 2008), and many reports have described elevated cytokine levels in individuals with depressive disorders in comparison to well controls (Baumeister et al. 2014; Dowlati et al. 2010).

Increased inflammation may explain, at least in part, links between specific underlying risk factors and the onset of depressive illness. Supporting evidence exists for adiposity (Bond et al. 2016; Miller et al. 2003), childhood trauma (Cattaneo et al. 2015; Danese et al. 2007; Li et al. 2013), metabolic syndrome (Capuron et al. 2008; Vogelzangs et al. 2014), and relative deficiencies in omega-3 fatty acids (Dinan et al. 2009). Some studies have also reported elevations in cytokine levels among individuals who have depressive illness and a history of suicide attempts in comparison to those with depressive illness but without past suicide attempts. Other reports have shown that levels of inflammatory markers decrease with antidepressant treatment (Li et al. 2013; Basterzi et al. 2005), but some have not (Brunoni et al. 2015; Eller et al. 2008; Hernandez et al. 2008), and it is unclear whether the benefits of conventional antidepressants accrue at least in part, through their anti-inflammatory effects.

There have been efforts to take a more direct approach and to use medications known as anti-inflammatory agents as antidepressants. These have included polyunsaturated fatty acids, cyclooxygenase (COX) inhibitors, anti-TNF-alpha, and minocycline (Fond et al. 2014). Efforts have met with some success (Akhondzadeh et al. 2009; Kappelmann et al. 2018; Muller et al. 2006) though this approach may have more benefit for those with elevated inflammatory levels at baseline (Raison et al. 2013).

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Tricyclic Antidepressants and Monoamine Oxidase Inhibitors: Are They Too Old for a New Look?

Ravikumar Chockalingam, Britt M. Gott, and Charles R. Conway

Contents

Abstract

Through unintentional discovery, monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) were the first antidepressant classes to be used clinically and have been widely available for over half a century. From the 1950s to the 1980s, these two classes of antidepressants were the sole antidepressant tools available to psychiatrists. With the advent of the selective serotonin reuptake inhibitors (SSRIs) in the 1980s and 1990s, the prescribing of the MAOIs and TCAs has fallen significantly worldwide. In this chapter, we take a closer look at the arc of MAOI discovery and clinical use, and how these two classes of drugs compare to each other. This is important because relatively few studies compare these older classes of drugs to the newer classes of antidepressants. Finally, we

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argue that TCAs, and particularly MAOIs, should continue to play an important role in the modern treatment of depression, especially in the treatment-resistant patient.

Keywords
Antidepressant classes · Major depression · Monoamine oxidase inhibitors · Prescribing considerations · Psychopharmacology · Treatment-resistant depression · Tricyclic antidepressants

1 Historical Background

The "golden age" of psychopharmacology of the 1950s saw the serendipitous discovery of two distinct classes of psychotropic medications, monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs). This was a critical period for psychiatry as the field was experiencing a paradigm shift with the emergence of the "medical model" of psychiatric illness (i.e., that psychiatric illnesses consisted of reliably identifiable symptoms that could respond to somatic treatments).

The systematic use of hydrazine compound derivatives as antidepressants may have occurred in the early 1950s, but the original concept of using such compounds dated back to the research laboratories of Emil Fischer as early as the 1870s. While Emil Fischer went on to synthesize phenyl hydrazine a few years later, the drug appeared largely dormant in terms of its research and clinical use over the next four decades. In the early 1950s, its use as a prominent therapeutic modality was better elucidated. The antituberculosis drug iproniazid, with known MAOI properties, is credited with the first documented case of serotonin syndrome in a patient treated for tuberculosis in the mid-1950s. The observed mood benefits, which were an accidental finding, planted the seed for the first antidepressant in the 1950s. As one observer noted:

> Patients were dancing in the halls tho there were holes in their lungs. – Observation of tuberculosis patients receiving iproniazid at the Sea View Hospital, NY, 1953 (Sandler 1990).

The effects of this random discovery were monumental with close to half a million early adopters within the first year. Though touted as a "psychic energizer," the fall of iproniazid was heavily influenced by liver toxicity and hypertensive crisis, which significantly dampened enthusiasm for the drug's clinical use. However, the overall development of MAOI antidepressants in this time period arguably became a cornerstone in psychopharmacology, inspiring numerous advancements that followed.

Unlike MAOIs, the TCAs were a novel class of drugs created by modifying the phenothiazine ring and substituting sulfur for an ethylene bridge. It was the search for better antipsychotic drugs, following the relative success of chlorpromazine, that led clinicians and researchers down the path to the development of imipramine, the prototypical TCA, which was subsequently FDA approved in 1959. At that time,

the mechanism of action of imipramine was unknown, and it was classified based on the drug's benzene ring, in contrast to current antidepressant nomenclature, which classifies medications based on their actions on specific neurotransmitter systems (Hillhouse and Porter 2015). Though imipramine failed as an antipsychotic, patients had significant mood benefits. In his famous 1958 essay, Kuhn described the differences noted in psychiatric patients receiving imipramine:

> The patients get up in the morning of their own accord, they speak louder and more rapidly, their facial expression becomes more vivacious. They commence some activity on their own, again seeking contact with other people, they begin to entertain themselves, take part in games, become more cheerful and are once again able to laugh. (Kuhn 1958).

In the 1960s, Sulser and Axelrod converged on the idea that both TCAs and MAOIs exerted their therapeutic effects by increasing synaptic serotonin and catecholamine concentrations. This in turn set the stage for an era of rational drug development with newer medication classes targeting specific neurotransmitter classes across a multitude of sites (Ramachandraih et al. 2011).

In the coming years, newer MAOIs (i.e., isocarboxazid, phenelzine, and tranylcypromine, referred to as the "classic MAOIs") emerged with higher potency and fewer side effects relative to iproniazid. The classic MAOIs, along with selegiline, are currently the four FDA-approved MAOIs in the USA. The use of selegiline for depression is relatively recent: it was initially restricted to Parkinson's disease, but over time lower dose selegiline transcutaneous patches (e.g., Emsam) have demonstrated therapeutic benefit for depressive symptoms, while bypassing dietary restrictions with fewer side effects.

Historically, MAOIs were classified either by chemical structure (e.g., hydrazine versus non-hydrazine [tranylcypromine]), or through receptor isoform selectivity (MAO-A, MAO-B, or both), as well as their reversibility (reversible or irreversible) (Thase et al. 1995). Two MAO receptor isoforms, MAO-A and MAO-B, were identified with the older drugs irreversibly inhibiting both isoforms. It was later shown that selective blockade of MAO-A alone also offered similar therapeutic benefits compared to inhibition of both MAO-A and MAO-B. Adrenaline, noradrenaline, and serotonin are deaminated through MAO-A receptors, whereas benzylamine and B-phenylethylamine are substrates for MAO-B receptors. Dopamine and tyramine use both isoforms. This encouraged the search for both reversible and selective MAO-A inhibitors for depression and MAO-B for Parkinson's disease.

2 Studies Comparing MAOI and TCA Antidepressants: Do Certain Subtypes of Depression Respond Selectively to One Class of Antidepressant?

Compared to placebo, MAOIs and TCAs have consistently demonstrated superior treatment of depressive symptoms both in terms of response and remission, respectively, defined as a Hamilton Depression Rating Scale (HDRS) improvement of 50%

in depressive symptoms and a score of less than or equal to 7. Initially, there were relatively few studies comparing the efficacy of MAOIs and TCAs; these early studies pointed to TCAs having an efficacy advantage over MAOIs. However, subsequent studies demonstrated superior efficacy of the MAOIs, especially in depression with atypical features (Lecrubier and Guelfi 1990).

More recent studies focused on individual drugs within these two classes. Rowan et al. (1982) looked at the efficacy of phenelzine and amitriptyline compared to placebo for neurotic depression and found similar effect sizes, both demonstrating a significant improvement over placebo. The same studies also inferred that both phenelzine and amitriptyline improved symptoms of depressed mood and content of thought; phenelzine fared better for anxiety symptoms, and amitriptyline was superior at improving anergia. The authors also concluded that MAOIs may be a preferred class of medications for comorbid anxiety and depression (Rowan et al. 1982).

Thase et al. (1995) conducted a systematic review, which compared the efficacy of the three classic MAOIs between 1959 and 1992. This review of 55 randomized controlled trials (RCTs) included 36 RCTs involving MAOIs versus placebo and 44 RCTs involving MAOIs compared to one another. The authors found an estimated response rate of phenelzine to be 54.3% (±9.6%) in placebo-controlled studies; further, phenelzine demonstrated a small advantage over TCAs among outpatient studies, a gap that closed significantly when the sample of atypical depression was removed from the analysis.

As a result, the scientific community arrived at a consensus that atypical depression was a separate, distinct clinical presentation of major depressive disorder (MDD), which was then reflected in the Fourth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association 1994). Overall, studies from this era consistently demonstrated MAOIs to have superior clinical efficacy in this atypical subtype of depression.

Though the MAOI's appeared to be superior for atypical depression, imipramine, the prototypical TCA, had greater antidepressant efficacy in hospitalized, depressed patients than phenelzine (Martin 1963). In contrast, other TCA versus MAOI (imipramine versus phenelzine) studies in psychiatric inpatients found comparable efficacy at higher doses of phenelzine (Davidson et al. 1981). These differences could largely be explained by dose discrepancies, study design as well as study duration. For example, the target phenelzine dose was 81 mg/day; subsequent studies have determined this to be a reasonably effective dose among outpatients as well.

In 1992, Thase et al. (1992) published an open-label study with 60 patients who had failed a trial of imipramine (mean maximum dose of 260 mg), who were then treated with either phenelzine (60 mg/day) or tranylcypromine (38.5 mg/day). This study found that 58% of those failing to respond to imipramine responded to the MAOIs, with significant reversal of neurovegetative symptoms. In particular, the majority of the patients who received tranylcypromine experienced reversal of anergia. While the amphetamine-like properties of tranylcypromine are known to be more activating than phenelzine, it is unclear if this propensity had a significant

bearing on drug selection at the time of the study. Finally, another trial (Thase et al. 1995) further compared the four FDA-approved MAOIs from five previously published RCTs but could not conclude relative efficacy of one over another. However, the relative superiority of certain target symptoms, such as melancholia and anergia, favored tranylcypromine, whereas patients with anxious depression responded better to phenelzine (Thase et al. 1995). This symptomatic distinction is likely critical in identifying which depressed patients are most appropriate for a specific MAOI. Failure to do so may contribute to worsening of certain target symptoms, leading to potential MAOI discontinuation, biasing the perception of the relative ineffectiveness of this drug class.

A review of MAOIs by Quitkin et al. (1979) detailed the use of phenelzine in "non-endogenous depression." This depressive presentation terminology is not typically used in modern psychiatry: the authors defined endogenous depression as, "disabling depressive symptomatology," "anxious depressives," and a "concoction of anxiety with mild neurotic symptoms similar to the anxious hysteria" (Quitkin et al. 1979). In this trial, patients with non-endogenous depression who had previously failed TCAs or benzodiazepines were randomized to phenelzine at doses ranging between 45 and 75 mg/day or placebo. The phenelzine group had significant improvement in mood symptoms, anxiety, hypochondriasis-agitation as well as change in psychomotor status. A subsequent study by Robinson et al. (1978) reaffirmed these findings and inferred that response to phenelzine occurred most in patients with non-endogenous depressive symptoms at daily doses greater than 30 mg. The literature consensus of this era supported a significant benefit of both MAOIs and TCAs over placebo (Davidson et al. 1981; Himmelhoch et al. 1982; Rowan et al. 1982; Liebowitz et al. 1984; Paykel 1995; Birkenhager et al. 2004).

In summary, studies that compared TCAs to MAOIs did not offer a clear therapeutic distinction favoring either class; however, both classes of medications demonstrated convincing antidepressant efficacy in comparison to placebo. Studies did highlight possible niche uses of the two classes, with atypical depression and depression comorbid with personality disorder, or perhaps severe anxiety, being slightly more responsive to MAOIs, and TCAs offering an edge over MAOIs in hospitalized depressed patients. However, in general, these distinctions are no longer considered when discerning the class or type of medication initiated to treat depression.

3 More Recent Studies of Tricyclic Antidepressants and Monoamine Oxidase Inhibitors

Since the 1980s, there has been a paucity of literature comparing MAOIs to TCAs. One study by Liebowitz et al. (1984) compared phenelzine to imipramine in atypical depression in a double-blind, randomized placebo-controlled trial ($N = 60$) and demonstrated significantly higher response rates with phenelzine (67%) compared to imipramine (43%) or placebo (29%). Atypical depression included histrionic or labile symptoms and, along with borderline personality, was measured using the

Schedule for Affective Disorder and Schizophrenia rating scale (SAD-C) as well as the 90-item Hopkins Symptoms Checklist (SCL-90). Outcome measures were determined using the Clinical Global Impression-Improvement Scale (CGI-I), SAD-C, SCL-90, and Hysteria-Dysphoria Symptoms ratings (HDS; extracted from the SAD-C). Notably, imipramine did not perform better than phenelzine on any of the primary or secondary outcome measures (Liebowitz et al. 1984). While the preliminary report was published in 1984, the final report in 1988 outlined four broad atypical features including hyperphagia, hypersomnolence, leaden feeling, and rejection sensitivity.

Birkenhager et al. (2004) conducted a 5-week, inpatient, randomized trial comparing phenelzine to tranylcypromine in 77 patients who met DSM-IV criteria for MDD and had failed either a TCA (imipramine or clomipramine at therapeutic serum levels) or fluvoxamine. Response was defined as a 50% reduction in depressive symptoms as determined by the HDRS, and depression severity was measured using the HDRS and the CGI. Thirty-nine patients received tranylcypromine (mean dose 60.5 mg day $\pm$2.9) and thirty-eight patients received phenelzine (mean dose 79 mg day $\pm$2.7). Forty to fifty percent of subjects showed response with no clear difference between the two medications. This study further supported the contention that MAOIs may be of significant benefit in severely treatment-refractory depression (Birkenhager et al. 2004).

A review of the MAOI and TCA antidepressant classes would be remiss without reviewing the findings of the largest prospective, open-label study of more than 2,700 enrolled MDD patients: the STAR*D (Sequential Treatment Alternatives to Relieve Depression) trial (Rush et al. 2006). This National Institute of Mental Health-sponsored study was conducted at more than 40 sites over a 6-year period at a cost of ~$35 million dollars. From the perspective of MAOIs, the findings were disappointing for tranylcypromine (response rate of 7%), while phenelzine was not included as an antidepressant in this trial. Further, in order to receive tranylcypromine or nortriptyline, patients had to qualify for Level 4 of the trial, which means that they had failed the three previous levels of the study. Psychiatric epidemiologists concur that the rates of remission dramatically fall with each failed trial of medications (Little 2009); therefore, by Stage 4 of the study the overall potential for success was low. Hence, the STAR*D trial's use of both TCAs and MAOIs was relegated to those highly predisposed to nonresponse, i.e., only those patients who had already failed at least three antidepressant/augmentation trials. Due to the overall response rate in the trial, this design aided in supporting the belief that older classes of medication were perhaps superior for treatment-resistant depression. It may have served the STAR*D trial better had Stage 4 been symptom driven, e.g., a depressed patient with anxiety would preferentially be given phenelzine, whereas an anergic depressed patient given tranylcypromine. Further, one could argue that the dose of tranylcypromine was suboptimal (mean dose of 36.9 mg) and few participants completed an adequate trial of the drug. Finally, limited evidence exists to support the idea that MAOIs are superior in treating depressed patients with comorbid personality disorders (Hori 1998); although this points to a limitation of STAR*D: the trial made no effort to *apriori* identify personality disorders.

A relatively recent meta-analysis compared the newer class of selective serotonin reuptake inhibitors (SSRIs) to TCAs and placebo for treatment of depression in the primary care setting (Arroll et al. 2005). This work is particularly important as the majority of MDD is treated in the ambulatory primary care setting, while most TCA trials have been conducted in inpatient psychiatric settings. This meta-analysis gathered data from established medical and psychiatric databases up until February 2003, including MEDLINE and Cochrane Databases. The findings reinforced the notion that both TCAs and SSRIs significantly improved both discrete and continuous outcomes of depression in primary care. With 890 patients on SSRIs (sertraline, citalopram, or escitalopram), 596 subjects on TCAs (doxepin or imipramine), and 1,267 patients on placebo, the meta-analysis determined a relative response rate (relative risk) of 1.26 and 1.37 for the TCA and SSRI arms, respectively, both statistically superior to placebo. The number needed to treat (NNT) was 4 for TCAs and 6 for SSRIs, while the number needed for adverse effects was slightly higher for TCAs, consistent with the concept that fewer side effects are observed with SSRIs than TCAs. Perhaps surprisingly, the authors further observed that tolerance and discontinuation rates between the two classes were largely negligent; hence, the authors concluded that TCAs at lower doses may have comparable efficacy, safety, and tolerance compared to the SSRIs in the primary care setting (Arroll et al. 2005).

In summary, despite evidence showing comparable to superior efficacy with these medication classes, the emergence of SSRIs and serotonin and norepinephrine reuptake inhibitors (SNRIs), antidepressants with relatively fewer dangerous side effects and limited risks in overdose, significantly contributed to the decreased use of the TCAs and MAOIs. Further, the use of the MAOIs and TCAs in the landmark STAR*D trial was intentionally at a stage of greater treatment resistance, which did not allow these medications fair opportunity to demonstrate their potential efficacious advantages.

4 The Under-Prescribing of Monoamine Oxidase Inhibitors and Tricyclic Antidepressants: A Justifiable Phenomenon?

The meteoric rise of the MAOIs and TCAs profoundly influenced biological psychiatry and inspired the search for newer psychotropic medications. It led researchers and clinicians across the globe to search for neuroreceptor- and neurotransmitter-based treatment modalities to treat psychiatric illness. One outcome of this was the emergence of the SSRIs in the 1980s and newer antidepressants in the 1990s. These newer class antidepressant medications had safer side effect profiles, and greater safety (especially in regard to overdose), radically shifted psychiatrist and primary care physician prescribing practices away from the MAOIs and TCAs. Concurrently, patient and practitioner perception of these older classes were oftentimes detrimentally shaped by an exaggerated fear of their associated risks. While definitive risks exist, several perceived risks might have been mitigated by careful prescription practices. Instead, intelligent marketing by the pharmaceutical industry, fear of litigation, and promoting drugs that were relatively easy for primary care providers

to use led to the systematic exodus of MAOIs and TCAs from the psychotropic armamentarium starting in the early 2000s (Balon et al. 1999; Krishnan 2007). Two decades later, MAOIs and TCAs seemingly have become a historical footnote, with the current generation of early career psychiatrists rarely, if ever, using these vital classes of medications. A significant growing concern regarding the failure to employ these medications, particularly the MAOIs, exists in treatment-refractory depressed patients.

As previously mentioned, underutilization of MAOIs and their systematic withdrawal from clinical use started with the infusion of newer and safer medications. However, closer investigation of this under-usage suggests unwarranted fear and hesitancy on the part of treating clinicians. The perceived serious side effects of MAOIs, most notably serotonin syndrome and hypertensive crisis, have been demonstrated to be relatively rare, while the less serious and more common side effects (e.g., orthostatic hypotension, insomnia, weight gain, and sexual dysfunction) are not unique to the MAOIs. A 10-year population-based cohort study that looked at MAOI prescription practices in Canada between 1997 and 2007 found a drop in new prescriptions from 3.1/100,000 to 1.4/100,000. More alarming was the drop in overall prevalence of MAOI prescriptions from 400/100,000 to 216/100,000. During this period, only 1 in 500 prescriptions for MDD was an MAOI. Interestingly, the authors also tracked hospital visits during this same period in patients taking psychotropic medications. Out of 221 patients who presented to the hospital during the 10-year period, no reported cases of hypertensive urgency or serotonin syndrome were reported. While overdoses were observed, the perceived danger that contributed to lower prescription rates was not observed in the severity and frequency of observed side effects, further reiterating limited experiential bias over scientific rigor in selecting MAOI's for treating depression (Shulman et al. 2009).

A high profile editorial in the 1963 Lancet (Hypertensive crisis and monoamine oxidase inhibitors 1963) may have captured the tone for the hesitancy to use the MAOIs. This piece described reports of hypertensive crises induced by patients taking MAOIs who had cheese as a mainstay of their diets. While in some cases there was no cheese exposure, the authors' described accounts of "devastating headache," "intracranial bleeding," and urged the medical community to "reexamine use of MAOIs." Additionally, a few years later, a British pharmacist noticed severe headaches every time his wife consumed cheese while on an MAOI medication. It was later determined that consumption of aged cheeses mimics a clinical condition similar to pheochromocytoma (symptoms of sympathetic overdrive, i.e., palpitations, tachycardia, elevated blood pressure, increased respiratory rate, and headache) resulting from elevated levels of epinephrine and norepinephrine. This "cheese reaction" results from inhibition of tyramine breakdown that ordinarily occurs via the MAO enzymes in the lining of the gut (Sathyanarayana Rao and Yeragani 2009). A "high tyramine diet" (approximately 40 mg of tyramine/day) will have little effect on an unmedicated individual. However, in patients on an MAOI, even a small dose (i.e., 8 mg of tyramine) was shown to potentially induce a hypertensive urgency (Stahl and Felker 2008).

As critical as it is to effectively warn patients receiving an MAOI about dietary restrictions, it should be noted that commonly consumed foods in the modern era (e.g., pepperoni or cheese pizza), that were previously presumed to be dangerous if consumed while taking an MAOI, were found to be safe with no appreciable tyramine levels (Shulman and Walker 1999). A summary of sympathetic symptoms associated with tyramine doses as well as these revised dietary restrictions can be found in Tables 1 and 2, respectively. However, even the revised (reduced) tyramine dietary restrictions did not influence both patient and provider perceptions around MAOIs, as the rate of prescription of these medications continued to drop.

Not surprisingly and in light of perceived concerns, a 1990 survey of the prescription practices of 485 psychiatrists from Pennsylvania and Delaware showed that only 25% of psychiatrists prescribed MAOIs regularly (Clary et al. 1990). Similarly, a 1999 study of the prescribing practices of the psychiatrists by the Michigan Psychiatric Association ($N = 573$) found that only 25% of psychiatrists

Table 1 Sympathetic symptoms associated with range of dietary tyramine consumed

Amount of tyramine in milligrams	Adverse effects
6–8	Hypertension, tachycardia, GI symptoms
10–25	Headache, increased risk of bleeding/stroke
>25	Hypertensive crisis

Table 2 Updated dietary restrictions for use of MAOI class antidepressants

	Food/drink	Weight	Estimated tyramine milligram equivalent
Cheese	New York cheddar	1 oz	42 mg
	Swiss	1 oz	28 mg
	All aged cheese	1 cup	Considered high
	All cheddar (especially with storage)	1 oz	Considered high
	Other types of cheese (American cheese, pasteurized American cheese, Parmesan cheese, and Farmer's cheese)	1 oz	Acceptable
	Romano, cottage, ricotta, and cream cheese	Up to 2 oz	
Alcohol	Tap beer	12 oz	38 mg
	Red wine	4 oz	0–0.6 mg
	Canned beer	1 can	1.5 mg
Meat	Dry sausage	1 oz	3–43 mg
	Salami	1 oz	1.2–5.4 mg
	Smoked fish	1 oz	Considered high
	Aged chicken liver	1 oz	60 mg
	Pepperoni	1 oz	1.75 mg
	All canned meat consumed immediately upon opening	2–4 oz	Insignificant
	All fresh meat, poultry, fish or chicken liver consumed on day of purchase	2–4 oz	Insignificant

regularly prescribed MAOIs. The reasons listed for not prescribing MAOIs included preference for newer antidepressants medications, avoidance of dietary modifications, and side effect profile. Interestingly, despite their failure to prescribe these medications, close to 94% of psychiatrists believed MAOIs to be superior for use in atypical depression, and more than half described MAOIs as advantageous for melancholic depression and panic disorder (Clary et al. 1990). Similarly, Conway et al. (2015) described a group of 79 severely treatment-resistant depressed patients seen in a treatment-refractory depression referral clinic in the Midwestern United States that despite having on average eight previous adequate dose/duration trials of antidepressants, 37% had never been exposed to an MAOI. This reflects the current hesitancy of clinicians to employ MAOIs and may contribute to chronic suffering in refractory MDD.

Finally, the "wash-out" period is critical to understanding the pharmacokinetics of MAO receptors. In the case of irreversible blockade of medications such as phenelzine and tranylcypromine, it is important to allow a 2-week wash out period, as that is the time required to generate new MAO receptors. This is an important consideration, as many patients with some degree of treatment resistance, or ongoing psychiatric decompensation, requiring a medication change may find it impractical to wait 2 weeks. Consideration of potential short-term use of inpatient psychiatric hospitalization for the purpose of initiating an MAOI might be reasonable. Further complicating prescription practices, deinstitutionalization (the move from inpatient care of psychiatric patients in the pre-1960s) likely played a role in the decreased use of MAOIs, as most clinicians felt uncomfortable switching from a "standard" antidepressant to an MAOI in the outpatient setting. Though, as we argue in this chapter, the fears are often unfounded; rapid initiation of an MAOI in patients recently on a "standard antidepressant" may represent a beneficial use of inpatient psychiatric hospitalization going forward.

In conclusion, the evolution of psychopharmacology, since the earliest serendipitous discovery of antidepressants, rests on the historic standing of these two classes of medications. An understanding of these antidepressants not only furthered our knowledge of the discipline, but it also paved the way for newer, and arguably safer, methods of treating and alleviating mental illness. While several of the risks posed by these medications are real and dangerous, many can be mitigated through careful patient selection and psychoeducation. As the symptomology of the unfortunate relatively common occurrence of treatment-refractory depressive illness is elucidated, the need for providers to use *every* resource available, including the TCAs and MAOIs, becomes vital.

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Clinical Implications of the STAR*D Trial

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Abstract

This chapter provides a synopsis of the clinically relevant findings derived from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study and selected ancillary studies appended to the primary trial. The chapter describes the participants, their recruitment and treatment, and the study design, primary outcomes, and clinically informative results. In particular, the chapter describes acute phase response and remission rates from each of the five treatment steps which entail antidepressant monotherapies and combinations, and psychotherapy alone or in combination with an antidepressant. In addition, longer-term outcomes beyond the 12 week acute trial are described for each treatment step. The treatment challenges described include patient retention and relapse, and longer-term follow-up. The chapter discusses the use of measurement-based care for delivering high-quality care, describes "treatment-resistant" depression and discusses its implications for clinical practice, and discusses the contributions of STAR*D to patient-oriented research and patient care.

Keywords

Depression · Pharmacotherapy · Practical clinical trial · Sequence treatment alternatives to relieve depression · Treatment resistance · Treatment steps

1 Introduction and Overview of STAR*D

This chapter provides a synopsis of the clinically relevant findings derived from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (Rush et al. 2004) and selected ancillary studies that were appended to the trial. Several reports summarizing some STAR*D findings are available elsewhere (Rush 2011; Rush et al. 2009; Warden et al. 2007a). The main aim of STAR*D was to determine the "next best treatment" for outpatients with nonpsychotic major depressive disorder (MDD) who had not achieved a satisfactory response after the initial or several treatment steps. The following highlights the key elements in trial design, clinical processes, recruitment, treatment delivery, and outcome assessments used in STAR*D. An understanding of these elements sets the stage for discerning what results apply in which circumstances and to which patients.

1.1 Participants

By design, STAR*D participants were representative outpatients who were seeking treatment for at least moderately severe nonpsychotic major depression diagnosed by clinical interview and confirmed with a checklist using DSM-IV symptomatic criteria for a major depressive episode. Participants were patients in public- or private-sector primary or psychiatric care clinics/practices. The design did not

Table 1 Demographic features of STAR*D participants by treatment step (Adapted from Rush et al. 2006a, b, c, d)[a]

Feature	Treatment step[b]			
	Step 1 ($N = 3,671$)	Step 2 ($N = 1,439$)	Step 3 ($N = 390$)	Step 4 ($N = 123$)
	Mean	Mean	Mean	Mean
Age	40.7	41.5	43.6	46.4
Education (years)	13.5	13.4	13.1	13.1
Monthly household income	2,456	2,161	1,979	1,861
	%	%	%	%
% Female	62	59	51	49
% Races				
White	76	77	80	82
Black	17	17	16	15
Other	7	6	5	2
Hispanic	12	12	14	15
% Employment status				
Employed	58	54	49	46
Unemployed	36	41	45	47
Retired	6	5	6	7
% Medical insurance				
Private	53	47	45	43
Public	13	14	15	13
None	34	39	39	43
% Marital status				
Single	29	28	24	19
Married/cohabiting	42	40	42	46
Divorced/separated	26	28	29	30
Widowed	3	4	5	5
% Psychiatric care	62	63	63	62

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[b]Sums do not always equal *N* because of missing values. Percentages are based on available data

allow symptomatic volunteers or recruitment from academic research clinics to ensure that the participants in the study were highly representative of patients at large who are diagnosed and treated in outpatient circumstances. Few exclusion criteria were used so that participants could and did have common comorbid general medical as well as psychiatric conditions. They could be suicidal or substance abusing as long as outpatient care was clinically appropriate and the substance abuse was not so severe to call for an independent substance abuse program. Tables 1 and 2 describe the demographic and clinical features of the sample at both study entry (under the column labelled Step 1) and at each subsequent treatment step (Fig. 1).

Table 2 Baseline clinical features of STAR*D participants by treatment step[a] (Adapted from Rush et al. 2006a, b, c, d)[b]

Feature	Treatment step			
	Step 1 ($N = 3,671$)	Step 2 ($N = 1,439$)	Step 3 ($N = 390$)	Step 4 ($N = 123$)
	%	%	%	%
First episode occurrence before				
Age 18	37	38	35	39
Recurrent depression	75	78	75	75
Family history of depression	55	54	51	55
Ever attempted suicide	17	18	19	20
Duration of current episode	25	27	27	30
≥2 years				
	Mean	Mean	Mean	Mean
Age at first episode (years)	25	25	26	26
Illness duration (years)	15	17	17	20
Number of episodes	6	7	7	8
Duration of current episode (months)	25	28	32	42
Median duration of current episode (months)	8	8	9	9
Quality of life and enjoyment	42	38	35	33
Satisfaction questionnaire score				
SF-12 mental	27	26	25	25
SF-12 physical	49	48	45	45
Work and social adjustment scale	24	25	28	28
Score				
$HRSD_{17}$ score	20	21	23	23
IDS-C_{30} score	35	38	41	42
QIDS-SR_{16} score	15	16	17	17
Cumulative illness rating scale				
Categories endorsed	3	3	3	4
Total score	4	5	5	6
Severity index	1	1	1	1
	%	%	%	%
Anxious features	45	50	57	57
Atypical features	17	19	21	25
Melancholic features	20	23	27	31
Psychiatric diagnostic screening				
Questionnaire	11	12		
Agoraphobia			17	21

(continued)

Table 2 (continued)

Feature	Treatment step			
	Step 1 ($N = 3,671$)	Step 2 ($N = 1,439$)	Step 3 ($N = 390$)	Step 4 ($N = 123$)
Alcohol abuse/ dependence	12	12	11	8
Bulimia	12	12	12	11
Drug abuse/dependence	7	7	7	7
Generalized anxiety disorder	21	23	27	33
Hypochondriasis	4	4	4	4
Obsessive-compulsive disorder	13	14	19	19
Panic disorder	11	15	18	18
Post-traumatic stress disorder	18	20	22	21
Social phobia	29	32	37	37
Somatoform disorder	2	3	4	3
Number of axis I comorbid conditions				
0	39	36	32	28
1	27	26	22	25
2	15	16	20	19
3	8	9	8	10
4+	11	13	18	17

[a]Sums do not always equal *N* due to missing values. Percentages are based on available data
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1.2 Treatment Outcomes

Remission was the primary outcome for each treatment in every STAR*D treatment step. It was defined by a score of 7 or less on the 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$) collected by trained, treatment-masked, physically remote raters via telephone with each participant. The clinician-rated 16-item Quick Inventory of Depressive Symptomatology (QIDS-C_{16}) (Rush et al. 2003a) was obtained at each treatment visit by the research coordinator or practicing clinician to guide treatment decisions and dosing. A total QIDS-C_{16} score of 5 or less (which approximates $HRSD_{17} = 7$) (Rush et al. 2003a; Trivedi et al. 2004a) (www.ids-qids.org) signaled remission to the clinician, who was masked to the $HRSD_{17}$. Remission of depression was chosen as the primary outcome and the aim of treatment because at the time of the study it was believed to be associated with better function and a better prognosis (Miller et al. 1998; Fava et al. 2003; Rush et al. 2004, 2006b).

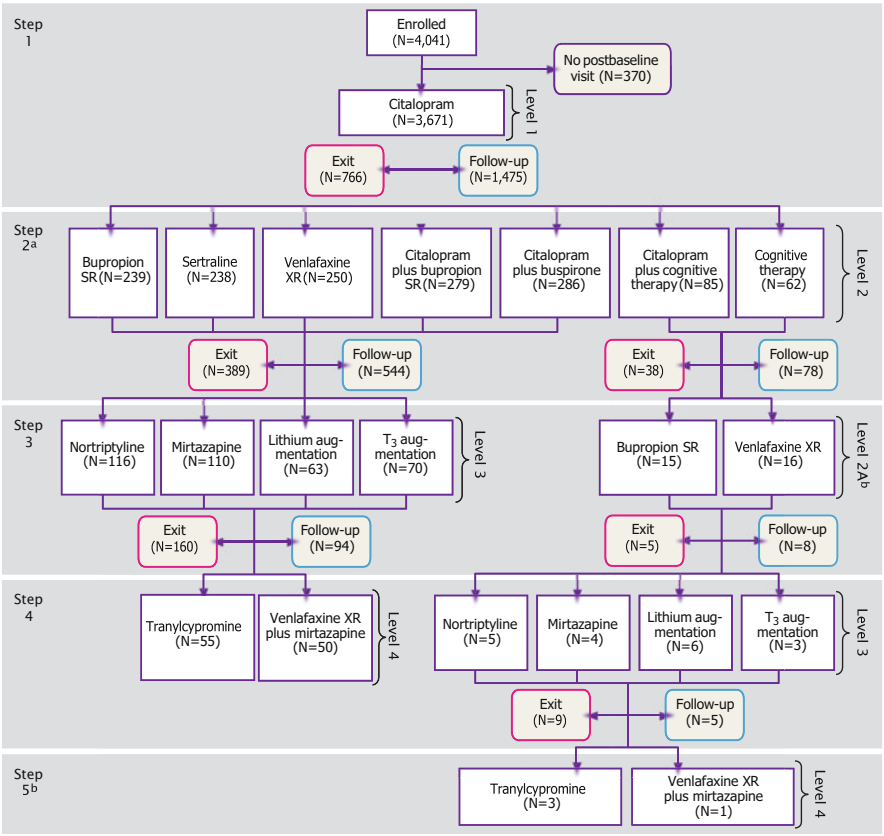

Fig. 1 Overall STAR*D participant flow (from Rush et al. Am J Psychiatry 2006a) (Reprinted with permission from *The American Journal of Psychiatry* (Copyright © 2018). American Psychiatric Association. All Rights Reserved). [a]Nine participants entered Step 2 without a Step 1 post-baseline visit being recorded. [b]Only possible for participants who received cognitive therapy alone or cognitive therapy plus citalopram at Step 2

STAR*D response and remission rates were calculated for each treatment at each step based on all the patients who began a treatment (the "full intent-to-treat" sample), which is distinct from the "modified intent-to-treat" analysis used in many trials. The latter counts only persons with both a baseline and at least one post-baseline measurement. Treatments can cause adverse effects that may lead to treatment discontinuation within a few days or a week, even before a single post-baseline measure can be obtained. Therefore, the "full intent-to-treat" sample provides a more realistic estimate of real-world outcomes, but it may have lower response and remission rates than the "modified intent-to-treat" sample. In addition, in STAR*D, when patients did not have a final $HRSD_{17}$ rating at exit, they were designated a priori as "non-remitters."

1.3 Treatment Steps

Figure 1 summarizes the treatment steps. Antidepressant treatment began with up to 14 weeks of citalopram (up to 60 mg/day), which was the first medication treatment that occurred at Level 1 (Step 1). Those who did not reach remission or had unacceptable side effects could proceed to Step 2. A patient who had a response to citalopram, but without remission, was eligible to enter follow-up but was strongly encouraged to enter Step 2 with the aim of achieving remission. Those without at least a response in Step 1 could either enter Step 2 or exit the study.

In the second treatment step (Level 2), up to seven treatment options (three augmentation and four switch options) were available. In both augmentation and switch strategies, cognitive therapy was an option (provided by trained certified cognitive therapists, sometimes located on-site and sometimes off-site in both primary and psychiatric care settings).

STAR*D employed an innovative "equipoise-stratified randomized design" (Lavori et al. 2000) that enabled the investigators to retain randomization at each treatment step while mimicking practice by allowing participants to make choices that reflect their preferences and real-world circumstances. The study team expected some Level 2 options would be strongly preferred and others would be declined depending. For example, those who had prior psychotherapy might want to decline either randomization scheme (switch and augmentation) that included cognitive therapy, so they could opt out of the therapy arm. Another example is participants who have a high intolerance to citalopram. These individuals would clearly decline augmentation of citalopram, but they might accept randomization to one of several switch treatments whether cognitive therapy was included or not. Conversely, those with some benefit and reasonable tolerance to citalopram might decline switching but accept augmentation provided they could continue the citalopram.

The equipoise-stratified randomized design enabled the investigators to adapt the randomization scheme to patient preferences regarding strategies or particular interventions but without allowing them to choose the treatment at the second step (Lavori et al. 2000). A similar approach was used for the third medication step (Level 3) in which participants could choose to be randomized to augmentation, switch to another drug, or both.

Following Level 2 (the second medication treatment step), only those patients who received cognitive therapy in Level 2 – as either a switch or augmentation – were offered a second medication step (Level 2A) before they could enter Level 3, which was the third medication treatment step. Thus, all participants who entered Level 3 had an inadequate benefit from two prior medications.

The third medication step (Level 3) offered a switch strategy that included nortriptyline or mirtazapine, and an augmentation strategy that included either lithium or triiodothyronine (T-3). Those without a satisfactory response to this third medication step could enter medication Step 4 (Level 4), which provided either tranylcypromine (TCP) or a mirtazapine and extended-relief venlafaxine (venlafaxine-XR), a combination thought to be particularly powerful (Stahl 2000; Blier 2001).

1.4 Treatment Delivery

A treatment can fail either due to poor treatment delivery (e.g., under-dosing), or it can simply fail even if well-delivered. STAR*D sought to ensure that treatment was optimally delivered because the study was to determine what to do when the prior treatment(s) was (were) innately ineffective, rather than failing due to poor delivery. The investigators borrowed from their experiences in the Texas Medication Algorithm Project (Rush et al. 2003b) where they developed ways to ensure high-quality medication treatment occurred "in the real world." Later dubbed measurement-based care (MBC) (Trivedi et al. 2006a), the study team aimed to have clinicians personally tailor the dose and treatment elements (such as side effect management, treatment strategy changes, etc.) based on the individual patient's therapeutic and adverse outcomes that were measured regularly during the study, thereby enhancing the chances of an adequate multi-week exposure to a maximally tolerated dose for each person.

At each treatment visit, MBC required (1) the regular measurement of depressive symptom severity, in this case using the QIDS-C_{16} (Rush et al. 2003a); (2) the regular assessment of side effects, in this case using the Frequency, Intensity, and Burden of Side Effects Rating (FIBSER) scale (Wisniewski et al. 2006); and (3) the adherence to specific dose escalation guidance that was reinforced by the clinical research coordinator (Rush et al. 2004). This effort aimed to ensure that the dose would be raised in the context of a modest clinical benefit and modest side effects. Treatment visit frequency, while determined by the clinicians, was by design more frequent than is typically seen in many clinical practices to ensure timely dose escalations. Treatment visits were recommended every 2 or at least every 3 weeks.

Each acute phase treatment trial in each level had a duration of up to 14 weeks, which is far longer than the average duration needed to ensure that remission – which takes longer than response – could be identified if it occurred, thereby avoiding the next treatment step. In sum, STAR*D did not study "routine care" in either primary or psychiatric care settings. Rather, STAR*D took particular pains to ensure diligent, personally tailored pharmacological management using MBC throughout all acute treatment steps (for more detail see Sect. 9).

1.5 Continuation Phase Treatment

Continuation phase treatment was provided in a naturalistic follow-up for up to a year. While STAR*D acute phase antidepressant treatment was diligently managed, no research oversight was provided during this follow-up, though symptomatic and functional outcome measures were obtained on a regular basis. Thus, the visit frequency, medication management and dosing, and all treatment decisions were based on clinician judgment. As noted above, entry into follow-up generally required reaching at least an acute phase treatment response.

2 Who Is Being Treated for Depression in Practice?

2.1 How Comparable Are Depressed Patients in Primary and Psychiatric Care Settings?

Tables 1 and 2 show the features of the STAR*D participants who entered each treatment level. Most study participants had recurrent MDD (>75%). More than 25% had a chronic index episode; more than 60% had their first major depressive episode before age 18. About one in five participants (18%) had made a previous suicide attempt (Rush et al. 2006a, b, c, d; Gaynes et al. 2008). About one in three had at least two concurrent Axis I disorders. On average participants had three concurrent general medical conditions as designated by the number of categories in the Cumulative Illness Rating Scale (Linn et al. 1968).

STAR*D participants were recruited from psychiatric (60%) and primary care (40%) settings (Gaynes et al. 2008). Overall, they had comparable depressive symptom levels and presentations, likely due to the minimal exclusion criteria beyond requiring a modest level of depressive symptoms ($HRSD_{17} \geq 14$) to enroll in the study. Primary care participants were older (44 vs. 39 years of age) with more concurrent general medical comorbidities. They were also more likely to have an age of first MDE onset after 18 years of age and have longer current major depressive episodes (9.5 vs. 6.0 months) (Gaynes et al. 2005). Participants in psychiatric care settings reported more previous suicide attempts (20% vs. 14%) and more current suicidal ideation (51% vs. 45%) (Gaynes et al. 2008).

2.2 Are FDA Registration Trial Participants Representative of Depressed Patients Treated in Practice?

The STAR*D study enrolled only treatment-seeking patients with a clinical diagnosis of nonpsychotic MDD of at least moderate symptom severity, defined by an $HRSD_{17} \geq 14$. FDA registration trials often set entry at an $HRSD_{17}$ score of 20–24 in an attempt to maximize drug/placebo differences because higher baseline depression symptom severity is associated with a greater chance of differentiating drug effects from placebo effects. The lower level of symptoms was chosen for STAR*D while retaining a high likelihood of meeting DSM-IV symptom criteria for a major depressive episode as well as having substantial distress or impairment. In addition, regulatory trials require that concurrent comorbidities be limited and that participants are not at substantial suicidal risk due to the blinded placebo control.

When we applied inclusion/exclusion criteria that are commonly used to define eligibility for regulatory trials, we found that less than 25% of STAR*D participants would have qualified for a typical efficacy clinical trial conducted for registration purposes (Wisniewski et al. 2009). In other words, 75% of depressed patients being treated in practice would not have qualified. For these patients, no placebo-controlled, randomized trials have established either the efficacy or safety of antidepressant medications.

We also found that the STAR*D participants who would have been excluded from registration trials had worse outcomes than those who would have been included, likely because they often had chronic current major depressive episodes ($\geq$2 years) and more concurrent general medical and psychiatric conditions – all features associated with poorer antidepressant outcomes (Trivedi et al. 2006a). These findings raise the important but rarely studied question as to whether certain concurrent general medical or psychiatric conditions are simply unresponsive to current antidepressants. For example, Hedayati et al. (2017) recently found that sertraline was no better than placebo in a large study of patients with major depression and chronic kidney disease. Specifically, some patients with major depression that co-present with certain other conditions may simply not benefit from our current agents.

2.3 Clinical Implications

In STAR*D, the cohort of non-treatment-resistant patients found in both primary and psychiatric care settings was very similar. In addition, evidence for efficacy and safety is largely lacking for the majority of depressed patients who are treated in practice because they are typically excluded from registration trials. Furthermore, these excluded patients seem to have poorer outcomes than those included in registration trials. These findings underscore the need for more pragmatic trials in representative patients.

3 Treatment Outcomes with the Initial Medication Treatment Step with a Selective Serotonin Reuptake Inhibitor (SSRI)

3.1 When and How Often Does Response and Remission Occur with an SSRI

Table 3 shows that overall from the first step onward, times to respond and to remission across the steps gradually increased. After up to 14 weeks of treatment with citalopram, overall remission defined by the $HRSD_{17}$ was 27%. The $HRSD_{17}$ remission rates were comparable in primary and psychiatric care (27% vs. 28%, respectively). Patients who achieved $HRSD_{17}$ remission had lower rates of side effect frequency and intensity and lower rates of serious adverse effects than those who did not which is likely a reflection of the practice of increasing the dose when remission has not yet been achieved.

Non-remission was ascribed when the exit $HRSD_{17}$ was missing. The study team could not compute response rates when the $HRSD_{17}$ was missing. Consequently, the QIDS-SR_{16} – which was obtained at every clinic visit – was used to calculate both response and time to response. The QIDS-SR_{16} remission rates were also

Table 3 Acute treatment outcomes after each treatment step (Adapted from Rush et al. 2006a, b, c, d)[a]

Feature	Treatment step[b]			
	Step 1 (N = 3,671)	Step 2 (N = 1,439)	Step 3 (N = 390)	Step 4 (N = 123)
	Mean	Mean	Mean	Mean
QIDS-SR_{16} score at entry to step	15	12	13	14
QIDS-SR_{16} score at exit from step	9	9	11	12
Change in QIDS-SR_{16} during step (%)	–43	–20	–12	–12
Weeks to remission[c] (for those	6	5	6	7
remitting)				
Weeks to response[d] (for those responding)	5	7	6	8
Weeks in treatment	10	9	9	9
Cumulative weeks in treatment	10	19	28	38
	%	%	%	%
Remission at each step exit	37	31	14	13
Response in each step	49	29	17	16
Intolerable side effects[e]	16	19	26	30

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[b]Sums do not always equal N due to missing values. Percentages are based on available data
[c]Exit QIDS-SR_{16} ≤5
[d]50% or more reduction in QIDS-SR_{16} score from entry score at each step
[e]Proportion of participants who left the level prior to 4 weeks for any reason and those who left thereafter whose exit form indicated intolerance

comparable between primary and specialty care (33% vs. 33%) (Gaynes et al. 2008). For those who reached QIDS-SR_{16} remission, the mean time to remission was 6.7 weeks (SD = 3.8), with times comparable in primary care (approximately 6 weeks) and psychiatric care (approximately 7 weeks).

Overall, the QIDS-SR_{16} rate of response was 47% (n = 1,343) (primary care, 46%; psychiatric care, 48%). For those who achieved a QIDS-SR_{16} response, the mean time to response was approximately 5.7 weeks, with times comparable in primary care (5.7 weeks) and psychiatric care (5.6 weeks). Of those who responded, 33% did so after the first 6 weeks (Trivedi et al. 2006a, 2007). About one-half of those who remitted did so after 6 weeks. Of all the steps in the study, Step 1 was associated with the greatest overall QIDS-SR_{16} reduction and the largest response and remission rates.

3.2 Can Baseline Features Tell Us Who Will Respond or Remit with the Initial SSRI?

Several pretreatment sociodemographic and clinical features were associated with the likelihood of response or remission. Women (29%) had higher $HRSD_{17}$ remission rates than men (24%) (Marcus et al. 2008), as well as higher QIDS-SR_{16} remission rates (34% and 31%, respectively) (Trivedi et al. 2006a). Caucasians had a higher $HRSD_{17}$ remission rate than Hispanics. Married or cohabitating (vs. never married, divorced, or widowed) and employed (vs. unemployed or retired) participants had higher remission rates, as did those with higher income, higher education, private insurance (vs. public or no insurance), higher function, and better quality of life. There was no statistical differences in $HRSD_{17}$ remission rates in relation to family history of depression, history of suicide attempts, age, age at onset of depression, or length of recurrent major depressive episode (more or less than 2 years of duration).

More concurrent general medical conditions as well as more concurrent psychiatric conditions were associated with lower response and remission rates to citalopram (Trivedi et al. 2006a). Several comorbid conditions influenced achieving remission as measured by the $HRSD_{17}$. Lower remission rates were seen in participants with generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, agoraphobia, alcohol abuse/dependence, and somatoform disorder. Those having no comorbid psychiatric disorder had a remission rate of 34%, while those having four or more comorbid conditions had a remission rate of 16% ($p = 0.0001$). The $HRSD_{17}$ remission rate for depression with anxiety was lower (22%) than the rate without anxiety (33%) (Trivedi et al. 2006a; Fava et al. 2008).

3.3 What Are the Long-Term Outcomes Following a Successful First-Step SSRI?

Table 4 and Fig. 2 show the longer-term outcomes for each treatment step. More patients entered follow-up in remission (74%) from Step 1 (citalopram) than from any of the subsequent steps, and they had the lowest average overall QIDS-SR_{16} score at entry into follow-up. Figure 1 shows that after Step 1, overall, fewer people relapsed in follow-up as compared to the subsequent steps. Further, relapse rates were lower for those who entered follow-up in remission (34% relapsed) and for those who entered with only a response (59% relapsed).

3.4 Does the Prior Course of MDD Predict Acute or Longer-Term Treatment Outcomes with Citalopram?

The study team also determined whether the prior course of illness, as well as the length of the current index episode, might affect longer-term outcomes to citalopram. Based on each person's prior course of illness, single or recurrent

Table 4 Status at follow-up entry and relapse rates for each treatment step (Adapted from Rush et al. 2006a, b, c, d)[a]

Treatment step and remission status at follow-up entry	# entering follow-up	Remission rate at follow-up entry (%)[b]	QIDS-SR_{16} score at entry[c]	# with at least one post-baseline contact[d]	Relapse rate (%)[e]	Months to relapse (of those relapsing)
Step 1 (N = 3,671)[f]	1,475	74	4.0	1,133	40	4.1
In remission	1,085		2.7	841	33	4.4
Not in remission	388		7.7	290	59	3.6
Step 2 (N = 1,439)[f]	622	62	5.1	479	55	3.9
In remission	383		3.0	291	47	4.5
Not in remission	237		8.3	186	68	3.2
Step 3 (N = 390)[f]	102	35	6.8	79	65	3.1
In remission	35		3.3	28	43	3.9
Not in remission	66		8.6	50	76	3.0
Step 4 (N = 123)[f]	49	31	8.3	38	71	3.3
In remission	15		3.3	14	50	2.5
Not in remission	34		10.5	24	83	3.5

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[b]All treatment step pairwise comparisons significant at $p < 0.0001$ except for Step 3 vs. Step 4 ($p < 0.63$)

[c]All treatment step pairwise comparisons significant at $p < 0.0001$ except for Step 3 vs. Step 4 ($p < 0.05$)

[d]Patients who made at least one call to the interactive voice response system

[e]Proportion of subjects relapsing of those who made at least one post-baseline call to the interactive voice response system. Treatment step pairwise comparisons showed only Step 1 to be significantly different from the rest ($p < 0.0001$)

[f]Ns represent the number of subjects who entered the step

MDD (DSM-IV) and with or without a chronic index episode (at least 2 years in duration), the investigators formed four groups (Rush et al. 2012). The participants with the best prognosis had neither a recurrent course nor a chronic index episode, while both of these features predicted worse acute and longer-term outcomes on citalopram. For those who entered follow-up either in remission ($p = 0.021$) or in response without remission ($p = 0.069$), relapse rates were highest for those with both a chronic current episode and a recurrent course. Relapse rates were intermediate for those with only a chronic current episode or only a recurrent course and were best for those with neither a chronic episode nor a recurrent course.

These results suggest that earlier intervention may be especially effective before either a propensity to recurrence or an inability to recover from the episode has been established. Further, while remission remains the aim of acute treatment, psychotherapy may play an important role in reducing the risk of relapse in both responders and remitters that enter longer-term medication treatment (Guidi et al. 2011). Further studies of this question are needed.

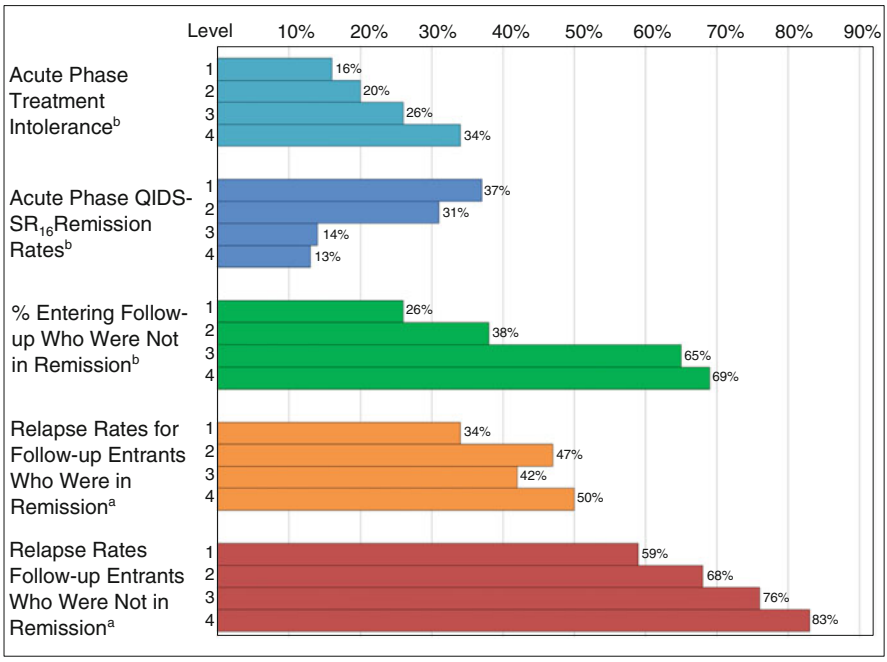

Fig. 2 STAR*D outcomes by number of treatment steps (Based on total number of treatment steps attempted [Levels 1, 2, 2A, 3, 4]) (Adapted from Rush et al. 2008a) (Reprinted with permission from Springer Customer Service Centre GmbH: Springer Nature. CNS Drugs. STAR*D Revising Conventional Wisdom. Rush AJ, Warden D, Wisniewski SR et al. Copyright © 2018). [a]Sample = 2,248 (participants who made at least one post-baseline call to the interactive voice response system). [b]Sample = 3,671 (participants who made at least one post-baseline visit)

3.5 Clinical Implications

It would appear that the use of MBC enhanced dosing, quality of care, and symptomatic outcomes – findings that have since been replicated (e.g., see Guo et al. 2015) (see Sect. 9). Since STAR*D revealed about one-third of eventual responders to SSRIs did so after 6 weeks, acute phase trials should be at least 6- and ideally 8-week long, with at least 4 weeks at the maximally tolerated dose before declaring treatment failure. A rough clinical guide might be to ascribe treatment failure when a less than 30% reduction in baseline symptoms has occurred after at least 6 weeks of treatment. Furthermore, since at least half of the remissions occurred after 6 weeks with the initial SSRI, it would seem best to defer the decision to combine or augment the initial SSRI monotherapy in order to reach remission until after 10–12 weeks. Since concurrent general medical and psychiatric conditions as well as a chronic index episode and a recurrent course of depression are indicators of a slower or lower chance of response or remission, these particular patients may be especially benefited by a longer medication trial before switching or augmenting. Finally, the

follow-up after Step 1 provided strong support for targeting remission whenever possible, given its association with lower relapse rates.

4 Treatment Outcomes with the Second Medication Treatment Step

4.1 Which Second-Step Treatment Options Are Preferred by Which Patients?

Tables 1 and 2 describe the participants who entered the second treatment step (Level 2). About 50% accepted randomization to the two medication augmentation options, while 57% accepted randomization to the three medication switch options. About one-fourth of participants were willing to accept the chance of being randomized to a strategy (switch or augment) that included cognitive therapy. Only 7% accepted randomization to both medication switch and augmentation. Only 1% accepted randomization to all seven Step 2 (Level 2) treatment options. Those with recurrent MDD and concurrent drug abuse preferred augmentation, while those who experienced greater intolerance or less improvement with citalopram preferred to switch as opposed to augment. Thus, as might be expected, those with meaningful benefit from Step 1 preferred to persist and augment, while those with less favorable outcomes from Step 1 (more side effects and less symptomatic benefit) seemed to prefer switching.

4.2 When the Initial SSRI Fails and a Medication Switch Is Provided, Do Pharmacological Differences Matter?

The second-step switch medications affect different but related neurotransmitter systems (sertraline, another SSRI; sustained-release bupropion (bupropion-SR), an agent with no direct serotonergic effect; venlafaxine-XR, an agent that at higher doses inhibits both serotonin and norepinephrine reuptake). However, these distinctions did not translate into clinically meaningful differences. Similar $HRSD_{17}$ remission rates (bupropion SR, 26%; sertraline, 27%; venlafaxine-XR, 25%) (Rush et al. 2006c) and similar mean times to achieve remission (5–6 weeks) were found. Mean $QIDS\text{-}SR_{16}$ response and remission rates were also comparable (Rush et al. 2006c). The three medications had comparable tolerance and adverse effects. Thus, the pharmacological differences were not reflected in clinical outcomes (see Fig. 3).

4.3 Which Augmentation Strategy Is More Effective, Bupropion-SR or Buspirone?

Participants who accepted randomization to augmentation often had already experienced some benefit with the first-step citalopram monotherapy before entry into

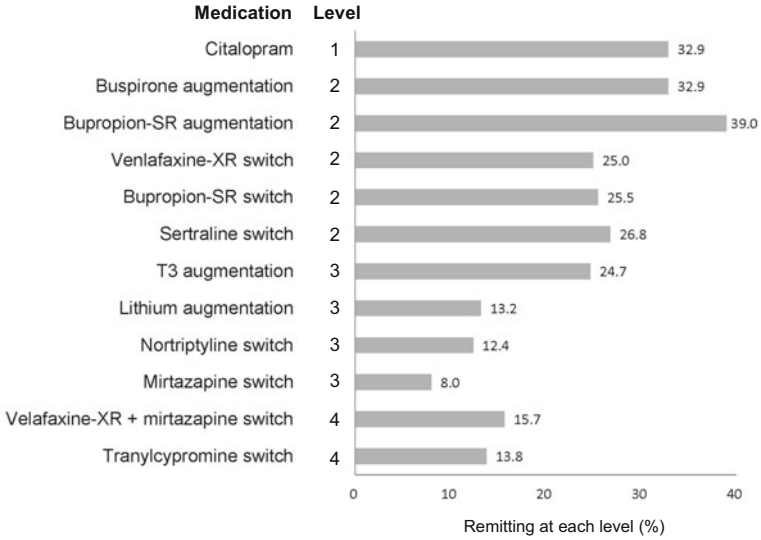

Fig. 3 Remission rates by treatment cell in STAR*D (Adapted from Rush et al. 2009) (Reprinted with permission from Springer Customer Service Centre GmbH: Springer Nature. CNS Drugs. STAR*D Revising Conventional Wisdom. Rush AJ, Warden D, Wisniewski SR et al. Copyright © 2018). Remission rates for various STAR*D treatments in each treatment level. Defined by exit: 16-item Quick Inventory of Depressive Symptomatology – Self-Rated (QIDS-SR_{16}) $\leq$5 (Reproduced from Warden et al., with kind permission from Current Medicine Group LLC). *SR* sustained release, T_3 triiodothyronine (liothyronine), *XR* extended release

medication augmentation (mean $HRSD_{17} = 15.4$ at entry for bupropion-SR and 16.2 for buspirone) (Trivedi et al. 2006b). The $HRSD_{17}$ remission rates were comparable for bupropion-SR and buspirone (30% each) (Trivedi et al. 2006b; Rush et al. 2006a).

There were no significant differences in time to remission between bupropion-SR (6.3 weeks) and buspirone (5.4 weeks) (Trivedi et al. 2006b) or times to QIDS-SR_{16} response (6.3 weeks and 6.8 weeks for buspirone, respectively). Bupropion-SR was apparently better tolerated and had a lower dropout rate (13%) compared to buspirone (29%).

In a secondary analysis, Bech et al. compared these two augmentations using a pharmacopsychometric triangle (Bech et al. 2012) which considered symptoms, side effect burden, and quality of life as a tripartite outcome. This analysis – using a modified intent-to-treat sample, unifactorial symptom scales, and measures of side effects and quality of life – revealed that bupropion-SR had superior results compared to buspirone. This analysis also showed that more participants dropped out of treatment with buspirone (20.6%) than bupropion-SR (12.5%) due to intolerable side effects.

4.4 How Did Augmentation with Cognitive Behavior Therapy Compare with Medication Augmentation?

In Level 2, cognitive therapy was available as either an augmentation to or a switch from citalopram. We compared outcomes for cognitive therapy vs. medication in each strategy group separately (Thase et al. 2007). Medication ($n = 117$) and cognitive therapy ($n = 65$) augmentation groups were comparable at entry into this second step except that the cognitive therapy augmentation participants had lower quality of life than medication augmentation participants. On average, cognitive therapy augmentation entailed 11.4 sessions (SD = 4.9). Altogether, 26% (17/65) of cognitive therapy participants completed the full 16-session course of therapy.

$HRSD_{17}$ remission rates were 33% for medication augmentation and 23% for cognitive therapy augmentation (no significant difference). Similarly, the QIDS-SR_{16} remission rates (33% for medication; 31% for cognitive therapy) and the QIDS-SR_{16} response rates (28% for medication; 35% for cognitive therapy) were not different. Of those who achieved remission, the mean time to first remission was 40 days (SD = 26) with medication and 55 days (SD = 31) with cognitive therapy. There was no differential effect of cognitive therapy as a function of practice setting type (i.e., primary care vs. psychiatric care settings).

4.5 How Did Switch to Cognitive Therapy Compare with Switch to Medication?

The participants who switched to cognitive therapy ($n = 36$) and those who switched to medication ($n = 86$) for the second treatment step spent a comparable time (about 8 weeks) in second-step treatment. Medication switch was associated with a substantial number of side effects, with roughly one-third reporting moderate-to-severe side effect burden and nearly 50% reporting side effects at least 50% of the time. In contrast, the cognitive therapy recipients reported no side effects. The two groups were not significantly different in terms of $HRSD_{17}$ remissions (cognitive therapy, 25%; medication, 28%), QIDS-SR_{16} remission rates (cognitive therapy, 31%; medication, 27%), or QIDS-SR_{16} response rates (22% of cognitive therapy vs. 27% for medication) (Thase et al. 2007). Thus, one can expect about a 25%–30% response or remission rate whether switching to medication or therapy.

4.6 Follow-Up After the Second Treatment Step

After the second treatment step (Level 2), over one-third of participants were willing to enter follow-up without remission (Rush et al. 2009). Relapse rates over the following 12 months were lower (47%) for those who achieved remission than for those who had not (68%). The mean time to relapse was 4.5 months for those who entered follow-up in remission and 3.2 months for those who entered follow-up

without being in remission. The relapse rates were higher than for those entering follow-up after only the first treatment step. In both follow-up cohorts, however, remission was associated with a better prognosis than response without remission to a clinically meaningful and statistically significant degree (Fig. 2).

4.7 Clinical Implications

The mechanistic differences among monoaminergic antidepressants used as switch medications did not translate into meaningful safety, efficacy, or side effect differences following an unsatisfactory response to the initial SSRI. Consequently, when choosing among second-step switch medications, as well as second-step augmentation medications, the risks and types of adverse effects, potential drug-drug interactions, patient preference, cost, and other factors should be considered.

In second-step augmentation, bupropion-SR had some advantages over buspirone in terms of symptoms, side effects, quality of life, and attrition from treatment. Although cognitive therapy and medication appeared to be equivalent as either a switch from or augmentation to citalopram, remission was somewhat slower with cognitive therapy than with medication, especially when used as augmentation, but side effects were minimal. Choosing among medications whether switching or augmenting should be strongly influenced by patient preference as to expected side effects and burden of treatment.

5 Selecting Among Switch Treatments at the Second Medication Treatment Step

5.1 What Are the Overall and Differential Predictors of Remission (Baseline Sociodemographic, Clinical, and First-Step Treatment Features) for Participants Who Received Any Second-Step Switch Medication?

Rush et al. (2008b) used logistic regression models to identify baseline socio-demographic, clinical, and first-step (citalopram) treatment features that were associated with remission or with intolerance or with both – that is, across all three second-step switch medication treatments – and in terms of moderating (or differentiating) among the three switch treatments (a moderator analysis). The variables that were evaluated in these analyses included age; gender; race; employment and insurance status; marital/cohabiting status; family history of depression; number and types of comorbid psychiatric conditions; number of general medical conditions; presence of anxious, atypical, or melancholic symptom features; chronicity of the index episode; and both intolerance and symptomatic response to citalopram in the first medication treatment step.

Table 5 Features associated with remission overall and with each individual medication (Rush et al. 2008b)[a,b]

			Remission by medication		
	Remission		Sertraline	Venlafaxine-XR	*P*
Feature	Overall	($n = 239$)[c]	($n = 238$)[c]	($n = 250$)[c]	Value[d]
Age range, years					
18–25	1 [Reference]				
26–35	**1.81 (0.97–3.38)**	1.27 (0.40–4.03)	**1.36 (0.45–4.13)**	**3.06 (1.10–8.51)**	
36–50	**1.43 (0.78–2.59)**	**1.79 (0.61–5.26)**	1.17 (0.42–3.27)	1.25 (0.45–3.48)	.42
51–75	1.24 (0.67–2.32)	**1.35 (0.44–4.12)**	0.83 (0.28–2.47)	**1.63 (0.58–4.59)**	
Male sex (vs. female)	0.96 (0.69–1.35)	0.89 (0.49–1.61)	1.25 (0.70–2.23)	**0.79 (0.43–1.45)**	.53
White race (vs. nonwhite)	**1.99 (1.28–3.10)**	**2.32 (1.07–5.05)**	**1.97 (0.90–4.32)**	**1.75 (0.85–3.62)**	.87
Hispanic ethnicity (vs. non-Hispanic)	**1.36 (0.82–2.26)**	**2.03 (0.83–4.95)**	**1.64 (0.71–3.76)**	**0.76 (0.29–1.96)**	.30
Employed (vs. unemployed/retired)	**1.60 (1.14–2.25)**	**1.46 (0.80–2.65)**	**1.83 (1.02–3.28)**	**1.52 (0.84–2.75)**	.85
Medical insurance					
Any private insurance	1 [Reference]				
Public only	**0.53 (0.31–0.93)**	**0.54 (0.22–1.29)**	**0.35 (0.11–1.11)**	**0.73 (0.29–1.86)**	.92
None	**0.78 (0.54–1.12)**	**0.77 (0.40–1.47)**	**0.75 (0.41–1.38)**	0.81 (0.43–1.51)	
Married/cohabiting (vs. neither)	**1.52 (1.08–2.13)**	**1.36 (0.75–2.45)**	1.28 (0.71–2.29)	**2.01 (1.12–3.60)**	.50
Age at first episode (<18 years vs. ≥18 years)	**0.76 (0.53–1.08)**	0.88 (0.48–1.62)	**0.74 (0.40–1.38)**	**0.66 (0.36–1.24)**	.80
Recurrent depression (vs. first episode)	**0.78 (0.53–1.16)**	1.05 (0.54–2.02)	**0.76 (0.37–1.52)**	**0.58 (0.29–1.15)**	.48
Ever attempted suicide (vs. never)	**0.60 (0.37–0.98)**	**0.56 (0.23–1.35)**	**0.62 (0.28–1.36)**	**0.64 (0.27–1.53)**	.98
Family history of depression (vs. none)	1.03 (0.74–1.45)	**1.38 (0.77–2.48)**	**0.80 (0.45–1.43)**	1.01 (0.56–1.81)	.43
Presence of Axis I disorders[e] (vs. absent)					
Generalized anxiety	**0.59 (0.38–0.92)**	**0.63 (0.29–1.34)**	**0.52 (0.23–1.14)**	**0.63 (0.30–1.35)**	.92
Obsessive-compulsive	**0.42 (0.23–0.76)**	**0.64 (0.23–1.79)**	**0.32 (0.11–0.94)**	**0.38 (0.14–1.03)**	.62

Panic	**0.42 (0.24–0.75)**	**0.36 (0.13–0.96)**	**0.38 (0.13–1.12)**	**0.55 (0.22–1.38)**	.80
Post-traumatic stress	**0.55 (0.35–0.85)**	**0.60 (0.29–1.26)**	**0.49 (0.22–1.08)**	**0.55 (0.25–1.20)**	.93
Social phobia	**0.58 (0.40–0.86)**	**0.63 (0.33–1.21)**	**0.41 (0.19–0.86)**	**0.72 (0.38–1.34)**	.50
Substance use	1.00 (0.63–1.59)	1.29 (0.53–3.11)	**1.66 (0.83–3.31)**	**0.38 (0.14–1.01)**	**.05**
No. of Axis I disorders[f]					
0	1 [Reference]				
1	0.99 (0.65–1.49)	**0.55 (0.25–1.18)**	**2.09 (1.04–4.21)**	**0.72 (0.34–1.54)**	.22
2	**0.66 (0.39–1.12)**	**0.40 (0.15–1.08)**	0.81 (0.30–2.16)	0.85 (0.38–1.91)	
3	**0.58 (0.30–1.12)**	**0.38 (0.12–1.22)**	**0.56 (0.15–2.14)**	0.85 (0.30–2.42)	
≥4	**0.33 (0.17–0.64)**	**0.32 (0.11–0.92)**	**0.48 (0.15–1.56)**	**0.23 (0.07–0.84)**	
No. of Axis III disorders[g]					
0	1 [Reference]				
1	1.07 (0.71–1.62)	**1.45 (0.71–2.97)**	1.16 (0.57–2.35)	**0.73 (0.35–1.52)**	.81
2	**0.74 (0.45–1.22)**	0.84 (0.36–2.00)	**0.65 (0.28–1.52)**	**0.76 (0.31–1.89)**	
3	**0.67 (0.35–1.30)**	0.99 (0.35–2.78)	**0.49 (0.10–2.37)**	**0.52 (0.18–1.50)**	
≥4	**0.38 (0.19–0.77)**	**0.14 (0.02–1.10)**	**0.58 (0.20–1.69)**	**0.37 (0.12–1.14)**	
Psychiatric care (vs. primary care)	1.00 (0.71–1.41)	**0.63 (0.35–1.14)**	1.00 (0.56–1.80)	**1.60 (0.87–2.95)**	**.10**
Chronic index episode (vs. nonchronic)[h]	**0.74 (0.50–1.09)**	1.22 (0.64–2.33)	**0.52 (0.26–1.05)**	**0.61 (0.30–1.24)**	**.17**
Anxious features (vs. absent)	**0.30 (0.20–0.45)**	**0.25 (0.12–0.52)**	**0.44 (0.23–0.83)**	**0.23 (0.11–0.48)**	.35
Atypical features (vs. absent)	1.04 (0.67–1.61)	1.06 (0.46–2.45)	1.10 (0.54–2.24)	0.96 (0.46–2.02)	.97
Melancholic features (vs. absent)	**0.43 (0.25–0.73)**	**0.40 (0.16–1.02)**	**0.60 (0.26–1.39)**	**0.29 (0.10–0.85)**	.57
Severe depression (vs. mild/moderate)[i]	**0.34 (0.22–0.52)**	**0.38 (0.19–0.78)**	**0.38 (0.18–0.78)**	**0.25 (0.11–0.58)**	.70
Intolerance during the first-step treatment (vs. tolerance)[j]	**1.57 (1.11–2.21)**	**1.55 (0.85–2.82)**	**1.74 (0.96–3.16)**	**1.43 (0.79–2.58)**	.90

(continued)

Table 5 (continued)

			Remission by medication		
	Remission		Sertraline	Venlafaxine-XR	*P*
Feature	Overall	($n = 239$)[c]	($n = 238$)[c]	($n = 250$)[c]	Value[d]
Response during the first-step treatment (vs. nonresponse)[k]	**2.78 (1.77–4.38)**	**2.96 (1.38–6.34)**	**2.31 (1.02–5.20)**	**3.10 (1.41–6.80)**	.86

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[b]$N = 727$. Data are presented as odds ratio (95% confidence interval) unless otherwise indicated. Sertraline was given as sertraline hydrochloride

[c]Boldface type indicates clinical significance (odds ratio, ≤ 0.8 or ≥ 1.3)

[d]*P* value for interaction between clinical or demographic feature and treatment group. Boldface type indicates clinical significance ($P < 0.20$)

[e]Assessed by the Psychiatric Diagnostic Screening Questionnaire (PDSQ)

[f]Maximum equals 11 of 13 disorders assessed by the PDSQ

[g]Maximum equals 13 of 14 disorders assessed by the cumulative illness rating scale

[h]Duration of index episode for more than 2 years

[i]Score of 16 or more on the 16-item Quick Inventory of Depressive Symptomatology, Self-Rated (QIDS-SR_{16})

[j]Exited the study at the first step before week 4 for any reason or after week 4 citing intolerable adverse effects

[k]Percentage reduction in baseline QIDS-SR_{16} score of 50% or more at the end of treatment

Table 5 shows how these various features relate to remission as an outcome overall and for each individual medication switch. Figures in bold in the first column, "remission overall," identify significant overall effects. Figures in the subsequent three columns identify significant findings for each of the three switch medications individually.

To illustrate, consider the rows showing age groups: the far left-hand column shows that participants in the 26–35 and 36–50 age groups had higher odds ratios of achieving remission (1.8 and 1.4) (both statistically significant as shown in bold) than the reference group (participants aged 18–25). As a further example, compared to those with private insurance, those with public insurance had a lower odds ratio (0.53) of reaching remission than did those without insurance (0.78).

For overall predictions, Table 5 shows that being in the age bracket of 26−50 years of age (compared to being 18–25 years of age), being white (vs. nonwhite), being Hispanic (vs. non-Hispanic), being employed (vs. unemployed), having private insurance, cohabiting or being married, having suffered intolerance with citalopram in the first treatment step, and having had a response to citalopram were all associated with a better chance of remission regardless of the specific switch treatment provided.

In Table 5, the odds ratios in bold below 1.0 are all associated with poorer chances of remission. Thus, for example, the presence of more concurrent psychiatric conditions or more general medical conditions (Axis III); a chronic index episode; the presence of anxious, atypical, and melancholic features; and more severe depression severity at entry into Step 2 were all significantly associated with lower chances of achieving remission regardless of the specific switch treatment.

Despite relatively robust sample sizes, few variables provided any statistically significant indication as to which of the three switch medications should be preferred or avoided. In the fifth column (Table 5), significant p values are noted in bold, and a value up to $p = 0.20$ was accepted and bolded as a "potential indicator" of significance given the exploratory nature of these analyses.

For example, the presence of substance abuse was associated with lower odds of achieving remission with venlafaxine-XR and a higher odds ratio of achieving remission with sertraline. Similarly, treatment conducted in psychiatric (vs. primary) care settings tended to be associated with a higher likelihood of remission when the treatment includes venlafaxine-XR. This finding might have been due to more aggressive dosing in psychiatric settings. Further, for participants with a chronic index episode, the chances of remission were somewhat higher with bupropion-SR at a trend level (0.17). Overall, there were no statistically strong, clinically actionable findings to recommend one as opposed to another switch medication based on remission as the outcome.

5.2 What Are the Overall and Differential Predictors (Baseline Sociodemographic, Clinical, and First-Step Treatment Features) of Intolerance for Participants Who Received Any Second-Step Switch Medication?

Turning to the question of intolerance, Table 6 shows a greater risk of intolerance for participants who were 51–75 years of age, were non-Hispanic, and had a prior suicide attempt, panic disorder, other Axis I disorders, or melancholic symptom features. Previous intolerance to citalopram was associated with higher risk of intolerance to both sertraline and venlafaxine-XR as a Step 2 switch. Thus, bupropion-SR would seemingly be preferred for patients with SSRI intolerance at Step 1. Those with a chronic index episode seem to have a higher likelihood of intolerance with sertraline, although at a trend level of significance (0.18). For those with substance abuse, venlafaxine-XR was more likely to be associated with intolerance than the other two switch medications ($p = 0.07$). Early onset depression (before age 18) and recurrent depression (vs. single episode) are seemingly associated with a greater risk of intolerance to sertraline than the other agents.

5.3 Clinical Implications

These data suggest that (1) the usual clinical and sociodemographic correlates of lower chances of remission found in Step 1 with citalopram all appear to be confirmed in Step 2 regardless of the type of medication to which participants switch, (2) depressions associated with selected general medical conditions or perhaps selected anxiety disorders may have a different etiology and thus require different treatments than we currently use (e.g., persons with elevated inflammatory cytokines seem to do poorly on SSRIs) (Jha et al. 2017; Uher et al. 2012) and perhaps other monoamine active agents, (3) the lack of predictive value from this wide range of clinical and sociodemographic variables makes a strong case for the development of biomarkers to inform treatment selection (Rush and Ibrahim 2018), and (4) intolerance to an SSRI might recommend a medication with minimal to no serotonin reuptake blockade as the next step.

6 Treatment Outcomes with the Third Medication Treatment Step

6.1 Overview of the Third Medication Treatment Step

The third medication treatment step entailed either switching to two different antidepressants – mirtazapine or nortriptyline – or augmenting an antidepressant medication that the participant had been receiving from Level 2 or Level 2A (sertraline, venlafaxine-XR, or bupropion-SR) with either lithium or triiodothyronine (T-3) using the equipoise-stratified randomized design (Rush et al. 2004; Lavori et al.

Table 6 Features associated with intolerance overall and with each individual medication (Rush et al. 2008b)[a, b]

			Intolerance by medication		
	Intolerance	Bupropion-SR	Sertraline	Venlafaxine-XR	*P*
Feature	Overall	($n = 239$)[c]	($n = 238$)[c]	($n = 250$)[c]	Value[d]
Age range, years					
18–25	1 [Reference]				
26–35	1.17 (0.62–2.21)	1.22 (0.41–3.62)	**0.77 (0.24–2.44)**	**1.59 (0.55–4.61)**	
36–50	0.99 (0.54–1.80)	1.27 (0.45–3.54)	**0.74 (0.26–2.12)**	0.89 (0.31–2.56)	.76
51–75	**1.34 (0.73–2.45)**	**1.33 (0.47–3.81)**	0.83 (0.28–2.47)	**2.00 (0.72–5.54)**	
Male sex (vs. female)	1.19 (0.84–1.69)	1.09 (0.61–1.93)	1.17 (0.63–2.18)	**1.35 (0.72–2.50)**	.88
White race (vs. nonwhite)	0.95 (0.64–1.42)	1.04 (0.54–2.00)	1.15 (0.53–2.49)	**0.74 (0.38–1.46)**	.67
Hispanic ethnicity (vs. non-Hispanic)	**0.50 (0.26–0.98)**	**0.53 (0.17–1.64)**	**0.59 (0.20–1.80)**	**0.39 (0.11–1.36)**	.88
Employed (vs. unemployed/retired)	1.05 (0.74–1.48)	0.88 (0.49–1.56)	1.25 (0.67–2.34)	1.07 (0.58–1.98)	.71
Medical insurance (vs. any private insurance)					
Public only	0.93 (0.54–1.58)	**1.76 (0.82–3.75)**	**0.09 (0.01–0.70)**	1.19 (0.43–3.29)	**.01**
None	1.07 (0.74–1.56)	1.11 (0.58–2.12)	**0.59 (0.31–1.14)**	**1.86 (0.96–3.64)**	
Married/cohabiting (vs. neither)	1.06 (0.74–1.51)	0.98 (0.54–1.77)	1.24 (0.66–2.33)	1.00 (0.54–1.84)	.84
Age at first episode (<18 years vs. ≥18 years)	1.04 (0.73–1.49)	0.98 (0.55–1.76)	**1.72 (0.91–3.24)**	**0.68 (0.36–1.31)**	**.13**
Recurrent depression (vs. first episode)	1.29 (0.84–2.00)	0.81 (0.42–1.55)	**5.20 (1.54–17.6)**	1.00 (0.47–2.13)	**.03**
Ever attempted suicide (vs. never)	**1.59 (1.04–2.45)**	1.16 (0.55–2.46)	**1.83 (0.89–3.76)**	**1.92 (0.90–4.13)**	.59
Family history of depression (vs. none)	1.12 (0.79–1.59)	0.88 (0.50–1.57)	**1.47 (0.77–2.80)**	1.14 (0.61–2.12)	.52
Presence of Axis I disorders[e] (vs. absent)					
Generalized anxiety	0.81 (0.52–1.25)	**0.73 (0.36–1.49)**	**0.68 (0.29–1.56)**	1.05 (0.51–2.17)	.69
Obsessive-compulsive	1.27 (0.78–2.05)	1.14 (0.47–2.74)	0.95 (0.39–2.32)	**1.74 (0.81–3.70)**	.57
Panic	**1.43 (0.90–2.25)**	**1.48 (0.72–3.05)**	**2.05 (0.89–4.72)**	0.97 (0.42–2.27)	.47

(continued)

Table 6 (continued)

Feature	Intolerance Overall	Bupropion-SR ($n = 239$)[c]	Intolerance by medication: Sertraline ($n = 238$)[c]	Intolerance by medication: Venlafaxine-XR ($n = 250$)[c]	P Value[d]
Post-traumatic stress	1.27 (0.85–1.89)	0.87 (0.45–1.71)	**1.93 (0.96–3.88)**	1.28 (0.63–2.63)	.27
Social phobia	0.88 (0.60–1.28)	0.90 (0.49–1.65)	**0.78 (0.38–1.61)**	0.95 (0.50–1.79)	.92
Substance use	0.86 (0.52–1.41)	**0.57 (0.21–1.58)**	**0.51 (0.20–1.28)**	**1.77 (0.83–3.78)**	**.07**
No. of Axis I disorders[f]					
0	1 [Reference]				
1	**1.43 (0.91–2.25)**	**1.40 (0.66–2.93)**	0.95 (0.42–2.13)	**2.30 (1.01–5.20)**	.92
2	**1.64 (0.98–2.75)**	**1.44 (0.61–3.40)**	**1.77 (0.70–4.49)**	**1.85 (0.75–4.55)**	
3	1.09 (0.56–2.13)	1.01 (0.36–2.87)	**0.76 (0.20–2.96)**	**1.63 (0.51–5.19)**	
≥4	0.90 (0.50–1.64)	**0.77 (0.30–2.01)**	0.85 (0.28–2.59)	1.19 (0.41–3.43)	
No. of Axis III disorders[g]					
0	1 [Reference]				
1	1.12 (0.72–1.74)	**1.30 (0.61–2.76)**	**1.39 (0.60–3.18)**	**0.74 (0.33–1.66)**	.86
2	1.01 (0.61–1.70)	**1.46 (0.64–3.32)**	**0.74 (0.24–2.02)**	0.91 (0.35–2.36)	
3	0.90 (0.46–1.76)	**1.44 (0.53–3.91)**	**0.23 (0.00–1.51)**	0.93 (0.34–2.57)	
≥4	1.15 (0.64–2.07)	**1.65 (0.60–4.55)**	**1.40 (0.44–4.09)**	**0.65 (0.22–1.88)**	
Psychiatric care (vs. primary care)	1.26 (0.88–1.80)	1.15 (0.64–2.07)	**2.08 (1.05–4.10)**	0.89 (0.48–1.64)	**.18**
Chronic index episode (vs. nonchronic)[h]	0.96 (0.65–1.42)	1.08 (0.57–2.05)	0.98 (0.49–1.97)	0.81 (0.39–1.66)	.84
Anxious features (vs. absent)	1.16 (0.80–1.70)	**1.54 (0.83–2.87)**	1.11 (0.56–2.18)	0.88 (0.45–1.72)	.48
Atypical features (vs. absent)	0.95 (0.59–1.53)	0.90 (0.38–2.15)	0.95 (0.42–2.17)	0.99 (0.45–2.17)	.99
Melancholic features (vs. absent)	**1.44 (0.91–2.27)**	1.20 (0.56–2.55)	**2.50 (1.15–5.43)**	0.99 (0.42–2.32)	.23
Severe depression (vs. mild/moderate)[i]	1.00 (0.69–1.46)	**0.67 (0.35–1.26)**	0.99 (0.50–1.96)	**1.59 (0.83–3.03)**	**.17**

Intolerance during the first-step treatment (vs. tolerance)[j]	**1.92 (1.33–2.77)**	1.25 (0.70–2.23)	**4.17 (1.97–8.83)**	**1.67 (0.89–3.15)**	**.04**
Response during the first-step treatment (vs. nonresponse)[k]	1.19 (0.72–1.97)	**1.64 (0.76–3.56)**	1.00 (0.38–2.61)	0.91 (0.35–2.37)	.58

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[b]$N = 727$. Data are presented as odds ratio (95% confidence interval) unless otherwise indicated. Sertraline was given as sertraline hydrochloride

[c]Boldface type indicates clinical significance (odds ratio, ≤ 0.8 or ≥ 1.3)

[d]P value for interaction between clinical or demographic feature and treatment group. Boldface type indicates clinical significance ($P < 0.20$)

[e]Assessed by the Psychiatric Diagnostic Screening Questionnaire (PDSQ)

[f]Maximum equals 11 of 13 disorders assessed by the PDSQ

[g]Maximum equals 13 of 14 disorders assessed by the Cumulative Illness Rating Scale

[h]Duration of index episode for more than 2 years

[i]Score of 16 or more on the 16-item Quick Inventory of Depressive Symptomatology, Self-Rated ($QIDS\text{-}SR_{16}$)

[j]Exited the study at the first step before week 4 for any reason or after week 4 citing intolerable adverse effects

[k]Percentage reduction in baseline $QIDS\text{-}SR_{16}$ score of 50% or more at the end of treatment

2001). Participants were randomly assigned in 1:1 ratio to either the augmentation medications or the switch medications, each stratified by acceptability to participants and regional centers (Fava et al. 2006). Most participants in medication Step 3 chose to be randomized to either the switch or augmentation options, declining randomization to all four treatment options, analogous to our experience in medication Step 2.

As with all medication steps, participants who entered Step 3 had either not reached remission or could not tolerate two prior medications. A subset of participants entering Step 3 (Level 3) had also failed to benefit from cognitive therapy. Participants discontinued their previous medications (either citalopram combined with bupropion-SR or buspirone or monotherapy regimens of bupropion-SR, sertraline, or venlafaxine-XR from Level 2 or 2A) without a washout period. Recommended mirtazapine doses began with 15 mg/day and could be elevated to 60 mg/day over 6 weeks. Nortriptyline began at 25 mg/day for 3 days with doses rising to 50 mg/day by 7 days and up to 150 mg/day by 6 weeks. Both switch and augmentation medications at medication Step 3 were managed through an MBC process. Tables 1 and 2 show the clinical and sociodemographic features of participants entering Step 3 and compare them to those entering the other treatment steps.

6.2 What Were the Demographic and Clinical Characteristics of Participants Entering Medication Switch at Step 3?

The two medication switch groups were similar except more participants on mirtazapine (25%) had previously attempted suicide than those receiving nortriptyline (12%). Four of ten had early onset MDD (before age 18), and almost 30% had a chronic index episode. Nearly half of the participants who entered Step 3 switch had been unable to tolerate their prior antidepressant medication (Level 2 or 2A), operationalized as exiting their prior medication treatment before 4 weeks for any reason or exiting after 4 weeks due to intolerable side effects. Most participants (two-thirds) had at least one concurrent psychiatric diagnosis based on the Psychiatric Diagnostic Screening Questionnaire (PDSQ). Also, most enrollees (70%) in the Level 3 switch had received a medication switch at Level 2 or 2A. The mean $HRSD_{17}$ was 19 at medication switch Level 3 entry. About one-third of participants completed the full 12 weeks of either nortriptyline or mirtazapine.

6.3 What Were the Treatment Outcomes for Medication Step 3 Switch?

$HRSD_{17}$ remission rates overall were 16% (mirtazapine, 12%; nortriptyline, 20%). QIDS-SR_{16} remission rates were 8% for mirtazapine and 12% for nortriptyline. The QIDS-SR_{16} response rates were 13% for mirtazapine and 17% for nortriptyline. None of these outcomes were significantly different, nor were there significant between-group differences in time to either QIDS-SR_{16} remission or response. For

those who achieved QIDS-SR_{16} remission, the mean times to remission were 5.7 weeks for mirtazapine and 6.3 weeks for nortriptyline. The mean time to achieve response was 6.9 weeks for mirtazapine and 6.3 weeks for nortriptyline, both of which were longer than times seen at medication Level 1 (Gaynes et al. 2009). The two antidepressant switch treatments did not differ in overall side effects or in the proportion of participants with any psychiatric serious adverse events.

6.4 Clinical Implications from STAR*D Medication Step 3 Switch

Less than one in five depressed patients achieved remission upon switching to another antidepressant medication after two unsuccessful medication treatments. This is in contrast to other efficacy studies (Quitkin et al. 2005; Poirier and Boyer 1999) that reported 27–50% remission rates in small samples upon switching to another antidepressant in participants who have not benefited adequately from two antidepressant trials. However, the duration of the prior trials (Levels 1 and 2) was 4–6 weeks rather than 12 weeks in STAR*D, and the samples were not as generally representative (i.e., some had come from efficacy trials with restrictive intake criteria). Consequently, STAR*D included more people with more concurrent psychiatric and general medical conditions and chronic depressions that adversely affect outcomes at Steps 1 and 2.

In addition, the somewhat distinct pharmacological mechanisms characterizing mirtazapine and nortriptyline did not translate into differential efficacy, side effects, or tolerability. Results further suggest that after successive use of two monotherapies – each being well delivered – one might consider augmentation as the third step. However, due to limited participant acceptance of randomization in STAR*D to both switch and augment strategies in medication Step 3, we could not directly compare switch and augmentation due to insufficient sample size.

6.5 How Was Medication Step 3 Augmentation Implemented?

The two augmentation options used at treatment Level 2, buspirone and bupropion-SR, were discontinued without tapering at the initial Level 3 treatment visit. Lithium or T-3 was added to ongoing treatment with citalopram, sertraline, bupropion-SR, or venlafaxine-XR. Lithium was started at 450 mg per day; at week 2 it was increased to the recommended dose of 900 mg per day. T-3 was started at 25 μg per day for 1 week and then increased to the recommended dose of 50 μg per day. This protocol was flexible, allowing a role for clinical judgment and ratings of symptoms and side effects.

6.6 Who Were the Participants in Medication Step 3 Augmentation?

Tables 1 and 2 summarize the clinical and sociodemographic features of enrollees in medication Step 3 augmentation. All had failed on citalopram as a first step. Nine then failed on cognitive therapy alone or combined with citalopram. All had also failed on a second medication. Participants who received lithium or T-3 were comparable except significantly more participants on lithium (26%) had their first major depressive episode before age 18 than did those on T-3 (21%).

The mean duration of augmentation treatment was 9.6 weeks, with 18% of participants receiving augmentation treatment for less than 4 weeks and 35% for less than 8 weeks. The two treatment groups were comparable in terms of duration of treatment. The main dose of lithium was 860 mg/day (lower than the desired target dose). The main dose of T-3 was 45.2 μg/day.

6.7 What Were the Outcomes of Medication Step 3 Augmentation?

$HRSD_{17}$ remission rates were 16% for the lithium group and 25% for the T-3 group (no significant difference) (Nierenberg et al. 2006). There was no significant difference between augmentation with lithium and T3 for those taking citalopram, sertraline, bupropion-SR, or venlafaxine-XR though sample sizes were small, which would prevent detecting a modest effect if it existed.

Among participants who responded, the mean time to response was 5.7 weeks for lithium augmentation and 6.0 weeks for T-3 augmentation. Among those who remitted, the mean time to remission was 7.4 weeks for lithium and 6.6 weeks for T-3. Of the participants on lithium who eventually remitted, 55% did so by week 4, and 66% did so by week 6. For those on T-3 who eventually remitted, 45% did so by week 4, and 67% did so by week 6. However other participants took longer such that 22% of the lithium recipients and 28% of the T-3 recipients achieved remission but not until week 14. Lithium-treated participants had more frequent side effects than those receiving T-3, and significantly more participants left lithium than left T-3 treatment due to side effects.

6.8 Clinical Implications of Medication Step 3 Augmentation in STAR*D

While the $HRSD_{17}$ remission rates were comparable for the two augmentation medications, T-3 augmentation was closer to the intended dose and had fewer side effects and dropouts due to side effects than for those receiving lithium augmentation. Modest remission rates were found with both treatments despite an adequate trial duration of more than 9 weeks. It would appear that T-3 augmentation would be preferred over lithium augmentation, and the latter might need to be performed in a

specialty care setting that can provide greater time and expertise in managing this treatment. Due to the lack of a placebo control and given the modest remission rates, we cannot be sure whether some or many of those who did remit in Step 3 would have done so spontaneously.

7 Treatment Outcomes with the Fourth Medication Treatment Step

7.1 Participants and Treatment

Tables 1 and 2 describe the participants entering Step 4. Roughly 75% had recurrent depression, 55% had a family history of depression, 20% had a history of suicide attempts, and 30% were in a chronic current episode. Compared to those entering the study at the first step, those who entered this last step had more anxious, atypical, and melancholic features, as well as more comorbid psychiatric conditions and comorbid general medical conditions. These clinical features are characteristic of treatment-resistant depression. These participants were randomly assigned to either the tranylcypromine (TCP) (up to 60 mg/day) ($n = 58$) or a combination ($n = 51$) of venlafaxine-XR (up to 300 mg/day) and mirtazapine (up to 45 mg/day).

After a 2-week washout from the prior medications, TCP began at 10 mg/day (first 2 weeks), followed by weekly increases of 10 mg/day (maximum of 60 mg/day). For the combination ($n = 51$), venlafaxine-XR began at 37.5 mg/day (week 1) was increased to 75 mg/day (week 2), 150 mg/day (weeks 3–5), 225 mg/day (week 6–8), and 300 mg/day thereafter. Mirtazapine began at 15 mg/day (first 3 weeks) was increased to 30 mg/day (following 8 weeks) and then to 45 mg/day. Participants in the TCP group remained in treatment for less time than those in the combination group (about 8 vs. 11 weeks on average, respectively). Neither treatment group achieved the higher levels of medication dosing thought to be optimal for highly treatment-resistant patients. Thus, conclusions about the potential value of each treatment at Step 4 are tentative at best.

7.2 What Were the Clinical Outcomes?

$HRSD_{17}$ remission rates were very modest (7% for TCP; 14% for the combination). The QIDS-SR_{16} remission rates were comparable for TCP and the combination. Remission rates were more modest due in part to difficulty in tolerability that caused people to leave the treatment without an exit rating (which automatically assigned them to $HRSD_{17}$ non-remission status). QIDS-SR_{16} response rates were also low (12% for TCP; 23% for the combination). Neither remission nor response rates nor time to QIDS-SR_{16} response (8.6 weeks for TCP; 8.1 weeks for the combination) differentiated the two groups, perhaps due in part to small sample sizes.

7.3 Naturalistic Follow-Up

Figure 2 and Table 4 highlight the high and rather rapid relapse rates for both Step 4 treatments, both for participants who entered follow-up in remission (the minority) and for those who entered with only response.

7.4 Clinical Implications

The two medications used in this fourth medication treatment step were chosen to offer alternative mechanisms that entailed a broader spectrum of neurotransmitter effects. Substantial difficulty was encountered implementing the monoamine oxidase inhibitor (MAOI), which likely accounts for both the low dose and the poor response. While easier to use, the combination of venlafaxine-XR and mirtazapine did produce meaningful response rates (23% by the QIDS-SR_{16}), but tolerability was also an issue. In addition, we must factor into our understanding of this level that participants had typically gone through at least three prior trials which could have been as long as 14 weeks each. In addition, these participants especially burdened with concomitant general medical and psychiatric comorbidity. This context likely added to the difficulty in tolerating the agents. Finally, this group is characterized by greater intolerance at the outset given their experience with earlier medication steps (McGrath et al. 2006).

These results cannot be used to eliminate MAOIs as a valid treatment for these difficult-to-treat patients. The low remission rates observed in both treatment groups suggest that switching antidepressants after failure to achieve remission in three prior antidepressant medication trials provided only modest chances of remission. This conclusion must be tempered by the fact that its use in this study did not approach the maximum recommended doses.

8 The Challenge of Treatment Engagement and Retention

Participants leaving treatment prematurely – so-called treatment attrition – are both common and concerning. These patients often leave treatment when they are still in a symptomatic state. They typically return weeks or months later after additional suffering and with increasingly poor function. From a care system perspective, these patients are costly. STAR*D provided an opportunity to evaluate engagement and attrition in a representative outpatient sample that was provided with additional clinical care resources and care without cost.

We defined acute phase "attrition subjects" as those who enrolled in the first treatment step and who then exited the study at any point following their baseline visit but before completing 12 weeks of acute treatment with citalopram, *except* for those who left the study for valid medical reasons (e.g., a cardiovascular event required study exit). In contrast to "attrition subjects," those who persisted in treatment could have done so either by completing the full 12 weeks of the first

treatment step or by either entering follow-up or the second treatment step (Level 2). We divided the attrition subjects into an immediate attrition group (those who left after completing *only* the baseline visit, apparently with difficulty engaging in treatment at all) and a later attrition group (those who completed at least one post-baseline treatment visit but who then left in an incompletely treated state, instead of persisting with either the first step or entering the second step or follow-up).

8.1 How Common Was Attrition in the First Treatment Step and Who Is at Risk?

In the sequence of acute phase trials in STAR*D, despite additional clinical staff and research support, the absence of a placebo, no cost treatment, and the use of standard antidepressant medications, attrition was significant. Of the 4,041 study enrollees, 1,439 (36%) completed Level 1 and moved to Level 2. Another 37% ($n = 1{,}475$) responded well enough to citalopram to move to follow-up. However, 28% ($n = 1{,}127$) left treatment prematurely, almost all of whom (92%) dropped out for nonmedical reasons.

Of those who left treatment for no medical reason, 34% left *immediately* after their baseline citalopram treatment initiation visit. Later acute phase attrition subjects attended at least one post-baseline visit but exited before week 12 (59%). The remainder (7%) failed to complete the visit that was scheduled after week 12. Among the later attrition group, 59% exited before 6 weeks, while 41% exited after the week 6 visit (Warden et al. 2007b).

For all attrition subjects (both immediate and later attrition groups), younger age, fewer years of education, and African-American race – especially in the later attrition group – were associated with attrition. A personal history of more than one episode of depression was associated with less attrition. The immediate attrition group was characterized by higher perceived mental health functioning. Those with public insurance dropped out more frequently than those with private insurance, and Hispanic participants dropped out more often later in treatment. Larger numbers of comorbid conditions (especially three or more) were associated with higher attrition rates. Specific comorbidities such as alcohol or drug abuse, panic disorder, agoraphobia, hypochondriasis, and obsessive-compulsive disorder were associated with attrition. Attrition was less likely when the duration of the MDD was longer (longer time from onset of the first episode to study entry).

Compared to participants who did not leave treatment prematurely, those who did – after at least one post-baseline visit – left with more severe depressive symptoms; lower side effect frequency, intensity, and burden; and a lower average dose of citalopram at exit (Warden et al. 2007b). This finding indicates that treatment attrition results in poor depression outcomes and is not by in large due to medication side effect burden.

8.2 How Common Is Attrition in the Second Medication Step and Who Is at Risk?

We looked at attrition for those who switched and those who received augmentation separately in this second medication treatment step. Of those receiving medication augmentation, 20% of those on bupropion-SR and 21% of those on buspirone left treatment prematurely. Those leaving were more likely to be non-Caucasian or Hispanic, less educated, and younger and to have a family history of drug abuse, more concurrent psychiatric conditions – especially panic disorder or drug abuse – and a lower household income. Those who left prematurely also had less improvement with the first treatment (citalopram) and thus entered the augmentation step with higher overall depression severity (Warden et al. 2009). Participants leaving treatment, whether from augmentation or switching at Step 2, were leaving with substantially lower remission rates than those who persisted (7% vs. 43% for augmentation; 12% vs. 31% for medication switch).

Attrition rates for the three switch medications were comparable: 29% for bupropion-SR, 24% for sertraline, and 27% for venlafaxine-XR. For medication switch, the attrition subjects were more likely to be African-American or of other non-Caucasian races, non-Hispanic, divorced or never married, and younger and more likely to have had onset of their depression before 18 years of age. The attrition group was also characterized by more melancholic symptom features and having lower exit doses but more severe side effects with citalopram in the first step.

8.3 Clinical Implications

Difficulty engaging patients in treatment after *only* their initial evaluation/treatment is common, accounting for one-third of all patients who left inadequately cared for. However, two-thirds of the acute phase attrition subjects had a baseline visit and at least one treatment visit thereafter. The overall attrition rate (26%) in the second-step treatment was similar to the attrition rate in the first step with citalopram (28%) after at least one post-baseline visit (Warden et al. 2007b, 2009).

The clinical and sociodemographic features associated with attrition are consistent across treatment steps. Namely, patients who are younger, socially and educationally disadvantaged, or of racial and ethnic minorities are at particular risk both for not engaging in treatment to begin with and for leaving during the course of treatment in both Steps 1 and 2. Scrutiny and attention are needed to determine whether attrition is due to misconceptions about treatment itself, difficult patient/provider relationships, treatment accessibility or setting, efficacy of the treatment, or other issues. Those with greater histories of depression (e.g., recurrent depression or early age of onset) have less attrition, perhaps due to prior experiences in leaving treatment.

Additional time and effort, potentially motivational interviewing, and specific attempts to correct the patient's misconceptions about treatment risks and benefits or to provide a more concrete picture of what to expect and when to expect it could help

engagement or retention. Perhaps telephone or videoconferencing within a few days of the first visit could reduce the challenge of engagement. In addition, Internet access to the provider of the treatment course might also induce patients to stay the course in busy practice settings with poorly educated patients. That could affect engagement or retention, including the quality of the participant/clinician relationship, clinician experience or commitment, patient perception of regimen complexity, ease of access to the clinic, ability to attend appointments, and adherence to prescription medications. Regardless of the cause(s), a focused effort on this very common problem could remarkably improve outcomes for many depressed patients.

9 Lessons for Delivering High-Quality Care

9.1 The Why and How of Measurement-Based Care in STAR*D

In the design of STAR*D, we were aware of the large disparity between best practices and actual practice in the treatment of depression, both in primary and psychiatric care. It is estimated that only 19% of patients in primary care receive appropriate treatments (Young et al. 2001). In actual practice, patients often receive too modest doses for too brief periods of time (Trivedi et al. 2004b; Trivedi and Kleiber 2001).

Since STAR*D aimed at identifying the next best step after one or more failed but well-delivered treatment attempts. Our prior experience in the Texas Medication Algorithm Project (Rush et al. 2003b) was the basis for developing measurement-based care (MBC) in the STAR*D project in order to enhance treatment implementation and thereby minimize undertreatment in terms of both dose and duration (Trivedi et al. 2006a).

The essence of MBC actually entails the use of standard clinical tools and systematic clinical processes *to accomplish nearly every essential clinical task*, such as early detection, diagnosis, treatment selection, treatment implementation, and side effect and longer-term management to achieve a clinically important level of precision. STAR*D focused on the implementation of medication treatment in particular as a major target for MBC to ensure that each study medication was used for an adequate period of time at a maximally tolerated dose while allowing for flexibility, such as slower dose increases in the context of higher side effects or greater medical fragility.

The MBC procedures used in STAR*D entailed (1) the regular use of measurement to gauge symptomatic outcome (QIDS-C_{16}) (ids-qids.org) (eprovide.mapi-trust.org) (Trivedi et al. 2004a, 2007) and side effects (FIBSER) (Wisniewski et al. 2006); (2) an agreed-upon approach to dose initiation and the conditions and timing of dose escalations for each medication (provided in the MBC manual), disseminated with training to the practicing clinicians; and (3) a technology-based physician feedback system to monitor and prompt corrective actions when inappropriate deviations were noted (Trivedi et al. 2007; Wisniewski et al. 2006) at critical decision points (CDPs) (when a treatment adjustment was being considered). The information

provided by the QIDS-C_{16} and FIBSER enabled clinicians to systematically tailor the treatment decision to each individual's response to that particular medication (Rush et al. 2003a; Trivedi et al. 2004a). The Texas Medication Algorithm Project used analogous MBC procedures (Rush 2015; Gilbert et al. 1998) to find that MBC exceeded treatment as usual in symptom reduction and that vigorous dosing associated with MBC did not result in more adverse effects than treatment as usual (Trivedi et al. 2004c).

Of course, flexibility was built into these processes to incorporate clinical judgment in every treatment decision whether raising the dose or moving to the next treatment step or follow-up. Participants could be moved to the subsequent treatment step if they did not reach remission at CDPs at weeks 9 and 12 for each study medication or if side effects limited dose increase in the face of modest-to-minimal symptom benefit.

STAR*D also used a website and regular support from a clinical research coordinator located at each site to ensure that the MBC guidance was generally followed by the clinicians. A special computer program was used to report (1) current medication type and dose, (2) time on the current dose, (3) total QIDS-C_{16} score, (4) total FIBSER scale score, and (5) the specific MBC manual recommendations at critical decision points for adjusting the dose of each study medication.

This web-based report displayed flags highlighting deviations from specific decision rules at each treatment visit. The site included a prompting and feedback system that provided specific alerts when treatment deviated from the algorithm. Clinicians and coordinators could easily review their adherence to and deviations from the guidance. In brief, this interactive system provided resources and guidelines to clinicians to help ensure a maximally tolerated dose and sufficient duration for each medication.

9.2 Does MBC for Medication Treatment Implementation Work?

At each medication step in STAR*D (Rush et al. 2006a, c; Trivedi et al. 2004b, c), we used an MBC approach to ensure that a maximally tolerated dose was used for an adequate duration so that a poor response could be attributed to a true medication failure rather than to inadequate treatment delivery. We believe that MBC delivered high-quality care as evidenced by visit frequency and the antidepressant medication doses that were actually achieved.

In medication steps throughout the trial, protocol-recommended treatment visits were to occur at baseline and at weeks 2, 4, 6, 9, and 12, with an additional optional week 14 visit if needed. The mean number of visits during Level 1 for participants with no remission ($n = 2{,}086$) was 4.5 and for participants with remission ($n = 790$) was 5.5 (total mean visits for both achieving remission and not achieving remission was 4.8) (Trivedi et al. 2006a). In Level 2, the number of post-baseline clinic visits was 3.5 ± 1.6 (bupropion SR, $n = 239$), 3.7 ± 1.6 (sertraline, $n = 238$), and 3.8 ± 1.6 (venlafaxine-XR, $n = 250$). For Level 3, the total number of post-baseline visits was 3.8 ± 1.5 ($n = 142$) with a mean of 3.8 visits for lithium

Table 7 Dosages and durations of STAR*D treatment (Adapted from Rush et al. 2009)[a]

Dosages and duration of treatment			
Drug	Maximum dosage target (mg/day)	Exit dosage (mg/day) [Mean ± SD]	Duration (week) [Mean ± SD]
Citalopram (L-1)	60	41.8 ± 16.8	10.0 ± 4.2
Bupropion-SR (L-2)	400	282.7 ± 104.4	7.9 ± 4.2
Sertraline (L-2)	200	135.5 ± 57.4	7.7 ± 4.3
Venlafaxine-XR (L-2)	375	193.6 ± 106.2	8.4 ± 4.0
Bupropion-SR added to citalopram (L-2)	400	267.5 ± 99.8	10.2 ± 4.7
Buspirone added to citalopram (L-2)	60	40.9 ± 16.7	9.2 ± 5.0
Mirtazapine (L-3)	60	42.1 ± 15.7	7.7 ± 5.2
Nortriptyline (L-3)	150	96.8 ± 41.1	7.7 ± 5.2
T_3 (triiodothyronine, liothyronine) augmentation (L-3)	50[b]	45.2 ± 11.4[b]	9.9 ± 5.0
Lithium augmentation (L-3)	900	859.8 ± 373.1	9.3 ± 5.4
Tranylcypromine (L-4)	60	36.9 ± 18.5	~8
Mirtazapine (L-4)	45	37.5 ± 17.6	~11
Venlafaxine-XR (L-4)	300	210.3 ± 95.2	~11

L-1, L-2, L-3, L-4 levels 1, 2, 3 and 4, respectively, *SR* sustained release, *XR* extended release

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[b]μg

($n = 69$) and 3.7 for T-3 ($n = 73$) (Nierenberg et al. 2006). The mean number of post-baseline visits for Level 4 was 4.0 (McGrath et al. 2006) with a mean of 4.0 post-baseline visits for TCP ($n = 58$) and 3.9 for venlafaxine-XR and mirtazapine ($n = 51$). Hence, participants who achieved remission during the first level had the greatest number of visits.

In terms of medication dosing, Table 7 shows the average exit dose for each medication. These doses are substantially higher than doses typically found in routine clinical practice. Hence, wider use of the MBC approach in routine psychiatric and primary care is likely to enhance quality of care and patient outcomes for MDD (Trivedi et al. 2007; Rush 2015).

9.3 Clinical Implications

MBC processes and procedures bring some important elements used in research trials to real-world practice. MBC provides an action plan and benchmarks for dose revisions that are tailored to individual patients depending on the therapeutic and adverse effects. For physicians, the benefit is flexible, nonintrusive support and guidance with a monitoring system that takes minimal professional time. MBC

procedures that are focused on treatment implementation are analogous to those generally used for other chronic illnesses, which provide for revisions in treatment types and doses depending on outcomes. For patients, MBC can enhance their understanding of the goals and objectives of the treatment and help them to monitor their own progress as well as participate in shared decision-making and disease management (Trivedi et al. 2007).

10 Description and Implications of "Treatment-Resistant" Depression

10.1 Overall Acute Phase Treatment Outcomes by Treatment Level

"Treatment-resistant" depressions refer to those depressions that do not adequately benefit (i.e., either respond or remit) to several well-delivered, adequate treatments (Agency for Healthcare Research and Quality 2017). Treatment resistance seems to be on a continuum that can be gauged by the number of previously unsuccessful acute treatment trials (Thase and Rush 1997; Sackeim 2001; Agency for Healthcare Research and Quality 2017). However, whether there is a particular level of resistance that is clinically informative remains contentious.

STAR*D was the first large-scale trial to test prospectively 4–5 sequenced acute phase treatment steps after 1, 2, 3, etc. prior failed trials. These data provide a clinically informative picture about the response and remission rates that might be expected in successive treatment steps as well as indicating which clinical and sociodemographic features are associated with greater resistance (see Tables 1 and 2). These same data helped to clarify the relevance of the degree of resistance defined by failure to achieve at least a response if not a remission one or more acute phase trials to longer-term outcomes (See Tables 3 and 4 and Fig. 2).

Table 3 summarizes the acute phase outcomes by treatment level. At each level, the mean QIDS-SR_{16} scores drop from entry to exit. However, the greatest percentage of drop in the QIDS-SR_{16} rates (−43%) was seen between Level 1 entry and exit, and the smallest drop (−11.6%) was seen between entry and exit on Level 4, indicating the diminishing gains of antidepressant treatment gains with each successive acute phase medication treatment step.

Whether measured by $HRSD_{17}$ or QIDS-SR_{16}, each successive phase step was associated with a successively lower likelihood of both response and remission, regardless of the type of medication used at each step. To illustrate, the QIDS-SR_{16} remission rates were 37% and 31% for Steps 1 and 2, respectively, and were 14% and 13% for Steps 3 and 4, respectively (Table 3).

Overall, the cumulative QIDS-SR_{16} remission rate would have been something close to 67% after all four medication treatment steps (but ONLY if no participants had left the study and ONLY if those who did leave were to have had comparable outcomes to those who stayed in the study).

At the end of each successive acute phase treatment step, more patients were ending each successive step with a response without remission. Thus, those entering

follow-up were less likely to be in remission if they were entering from the later acute phase treatment steps. For example, after the third step, about 75% of participants entered follow-up with only a response without remission, whereas 75% were in remission at entry into follow-up from Step 1. Further, the time to remission and response for those who achieved either was minimally longer for those treated in the later treatment steps, perhaps due to the increasing burden from more comorbid general medical or psychiatric disorders which seem to slow somewhat the time to benefit as compared to those with little comorbidity (Rush et al. 2006a). Nevertheless, there remained a one in three patients who will respond after the 6th week regardless of the treatment level or degree of resistance – a fact that highlights the importance of retaining patients in treatment trials longer before declaring failure – especially for more resistant depressions. In addition, those entering the later treatment steps tended to have more clinical and sociodemographic features (more comorbidities, anxiety, melancholic features, more chronicity) that were associated with a poorer outcomes at pretty much every treatment step.

10.2 Is the "Degree of Resistance" Defined by the Number of Failed Acute Phase Treatment Trials Related to the Likelihood of or Time to Relapse Following Acute Phase Treatment?

During the naturalistic follow-up, relapse rates were always lower when remission was present at entry into the follow-up as compared to when only response without remission was present (see Table 4 and Fig. 1). Failure to achieve remission at follow-up entry raises the chances of relapse by 50% or more. Further, most relapses occur within the first 6 months of follow-up regardless of the number of prior failed trials (Rush et al. 2006a).

For both remitters and responders without remission at entry into follow-up, relapse rates were higher, and the mean time to relapse was shorter with more prior failed treatment trials (implying greater degrees of treatment resistance). The mean time to relapse for those who did relapse was shorter for those who required two or more treatment steps compared to those entering follow-up after only one treatment step.

10.3 What Clinical and Sociodemographic Features Are Associated with Greater Treatment Resistance?

Tables 1 and 2 reveal that greater general medical and psychiatric comorbidity seems to be associated with a greater degree of treatment resistance. More concurrent anxiety disorders, substance use disorders, and a more chronic course are indications of poor response that seems largely sustained across the treatment levels. These results suggest that clinicians need to especially attend those with more chronic

depression and those with more concurrent general medical and psychiatric disorders.

10.4 Clinical Implications

These results clearly demonstrate that remission is the strongly preferred aim of acute treatment because it is associated with better day-to-day functioning and a better prognosis (Rush et al. 2006a, b). Remission is associated with a better prognosis even if remission is not reached until after several treatment trials. Clinicians and patients must decide when remission is sufficiently unlikely that the patient will be best served by a chronic disease management approach as opposed to the relentless pursuit of remission. These results also indicate that whether response or remission is achieved, diligent follow-up is required – particularly in the first 6 months following the acute treatment phase – and especially for those who enter follow-up not in remission and for those who required three or four acute treatment steps to enter follow-up (Rush et al. 2006a).

In addition, with the recognition of diminishing outcomes, especially after the second medication treatment step, clinicians may want to consider other antidepressant medication or stimulation methods.

Finally, STAR*D results are consistent with the idea that there are two pathways (in terms of course) to "treatment resistance": (1) inability to end the index episode (acute phase treatment failure) and (2) inability to sustain that initial acute phase benefit whether a response or a remission (relapse). Acute phase treatments are less and less likely to work after more prior failures, and analogously the likelihood of relapse increases dramatically with the more failed trials. Whether these are two etiologically distinct pathways to failure is not known, but it appears that long-term prophylactic efforts are more and more tenuous even when acute remission is reached in the "more resistant" depressions. These findings suggest a great need for longer-term maintenance treatments (whether given intermittently or chronically) that may differ from treatments needed to acutely end the episode.

11 STAR*D Contributions to Patient-Oriented Research and Patient Care

STAR*D pioneered the development or the adaptation and application of a variety of scales to assess symptoms, function, and side effects and adapted existing scales to new uses such as the use of a screening scale to estimate comorbid conditions. The study was also one of the first to use laptop computers to acquire data from patients and research coordinators that was directly entered into the data base – largely avoiding paper records and the associated time and cost. The following provide a few highlights.

11.1 Measures of Symptoms: QIDS-C_{16}, QIDS-SR_{16}, and QIDS-IVR_{16}

While the primary outcome was a masked, interviewer-completed $HRSD_{17}$, STAR*D had to ensure that clinicians would safely but assertively maximize dose in a personally tailored way for each patient. Clinicians and patients used the QIDS-C_{16} to accomplish this task. One of the outputs was that STAR*D provided substantial evidence that the QIDS-SR_{16}, a self-report, provided very comparable results to the clinician-rated $HRSD_{17}$ or QIDS-C_{16} in assessing depressive symptom severity as an outcome (Rush et al. 2006d). Indeed, QIDS-SR_{16} results appear to be a valid outcome in outpatients with nonpsychotic major depression. We (Rush et al. 2003a; Trivedi et al. 2004a) also created conversion tables using the STAR*D and other data project by which to convert between various symptom scale ratings of depressive symptoms, $HRSD_{17}$ to a QIDS score or Inventory of Depressive Symptomatology score (www.ids-qids.org).

In another to further explore innovative technologies, STAR*D was one of the first large multisite effectiveness trials to use the interactive voice response (IVR) system that automated data collection. We found the QIDS-IVR to be extremely comparable to self-report and clinician-rated versions of the same scale (Rush et al. 2006d). This IVR could be readily used in other trials or in care systems seeking patient-reported outcomes.

11.2 Measures of Function: The Work and Productive Activity Inventory (WPAI) and the Work and Social Adjustment Scale (WSAS)

The IVR was also used to acquire a brief rating of work productivity: the Work and Productive Activity Inventory (WPAI) (Reilly et al. 1993). The WPAI, a 6-item self-report, assesses the quantity of work and productive activity. The construct validity of a quantitative WPAI measure of health outcomes was tested for use in clinical trials, along with its reproducibility when administered by either self-report or interviewer. The WPAI measures time missed from work and impairment of work and regular activities due to overall health and symptoms. Its construct validity was assessed relative to measures of general health perceptions, role (physical), role (emotional), pain, symptom severity, and global measures of work and interference with regular activity. The interviewer-administered WPAI (as opposed to the self-report) had better construct validity and fewer omissions, but the self-report had adequate reproducibility (Reilly et al. 1993).

STAR*D also used the IVR to acquire a 5-item rating of social adjustment: the Work and Social Adjustment Scale (WSAS) (Mundt et al. 2002). Patients readily understand the functional domains assessed and provide the numeric ratings of functional impairment. Scores are stable over intervals of at least 2 weeks, in the absence of intervention or treatment, and robust across different modes of administration. Cronbach's α is satisfactory (0.70–0.94) as is test-retest reliability (0.73). IVR administrations of the WSAS correlated highly (0.81 to 0.86) with clinician

interviews. Correlations of WSAS with severity of depression and obsessive-compulsive disorder symptoms were 0.76 and 0.61, respectively. WSAS scores were sensitive to differences in disorder severity and change with treatment (Mundt et al. 2002). Early changes in function as assessed by the IVR in STAR*D were predictive of longer-term outcomes (Jha et al. 2017a, b).

11.3 The Frequency, Intensity, and Burden of Side Effects Rating (FIBSER)

STAR*D also developed a global measure of side effects as an essential tool to be used in MBC. The FIBSER (Wisniewski et al. 2006) is a 3-item self-report assessing three domains, each on a Likert scale ranging from 1 to 7. The FIBSER measures the frequency, intensity, and burden of side effects that the patient attributes to the treatment. This simple tool allowed clinicians to rapidly and systematically gauge the overall side effect burden of the medication to more precisely determine whether to raise the dose.

The FIBSER was shown to be reliable, with high correlations between observations taken a short time apart and correlations decreasing as the time between observations increased. There were also consistent relationships between items over time. The FIBSER has both face and construct validity. Ratings of intensity and frequency are highly related (correlations range, 0.83–0.89). The correlation between intensity and burden (range, 0.79–0.83) was higher than the correlation between burden and frequency (range, 0.68–0.75) but lower than the correlation between frequency and intensity. Cronbach's α, measured at each assessment time, ranged from 0.91 to 0.93, indicating excellent internal consistency.

11.4 Design Innovations

The development and implementation of the equipoise-stratified randomized design (Lavori et al. 2001) was an innovative advance in adaptive treatment design that can be used in other investigations. The design allows individual patient considerations to be "adapted to" while retaining randomization. In essence, the participants who agreed to randomizations that are available are actually reflecting the kinds of patients willing to consider similar treatments in the "real world."

To enhance patient safety in the context of tailored but aggressive dose escalations and to reflect practice in the "real world" as MBC was being implemented, both clinicians and participants were aware of the treatments being delivered, and with MBC, both were aware of symptomatic outcomes. But to blind the trial, we used off-site treatment-masked raters who attain the primary outcome: the $HRSD_{17}$ patient rating. These days, videoconferencing methods could just as easily be used and might be even more reliable or valid than the telephonic (voice-only) assessment.

STAR*D required the recruitment of actual treatment-seeking patients in "real-world" clinics while also requiring particularly diligent care in treatment delivery under the control of researchers and MBC processes. The resulting study design was a hybrid of an effectiveness and an efficacy study. Such an approach has been used subsequently in point-of-care trials where the participants may be representative of the population of interest, but the processes used to deliver care might need to be more carefully controlled or delivered in a particular way to address specific questions. STAR*D demonstrated that this approach was feasible in a large multisite study engaging busy private- and public-sector primary and specialty care practices.

12 Summary

The STAR*D study cost roughly $23 million and produced directly over 120 manuscripts and scores of additional reports from data placed in the public domain. At this writing (February 2018), analyses and publications using these data are still ongoing. STAR*D provided information on a range of topics, including evaluation of treatment options at multiple sequenced steps, characterization of "treatment-resistant" depression, factors affecting the risk of relapse, treatment tactics, clinical tools and processes to enhance the quality of care, and methodological contributions (e.g., the development, psychometric evaluation, and use of new clinical scales and outcome measures for clinical research) among others.

Table 8 highlights selected but important clinical take-away messages from STAR*D. The very similar outcomes among second and third medication treatment steps – both switch and augmentation treatments – were a surprise to some. Just as important and perhaps as surprising was the challenge in engaging and retaining depressed persons who were seeking treatment at a site of their choosing, even when staff were added to assist in clinical care and treatment was provided at no cost to the patients.

In addition, the increasing relapse rates in relation to the increasing number of failed acute phase treatment trials argue strongly for the development of new and better medication treatments as well as more innovative psychotherapeutic interventions for patients with difficult-to-treat depressions.

The advantage of a study like STAR*D, which was conducted in "real-world" care settings, was that the results are immediately applicable to everyday practice. Mechanisms by which to create networks and inexpensive outcome assessments on an ongoing basis – not just for depression but for other mental illnesses – would help to reduce the well-recognized gap between research discoveries and their application and evaluation in actual practice. Greater efforts in this direction have the potential to deliver more personalized, efficient, and cost-effective care that is already being realized in areas such as cardiology and oncology. Such networks also provide a much-needed platform for developing and evaluating biomarkers that could serve a variety of clinical functions including early detection, differential diagnosis, treatment selection, and prognostication (Rush and Ibrahim 2018).

Table 8 Clinical take-away lessons from STAR*D

1	Major depression is a chronic, recurrent, and often relapsing condition that requires diligent care
2	Measurement-based care (MBC) helps to achieve optimal outcomes and should be widely implemented. It entails: 1. *MEASUREMENT* of symptoms and side effect burden at each critical decision point 2. *ACTION PLAN* that makes specific recommendations based on the measures obtained 3. Methods *to ENSURE IMPLEMENTATION* of the plan
3	Remission, when feasible, must be the goal of treatment because relapse rates are lower in those who have remitted compared to those without remission
4	Acute phase response and remission rates become ever lower with more prior failed treatment trials
5	Relapse rates become ever higher with more failed treatment trials
6	Symptom remission cannot be achieved with all depressions. Non-remission is associated with more concurrent general medical conditions; more concurrent psychiatric conditions; a chronic index episode; a recurrent course; more anxious, atypical, or melancholic symptom features; more prior treatment failures; and greater initial depressive symptom severity
7	In selecting among antidepressant medications: 1. Few clinical or sociodemographic features were not informative 2. Patient acceptance is more important than the particular monoaminergic pharmacology
8	Depression-targeted psychotherapy (e.g., cognitive behavioral therapy) should be offered before a third medication step is taken given its high tolerability and apparent effectiveness
9	Depression concurrent with alcohol or other substance use disorders, which themselves do not require independent intervention, can be treated with antidepressant medications, but expect poorer antidepressant outcomes, especially in patients who abuse both alcohol and other substances. Expect higher dropout rates especially among drug abusers
10	Augmentation strategies are preferred by those with some benefit from the prior treatment along with tolerable side effects. Medication switches are preferred by patients with minimal-modest symptom reduction and substantial side effects from their prior treatment
11	Behavior problems in children of depressed mothers are common. Some may be responses to mothers' unrecognized or untreated depression. Some children benefit when their mother's depression responds to treatment
12	Clinicians should focus efforts on – and care systems should support – the development of methods to engage and retain depressed patients in treatment given the high treatment attrition rates (about 25–30%). Those at greatest risk for leaving treatment prematurely are younger and socioeconomically and educationally disadvantaged persons who have had less past depression but may carry a greater burden of general medical or psychiatric comorbidities
13	Patients entering follow-up, especially those not in remission, should be contacted monthly for the first 6 months, which is when relapses most often occur
14	Three out of four patients seen in practice and treated for depression are ineligible for placebo-controlled randomized trials conducted for product registration purposes
15	Patients who find two medications difficult to tolerate should be considered for pharmacogenomic testing to rule out slow metabolism
16	Measurement-based care results in higher average dosing of antidepressant medication

The limitations of STAR*D should be highlighted. Of course, we have many questions that we could not answer at the time that now plague clinicians. For example, when and for whom should we choose atypical antipsychotic agents for augmentation in difficult-to-treat depression? In addition, various brain stimulation

interventions (transcranial magnetic stimulation, vagus nerve stimulation, etc.) were not evaluated at all. Also, while some reports (Rosenblat et al. 2017; Perlis et al. 2007, 2009; Paddock et al. 2007) suggest some value to pharmacogenetic testing, it is unknown exactly where these tests best fit in care delivery. In the trial, we found some participants switched medications twice and encountered intolerance at both points. Perhaps these patients are the best candidates for such testing and appropriate dose adjustment or treatment changes – a speculation. A final limitation is that the follow-up was "naturalistic" meaning not supported by additional clinical staff or clinical care oversight. The high relapse rates might have been lower had there been better clinical support. Regardless, the longer-term care of persons with depressions deserves greater clinical and research focus.

In sum, STAR*D answered a series of clinically important questions while developing new methods and tools for clinical care and future patient-oriented research. It also raised important questions and challenges for subsequent investigations. Finally, it established the feasibility and value of engaging clinicians and patients in real-world practice settings in research that can directly benefit patients.

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Dr. Rush is named as co-inventor on two patents:

1. US Patent No. 7795033: Methods to Predict the Outcome of Treatment with Antidepressant Medication, Inventors: McMahon FJ, Laje G, Manji H, Rush AJ, Paddock S, Wilson AS
2. US Patent No. 7906283: Methods to Identify Patients at Risk of Developing Adverse Events During Treatment with Antidepressant Medication, Inventors: McMahon FJ, Laje G, Manji H, Rush AJ, Paddock S

Dr. Jain has no disclosures to report.

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Pharmacogenomics and Biomarkers of Depression

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Contents

Abstract

The standard of care for antidepressant treatment in major depressive disorder (MDD) is a trial-and-error approach. Patients often have to undergo multiple medication trials for weeks to months before finding an effective treatment. Clinical factors such as severity of baseline symptoms and the presence of specific individual (anhedonia or insomnia) or cluster (atypical, melancholic, or anxious) of symptoms are commonly used without any evidence of their utility in selecting among currently available antidepressants. Genomic and proteomic biomarker have gained recent attention for their potential in informing antidepressant medication selection. In this report, we have reviewed some of the major pharmacogenomics studies along with individual genetic and proteomic biomarker of antidepressant response. Additionally, we have reviewed the blood-based protein biomarkers that can inform selection of one antidepressant over another. Among all currently available biomarkers, C-reactive protein (CRP) appears to be the most promising and pragmatic choice. Low CRP (<1 mg/L) in patients with MDD predicts better response to escitalopram while higher levels are associated with better response to noradrenergic/dopaminergic antidepressants. Future studies

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are needed to demonstrate the superiority of a CRP-based treatment assignment over high-quality measurement-based care in real-world clinical practices.

Keywords
Antidepressant treatment selection biomarkers · C-reactive protein · Inflammation · Major depressive disorder · Pharmacogenomics

1 Introduction

Biological markers (or biomarkers) are objective measures of biological function that can be measured externally (Strimbu and Tavel 2010). As the name suggests, pharmacogenomics combines pharmacology (the study of medications) and genomics to evaluate the role of genetics in an individual patients' response to medications. The interest in pharmacogenomics and biomarkers of depression has been driven by the limited utility of clinical markers in improving treatment outcomes of patients with major depressive disorder (MDD). Despite lacking supportive evidence, the standard of care for antidepressant prescription in clinical practice is based on subjective factors such as anticipated side effect profile of medications, patient or provider preference, cost, and availability on insurer's approved drug lists (Gelenberg et al. 2010). Comparison of antidepressant medications in head-to-head trials has failed to find any significant difference (Gartlehner et al. 2011). Previous studies that have evaluated clinical factors such as baseline depression severity (Friedman et al. 2012), early age of onset (Sung et al. 2013), chronic depression (Sung et al. 2012), presence of insomnia (Sung et al. 2015), or presence of atypical, melancholic, or anxious features (Bobo et al. 2011; Arnow et al. 2015) have failed to find any significant difference in treatment outcomes among currently available antidepressant medications. Thus, a biomarker-driven approach is advocated to individualize selection of antidepressant treatments in order to enhance recovery and treatment adherence and minimize the likelihood of adverse events and attrition from care (Trivedi 2016; Gadad et al. 2018a). Due to the broad scope, we will restrict the discussion to biomarkers that can be assayed from blood and predict response to antidepressant medications in patients with major depressive disorder (MDD).

2 Major Pharmacogenomic Studies of Antidepressant Response

1. *Sequenced Treatment Alternatives to Relieve Depression (STAR*D):* The STAR*D study enrolled treatment seeking outpatients from primary care and psychiatric outpatient clinics who were enrolled in open-label monotherapy with citalopram during the first level. A large proportion of STAR*D participants ($n = 1914$) provided samples for genetic analyses that were used to predict improvement and adverse events with antidepressant treatment (Laje et al. 2009). Laje et al. reviewed the strengths and limitations of STAR*D sample

along with the findings of pharmacogenomic results until 2009 in an exhaustive report (Laje et al. 2009). Briefly, novel variants in serotonin receptor (HTR2A), glutamate receptor (GRIK4), and potassium channel (KCNK2) predicted improvement with citalopram. Notably, association of improvement with polymorphisms in pharmacokinetic genes was not significant. Treatment-emergent suicidal ideations and sexual dysfunction were associated with polymorphisms in genes coding for glutamate receptor and immune regulatory pathways (Laje et al. 2009). In the last few years, STAR*D data has also been used to replicate findings from other studies, as described below.

2. *Munich Antidepressant Response Signature (MARS):* The MARS project enrolled patients ($n = 842$) with MDD or bipolar disorder who were admitted to a psychiatric hospital for an ongoing major depressive episode in order to understand the biological mechanisms (genetic and hormonal markers) of response to antidepressant treatment (Hennings et al. 2009). Among genetic markers, the MARS project focused on both pharmacokinetic (related to drug efflux) and pharmacodynamic (related to regulation of glucocorticoid receptor) genetic markers (Holsboer 2001). Among hormonal markers, the MARS project focused on the release of cortisol using the dexamethasone suppression/corticotropin-releasing hormone (CRH) stimulation test. More recent reports from the MARS project have identified polymorphisms in brain-derived neurotrophic factor (BDNF) and its receptor as predictive of antidepressant response (Hennings et al. 2013).
3. *Genome-Based Therapeutic Drugs for Depression (GENDEP):* This open-label study enrolled patients with MDD for treatment with flexible doses of either escitalopram or nortriptyline (Uher et al. 2009). The initial report ($n = 760$) from the GENDEP study utilized a candidate gene approach evaluating 116 single-nucleotide polymorphisms (SNPs) from 10 candidate genes and found and association of serotonin receptor genes (HTR2A) with response to escitalopram and an association of the norepinephrine transporter (SLC6A2) with response to nortriptyline (Uher et al. 2009). In a subsequent study ($n = 796$) that utilized a candidate gene approach for treatment-emergent suicidal ideation, there was a significant association of polymorphism in BDNF (rs962369) and its receptor (Perroud et al. 2009).
4. *Pharmacogenomics Research Network Antidepressant Medication Pharmacogenomic Study (PGRN-AMPS):* This study enrolled patients ($n = 529$) with nonpsychotic MDD for an 8-week trial of either citalopram or escitalopram (Mrazek et al. 2014). Reports from this study have focused on the role of pharmacokinetic genes on levels of antidepressant medications. Specific SNPs were associated with levels of escitalopram (s-enantiomer of citalopram) and its metabolite in or near cytochrome p450 2C19 and 2D6 genes (Ji et al. 2014). Investigators from this study also informed the development of commercially available combinatorial genetic testing to prescribe antidepressant treatment (Mrazek et al. 2014; Altar et al. 2013). In a recent report, such a combinatorial approach was shown to be superior in efficacy rates as compared to a treatment as usual approach (Altar et al. 2015).

5. *International Study to Predict Optimized Treatment in Depression (iSPOT-D):* In this large multi-site study conducted in five countries, genetic information from patients with MDD ($n = 683$) was analyzed to predict differential rates of improvement and adverse events to escitalopram, sertraline, or venlafaxine (Schatzberg et al. 2015). The genetic analyses, described below, have focused on SNPs in genes regulating drug efflux across the blood-brain barrier and hypothalamic-pituitary-adrenal (HPA) axis (Schatzberg et al. 2015; O'Connell et al. 2018b).
6. *International SSRI Pharmacogenomics Consortium (ISPC):* This consortium focused predominantly on genes involved with response to selective serotonin reuptake inhibitors (SSRIs) and enrolled patient with MDD at seven sites from five different countries including those in North America, Europe, and Asia (Biernacka et al. 2015). In a large sample of patients ($n = 865$), there was no SNP that attained genome-wide level of significance (Biernacka et al. 2015).
7. *Combining Medications to Enhance Depression Outcomes (CO-MED) trial:* In this large single-blind study of outpatients with MDD comparing escitalopram monotherapy with combinations of escitalopram and bupropion and of venlafaxine and mirtazapine, blood samples were obtained from a subgroup of participants ($n = 459$) for genetic analyses. In a recent genome-wide association study (GWAS) of the three treatment arms, a SNP (rs10769025) in the ALX4 gene on chromosome 11 was significantly associated with response ($\geq$50% reduction in symptoms) at week 6 with escitalopram but not with the other two antidepressant combinations (Gadad et al. 2018b).
8. *Genome-wide association studies (GWAS) meta-analyses:* Multiple reports have now combined samples from the above-described studies to conduct GWAS meta-analyses to identify differences using a larger sample size. In a GWAS analyses of 1.2 million SNPs in individuals of northern European ancestry ($n = 2{,}256$) from the GENDEP, MARS, and STAR*D studies, there was no SNP that met the threshold for genome-wide association with symptom improvement over a 12-week period (Investigators et al. 2013). Additionally, a polygenic risk score derived from the GENDEP and MARS studies accounted for only 1.2% variance in outcomes in the STAR*D study (Investigators et al. 2013). Similarly, a meta-analysis of ISPC, STAR*D, and PGRN-AMPS failed to find any SNP with genome-wide significance for predicting response to SSRI antidepressants (Biernacka et al. 2015).

3 Genetic Biomarkers of Antidepressant Response

1. *Drug Efflux:* Genetic polymorphisms also known as ABCB1 have been investigated for predicting response to antidepressant medications. Polymorphisms in MDR1/ABCB1 genes that code for P-glycoprotein (P-gp), an efflux pump at the blood-brain barrier that regulates the level of antidepressants such as citalopram and venlafaxine that are substrates of P-gp (Uhr et al. 2008), have been widely studied for predicting antidepressant response. While there are multiple studies showing an association of MDR1/ABCB1 SNPs with response

to antidepressant medications that are P-gp substrates (Uhr et al. 2008; Gex-Fabry et al. 2008; Kato et al. 2008; Nikisch et al. 2008; Dong et al. 2009), others have failed to find any significant association of these SNPs with either response or adverse events (Laika et al. 2006; Peles et al. 2008; Peters et al. 2008). In a recent report, Schatzberg et al. tested for ten SNPs in or near the ABCB1 location for their association with either improvement (remission of depressive symptoms) or side effect severity (Schatzberg et al. 2015). Of the nine SNPs investigated, they found that one (rs10245483, a functional SNP upstream of ABCB1) was differentially associated with improvement and side effect severity. The major G allele and minor T allele of this SNP predicted differential outcomes with SSRIs (escitalopram or sertraline) and venlafaxine [serotonin and norepinephrine reuptake inhibitor (SNRI)]. Remission rates were higher with SSRIs than venlafaxine in G/G homozygotes for this SNP. Conversely, in T/T homozygotes, remission rates were significantly higher with venlafaxine than SSRIs (Schatzberg et al. 2015).

2. *Neurotransmitter Transport and Transmission*
   (a) *Serotonin transporter:* Polymorphisms in the serotonin transporter linked polymorphic region (5-HTTLPR) of the SLC6A4 gene influence serotonin reuptake and have been investigated widely for antidepressant response. In the STAR*D study, while an initial report suggested no significant association (Kraft et al. 2007), a follow-up study showed differential treatment outcomes with citalopram only in non-Hispanic white subjects and not in Hispanic white and black subjects (Mrazek et al. 2009). In a systematic meta-analysis, Procelli et al. found a strong association between polymorphism in 5-HTTLPR and treatment outcomes with selective serotonin reuptake inhibitors (SSRIs) in Caucasians but not in Asians (Porcelli et al. 2012). Notably, several studies have failed to find association of 5-HTTLPR polymorphism with antidepressant outcomes (Maron et al. 2009; Perlis et al. 2010).
   (b) *Serotonin receptor:* A specific SNP (rs7997012) of the serotonin receptor 2A (HTR2A) gene was significantly associated with antidepressant response in both STAR*D and the MARS studies (McMahon et al. 2006; Peters et al. 2009; Lucae et al. 2010). However, other studies failed to replicate this association but found associations with other SNPs of HTR2A and antidepressant treatment outcomes (Uher et al. 2009; Horstmann et al. 2010). Adding to the variability of these findings, other studies did not find an association of HTR2A SNPs with outcomes but implicated other serotonin receptors (HTR1A) (Hong et al. 2006).
   (c) *Dopamine metabolism:* The catechol-O-methyltransferase (COMT) val/met polymorphism (rs4680) has been associated with response to antidepressant medications. The val/val genotype is associated with higher activity of the COMT enzyme than the val/met and met/met genotypes (Chen et al. 2004). In a study of Caucasian patients with MDD ($n = 256$), the val/val genotype was associated with significantly less likelihood of response from weeks 4 to 6 (Baune et al. 2007). Interestingly, in MDD patients who have failed to respond to multiple antidepressant treatments, those with the val/val

genotype had a much higher chance of responding with electroconvulsive therapy (Anttila et al. 2008). These findings were partially replicated in a separate sample of treatment-resistant depressed patients where the association of val/val genotype was associated with greater improvement only in females but not males (Katharina et al. 2010).

(d) *Glutamate:* Association of response to antidepressant treatment with polymorphisms in ionotropic glutamate receptors (GRIK4) has been reported in STAR*D, MARS, and other studies (Horstmann et al. 2010; Paddock et al. 2007; Pu et al. 2013). However, these findings were not replicated in studies by Perlis et al. (2010) and Serretti et al. (2012) who failed to replicate these associations.

(e) *Monoamine* metabolism: While variations in genes coding for the type A monoamine oxidase A (MAO-A) enzyme exist, the principal catabolic enzyme of monoamine neurotransmitters has been associated with response to mirtazapine in female patients with MDD (Tadić et al. 2007). Studies of bupropion (Tiwari et al. 2013) and fluoxetine (Peters et al. 2004) failed to replicate these findings.

3. *Liver Enzymes:* Tests for common polymorphisms in genes encoding for cytochrome P450 (CYP) enzymes, which can affect the metabolism of antidepressant medications, are included in commercially available kits (O'Connell et al. 2018b) and may be used to classify patients on the basis of their metabolism of individual drugs (extensive, intermediate, poor, or ultrarapid metabolizers) (Porcelli et al. 2011). The utility of these polymorphisms is mainly restricted to predicting adverse events (Porcelli et al. 2011). The association of CYP SNPs with response to antidepressant medications was negative in the STAR*D and GENDEP studies (Peters et al. 2008; Hodgson et al. 2015). Consistent with these reports, a recent review of combinatorial pharmacogenetic tests found that the clinical utility of these tests is limited and may be informative in predicting adverse events with antidepressants (Zeier et al. 2018).
4. *Hypothalamic-Pituitary-Adrenal (HPA) Axis*

(a) *FK506-binding protein 5 (FKBP5)*: Variants in gene coding for FKBP5, a protein regulating glucocorticoid receptor, were initially identified by Binder et al. to show strong association with response to antidepressant medication and risk of recurrence using sample from MARS study ($n = 233$) and replicated in an independent sample of patients ($n = 85$) (Binder et al. 2004). Interestingly, they found an association of these polymorphisms with levels of FKBP5 protein but not with mRNA (Binder et al. 2004). The levels of FKBP5 protein, in turn, were associated with levels of cortisol after dexamethasone suppression/CRH stimulation. The association of functional genetic variants of FKBP5 with antidepressant response was replicated in independent samples using STAR*D and PGRN-AMPS studies (Ellsworth et al. 2013). However, Uher et al. failed to find any association of FKBP5 polymorphisms with antidepressant response in GENDEP (Uher et al. 2009).

(b) *Corticotropin-releasing hormone (CRH)*: A recent report evaluated 16 candidate polymorphisms in 5 CRH and cortisol-associated genes and found 1 (rs28365143) that was differentially associated with treatment response in the iSPOT-D study (O'Connell et al. 2018a). Participants of iSPOT-D who

were homozygotes for the G allele and were treated with SSRIs (escitalopram or sertraline) had significantly higher response and remission rates than those who carried A alleles (A/G and A/A) (O'Connell et al. 2018a). This pattern of association was replicated in a separate sample of depressed outpatients (O'Connell et al. 2018a).

4 Protein Treatment Selection Biomarkers (Moderators)

In contrast to clinical markers which have failed to guide antidepressant treatment selection, several biomarkers have shown potential in guiding antidepressant treatment selection in recent reports. Most of these are related to immune dysfunction or inflammation. Notable in this regard is the role of obesity, which has been shown to partly account for elevated inflammatory markers in patients with MDD (Shelton et al. 2015). Two recent reports suggest that body mass index (BMI), a commonly used measure of obesity, can guide selection of antidepressant medications. While depressed patients with normal BMI respond better to SSRIs, those with BMI >35 respond better to either venlafaxine monotherapy or a combination of SSRI's and bupropion (Jha et al. 2018a; Green et al. 2017). A variety of protein biomarkers have been shown to differentially predict antidepressant response (Jha and Trivedi 2018).

1. *C-reactive protein (CRP):* CRP is a plasma protein which is synthesized mainly by the liver and increases markedly in response to acute infection or injury and thus is also labelled as an acute-phase reactant. Levels of CRP below 1 mg/L have been associated with low likelihood of cardiovascular mortality than those about CRP >3 mg/L. In a recent report, CRP in plasma was shown to have very high correlation (coefficient = 0.855) with CRP in cerebrospinal fluid suggesting the utility of CRP in blood as a marker of central nervous system inflammation. In the GENDEP study, Uher et al. studied differential treatment outcomes with escitalopram vs. nortriptyline at three thresholds of CRP (<1 mg/L, 1–3 mg/L and >3 mg/L). They found that escitalopram was significantly superior to nortriptyline in MDD patients with CRP <1 mg/L. Conversely, among those with CRP ≥1 mg/L, nortriptyline was superior to escitalopram (Uher et al. 2014). These findings were partly replicated in the CO-MED trial where the combination of bupropion-escitalopram was considered analogous to nortriptyline in pharmacological profile. In the CO-MED trial, patients with CRP <1 mg/L had significantly higher remission rates with escitalopram monotherapy (57.1%) than bupropion-escitalopram combination (33.3%). Conversely, among those with CRP ≥1 mg/L, remission rates were significantly higher with bupropion-escitalopram combination (51.4%) than escitalopram monotherapy (29.7%) (Jha et al. 2017a). Taken together, these findings support the utility of CRP in blood as treatment selection biomarker (Miller et al. 2017).
2. *Interleukin 17 (IL-17):* Recent reports suggest the role of IL-17-mediated immune response in pathophysiology of depression (Beurel et al. 2013). Elevated levels of IL-17 have also been associated with greater severity of anhedonia in male

patients with MDD (Jha et al. 2018b). Hence, a recent report from CO-MED trial explored a panel of cytokines containing IL-17, Th1- (interferon gamma and tumor necrosis factor alpha), Th2- (IL-4, IL-5, IL-9, and IL-13), and non-T-cell-related (IL-1β, IL-1 receptor antagonist, IL-6, IL-8, and macrophage inflammatory protein (MIP) 1 α and β) markers as moderators of antidepressant treatment outcomes. In this report, only IL-17 was associated with differential treatment outcomes. Elevated IL-17 levels were associated with greater reduction in depression severity with the bupropion-escitalopram combination only. There was no such association with either escitalopram monotherapy or venlafaxine-mirtazapine combination (Jha et al. 2017b).

3. *Biomarkers of blood-brain barrier (BBB) dysfunction:* Disruption of the blood-brain barrier has gained recent attention for its role in pathogenesis of depressive symptoms (Cheng et al. 2018). In response to BBB disruption, pericytes can be recruited to breach the disruption. Platelet-derived growth factor (PDGF) has been shown to be critical in the activity of pericytes and increase in response to BBB disruption. Additionally, BBB disruption can also lead to increase in levels of astrocytic markers such as S-100 calcium binding protein B (S100B) as they escape out of CNS into peripheral circulation. The hypotheses of BBB dysfunction in predicting antidepressant response were tested in two different reports in the CO-MED trial. Elevated levels of PDGF were associated with greater reduction in overall depression severity and anhedonia with bupropion-escitalopram combination with no similar association seen for escitalopram monotherapy or venlafaxine-mirtazapine combination (Jha et al. 2017c). Interestingly, improvement in anhedonia completely accounted for the change in depressive symptom severity suggesting that these differences were driven by changes in severity of anhedonia. In a separate report, pre-treatment levels of S100B were differentially associated with changes in anhedonia severity. Among those treated with escitalopram monotherapy, low S100B (reflecting greater BBB integrity) was associated with better outcomes (Jha et al. 2018c). Among those treated with bupropion-escitalopram or venlafaxine-mirtazapine combinations, there was no similar association.

5 Conclusions and Recommendations

The last few decades have seen tremendous advances in our understanding of the biological underpinnings of depression. However, these findings have not translated in improved outcomes for patients with MDD. Pharmacogenomic tools, while in wide use, have proven to be of little benefit in predicting improved treatment outcomes. In this regard, CRP seems to be the most promising and pragmatic biomarker. It is readily available through commercial laboratories, is stable in biospecimens under varying conditions of storage and processing, and can even be measured with point-of-care finger-stick devices. However, future trials are needed to test if implementing a CRP-based treatment assignment in real-world clinical practices will result in higher rates of remission as compared to high-quality care delivered by clinicians.

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Therapeutic Drug Monitoring of Antidepressants

Najla Fiaturi and David J. Greenblatt

Contents

Abstract

For a number of antidepressants in current clinical use, concentrations in serum or plasma are a more reliable index of target drug concentrations than is dosage. For such drugs, therapeutic drug monitoring (TDM) may be a useful clinical guide for the purpose of maximizing the likelihood of favorable therapeutic outcome while minimizing the probability of clinical ineffectiveness or adverse side effects. TDM is of greatest benefit when a therapeutic range of serum concentrations

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has been well established. Even if such a range is not definitively determined, TDM can be of help in situations in which patients are refractory to therapy despite adequate or high dosages, when adverse events supervene even with low doses, or when noncompliance with the intended dosage plan is suspected. Serum antidepressant concentrations from TDM should be interpreted in the full context of the patient's demographic characteristics and clinical status, along with an understanding of the pharmacokinetics of the medication being taken, the timing of the sample in relation to the dosage regimen, and the specific laboratory assay procedure. TDM measurements may be costly, and the potential benefits of the information need to be weighed against the cost to the patient or to the health care system.

Keywords

Antidepressants · Pharmacokinetics · Plasma drug concentrations · Selective serotonin reuptake inhibitor · Therapeutic drug monitoring · Tricyclic antidepressant

1 Introduction

Physicians often face the challenge of managing patients who respond to treatment initially and then lose response. This can be frustrating for both patient and physician. In addition, adverse drug reactions are an important health issue that can affect treatment decisions. In 1994, adverse drug reactions were reported to account for over two million serious events per year, including 106,000 deaths per year (Lazarou et al. 1998). However, these numbers do not consider the benefits of pharmacologic treatment, in that failure to use appropriate medications, as well as use of inadequate doses of the medications, can in themselves lead to morbidity and mortality. Nonetheless, adverse drug reactions and loss of response are areas where therapeutic drug monitoring can play a role in improving outcome.

There are three pharmacologic concepts that determine the safety and effectiveness of a medication in an individual patient: (1) pharmacokinetics, which describes the body's effect on a drug and the processes of absorption, distribution, metabolism, and elimination; (2) pharmacodynamics, which describes the drug's effect on the body; and (3) pharmacogenomics, which is the study of inherited differences in drug disposition and effects or the influence of genetics on pharmacokinetics and pharmacodynamics.

The major therapeutic drug classes used to treat psychiatric illnesses are the antidepressants, antipsychotics, anxiolytics, mood stabilizers, and psychostimulants. The first two are prescribed frequently through various mental health services, and the anxiolytics are prescribed by nearly all medical specialties. Clinical laboratories will ordinarily receive only a few requests for analysis of samples containing these drugs. The utility of antipsychotic serum concentration monitoring is still subject to controversy, and only a few centers routinely provide these measurements.

Therapeutic drug monitoring (TDM) includes the analysis, assessment, and evaluation of drug concentrations in serum or plasma (Koch-Weser 1972, 1975; Kang and Lee 2009; Friedman and Greenblatt 1986). TDM can guide clinicians to achieving optimal therapeutic effects with commonly used antidepressants. The goal is to provide individualized drug dosing to optimize safety and efficacy. What is needed for that purpose is a clinically meaningful therapeutic range of drug concentrations that are associated with the drug's pharmacologic effect. Serum concentration information must always be viewed in a clinical context and with a working knowledge of the drug's pharmacokinetic profile. Understanding relationships between drug dosage and resulting drug concentrations will make serum levels more meaningful. However, these relationships do not allow clinicians to more reliably predict a patient's response to a dosage regimen. The relationships between drug concentration and ultimate pharmacologic response are determined by several factors, including patient compliance with the prescribed regimen, access of drug to receptor sites, and receptor sensitivity, along with pharmacokinetic factors including drug absorption, distribution, elimination half-life, steady-state concentration, etc. (Levy 1994; Friedman and Greenblatt 1986). Similarly, factors such as age, drug interactions, and concomitant disease can also influence a drug's pharmacokinetic properties and serum level profile (Koch-Weser 1975).

Clinical questions of efficacy, toxicity, and patient compliance will often prompt the need for therapeutic drug monitoring. If TDM is to be used optimally, the physician and clinical laboratory must collaborate closely. This means that laboratories and physicians should be aware of the clinical application of basic pharmacokinetic principles and the patient's underlying clinical status. Understanding the pharmacokinetics of a given agent can help physicians to individualize each patient's treatment, enhance clinical benefit, and reduce the incidence of drug-related toxicity. Because of interindividual differences in pharmacokinetic properties of a given drug, TDM can provide an advantage over simply knowing the dose. There are various conditions where TDM can be beneficial, including:

1. A narrow therapeutic range, which occurs when the same dose of a drug produces the desired therapeutic concentrations in one patient and toxicity in another
2. When toxicity or lack of effectiveness of the drug is potentially hazardous
3. A poor response to the drug, suspected noncompliance with the dosage regimen, or signs of toxicity despite seemingly appropriate dosage
4. Drugs for which serum concentrations are associated with drug efficacy and/or toxicity, as in the case of a number of antidepressants (Perry et al. 1994)
5. Drugs that have unpredictable pharmacokinetics, for example, drugs that have nonlinear pharmacokinetics with increasing dose or have unexpectedly high within- and between-patient variability
6. When a rapid, reliable, specific, and inexpensive drug assay is available

These factors also form the basis for understanding the value of TDM with psychiatric medications such as antidepressants.

2 Basic Concepts of TDM

2.1 The Relationship Between Dosage, Plasma Concentration, and Clinical Effect

Pharmacokinetics (PK) utilizes mathematical models to portray and study metabolic processes and relationships between drug dose and drug concentration in plasma and other biologic fluids (Greenblatt and Koch-Weser 1975; Greenblatt and Shader 1985; Greenblatt and Abourjaily 2016). Pharmacodynamics (PD) applies similar models to understand the time course of drug effects on the body. Physicians are most worried about pharmacodynamics – they need to know how dosage, route of administration, and frequency of administration can be used to maximize the likelihood of attaining the desired therapeutic effect and at the same time minimize the probability of adverse effects.

Bioavailability is an important determinant of the relationship between drug dosage and plasma concentration (Greenblatt and Koch-Weser 1975; Aronson et al. 1992). The actual drug dose by itself may have limited predictive value, and knowledge of drug concentration can make the difference between a failed versus an optimal treatment response. The availability of a drug after oral dosage depends on the extent of absorption and, for some drugs, the extent of first-pass metabolism (Gibaldi et al. 1971; Greenblatt and Koch-Weser 1975). The decrease in the net fraction of systemically available drug is equivalent to a decrease in the dose given.

Decreased rates of drug absorption are clinically important for drugs that are given as a single dose in situations requiring rapid onset of action, as with analgesics or hypnotics. Drug absorption rate and systemic availability can be affected by the product formulation. As with drugs that undergo first-pass metabolism, drugs that are incompletely absorbed after oral administration will have higher blood concentrations when they are administered intravenously. Intramuscular and subcutaneous administration may yield lower peak blood concentrations than drugs administered intravenously. On the other hand, the rate of absorption is usually of less importance for compounds which are given in multiple-dose regimens to achieve a desired steady-state plasma concentration. However, even if the drug is completely absorbed, the rate of absorption might be slow enough that effective blood concentrations are never reached, or the rate of onset may be too slow when prompt action is required.

2.2 Plasma-Tissue Partitioning

In order for a drug to exert its characteristic effect, it must reach its site of action. Though it would be optimal to monitor concentrations at these sites, receptor concentrations of drugs are usually inaccessible or are widely distributed in the body. Thus the measurement of drug concentrations at these sites is generally not possible (Rizk et al. 2017). Unless a drug is purposely administered to produce its effect locally or is injected directly into the blood, getting to the site of action

involves two separate processes. The first of these is absorption (covered in Sect. 2.2 of this chapter). The second process is distribution, defined as the diffusion or transport of a drug from vascular to extravascular sites.

Clinically, the body is often characterized as a single compartment, with the assumption of rapid and homogenous distribution throughout the hypothetical volume of distribution. However, it is more realistic that the body consists of several compartments, with specific compartments requiring longer periods of time to achieve equilibrium (Greenblatt and Koch-Weser 1975; Stangier 2008). In the pharmacokinetic sense, these drugs are described best by multi-compartment models. Factors that influence drug distribution from plasma to specific body compartment include the mechanism of transport (active or passive), the permeability of membranes, lipid solubility, the extent to which drug molecules are ionized or charged, and the extent of drug binding in to plasma protein (Burton 2006). For example, passage across the intact blood-brain barrier is favored for highly lipid-soluble drugs, but does not occur for relatively polar antibiotics that exist largely in an ionized state in serum, such as penicillin G. Another aspect of drug distribution involves the binding of drug to plasma proteins (Greenblatt et al. 1982).

Ideally a drug would remain in solution in the various compartments of the body, but this is characteristic of very few drugs. More commonly a drug will interact with other molecules like plasma proteins, similar to the interactions that occur between a drug and its receptors (Ambrose and Winter 2004). The major difference is that the drug-receptor combination leads to a biologic effect, whereas binding with non-receptor sites does not.

2.3 Analytical Issues in TDM

The practice of therapeutic drug monitoring requires the integration of several disciplines, including pharmacokinetics, pharmacodynamics, and laboratory analysis. When it comes to blood sample collection, timing of the sample is of critical importance (Greenblatt et al. 1994; Friedman and Greenblatt 1986; Bowers 1998). Usually, there are two specific times that a blood sample is drawn from a patient. One of these sampling times is intended to determine what is termed the "trough" concentration, which is the concentration just prior to the next dose. The second is to determine the peak concentration, which is usually 1–2 h after oral dosing. Peak concentration determinations have the inherent limitation of extensive and unpredictable within- and between-individual variations in the rate and extent of drug absorption.

A principal objective in designing a dosage regimen in general is to attain a trough concentration that is within the therapeutic range and peak concentration that does not reach the potentially toxic range. Similarly, in relation to TDM, the timing of blood sample collection is critical for correct interpretation of the result. The absorption and distribution phases should be complete and a steady-state concentration reached before the sample is collected (Linder and Keck 1998; Friedman and Greenblatt 1986). Samples obtained before a steady-state condition is reached may

underestimate the actual steady-state drug concentration (Greenblatt and Abourjaily 2016). In such cases, increasing the dose based on the result could lead to excessively high concentrations and possible toxicity (Greenblatt and Abourjaily 2016). The timing of sampling in relation to drug administration should be based on the pharmacokinetic properties of the drug, its dosage regimen, and the clinical reason for sample collection. For drugs with short half-lives, both a steady-state peak and trough sample may be collected to characterize the concentration profile ("interdose fluctuation"). For drugs with a long half-life, steady-state trough samples alone are generally sufficient.

Historically, spectrophotometry and colorimetry were the main techniques utilized for estimation of drug levels. However, these strategies are constrained by poor sensitivity and variable specificity. Chromatography is a technique for isolating mixtures of substances based on their physicochemical qualities, so at least one of those substances can be specifically detected. Generally it is possible to distinguish and quantitate the parent medication and some or all of its major metabolites at the same time (Friedman and Greenblatt 1986).

In the last 10 years, the technology for determining drug concentrations in body fluids has progressed from relatively nonspecific, time-consuming, complex procedures, to those using micro-samples with high sensitivity and specificity. Serum drug analysis as a clinical tool requires that the methods selected be sufficiently sensitive and highly specific; interference from other drugs or endogenous substances should be minimal. The assays that have been developed include radioimmunoassay (RIA) and enzyme-linked immunosorbent assay (ELISA, the most commonly used assay) (Uglietti et al. 2007). Lack of specificity is the principal limitation of immunoassays. Another limitation of double antigen ELISA, the most common type of ELISA, is the inability of accurately measure antidrug antibody in the presence of the drug.

We have been using serum and plasma drug concentrations as interchangeable quantities. For the great majority of drugs, serum and plasma concentrations are in fact essentially identical. However, whole blood concentrations are another matter. The relation of serum/plasma drug concentrations to those in hemolyzed whole blood will depend on the extent of red blood cell uptake of the drug, which is variable from drug to drug depending on a variety of factors.

2.4 Practical Issues in TDM

In clinical use, therapeutic drug monitoring is somewhat analogous to the electrocardiogram or X-ray studies, for which the interpretation of the test is as important as the test itself. If an assay result is to be realistically interpreted, results must be considered in light of the patient's full clinical profile (Misan et al. 1990; Reynolds and Aronson 1993). Examples of patient factors that may influence serum concentration monitoring and interpretation are:

1. Pregnancy
2. Age, weight, and body habitus
3. Gender
4. Genetics
5. Renal, hepatic, and cardiac diseases
6. Diseases affecting renal and/or hepatic perfusion
7. Malabsorption or nutritional status
8. Hypoalbuminemia
9. Concomitant drug therapy

2.5 Economic Considerations for TDM

Regardless of the methodology used in measuring serum drug concentration, the cost to the patient and the healthcare system should be considered. The methodology must have an acceptable level of precision, accuracy, specificity, and sensitivity for the drug being monitored (Touw et al. 2005). The results should be attainable by a technologist or technician level personnel. The assay instrumentation should be reasonably priced and easily maintained. The assay reagents must be inexpensive and stable for a reasonable period of time. The calibration curve should be stable and not require daily adjustments. Reasonably rapid result generation capabilities should be available at reasonable cost.

It is difficult to put a dollar value on quality patient care, especially when it involves preventive medicine. However, the resources utilized by TDM methods will likely be justified by positive clinical outcomes, including decreased morbidity and hospitalizations (Schumacher and Barr 1998).

3 Utility of TDM with Antidepressant Pharmacotherapy

3.1 Serotonin Selective Reuptake Inhibitors

The need for effective antidepressant medication options with improved tolerability compared to the tricyclic antidepressants (TCAs) led to the development of the selective serotonin reuptake inhibitors (SSRIs), which have relatively high affinity for serotonin reuptake receptors, lower affinity for noradrenergic reuptake receptors, and low affinity for postsynaptic neurotransmitter receptors (Frazer 1997). SSRIs are hence the first class of rationally designed therapeutic medications in psychiatry. After the introduction of fluvoxamine in Great Britain in 1983, fluoxetine became generally available in multiple countries, followed by paroxetine, citalopram, sertraline, fluvoxamine, and escitalopram (Catterson and Preskorn 1996). Based on clinical trials, SSRIs are viewed as an alternative option to TCAs. With respect to therapeutic efficacy, SSRIs and TCAs are essentially equivalent (Bech 1988; Rickels et al. 1990). Because of the absence of postsynaptic receptor antagonism, SSRIs have reduced adverse effects such as cardiotoxicity and CNS toxicity. SSRIs are

reasonably safe, and straightforward to dose and manage clinically. Due to the beneficial safety profile of SSRIs, the treatment of depression with antidepressant medications has largely changed from hospitalized inpatients to an outpatient setting (Sheehan et al. 1998). Also, the use of SSRIs has been expanded from major depression to less severe forms of depression (Szegedi et al. 1997), and other psychiatric disorders suggested to be related to serotonergic dysfunction. These include anxiety, obsessive-compulsive disorder (Fineberg 1996), and premenstrual dysphoric disorders (Epperson et al. 2012; Gunasekara et al. 1998).

In addition to the greater safety and tolerability of SSRIs, the pharmacology of SSRIs has been viewed as less perplexing compared to their predecessors, the TCAs. The metabolism of TCAs yields various metabolites with pharmacologic properties that are not necessarily equivalent to those of the parent medication. After the introduction of SSRIs, little consideration was given to their pharmacokinetics in depressed patients, and TDM still is not a common component of clinical use of SSRIs.

Currently, one important criterion for drug selection is based on the potential for drug-drug interactions (Baumann 1996; Brøsen 1996; Greenblatt et al. 1999). Although not all SSRIs inhibit the activity of specific cytochrome P450 (CYP) isoenzymes (Harvey and Preskorn 1996; Preskorn 1996b), nonetheless drug-drug interactions are a consideration with SSRIs, as well as with other drugs (Preskorn and Magnus 1994; Harvey and Preskorn 1995; Shader et al. 1996; Nemeroff et al. 1996; Greenblatt et al. 1999; von Moltke et al. 2001).

3.1.1 Concentration-Response Relationships

An issue with SSRIs is that the response rate generally does not improve at doses greater than the "minimum effective dose." This may account for some of the popularity of the SSRIs, since dose titration was of reduced importance, and the starting dose might correspond to the eventual effective dose. In double-blind, controlled studies of patients with major depressive disorder, daily doses of 20, 40, and 60 mg daily of fluoxetine produced almost equivalent remission rates (Altamura et al. 1988; Wernicke et al. 1988; Schweizer et al. 1990). Correspondingly, no distinction was found in the remission rates in patients treated with 20, 30, or 40 mg/day of paroxetine or 50, 100, 150, or 200 mg/day of sertraline (Dunner and Dunbar 1992; Preskorn and Baker 1997). Nonetheless there are patients who benefit from a dose other than the usually effective minimum dose, and studies have not been done to evaluate the utility of TDM in such patients.

The level of serotonin reuptake inhibition is associated with SSRI plasma concentration (Preskorn 1993). Nonetheless it is likely that the flat dose-response curve of the SSRIs is because 70–80% of serotonin reuptake sites are inhibited at the "usually effective minimum dose," and minimal additional reuptake is inhibited as the dose is increased (Lemberger et al. 1985; Routledge and Marsden 1987; Preskorn 1996b). This is similar to the monoamine oxidase inhibitors (MAOIs), for which inhibition of 70–80% of monoamine oxidase (MAO) activity is needed for optimal antidepressant effect.

The flat dose-response curve for the SSRIs may in part explain why attempts to identify associations between SSRI plasma levels and antidepressant efficacy have not been definitive (Preskorn and Fast 1991; Goodnick 1994; Amsterdam et al. 1997). There are limitations in statistical approaches to establishing associations between drug concentration and response, particularly in view of complexities such as enantiomers of a drug that have different biological activity, delayed time to achieve steady-state, plasma/tissue drug partitioning, a delay in attainment of optimal clinical response, and interpatient variability in pharmacokinetic characteristics (Koran et al. 1996).

The SSRIs that are presently available to treat depression or other conditions with dysfunctional serotonergic transmission have comparable therapeutic efficacies and adverse reaction profiles, regardless of a moderately wide range of affinities for serotonin transporters. There are substantial differences in the frequency and degree of less common effects, for example, hyponatremia (Cotton et al. 1999; Greenblatt and Greenblatt 2016), extrapyramidal movement disorders (Leo 1996), or withdrawal symptoms after drug cessation (Haddad 1997), presumably because of interactions with sites other than the serotonin transporters, as well as pharmacokinetic differences (Goodnick and Goldstein 1998).

SSRIs vary in their pharmacokinetic properties. To choose a particular SSRI, its half-life, linearity of kinetics, pharmacologic activity of metabolic products, and drug-drug interactions should all be considered. For example, the long half-life of fluoxetine, and of its active metabolite norfluoxetine, might be of benefit for a patient with poor compliance, since drug concentrations decrease only slightly when the patient misses a dose. On the other hand, in cases of fluoxetine nonresponse, long washout periods are recommended before switching to another antidepressant agent, in order to avoid drug interactions or the development of serotonin syndrome.

An important difference among the SSRIs is their potential for drug-drug interactions. Paroxetine, fluoxetine, and norfluoxetine are strong inhibitors of CYP2D6, and fluvoxamine strongly inhibits CYP1A2 and CYP2C19 (Greenblatt et al. 1999). The concomitant use of SSRIs with other drugs that are substrates of the CYP enzymes can lead to potential toxicity unless they are appropriately monitored. In addition, the nonlinear kinetics of fluvoxamine, fluoxetine, and paroxetine complicate dosing. Dosage escalation may cause disproportionate increases in drug concentrations. TDM might be helpful to monitor drug concentrations in patients treated with drugs having nonlinear kinetics (Greenblatt and Abourjaily 2016).

3.1.2 Recommendation

Because of their wide therapeutic index, there is no convincing evidence to support routine monitoring of serum levels of any of the SSRIs as a standard of care to maximize efficacy or avoid toxicity. However, TDM might be valuable for individual dosage optimization in specific circumstances, such as apparent lack of any pharmacologic effect despite seemingly adequate dosage (Friedman and Greenblatt 1986; Lundmark et al. 2000). Roughly half or more of patients on any single dose of an SSRI do not achieve an ideal response in terms of alleviation of depressive symptoms (Preskorn 1996a). For these patients, TDM can give potentially important

data to rule out low plasma concentrations due to noncompliance (failure to take the medication as prescribed) or to identify those people who might be pharmacokinetic outliers (i.e., unusually high or low drug clearance). In the "non-responder," who is taking an adequate dosage of an SSRI for an adequate duration of time, determination of drug concentrations can be utilized to guide treatment choices (i.e., low drug concentration and absence of effectiveness or high drug concentration and poor tolerability). TDM may also be useful with the SSRI fluoxetine, where TDM can be used to determine whether its metabolite, norfluoxetine, is still present after discontinuation of treatment. Such plasma monitoring would help the clinician to decide when it is safe to begin treatment with another agent and avoid a potential drug-drug interaction (e.g., when changing to an MAOI or to a substrate for one of the drug-metabolizing enzymes inhibited by fluoxetine).

3.2 Serotonin Norepinephrine Reuptake Inhibitors

Venlafaxine and duloxetine are the two most commonly used SNRIs. They inhibit the reuptake of both serotonin and norepinephrine. These drugs are generally safer than the TCAs, which also block reuptake of both serotonin and norepinephrine.

3.2.1 Venlafaxine

Venlafaxine (VF) has linear pharmacokinetics. It is metabolized principally by CYP2D6 to give an active metabolite, O-desmethylvenlafaxine (ODV), and also to small extent by CYP3A4, which yields *N*-desmethylvenlafaxine (Fogelman et al. 1999; Shams et al. 2006). VF and ODV are both serotonin and norepinephrine reuptake inhibitors, and venlafaxine moderately inhibits dopamine reuptake. Because of extensive first-pass metabolism, only 40–45% of a dose of VF reaches the systemic circulation unchanged. Venlafaxine and its primary metabolite ODV are 27% and 30% bound to plasma proteins, respectively (Shams et al. 2006). Maximal blood levels are achieved 1–2 h (VF) and 3 h (ODV) after administration of the immediate-release preparations and 6 h (VF) and 9 h (ODV) after the delayed release form (Nichols et al. 2009). The usual steady-state half-lives of VF and ODV average 5 and 11 h, respectively. Steady-state plasma concentrations are reached after 3 days of dosing. The ratio of ODV/VF is a reasonable method for phenotyping patients regarding their CYP2D6 metabolizer status (Nichols et al. 2009). Plasma levels vary widely at each dosage level. Gender, age, and smoking should be considered for ideal dosing of patients with VF. Females had higher dose-corrected plasma levels of VF and ODV than males, and patients older than 60 years showed elevated levels of the two compounds. In smokers, mean plasma levels of ODV are lower than in non-smokers (Unterecker et al. 2012). A significant association was detected between VF plasma levels and its antidepressant efficacy (Charlier et al. 2002). A positive relationship was additionally found between VF plasma concentration and adverse reactions. Therefore there are some situations in which TDM of VF and ODV concentrations may have clinical value.

Recommendation

Specific quantitative analysis of venlafaxine and its active metabolite can be achieved with high-performance liquid chromatography (Vu et al. 1997). Preliminary data in light of these assays suggest a target plasma concentration range from 195 to 400 ng/ml for therapeutic response with venlafaxine (Veefkind et al. 2000).

3.2.2 Duloxetine

Duloxetine reaches maximum plasma concentrations at roughly 6–10 h after dosage. Duloxetine is highly protein-bound and is widely distributed to peripheral sites. Oral bioavailability is around 50%. It is metabolized in the liver by CYP1A2 and CYP2D6. The mean elimination half-life of duloxetine is in the range of 8–17 h (Carter and McCormack 2009; Knadler et al. 2011).

Recommendations

TDM of duloxetine and titration to steady-state serum concentrations above 58 ng/ml is recommended for treatment optimization (Waldschmitt et al. 2009).

3.3 Other Antidepressants

Mirtazapine, a serotonin-receptor blocker that additionally has an effect on norepinephrine by blocking alpha2-adrenergic receptors, and bupropion, which has an effect on norepinephrine and dopamine transport, provide alternative options to the SSRIs and SNRIs and for treatment-resistant depression. Bupropion is a strong inhibitor of CYP2D6. Mirtazapine significantly inhibits histamine (H1) receptors and 5-HT2 receptors, causing sedation and increased appetite/weight gain.

3.3.1 Mirtazapine

Mirtazapine is the first noradrenergic and specific serotonergic antidepressant (NESSA). After oral dosage, it is rapidly absorbed, reaching peak plasma concentrations within 2 h. Eighty-five percent of mirtazapine is plasma protein bound in a nonspecific and reversible way. Because of enteric and hepatic first-pass metabolism, the bioavailability of mirtazapine is only is 50%. Mirtazapine demonstrates linear pharmacokinetics, which is subject to gender and age variability. Females and the elderly show higher plasma concentrations than males and young adults. The time to reach steady-state for mirtazapine is 4–6 days, and the elimination half-life is 20–40 h. It is mainly metabolized by CYP enzymes (CYP2D6 and CYP3A4) and to a lesser extent by CYP1A2 and CYP2B6 (Störmer et al. 2000; Hiemke et al. 2011; Spina et al. 2008; Timmer et al. 2000).

Recommendations

Although a linear relationship was found between plasma concentration and mirtazapine dosage in the range of 15–80 mg/day (Sterr and Freivogel 2003), there is very limited information available on the concentration-effect relationship,

particularly in a clinical setting. It is still unclear whether controlling the variability of plasma concentrations can improve clinical outcome with mirtazapine treatment.

3.3.2 Bupropion

Bupropion is a dopamine-norepinephrine reuptake inhibitor. Oral bioavailability is 87%, and peak plasma concentration is achieved 3–5 h after dosing. Eighty-four percent of bupropion is plasma protein bound. Bupropion is largely metabolized by the liver via CYP2B6 and has an elimination half-life in the range of 8–26 h. Biotransformation leads to an active metabolite hydroxybupropion (Hesse et al. 2000). Maximum plasma concentrations of hydroxybupropion are fourfold to sevenfold higher than the parent drug (Hesse et al. 2006). The other two active metabolites of bupropion, threohydrobupropion and erythrohydrobupropion, are formed by non-microsomal pathways (Jefferson et al. 2005). Bupropion and its active metabolites exhibit linear pharmacokinetics, and steady-state concentrations are reached within 8 days of administration. Genetic polymorphisms in CYP2B6 may cause variability in bupropion pharmacokinetics (Faucette et al. 2000; Hesse et al. 2004). A curvilinear relationship between trough plasma bupropion concentrations and its antidepressant efficacy has been reported. Therefore plasma levels of bupropion and metabolites, especially hydroxybupropion, may be associated with antidepressant response in patients taking bupropion (Daviss et al. 2006).

Recommendations

The available data support the conclusion that TDM would probably increase the safe and effective utilization of bupropion. TDM, with a focus on hydroxybupropion, appears applicable to bupropion, since the risk of central nervous system toxicity is related to the use of higher doses, and effectiveness occurs at lower instead of higher plasma levels of bupropion and its metabolites. However, TDM is not yet routinely utilized with bupropion.

3.4 Monoamine Oxidase Inhibitors

Despite an extensive history of use, the pharmacokinetics of MAOIs are still not well understood (Mallinger and Smith 1991; Baker et al. 1999). The irreversible MAOIs are rapidly absorbed and eliminated, with plasma elimination half-life values of 1.5–4 h (Mallinger and Smith 1991; Fulton and Benfield 1996). However, due to their irreversible inhibition of MAO, the physiological impact of MAOIs such as phenelzine, isocarboxazid, and tranylcypromine can persist for 2–3 weeks after exposure (Cooper 1989). To prevent potentially important drug-drug interactions, a 14-day washout period is recommended before starting another antidepressant (Baker et al. 1999; Marangell 2001). Even after a 14-day washout, patients should be closely observed, since some patients have reported significant adverse events, including serotonin syndrome, even after 14-day washout periods, or when switching from one MAOI to another (Gitlin 1997; Marangell 2001; Szuba et al.

1997). A washout time of five half-lives for an antidepressant and its active metabolites should be heeded before starting a MAOI (Marangell 2001). Combining other serotonergic medications with MAOIs increases the risk of serotonin syndrome. Patients with serotonin syndrome typically present with mental status changes, restlessness, myoclonus, hyperreflexia, diaphoresis, and evidence of autonomic overactivity (Sternbach 1991; Bodner et al. 1995).

Due to their rapid elimination and their irreversible inhibition of MAOs, the relationship between plasma concentrations of MAOIs and outcome has been difficult to establish, since there is a disconnect between the pharmacologic effect and the systemic exposure. As such, TDM is not ordinarily recommended for MAOIs. Platelet MAO activity has been utilized as an alternative marker for central neuronal MAO action. Favorable antidepressant effect has been associated with 80% inhibition of platelet MAO (Preskorn and Burke 1992).

3.4.1 Recommendation

TDM as it applies to MAOIs is not through measurement of serum drug concentrations but rather via monitoring of a pharmacodynamic effect (i.e., inhibition of platelet MAO activity). The platelet assay for MAOI activity is costly, and not generally available. This, together with the relatively infrequent utilization of MAOIs, has restricted the use of this approach.

3.5 Tricyclic Antidepressants

TDM is a well-established tool to assist in identification of the individual optimal dose of a number of tricyclic antidepressants. TDM has been used to increase efficacy, safety, and cost-effectiveness in the treatment of depression and is recommended for most tricyclic antidepressants. The risk of adverse events is reduced, and for some TCAs, a concentration-effectiveness relationship has been established (Glassman 1985; Hiemke et al. 2011; Perry et al. 1994). However, TCAs are limited by their risk of toxicity with overdose and potential cardiac side effects (cardiac conduction disturbances and potential arrhythmias). TCAs may be additionally associated with orthostatic hypotension, sedation, and anticholinergic effects, depending on their propensity to block postsynaptic alpha-1 adrenergic, histamine-1, and cholinergic receptors (Huffman and Alpert 2010).

4 Summary

The clinical rationale for use of TDM for the guidance of psychopharmacological treatment is the uncertainty in dose-outcome relationships due to interindividual variability in pharmacokinetic properties. To exert pharmacologic effects, a medication must be present in appropriate concentrations at the intended site(s) of action. At the same dosage of psychotropic medications, there may be extensive interindividual variation in steady-state concentrations (Hiemke et al. 2011). Clinically significant

knowledge has been gained on the vital role of cytochrome P450 isoforms in the biotransformation of antidepressants. Genetic polymorphisms influencing CYP2D6 expression and function can be of clinical relevance for antidepressants which are substrates of this enzyme, including some tricyclic antidepressants, some selective serotonin reuptake inhibitors, and venlafaxine. Clinically, a poor metabolizer (PM) can be susceptible to side effects of antidepressants known to be substrates of the deficient enzyme, while ultra-rapid metabolizers (UMs) may be subject to a higher risk for nonresponse because of subtherapeutic plasma concentrations (Baumann et al. 2005). Automated laboratory alerts can identify drug concentrations above the recommended reference range and promptly alert the prescribing doctor to consider reducing dosage when the patient presents with signs of toxicity. On the other hand, when a high drug concentration is well-tolerated by the patient, or dose reduction might predispose to relapse, the dosage should remain unchanged. For various psychoactive medications, metabolites effectively add to the clinical impact of the parent drug. Hence, TDM must include the evaluation of active metabolites. The frequency of TDM requests might be increased if there is a suspected problem with patient compliance or if there is a change of co-medication or smoking that might influence the pharmacokinetics of the medication. Usually trough concentrations are measured, but in some circumstances, peak concentrations might show a better association with side effects. Blood samples should be collected after at least four drug elimination half-lives following the start of treatment or an adjustment in dosage. In clinical practice, the suitable sampling time for most psychoactive medications is 1 week after stable daily dosage, and immediately before the morning dose. For dosage titration with antidepressants, it is important to include patient assessments at baseline and at week 2, in addition to drug concentration measurements (Schoretsanitis et al. 2018).

In conclusion, TDM of antidepressants utilizes the measurements of drug serum/plasma concentrations, followed by interpretation and collaboration with the clinician. TDM can assist in achieving "personalized medicine" with respect to dosage individualization, leading to minimization of adverse reactions, decrease in mortality and morbidity, and a decrease in the cost of healthcare services.

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Selective Serotonin Reuptake Inhibitors

Dee Lochmann and Tara Richardson

Contents

Abstract

The first antidepressants were created by chance but brought the idea that central serotonin agonism produced an antidepressant effect. SSRIs were the first class of psychotropic medications to be rationally designed, meaning that researchers

The goal of this textbook is to briefly review the older and established treatments for depression and focus more on newer treatments and future directions of the field. The book contains an extensive chapter on STARD, which reviews the efficacy of SSRIs. Additional chapters cover proposed biomarkers as they relate to SSRI efficacy and safety including genetic markers. The reader is referred to those chapters as well as additional resources including Preskorn.com for a more exhaustive review of the SSRIs. Portions of this chapter are adapted with permission from Preskorn et al. (2004).

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intended to utilize a specific mechanism of action while avoiding adverse effects. In this way, SSRIs were created to be safer and more tolerable than previous antidepressants. SSRIs share many similarities, but differ in terms of pharmacokinetics and effects on CYP450 enzymes, which is detailed in this chapter. Further information will be provided regarding safety, clinical indications/uses, and dosing recommendations.

Keywords
Citalopram · Escitalopram · Fluoxetine · Fluvoxamine · Paroxetine · Rational drug development · Selective serotonin reuptake inhibitors · Sertraline · Side effects · Tolerability · Vilazodone · Vortioxetine

1 Introduction and History

The first antidepressants were created by chance but brought the idea that central serotonin agonism produced an antidepressant effect. SSRIs were the first class of psychotropic medications to be rationally designed, meaning that researchers intended to target a specific site of action using in vitro receptor binding affinity technology (Preskorn 1996). This was intended to utilize a specific mechanism of action while avoiding adverse effects. In this way, SSRIs were created to be safer and more tolerable than previous antidepressants (TCAs and MAOIs) (Preskorn 1990, 1995b). Fluoxetine was the first SSRI on the market, introduced in 1987. Since that time, the SSRIs have become the most widely prescribed antidepressants in many countries.

2 Currently Available SSRIs and Indications for Their Use

The following SSRIs are currently available in the United States and many other countries, for the following indications approved by the FDA (in adult patients unless otherwise specified). The brand name of the medication is in parentheses after the generic name. Vilazodone and vortioxetine will be included in this section as their mechanism of action is very similar to that of the SSRIs. Per the FDA package insert, both medications also "enhance serotonergic activity in the CNS through selective inhibition of serotonin reuptake." Vilazodone is also a partial agonist at 5-HT1A receptors, while vortioxetine is also an agonist at 5-HT1A and an antagonist at 5-HT3.

- Citalopram (Celexa): depression
- Escitalopram (Lexapro): depression in patients 12 and older, GAD
- Fluoxetine (Prozac): depression in patients 8 and older, panic disorder, OCD in patients 7 and older, bulimia nervosa, PMDD
- Fluvoxamine (Luvox): OCD in patients 8 and older
- Paroxetine (Paxil): depression

– Sertraline (Zoloft): depression, panic disorder, OCD in ages 6 and older, social anxiety disorder, PTSD, PMDD
– Vilazodone (Viibryd 2010): depression
– Vortioxetine (Trintellix 2017): depression

SSRI	Depression	Panic disorder	OCD	Social anxiety disorder	GAD	PTSD	Bulimia nervosa	PMDD
Citalopram	X							
Escitalopram	X (12+)				X			
Fluoxetine	X (8+)	X	X (7+)				X	X
Fluvoxamine			X (8+)					
Paroxetine	X	X	X	X	X	X		X
Sertraline	X	X	X (6+)	X		X		X
Vilazodone	X							
Vortioxetine	X							

3 Chemistry, Pharmacology, and Metabolism

The SSRIs share many similarities (Preskorn 1999b) as follows:

1. Equivalent acute and maintenance antidepressant efficacy
2. A flat dose-response curve for antidepressant efficacy
3. An ascending dose-response curve for adverse effects
4. An adverse effect profile consistent with excessive serotonin agonism
5. 60–80% Inhibition of serotonin uptake at their lowest, usually effective antidepressant dose
6. Efficacy in both depressive and anxiety disorder

Most of the SSRIs have similar half-lives, close to 24 h. One exception to this is fluoxetine, which has a half-life of 24–48 h (Preskorn 1999b). In addition, the active metabolite of fluoxetine, norfluoxetine, has an average half-life of 7–15 days in a normal adult patient and 3 weeks in a healthy patient over the age of 65. Because of this extremely long half-life, fluoxetine can take 4 months to reach steady-state conditions and another 4 months to clear the body after discontinuation. It can be conceptualized as an oral depot antidepressant. This can not only make adverse effects difficult to detect but can also be problematic if an adverse effect leads to discontinuation. Vortioxetine also has a longer half-life than most SSRIs at 66 h, so that steady-state concentration is typically achieved in approximately 2 weeks (vortioxetine package insert).

The goal in development of the SSRIs was to design an antidepressant that would both potently and selectively inhibit the serotonin uptake pump to increase central serotonin agonism. The SSRIs all have a similar mechanism of action, selectively blocking the serotonin uptake pumps, which lead to an increase in the availability of

serotonin. Selectivity is defined as "a separation of at least one order of magnitude (a tenfold separation) between the effects of a drug on its most potent site of action and its next most potent site of action; such a drug is capable of having pharmacologically and clinically meaningful effects on its most potent target while having no effects on any other target (i.e., the drug is 'selective')" (Preskorn 1995b, 1999a). The selectivity of the SSRIs allow them to achieve their desired effect (inhibition of the serotonin uptake pump) while having no effect on other transporter proteins (such as those associated with norepinephrine or dopamine). While both TCAs and SSRIs inhibit the serotonin transport protein, the SSRIS do not affect other receptors or sodium channels in the way that TCAs do (which is responsible for most of the associated adverse effects). However, SSRIs were rationally designed before the technology allowed isolation of the CYP enzymes, so this was not taken into account by the researchers at the time. Several of the SSRIs have substantial, unintended, inhibitory effects on cytochrome P450 enzymes that mediate the bulk of human oxidative drug metabolism. Despite similarity in mechanism of action, efficacy and side effect profiles, different SSRIs vary quite dramatically in terms of pharmacokinetics and their effects on CYP450 enzymes; and these differences in the pharmacokinetics of various SSRIs must be kept in mind when prescribing. Many prescribers are not aware of these differences between SSRIs. Fluoxetine, fluvoxamine, and paroxetine all substantially inhibit at least one CYP enzyme, and thus can cause significant pharmacokinetic drug-drug interactions (Preskorn 1999b). "Substantial inhibition of CYP enzymes means that the coadministration of these SSRIs causes a several fold increase in levels of co-prescribed drugs whose clearance is dependent on the CYP enzyme inhibited by the SSRI. Such an increase in levels of the affected drug can cause a variety of negative effects, including decreased tolerability, withdrawal syndromes, or increased adverse effects and toxicity" (Preskorn 1999b). There is no other advantage leading to use of these medications over those that do not inhibit CYP enzymes (citalopram, escitalopram, sertraline), and this should be taken into consideration when prescribing an SSRI. Neither Vilazodone nor Vortioxetine substantially inhibit or induce CYP enzymes (Viibryd [package insert], Trintellix [package insert]).

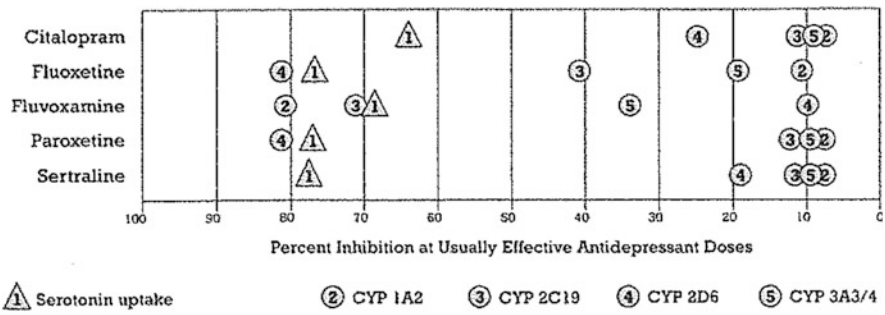

Fig. 1 In vivo profile of SSRIs: serotonin uptake inhibition versus CYP enzyme inhibition (based on data from Shad and Preskorn 2000) (copyright Preskorn 2003)

Table 1 Summary of the effect of the various SSRIs on the major human drug metabolizing cytochrome P450 enzymes (from Preskorn 1996, 1999b; Harvey and Preskorn 1996a, b; Madsen et al. 2001) (copyright Preskorn 2003)[a]

	1A2	2D6	2C9/10	2C19	3A3/4
Citalopram		++			
Escitalopram		++			
Fluoxetine		+++	+++	++	+
Fluvoxamine	+++		+++[b]	+++	++
Paroxetine		+++			
Sertraline		+			

Blank, no or minimal effect (<20%); +, mild effect (20–50%); ++, moderate effect (50–150%); +++, substantial effect (>150%)

[a]The information in this table is based on the results of formal in vivo studies in humans. The ratings are based on the following doses because the effects are dose dependent and the studies were principally conducted at these doses: 40 mg/day of citalopram; 20 mg/day of escitalopram, fluoxetine, and paroxetine; 150 mg/day of fluvoxamine; and 100 mg/day of sertraline, with some studies testing doses as high as 200 mg/day

[b]This table has been updated to reflect the results of a recent in vivo human study showing that fluvoxamine at a dose of 150 mg/day caused a 300% increase in tolbutamide levels (Madsen et al. 2001)

Pharmacodynamically mediated drug-drug interactions are limited to other medications which may also inhibit serotonin reuptake, leading to the development of serotonin syndrome (e.g., TCAs and MAOIs).

Neither vilazodone nor vortioxetine substantially inhibit or induce CYP enzymes (cite FDA drug inserts), which is why they are not included in Fig. 1 and Table 1.

4 Adverse Effects

As a class, the SSRIs are typically well-tolerated, without the other severe adverse effects seen with other classes of antidepressants. Because of the similar mechanism of action, each of the SSRIs has a similar adverse effect profile as well. Most adverse effects are dose-dependent and consistent with those expected with excess serotonin. Treatment can be started at a clinically effective dose, and as SSRIs all have a flat dose-response curve, there is little need to increase the dose in the first 2–4 weeks of treatment. However, some individuals may still benefit from a higher (or lower) dose due to variability in the ability to clear the medication.

Common early adverse effects include nausea and loose stool, both of which are dose-dependent and typically resolve with continued treatment. Nausea may be relieved by reducing the dose temporarily, or by taking the medication with food or an antacid. Other side effects that may occur early in treatment are as follows: headache, dizziness, somnolence or insomnia, sweating, tremor, dry mouth, anxiety, and restlessness (Janicak et al. 2001).

Less frequent adverse effects include weight gain, sexual dysfunction (inhibition of ejaculation or orgasm), bruxism, myoclonus, and paresthesia (Janicak et al. 2001). Sexual dysfunction may occur with all antidepressants that increase serotonin

reuptake and affect 30% of patients taking SSRIs. Unlike other adverse effects, sexual dysfunction may occur several weeks or months into treatment, and patients do not develop tolerance to this adverse effect. If patients discontinue the medication at this point into the maintenance phase of therapy, they are still at risk for recurrence or relapse of depression. Various treatment strategies exist for relieving sexual dysfunction due to SSRIs, including bupropion, cyproheptadine, yohimbine, sildenafil, and topical testosterone cream for female patients.

Patients may experience a withdrawal syndrome upon sudden discontinuation of treatment with SSRIs. This withdrawal syndrome may be recalled using the mnemonic FLUSH (Preskorn 1996, 1999b):

- Flu-like symptoms (fatigue/myalgia/loose stools/nausea)
- Lightheaded/dizziness
- Uneasiness/restlessness
- Sleep and sensory disturbances
- Headache

Withdrawal can mimic both depression and emerging mania, which may lead to inappropriate treatment. If symptoms resolve within 12–24 h of restarting the SSRI, it confirms that the symptoms were most likely related to withdrawal from the medication. Certain SSRIs are more likely to lead to a withdrawal syndrome upon discontinuation than others. Factors affecting the likelihood of withdrawal symptoms include the duration of time taken, drug potency, and half-life of the drug. A drug with a shorter half-life is more likely to lead to withdrawal due to the inability of the brain to "re-equilibrate" through upregulation of receptors after discontinuation. Fluvoxamine and paroxetine are more likely to cause withdrawal symptoms, whereas citalopram, escitalopram, and sertraline are less likely to cause withdrawal symptoms. Fluoxetine is the least likely to cause withdrawal symptoms due to the long half-life of both the parent drug and its active metabolite, norfluoxetine. Similarly, vortioxetine has an extremely long half-life though it produces no active metabolites (vortioxetine package insert).

4.1 Safety in Overdose

Overall, SSRIs are relatively safe in overdose, with no serious systemic toxicity even with large doses (Preskorn 1996, 1999b).

4.2 Teratogenicity

The majority of studies regarding SSRI use in pregnancy have focused on fluoxetine, given that the medication will persist in the body for weeks (well into the first trimester) after discontinuation due to its' long half-life. A large-scale study by Chambers et al. found more than a twofold increase in the incidence of three or

more minor structural anomalies, though there was no increase in major structural anomalies or the rate of spontaneous abortions (Chambers et al. 1996). There was also an increased incidence of premature deliveries, lower birth weight, admission to special care nurseries, cyanosis on feeding, and jitteriness compared with controls, particularly in those exposed during the last trimester. Pastuszak et al. did not find any difference in the rate of major structural anomalies but did find the miscarriage rate doubled. Goldstein (1995) found postnatal complications in 13% of neonates exposed in the last trimester. Per the Support Expert Consensus Guidelines on the Treatment of Depression in Women issued in 2001, the use of antidepressants in pregnancy should be first-line only if depression is severe or the patient has a high likelihood of relapse or recurrence upon discontinuation of the medication. SSRIs are considered the safest medication option, followed by TCAs (Altshuler et al. 2001).

4.3 Long-Term Safety

Maintenance treatment with antidepressants is often long-term in order to avoid recurrence of symptoms. Long-term studies have shown no safety problems associated with long-term maintenance treatment (Eric 1991; Doogan and Caillard 1992; Janicak et al. 2001).

5 Clinical Indications/Uses

In addition to being an effective treatment for depression, SSRIs have also proven beneficial in treating anxiety disorders. Many patients with depression suffer from anxiety as well, and thus having one effective treatment for both is desirable. SSRIs have been shown to be effective for acute response as well as long-term maintenance treatment, across the lifespan as well as in variable settings. SSRIs are appropriate for use even in patients with significant comorbid medical conditions. SSRIs have been shown to improve functioning in addition to reducing target symptoms of depression.

6 Acute Treatment

In the treatment of depression, the similar mechanism of action between the SSRIs equates to similar overall efficacy as well. Studies have shown that SSRIs are more tolerable than TCAs, with a lower dropout rate and fewer reported adverse effects. Studies have mostly focused on patients with moderate depression (on an outpatient basis); thus studies showing efficacy in patients with severe depression requiring hospitalization have been limited. If a patient is unable to tolerate the first trial SSRI, a prescriber may consider a trial of a second SSRI. However, because of the similar mechanism of action, a different class of medications may be preferable if the trial fails because of inadequate response despite correct dosing and duration.

7 Dosing Recommendations

As discussed above, all SSRIs have a flat dose-response curve, and as such, there is no significant benefit in using doses above the usually effective minimum dose though there are some variances in individual metabolism.

FDA-approved dose ranges for treatment of MDD

Drug	Usually effective lowest dose (mg/day)	Maximum approved dose (mg/day)
Citalopram	40	40
Escitalopram	20	20
Fluoxetine	20	80
Fluvoxamine	150–200	300
Paroxetine	20	50–60
Sertraline	50	200
Vilazodone	20	40
Vortioxetine	10	20

8 Onset of Action

SSRIs will take 1–2 weeks to produce a clinically meaningful response in depressed patients. No studies have been designed specifically to evaluate the onset of action: thus this data was taken retrospectively from trials with other aims. As discussed above, fluoxetine may have a slower onset of action due to the long half-life of both the parent drug and its active metabolite, norfluoxetine. It may take up to 75 days to reach steady-state conditions in a healthy adult patient and up to 105 days in a healthy patient over 65. Because of this, other options are typically preferable in elderly patients. Vilazodone was marketed to have a more rapid onset of action though this has not been proven in subsequent studies (Deardorff and Grossberg 2014).

9 Maintenance Treatment

There were six double-blind, placebo-controlled crossover studies involving adults with major depression who had responded to acute treatment with SSRI and then were randomly assigned to continue with SSRI versus placebo. Ten percent of patients on an SSRI relapsed over the next 24 weeks as compared to 35% of those who were switched to placebo. Over the course of 1 year, there was approximately a 30% greater relapse rate in patients who were assigned to placebo (Janicak et al. 2001).

The American Psychiatric Association provides the following recommendations for antidepressant use during maintenance treatment in the Practice Guideline for the Treatment of Patients with Major Depressive Disorder:

> Patients who have had three or more prior major depressive episodes should proceed to the maintenance phase of treatment after completing the continuation phase. Maintenance therapy should also be considered for patients with additional risk factors for recurrence, such as the presence of residual symptoms, ongoing psychosocial stressors, early age at onset, and family history of mood disorders. Additional considerations that may play a role in the decision to use maintenance therapy include patient preference, the type of treatment received, the presence of side effects during continuation therapy, the probability of recurrence, the frequency and severity of prior depressive episodes (including factors such as psychosis or suicide risk), the persistence of depressive symptoms after recovery, and the presence of co-occurring disorders. Such factors also contribute to decisions about the duration of the maintenance phase. For many patients, particularly for those with chronic and recurrent major depressive disorder or co-occurring medical and/or psychiatric disorders, some form of maintenance treatment will be required indefinitely. During the maintenance phase, an antidepressant medication that produced symptom remission during the acute phase and maintained remission during the continuation phase should be continued at a full therapeutic dose. Due to the risk of recurrence, patients should be monitored systematically and at regular intervals during the maintenance phase.

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Serotonin and Norepinephrine Reuptake Inhibitors

Richard C. Shelton

Contents

Portions of this chapter are adapted from Janicak et al. (2001), Preskorn et al. (2004) and articles by Preskorn (2004b) on milnacipran and duloxetine (Preskorn 2004a).

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Abstract

This chapter covers antidepressants that fall into the class of serotonin (5-HT) and norepinephrine (NE) reuptake inhibitors. That is, they bind to the 5-HT and NE transporters with varying levels of potency and binding affinity ratios. Unlike the selective serotonin (5-HT) reuptake inhibitors (SSRIs), most of these antidepressants have an ascending rather than a flat dose–response curve. The chapter provides a brief review of the chemistry, pharmacology, metabolism, safety and adverse effects, clinical use, and therapeutic indications of each antidepressant. Venlafaxine, a phenylethylamine, is a relatively weak 5-HT and weaker NE uptake inhibitor with a 30-fold difference in binding of the two transporters. Therefore, the drug has a clear dose progression, with low doses predominantly binding to the 5-HT transporter and more binding of the NE transporter as the dose ascends. Venlafaxine is metabolized to the active metabolite O-desmethylvenlafaxine (ODV; desvenlafaxine) by CYP2D6, and it therefore is subject to significant inter-individual variation in blood levels and response dependent on variations in CYP2D6 metabolism. The half-life of venlafaxine is short at about 5 h, with the ODV metabolite being 12 h. Both parent compound and metabolite have low protein binding and neither inhibit CYP enzymes. Therefore, both venlafaxine and desvenlafaxine are potential options if drug–drug interactions are a concern, although venlafaxine may be subject to drug–drug interactions with CYP2D6 inhibitors. At low doses, the adverse effect profile is similar to an SSRI with nausea, diarrhea, fatigue or somnolence, and sexual side effects, while venlafaxine at higher doses can produce mild increases in blood pressure, diaphoresis, tachycardia, tremors, and anxiety. A disadvantage of venlafaxine relative to the SSRIs is the potential for dose-dependent blood pressure elevation, most likely due to the NE reuptake inhibition caused by higher doses; however, this adverse effect is infrequently observed at doses below 225 mg per day. Venlafaxine also has a number of potential advantages over the SSRIs, including an ascending dose–antidepressant response curve, with possibly greater overall efficacy at higher doses. Venlafaxine is approved for MDD as well as generalized anxiety disorder, social anxiety disorder, and panic disorder. Desvenlafaxine is the primary metabolite of venlafaxine, and it is also a relatively low-potency 5-HT and NE uptake inhibitor. Like venlafaxine it has a favorable drug–drug interaction profile. It is subject to CYP3A4 metabolism, and it is therefore vulnerable to enzyme inhibition or induction. However, the primary metabolic pathway is direct conjugation. It is approved in the narrow dose range of 50–100 mg per day. Duloxetine is a more potent 5-HT and NE reuptake inhibitor with a more balanced profile of binding at about 10:1 for 5HT and NE transporter binding. It is also a moderate inhibitor of CYP2D6, so that modest

dose reductions and careful monitoring will be needed when prescribing duloxetine in combination with drugs that are preferentially metabolized by CYP2D6. The most common side effects identified in clinical trials are nausea, dry mouth, dizziness, constipation, insomnia, asthenia, and hypertension, consistent with its mechanisms of action. Clinical trials to date have demonstrated rates of response and remission in patients with major depression that are comparable to other marketed antidepressants reviewed in this book. In addition to approval for MDD, duloxetine is approved for diabetic peripheral neuropathic pain, fibromyalgia, and musculoskeletal pain. Milnacipran is marketed as an antidepressant in some countries, but not in the USA. It is approved in the USA and some other countries as a treatment for fibromyalgia. It has few pharmacokinetic and pharmacodynamic interactions with other drugs. Milnacipran has a half-life of about 10 h and therefore needs to be administered twice per day. It is metabolized by CYP3A4, but the major pathway for clearance is direct conjugation and renal elimination. As with other drugs in this class, dysuria is a common, troublesome, and dose-dependent adverse effect (occurring in up to 7% of patients). High-dose milnacipran has been reported to cause blood pressure and pulse elevations. Levomilnacipran is the levorotary enantiomer of milnacipran, and it is pharmacologically very similar to the racemic compound, although the side effects may be milder within the approved dosing range. As with other NE uptake inhibitors, it may increase blood pressure and pulse, although it appears to do so less than some other medications. All medications in the class can cause serotonin syndrome when combined with MAOIs.

Keywords
Desvenlafaxine · Duloxetine · Levomilnacipran · Milnacipran · Venlafaxine

1 Introduction

This chapter focuses on the following antidepressants that fall into the serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor (SNRI) class: venlafaxine, desvenlafaxine, duloxetine, milnacipran, and levomilnacipran. The pharmacodynamic properties of these antidepressants differ substantially from those of the tricyclic antidepressants (TCAs), the monoamine oxidase inhibitors, the selective 5-HT reuptake inhibitors (SSRIs), and, in some instances, from each other. Among the antidepressants described in this chapter, venlafaxine most closely approximates the binding affinity profile of an SSRI. It is 30 times more potent (i.e., has a higher binding affinity) as an inhibitor of the 5-HT compared with the NE transporter, although it is not as "selective" as the SSRIs (Bymaster et al. 2001). The rest of the medications have a more balanced profile of 5-HT and NE uptake inhibition.

1.1 Dose–Response Curves

Unlike the SSRIs, many of the antidepressants in this chapter have an ascending rather than a flat dose–response curve. That is, consistent with their in vitro pharmacology, all the medications in this class are more potent 5-HT than NE reuptake inhibitors. As a result, the primary binding at lower doses is for the 5-HT transporter (Harvey et al. 2000). As the dose ascends, maximal binding to the 5-HT transporter may occur before there is significant binding to the NE transporter. Further dose escalation, then, results in increasing binding to the NE transporter. This is most obvious with venlafaxine, which has a clear dose–response effect (Preskorn 1995).

1.2 Organization of the Chapter

The chapter will review chemistry, pharmacology, metabolism, safety and adverse effects, clinical use, and therapeutic indications for the medications in this class. For a more detailed discussion of the pharmacokinetics of these agents, see the chapter on "General Principles of Pharmacokinetics" by Preskorn and Catterson (this volume). For a discussion of the use of therapeutic drug monitoring of antidepressants, see the chapter by Burke and Preskorn. Summary tables on dosing, adverse effects, pharmacokinetic parameters, and plasma concentrations are provided in the Appendix.

2 Venlafaxine

2.1 Chemistry, Pharmacology, and Metabolism

Venlafaxine, a phenylethylamine, first inhibits the neuronal reuptake transporters for 5-HT and then, with dosage escalation, the reuptake transporter for NE (Harvey et al. 2000). Venlafaxine is approximately 30 times more potent in vitro as an inhibitor of the 5-HT than the NE transporter (Bymaster et al. 2001). The sequential effects of venlafaxine binding on the 5-HT transporters and then the NE reuptake transporters are dose- and concentration-dependent (Harvey et al. 2000). At 75 mg per day, venlafaxine is predominantly an SRI, like the SSRIs, whereas at 375 mg per day it produces NE uptake inhibition that is intermediate between SSRIs and TCAs (Harvey et al. 2000). TCAs also inhibit 5-HT and NE reuptake transporters; unlike the TCAs, venlafaxine has very low affinity for most other receptors (e.g., muscarinic, alpha adrenergic, or histamine receptors), and it does not inhibit sodium fast channels, making it relatively safe in overdose.

Venlafaxine is biotransformed by CYP2D6 to its active metabolite, O-desmethylvenlafaxine (ODV), also referred to as desvenlafaxine, which is discussed in greater detail below. ODV has pharmacological activity comparable to the parent drug and is believed to contribute equally with the parent drug to efficacy and adverse effects; ODV is then metabolized via CYP3A3/4 (Klamerus

et al. 1992; Preskorn and Burke 1992). The half-life of venlafaxine is approximately 5 h, while the half-life of ODV is approximately 12 h. Also, both venlafaxine and ODV have low protein binding (27% and 30%, respectively), which confers relative safety with other drugs with high protein binding (e.g., warfarin) (Gage et al. 2000).

2.2 Safety and Adverse Effects

2.2.1 Drug–Drug Interactions

Venlafaxine has modest binding to 5-HT and NE transporters (Owens et al. 1997), and it has a relatively safe profile regarding pharmacodynamically mediated drug–drug interactions (Ereshefsky and Dugan 2000). Venlafaxine does pose the risk of serotonin syndrome and hypertensive reactions when combined with MAOIs (Feighner 1995; Nelson 1997). Venlafaxine does not cause significant CYP enzyme inhibition in typical human doses. Finally, it has low protein binding (27% for venlafaxine and 30% for the ODV metabolite) (Ereshefsky and Dugan 2000). Therefore, venlafaxine may be a good choice in situations where drug–drug interactions are a concern.

The therapeutic action of venlafaxine is likely to depend on the combined effect of the concentrations of both the parent compound, venlafaxine, and the primary metabolite ODV. Conversion of venlafaxine to ODV is mediated by CYP2D6. Since CYP2D6 effect ranges from ultrarapid to poor metabolism, blood levels of venlafaxine have considerable inter-individual variation. Further, CYP2D6 inhibitors will increase venlafaxine and decrease ODV levels. ODV is metabolized primarily by CYP3A4 without producing significantly active metabolites. Therefore, ODV is subject to the effects of inhibitors and inducers of CYP3A/4. These effects can contribute to wide variation in both response (and hence the dose of medication required) and side effects. For CYP2D6 intermediate or poor metabolizers, desvenlafaxine (ODV) may be a better choice.

2.2.2 Adverse Effects

Unlike SSRIs that show the same profile of side effects throughout their dose range, the side effect profile of venlafaxine changes with higher doses. This is the result of the fact that side effects with low doses are mediated primarily by 5-HT transporter inhibition, while higher doses confer more side effects due to NE update blockade. At lower doses, consistent with its action on the 5-HT system, the adverse effect profile is similar to SSRIs: nausea, diarrhea, fatigue or somnolence, and sexual side effects (Janicak et al. 2001). The immediate-release (IR) formulation causes more nausea than the extended release (XR), although rates of nausea are relatively high even for the XR (Ereshefsky and Dugan 2000). Venlafaxine appears to have the same liability as the SSRIs for causing sexual dysfunction (Janicak et al. 2001). At higher doses, venlafaxine can produce the same adverse effects as any other norepinephrine reuptake inhibitor: diaphoresis, tachycardia, tremors, anxiety, and mild but sustained hypertension (Nelson 1997; Preskorn 1995). The elevated blood pressure is a dose-dependent effect and is infrequently observed at doses below 225 mg per

day (Grunder et al. 1996). Elevated blood pressure occurs in 3% or less of people treated with doses of 75–225 mg per day, while doses of 300 mg per day or higher have a rate of 13%. Antihypertensives are effective in lowering the blood pressure (Janicak et al. 2001). Blood pressure increases usually occur within the first 2 months of treatment and may increase over the first 6 months, so careful monitoring during this period is warranted.

Because of its blockade of the 5-HT transporter, and its relatively short half-life, venlafaxine is prone to causing a discontinuation syndrome (for a description, see the preceding chapter on the SSRIs) (Schatzberg et al. 2006). The incidence and severity of the 5-HT withdrawal syndrome is partly a function of the half-life of the agent involved—the half-life of venlafaxine is about 5 h, and the half-life of the active metabolite ODV is approximately 12 h (Klamerus et al. 1992). The XR formulation does not change the half-life of the drug, although it does delay absorption, and therefore it may increase the apparent half-life a small amount. Discontinuation reactions are not dangerous in and of themselves, but they can be acutely uncomfortable and, particularly when patients have not been warned about the possibility, frightening. These effects are not like withdrawal reactions to sedative hypnotics or opioids, but they can be very unpleasant for patients, who may mistake the withdrawal symptoms for a relapse of their depressive illness, and may even become so dysphoric or agitated that they experience suicidal ideation (Rosenbaum et al. 1998; Rosenbaum and Zajecka 1997). It can also cause transient mania-like reactions, which may lead to a misdiagnosis and inappropriate treatment (Landry and Roy 1997). These reactions typically occur for up to 3 weeks, although in most instances they are much shorter. They can be managed using several strategies, including patient education, slow tapering, and temporary substitution of a long half-life medication like fluoxetine, followed by tapering of venlafaxine and then fluoxetine (Giakas and Davis 1997).

Venlafaxine has been associated with adverse effects in babies exposed to venlafaxine during pregnancy in some pharmacoepidemiology studies (Berard et al. 2017). The most commonly reported negative effect has been persistent pulmonary hypertension of the newborn (Chambers et al. 2006), although the data are not consistent (Hayes et al. 2012). In addition, newborns can experience acute discontinuation reactions. Therefore, venlafaxine is not a good choice for treatment during pregnancy or in women who may become pregnant. Discontinuation reactions can be reduced in women taking venlafaxine by switching to a longer-acting medication like fluoxetine.

In 2003, the FDA issued a black box warning that antidepressants increase the risk of suicidal thinking and behavior in children and adolescents. This was followed by a decline in the prescriptions for antidepressants (Nemeroff et al. 2007) and an increase in suicide rate (Bridge et al. 2008). This warning was the result of an analysis of industry-sponsored clinical trials data in children and adolescents that included venlafaxine. This warning has been seriously criticized (Gibbons et al. 2007; Klein 2006), and subsequent analyses found no association between actual suicides and antidepressant use in these groups (Cooper et al. 2014; Gibbons et al. 2006). In fact, Gibbons et al. showed an inverse relationship between rates of

antidepressant prescription and suicide completion rates (Gibbons et al. 2006). Gibbons et al. also did a subsequent analysis of trials in children, adolescents, and adults and found that suicidal thoughts and behavior decreased over time for adults treated with either fluoxetine or venlafaxine compared with placebo. However, there was neither an increase nor a decrease in suicidal thoughts or behaviors in children and adolescents. This may have been the result of the fact that suicidal youth were not included in the trial. Nonetheless, venlafaxine is not FDA approved for treatment of children or adolescents.

2.2.3 Overdose

Venlafaxine inhibits the 5-HT and NE uptake transporters, which does not typically pose a significant overdose risk. It has low affinity for other receptors and does not inhibit sodium fast channels or potassium rectifying channels (as do the TCAs), making it relatively safe in overdose due to its wide therapeutic index (Feighner 1995; Janicak et al. 2001; Muth et al. 1991). During clinical trials, patients survived acute ingestion of over 6,750 mg of venlafaxine without serious effects (Janicak et al. 2001). Most acute overdoses required no specific therapeutic interventions other than observation. Moreover, the most common effect is nausea and vomiting, which further reduce the overdose risk.

2.3 Clinical Use/Therapeutic Indications

2.3.1 Major Depressive Disorder

There were several placebo- and active drug-controlled short-term registration and other trials of venlafaxine in patients with MDD, first with the IR formulation (with twice or three times per day dosing) (Cunningham et al. 1994; Mendels et al. 1993; Schweizer et al. 1991, 1994) and later with the once daily XR formulation (Cunningham 1997; Feighner et al. 1998; Mehtonen et al. 2000; Rudolph and Feiger 1999; Silverstone and Ravindran 1999; Thase 1997). The studies showed venlafaxine IR and XR to be well tolerated, more effective than placebo, and comparable to other antidepressant medications, including imipramine (Grunder et al. 1996; Schweizer et al. 1994) and fluoxetine (Clerc et al. 1994; Costa e Silva 1998; Einarson et al. 1999; Silverstone and Ravindran 1999). The studies included both inpatients and outpatients with MDD. The trials show escalating benefits in the range of 75–225 mg per day, but not greater benefit in doses above 225 mg per day. Note that these represent group effects, and certain individuals may benefit from higher doses.

There is some evidence that venlafaxine may be more effective than SSRI antidepressants. Ferrier (2001) reviewed findings from studies that reported rates of remission (defined as a score of 10 or less on the 17-item Hamilton Depression Rating Scale [HAM-D] or a clinicians' global impression [CGI] improvement score of 1, very much improved) for MDD and found remission rates of approximately 20–30% with SSRIs during short-term therapy and remission rates with venlafaxine that ranged from 37–62%. In these studies, the remission rates for venlafaxine

were greater than those seen with fluoxetine, sertraline, or paroxetine. However, the studies were not designed to test the superiority of venlafaxine over the comparator and, therefore, may not have used optimal dosing of the other medication. Nevertheless, some evidence exists in support of the idea that antidepressants that combine noradrenergic with serotonergic mechanisms of action, such as the TCAs and venlafaxine, may have a more robust effect than purely serotonergic antidepressants.

Studies have tested the longer-term benefits of venlafaxine. In one such study (Montgomery et al. 2004), patients with a history of recurrent MDD received open-label treatment with venlafaxine, 100–200 mg per day, for 6 months. Those who responded to treatment (as defined by a HAM-D21 score of $\leq$12 on day 56) and remained relapse-free were randomized to either a continuation of venlafaxine 100–200 mg per day or placebo for 12 months, observing for relapse. Survival analysis showed a 22% cumulative probability of recurrence in venlafaxine and 55% for the placebo group. A second study (Kocsis et al. 2007) titled "Prevention of Recurrent Episodes of Depression with Venlafaxine for Two Years" (PREVENT) initially randomly assigned patients with MDD to double-blind treatment with either venlafaxine XR (75–300 mg per day) or fluoxetine (20–60 mg per day) for 10 weeks of acute treatment. Responders then received 6 months of continuation treatment. Those who continued to show response proceeded into two 12-month sequential maintenance periods. Venlafaxine ER responders were randomly assigned to receive double-blind treatment with venlafaxine ER or placebo in each of these periods. Fluoxetine responders were not randomly assigned but continued taking fluoxetine. The mean daily dose of venlafaxine ER was 225 mg and for fluoxetine was 53 mg. The cumulative probability of recurrence through the initial 12 months, based on the primary definition, was 23.1% for venlafaxine XR and 42.0% for placebo. The cumulative probability of relapse across both maintenance periods was 28.1% for venlafaxine and 44.2% for fluoxetine; although this suggests that venlafaxine might be more effective in preventing relapse in initial responders, this finding did not meet statistical significance based on Kaplan-Meier survival analysis.

2.3.2 Other Indications

Venlafaxine is also approved in the USA and elsewhere for generalized anxiety disorder (GAD) (Davidson et al. 1999; Gelenberg et al. 2000; Lydiard 1999; Montgomery et al. 2002; Rickels et al. 2000), social anxiety disorder or social phobia (Allgulander et al. 2004; Liebowitz et al. 2005a, b; March et al. 2007; Rickels et al. 2004), and panic disorder (Bradwejn et al. 2005; Liebowitz et al. 2009; Pollack et al. 1996, 2007a, b). The approved doses for GAD are 75–225 mg per day and 37.5–225 mg per day for panic disorder but only 75 mg per day for social anxiety disorder. The approved doses are the product of the data submitted for FDA approval and may not be optimally effective for some people given the inter-individual variation in pharmacokinetics. There is also evidence that venlafaxine is effective in reducing vasomotor symptoms ("hot flashes") associated with menopause (Ramaswami et al. 2015).

2.4 Dosing Recommendations

Initial dose titration is not required, and most patients can tolerate 75 mg per day to start, although in some patients the clinician may choose the 37.5 mg dose to start. This would be true, for example, in the face of a CYP2D6 intermediate metabolism (venlafaxine should not be used in poor metabolizers). Dosing should also be reduced in the face of advanced hepatic disease. There is dose progression in that some patients who have not responded adequately to lower doses may respond to higher. The original immediate-release formulation was approved up to 375 mg per day, although the approved maximum dose on the extended release is 225 mg per day. However, there are wide inter-individual differences in blood levels, and, therefore, doses above 225 mg per day can be used safely in the absence of response to a lower dose. Note, however, that hypertension is more common at higher doses, and, therefore, blood pressure should be monitored.

3 Desvenlafaxine

3.1 Chemistry, Pharmacology, and Metabolism

Desvenlafaxine (O-desmethylvenlafaxine [ODV]) is the primary metabolite of venlafaxine mediated by metabolism via CYP2D6. Its basic pharmacology is almost identical to venlafaxine and will only be reviewed briefly here. Desvenlafaxine has a binding affinity that is similar to venlafaxine for the 5-HT transporter (approximate Ki = 40 nM and 30 nM, respectively) and the NE transporter (approximate Ki = 560 nM and 535 nM, respectively) (Deecher et al. 2006; Sabatucci et al. 2010). It has very low binding affinity for other receptors. Also like venlafaxine, desvenlafaxine has relatively low protein binding of about 30% (Ereshefsky and Dugan 2000) and no CYP interactions. Unlike venlafaxine that is metabolized primarily by CYP2D6, desvenlafaxine is metabolized by CYP3A4 and is subject to less variation based on genetics. However, it is affected by CYP3A4 inhibitors (e.g., ketoconazole) and inducers (e.g., carbamazepine). However, the primary mode of elimination is direct glucuronide conjugation mediated by UGT1A1, 1A3, 2B4, and 2B15 enzymes (Fossom 2008). Therefore, it has limited drug–drug interactions. The half-life is relatively short at about 12 h.

Desvenlafaxine is approved with a narrower dosing range of 50–100 mg per day, although doses up to 400 mg per day were tested in humans. There is relatively little in the way of ascending effect because of the narrow range. It is unclear whether doses in excess of 100 mg per day are more effective in people not responding adequately to lower doses. However, fixed-dose studies do not support additional benefit.

No dosage adjustment is recommended in patients with mild renal impairment. The recommendation is to limit the dose to 50 mg per day in moderate renal impairment (24-h CrCl = 30–50 mL/min), while those with severe renal impairment (24-h CrCl <30 mL/min) should take no more than 50 mg every other day. The

recommended dose limit for people with significant hepatic impairment is no more than 100 mg per day.

3.2 Safety and Adverse Effects

3.2.1 Drug–Drug Interactions

Desvenlafaxine has relatively low binding affinity to 5-HT and NE transporters in contrast to SSRIs and most other SNRIs (except for venlafaxine), and it is therefore relatively safe regarding pharmacodynamically mediated drug–drug interactions. Desvenlafaxine poses a risk of serotonin syndrome and hypertensive reactions when combined with MAOIs because of serotonin reuptake inhibition. Desvenlafaxine does not cause significant CYP enzyme inhibition in typical human doses, and it has low protein binding (30%). It is therefore a good choice in terms of relatively limited risk of drug–drug interaction. While it is a substrate of CYP3A4, the primary elimination pathway is via direct conjugation mediated by UGT1A1, 1A3, 2B4, and 2B15 enzymes (Fossom 2008). For this reason, it has limited interaction with CYP3A4 inhibitors, although inducers may affect levels a small amount.

3.2.2 Adverse Effects

Side effects of desvenlafaxine are typical of 5-HT reuptake inhibitors and include nausea, diarrhea, dry mouth, fatigue, dizziness, sexual side effects, and decreased appetite but also insomnia and diaphoresis, which are more typical of NE reuptake inhibitors. There is evidence of an escalation of side effects in doses exceeding 100 mg per day. There is no evidence of hypertension within the 50–100 mg per day range, suggesting limited NE reuptake inhibition. There is an increase in frequency of mild sustained hypertension in doses of 200 mg per day or more (Thase et al. 2015). Blood pressure monitoring in typical doses of 50–100 mg per day is not generally warranted.

Desvenlafaxine can cause discontinuation reactions as described in the section above on venlafaxine owing to its serotonin uptake inhibition and short half-life. There is at least some evidence to suggest that discontinuation reactions in the typical dose range of desvenlafaxine of 50–100 mg per day may not be as severe as seen with venlafaxine. In one study (Khan et al. 2014), 480 participants with MDD were treated with desvenlafaxine 50 mg per day for 24 weeks and then randomly assigned in a double-blind fashion to continued desvenlafaxine (no discontinuation) abrupt discontinuation without taper or a reduction to 25 mg per day. Outcomes were assessed using the Discontinuation-Emergent Signs and Symptoms (DESS) scale total score during the first 2 weeks of the double-blind phase. The mean DESS scores were 4.1 (SD = 0.72) for the group that continued medication, 4.8 (SD = 0.54) for the group that was tapered off the desvenlafaxine, and 5.3 (SD = 0.52) for abrupt discontinuation. A second report (Montgomery et al. 2009) analyzed data from nine short-term (8 weeks) double-blind, placebo-controlled studies of desvenlafaxine (50, 100, 200, or 400 mg per day), a relapse

prevention study (12-week, open-label 200 or 400 mg per day), and a 6-month double-blind study comparing placebo to desvenlafaxine. In the short-term studies, the maximum DESS ranged from 1.9 to 5.7. The DESS scores increased significantly for patients after being dosed with 12-weeks of open-label desvenlafaxine in doses of 200 and 400 mg per day compared with those continuing desvenlafaxine. After the 6-month blind phase, DESS scores increased significantly compared with placebo for patients discontinuing 400 mg per day only. These studies suggest that discontinuation symptoms for the 50 or 100 mg per day dosages tend to be modest and increase in doses higher than 100 mg per day. Although aggregate data indicate that discontinuation symptoms are relatively mild, that does not necessarily predict the severity of symptoms experienced by individual patients.

3.2.3 Overdose

Desvenlafaxine appears relatively safe in overdose. A paper reported on the results of 182 desvenlafaxine overdoses, which included 75 desvenlafaxine overdoses with or without alcohol and 107 combined with one or more other drugs. In the desvenlafaxine-only group (with or without alcohol), the median ingested dose was 800 mg, with a range of 250–3,500 mg. The Glasgow Coma Score (GCS) was 15 (the best score indicating minimal brain injury) in 92% of patients, 13–14 in 7% of patients, and 7 in 1 patient who also was noted to have aspirated. Mild hypertension occurred in 32% of cases and tachycardia in 39%. There was one case of serotonin syndrome based on standard criteria. In the 107 patients who overdosed with both desvenlafaxine and other drugs, 5% experienced seizures, although this may have been the result of the co-ingested medication. The Glasgow Coma Score was <10 in 14% of cases where patients overdosed on more than one medication. Mild hypertension was observed in 43% of cases, and severe hypertension occurred in one case. Serotonin syndrome was observed in 6%. There were no reported deaths, although one participant who died was excluded from the analysis because the death was assumed to occur because of other drugs (e.g., verapamil). Overall, these data indicate that overdose with desvenlafaxine alone or in combination with other drugs confers relatively low risk.

3.3 Clinical Use/Therapeutic Indications

3.3.1 Major Depressive Disorder

Desvenlafaxine is approved in a limited number of countries for the treatment of MDD. A meta-analysis reviewed the results of 17 controlled clinical trials of the medication (Laoutidis and Kioulos 2015). The overall assessment was that desvenlafaxine was more effective than placebo, although the differences were modest, with risk ratios for response of 1.24 and remission of 1.43. There were more dropouts due to side effects in the desvenlafaxine group (RR = 1.98). The analysis found no differences in dropouts for any doses in fixed-dose studies (doses = 50, 100, 200, and 400 mg per day).

The results were contrasted against earlier meta-analyses of duloxetine and venlafaxine, which found risk ratios of response and remission to be much higher than for desvenlafaxine (response RR = 1.99 and 2.04, remission RR = 1.91 and 1.97, respectively). In addition, three studies that compared desvenlafaxine against other antidepressant drugs were evaluated. One study compared desvenlafaxine to venlafaxine only and a second study compared desvenlafaxine to venlafaxine or duloxetine and found no differences. A third study found desvenlafaxine to be inferior to a group that included treatment with venlafaxine, duloxetine, or escitalopram. Notably, all the risk ratios for response and remission of desvenlafaxine against comparators were in the same range (RR approximately 0.90 and 0.85, respectively). These results indicate that desvenlafaxine may be less effective than other antidepressant medications.

3.3.2 Other Indications

Desvenlafaxine is not approved for indications other than major depressive disorder. There is evidence that it may be effective for vasomotor symptoms ("hot flashes") associated with menopause (Sun et al. 2013).

3.4 Dosing Recommendations

Desvenlafaxine is approved in doses of 50 or 100 mg per day, and there is scant evidence of benefit at higher doses. However, since it is a CYP3A4 substrate, there will be wide variation in blood levels between individuals. A dosage formulation below 50 mg per day is not available, and, therefore, desvenlafaxine should not be used in combination with potent CYP3A4 inhibitors. Doses higher than 100 mg per day may be needed when the drug is combined with CYP3A4 inducers.

4 Duloxetine

4.1 Chemistry, Pharmacology, and Metabolism

Duloxetine is a chiral compound [(+/−)-*N*-methyl-3-(1-napthalenyloxy)-3(2-thiophene) propanamine] which can be formed from the building blocks of (*S*)-3-chloro-1-(2-thienyl)-1-propanol and the corresponding (*R*)-butanoate (Liu et al. 2000; Wong et al. 1988). It is a potent inhibitor of the 5-HT and NE transporters (Ki approximately 0.8 and 7.5 nM, respectively) (Bymaster et al. 2001), and it has negligible inhibition of the dopamine transporter (Wong et al. 1993). It is a more "balanced" inhibitor of 5-HT and NE transporters than venlafaxine, in that the ratio of binding for duloxetine is about 10, while the ratio for venlafaxine is approximately 30 (Bymaster et al. 2001). It has very low affinity for muscarinic, histamine-1, adrenergic, dopamine, and 5-HT receptors (Wong et al. 1988). Therefore, it has low potential for causing adverse effects mediated by actions on these receptors, particularly as compared with tricyclic antidepressants. There is a very

large amount of preclinical literature indicating duloxetine is a potent 5-HT and NE uptake inhibitor in vivo and supporting an antidepressant effect via animal models of depression (Engleman et al. 1995; Fuller et al. 1994; Gobert and Millan 1999b; Gobert et al. 1997; Gongora-Alfaro et al. 1997; Kasamo et al. 1996; Katoh et al. 1995; Kihara and Ikeda 1995; Rueter et al. 1998a, b; Smith and Lakoski 1997; Wong et al. 1993). A brief summary of this in vivo preclinical work follows (adapted from Preskorn 2004a).

Intraperitoneal administration of duloxetine at 15 mg/kg to rats produced a large increase in extracellular levels of 5-HT (250%) and NE (1,100%) in both the hypothalamus and cerebral cortex (Engleman et al. 1995). In rats and mice, duloxetine prevented tetrabenazine-induced ptosis, inhibited reserpine-induced hypothermia, and potentiated the effects of 5-hydroxytryptophan (a precursor of 5-HT) but did not reverse the effects of the cholinergic agonist oxotremorine (lacrimation or salivation) (Katoh et al. 1995), which indicates that it blocks the uptake of 5-HT and NE at doses that do not block muscarinic cholinergic receptors. Oral administration of duloxetine produced a dose-dependent increase in the output of both 5-HT and NE from the frontal cortex and dopamine output from the nucleus accumbens. The latter is most likely an indirect effect mediated via its direct effects on the central 5-HT and/or NE circuits (Kihara and Ikeda 1995) and is consistent with the anatomical connections of these systems and other electrophysiological studies, including the observation that acute administration of duloxetine and other 5-HT reuptake inhibitors increases the firing frequency of DA neurons in the substantia nigra at the same time that they suppress the spontaneous firing of 5-HT neurons in the dorsal raphe. Duloxetine antagonized the 5-HT and NE-depleting effect of p-chloroamphetamine and 6-hydroxydopamine but not dopamine depletion in both mice and rats and decreased brain 5-hydroxyindoleacetic acid (5HIAA) and 5-HT turnover consistent with in vivo blockade of the 5-HT and NE reuptake transporters but had no direct effect on the DA reuptake transporter at the doses used (Fuller et al. 1994). The recovery times of dorsal hippocampal CA3 pyramidal neurons in rats were significantly prolonged after microiontophoretic applications of 5-HT and NE following treatment with duloxetine, consistent with inhibition of both the 5-HT and NE reuptake transporters (Rueter et al. 1998b). In the same study, electrically evoked release of 5-HT was enhanced in the midbrain and hippocampus presumably from desensitization of the 5-HT1D and 5-HT1A autoreceptors and a2-adrenergic heteroreceptors, respectively. Acute intravenous administration of duloxetine in rats suppressed spontaneous firing activity of both 5-HT and NE neurons in the dorsal raphe and locus coeruleus, respectively, with ED50 (i.e., median effective dose) values of 99 and 475 mg/kg, respectively (Kasamo et al. 1996). The firing rate of 5-HT neurons in the dorsal raphe nucleus was decreased after 2 days of duloxetine administration but returned to control levels after 21 days consistent with acute 5-HT reuptake inhibition followed by compensatory desensitization of the somatodendritic 5-HT1A autoreceptors (Rueter et al. 1998a). That conclusion was further supported in this same study by the finding that administration of the 5-HT1A antagonist WAY 100635 increased hippocampal firing rates in rats treated for 21 days to a greater extent than in either rats treated for 2 days or control rats.

The ability of duloxetine to inhibit 5-HT uptake has also been demonstrated in healthy human volunteers (Kasahara et al. 1996; Turcotte et al. 2001). In one study, duloxetine at doses up to 60 mg per day given for 14 days did not reduce the usual increase in blood pressure that follows an intravenous tyramine infusion, whereas clomipramine (a tertiary amine TCA) did (Turcotte et al. 2001). However, duloxetine at the 60 mg dose in this study did increase supine systolic blood pressure. Another study indicated that the threshold increase in systolic blood pressure after tyramine administration (change of 30 mmHg) was 120 mg per day. The results suggest that 60 mg per day may be the threshold dose for NE reuptake blockade with a progression of action up to 120 mg daily (Vincent et al. 2004).

Duloxetine at doses of 20–40 mg twice a day in 12 healthy male volunteers exhibited linear pharmacokinetics with a half-life of about 12.5 h (Sharma et al. 2000). As discussed in greater detail below, duloxetine is a substrate and inhibitor of CYP2D6 and a substrate of CYP1A2. Duloxetine should be avoided because of reduced clearance in patients with end-stage renal disease (Preskorn 2004a). As well, duloxetine should be avoided in patients with hepatic disease, as discussed below.

4.2 Safety and Adverse Effects

4.2.1 Drug–Drug Interactions

Duloxetine at a dose of 120 mg per day is also a moderate inhibitor of CYP2D6 (i.e., less than fluoxetine or paroxetine at their lowest usually effective dose but greater than escitalopram, citalopram, or sertraline at their lowest usually effective dose) (Skinner et al. 2003). Thus, modest dose reductions and careful monitoring will be needed when prescribing duloxetine in combination with drugs that are preferentially metabolized by CYP2D6, particularly those with narrow therapeutic indexes.

Duloxetine is a substrate of CYP2D6 and CYP1A2 (Knadler et al. 2011). Inhibitors of either enzyme can affect duloxetine blood levels. Co-administration with potent inhibitors of either should be avoided. For example, fluvoxamine, a potent inhibitor of CYP1A2, increased the duloxetine area under the curve after oral administration by 460% and C(max) by 141% (Knadler et al. 2011). Smoking induces CYP1A2 metabolism and can reduce duloxetine blood levels by 30% (Knadler et al. 2011). CYP2D6 inhibitors or genetic variants affect metabolism to a lesser extent. Combined effects on CYP1A2 and CYP2D6 would have marked effects on duloxetine blood levels.

Preclinical animal studies with duloxetine also provide some evidence of potential pharmacodynamic drug–drug interactions that may occur in humans (Preskorn 2004a). Systemic administration of buspirone, a 5-HT1A receptor partial agonist, transiently inhibited the duloxetine and fluoxetine-induced increases in 5-HT levels but markedly and synergistically increased duloxetine and fluoxetine-induced increases in DA levels (550% and 240%, respectively) and in NE levels (750% and 350%, respectively) in the frontal cortex (Gobert et al. 1997). Co-administration of the 5-HT1A antagonist, LY206130, produced a 570%, 480%, and 300% increase in duloxetine-induced increases in 5-HT, NE, and DA levels, respectively, in the

hypothalamus of conscious, freely moving rats consistent with antagonism of the normal auto-inhibitory feedback loop mediated by somatodendritic 5-HT1A autoreceptors (Engleman et al. 1996) with duloxetine. In addition, the major metabolite of buspirone is 1-(2-pyrimidinyl) piperazine (1-PP), an NE a2-adrenergic antagonist. 1-PP potentiated the duloxetine-induced increase in 5-HT, NE, and DA levels in the frontal cortex by 290%, 1,320%, and 600%, respectively, consistent with the fact that a2-adrenergic receptors tonically inhibit NE and DA and phasically inhibit 5-HT release in the frontal cortex (Gobert et al. 1997). Therefore, co-administration of buspirone with duloxetine may increase synaptic monoamines, which could either increase side effects or potentiate benefit. Pindolol, a 5-HT1A, 5-HT1B, and β adrenergic receptor antagonist, potentiated the increase in both 5-HT and DA levels but not NE in the frontal cortex produced by administration of duloxetine and fluoxetine (Gobert and Millan 1999a). While there have been no human clinical trials of pindolol combined with duloxetine, pindolol has been shown to accelerate response to SSRIs (Blier 2003).

There is also considerable preclinical data supporting the benefits of duloxetine on peripheral pain syndromes (Wang et al. 2015, 2016). These effects are similar to those observed with tricyclic antidepressants and appear to be mediated by inhibition of sensory transmission in nociceptive fibers in the dorsal horn of the spinal cord by serotonin and norepinephrine (Micó et al. 2006). Duloxetine also blocks voltage-gated sodium channels, which may mediate some of the benefit on pain (Wang et al. 2010).

4.2.2 Adverse Effects

The published literature suggests that duloxetine is well tolerated. In an early stress urinary incontinence study, the discontinuation rate for adverse effects was dose dependent: placebo 5%, 20 mg per day 9%, 40 mg per day 12%, and 80 mg per day 15%, with nausea being the most common symptom leading to discontinuation (Norton et al. 2002). Similar results were seen in the depression trials. In one study, the discontinuation rate of placebo was 4.3% vs 12.5% with duloxetine, 60 mg per day (Detke et al. 2002). In a forced titration trial to 120 mg per day, the only adverse effects that were reported to a statistically greater degree ($p < 0.05$) with duloxetine compared with placebo were insomnia and asthenia (Goldstein et al. 2002). The adverse effects in these trials are consistent with indirect 5-HT and NE receptor activation mediated by reuptake transporter inhibition. The overall discontinuation rate due to adverse effects with duloxetine in MDD trials was 8.4%. In trials in other conditions, the discontinuation rate due to side effects was as follows: generalized anxiety disorder = 13.7%; diabetic neuropathic pain = 12.9%; fibromyalgia = 17.5%; osteoarthritis pain = 15.7%; and low back pain = 16.5%, with the most common adverse effects being nausea, dry mouth, somnolence, constipation, decreased appetite, and sweating (2016).

There have been reports of serious hepatotoxicity consistent with hepatocellular injury, including hepatic failure in patients treated with duloxetine (McIntyre et al. 2008; Voican et al. 2014). Early clinical trials of duloxetine showed that elevations of alanine aminotransaminase of three times the upper limit of normal or higher

occurs in 0.9–1.7% of duloxetine-treated patients versus 0.0–0.3% of placebo-treated patients (McIntyre et al. 2008). Duloxetine should not be used in patients with clinically significant liver disease, including alcoholic liver disease, cirrhosis from other causes, or cholestatic jaundice. Use in patients with a recent alcohol use disorder even without obvious liver disease should be avoided. Patients treated with duloxetine should have periodic ALT and AST monitoring.

There are very little data on the use of duloxetine in pregnancy. In one analysis of 668 infants born to mothers taking duloxetine during the first trimester of pregnancy (Lassen et al. 2016), found a relative risk of 0.80 (CI = 0.46–1.29), suggesting that duloxetine may not increase in malformations in face of first trimester exposure. Eli Lilly and Company maintains a pregnancy registry (https://lillypregnancyregistry.com/). While there are no known risks associated with duloxetine exposure, it remains FDA category C. Preclinical studies showed decreased fetal weights but no evidence of teratogenicity (Eli Lilly and Company 2016). Infants with late pregnancy exposure do run a risk of drug discontinuation reactions and other adverse effects that can include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, and irritability (Eli Lilly and Company 2016). Duloxetine is secreted in breast milk with an exposure equivalent to only 0.14% of the maternal dose suggesting that administration during breastfeeding may be safe (Lobo et al. 2008).

4.2.3 Overdose

There are no published large-scale analyses on the risks associated with overdose with duloxetine. Overdose deaths with duloxetine alone have been reported but are rare (Scanlon et al. 2016). The preclinical pharmacology of the drug suggests that it should have a wide therapeutic index and have a limited risk of death due to overdose.

4.3 Clinical Use/Therapeutic Indications

4.3.1 Major Depression

A Cochrane Review assessed the existing data on safety and efficacy of duloxetine in 2012 (Cipriani et al. 2012). This review identified 16 randomized controlled trials involving 5,735 MDD participants that were included in this systematic review, including 3 that were previously unpublished. In addition, there were 15 studies involving 5,282 participants comparing duloxetine with other antidepressants (paroxetine, escitalopram, fluoxetine, venlafaxine, and desvenlafaxine). There was one other study comparing duloxetine with quetiapine. The placebo-controlled studies showed benefit, and there were no significant differences in this analysis with other antidepressants with regard to efficacy. When compared with escitalopram or venlafaxine, there were higher rates of dropouts due to all causes with duloxetine (OR = 1.62 and 1.56, respectively). Notably, an earlier analysis applied network meta-analysis (Shelton 2015) to the clinical trials data comparing

various antidepressants and found duloxetine to be less effective than mirtazapine, escitalopram, venlafaxine, and sertraline (OR's favoring the other medications ranged from 1.27 to 1.39) (Cipriani et al. 2012). Approved doses of duloxetine for MDD are from 30 to 120 mg per day.

Duloxetine is approved for use in children and adolescents age 7 and above (Atkinson et al. 2014; Emslie et al. 2014). Approved doses are the same as adults at 30–120 mg per day. As for all antidepressants, duloxetine has a black box warning for treatment-emergent suicidal ideation or self-injury in children, adolescents, and young adults. One network meta-analysis (Shelton 2015) of clinical trials in children suggested that duloxetine may be less effective than fluoxetine for MDD (Cipriani et al. 2016).

A pooled analysis of short- and longer-term (up to 36 weeks) MDD studies reported on the safety of duloxetine and fluoxetine (Emslie et al. 2015). Of patients who were suicidal at baseline, suicidal ideation improved in 81% of duloxetine- and 77% of fluoxetine-treated patients at endpoint in the 36-week studies. Suicidal behavior was reported in 1.8% of patients initially randomized to duloxetine and 1.3% randomized to fluoxetine. Treatment-emergent suicidal ideation during the 36 weeks of treatment occurred in 11.1% of patients treated with duloxetine and in 15.1% of patients treated with fluoxetine (Atkinson et al. 2014; Emslie et al. 2014). Treatment-emergent non-suicidal self-injury (e.g., cutting or burning) during the 36 weeks of treatment was seen in 5.5% and 4.5% of patients treated with duloxetine and fluoxetine, respectively. Duloxetine therefore appears to be about as safe as fluoxetine in longer-term treatment with regards to suicidal ideation and behavior and other self-injury.

4.3.2 Other Indications

In addition to duloxetine's antidepressant actions, it has been extensively studied in pain syndromes and is approved for the treatment of diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain (Lunn et al. 2014). A Cochrane review concluded that doses of 60 and 120 mg per day were effective in pain syndromes, but lower doses were not (Lunn et al. 2014). Duloxetine treatment also resulted in greater reduction in painful physical symptoms in patients with MDD, including overall pain, back pain, shoulder pain, and time in pain while awake (Detke et al. 2002; Goldstein et al. 2002).

Duloxetine is also approved in children over age 7, adolescents, and adults for generalized anxiety disorder (Alaka et al. 2014; Davidson et al. 2008; Hartford et al. 2007; Rynn et al. 2008; Sheehan et al. 2008; Strawn et al. 2015). One published trial showed benefit of duloxetine versus placebo for the longer-term relapse prevention in GAD patients (Davidson et al. 2008).

There are limited data on benefit in pain syndromes (Trouvin et al. 2017; VanderWeide et al. 2015), including migraine prophylaxis (Tarlaci 2009), but the data are not as robust as for duloxetine or milnacipran, which is also discussed in this chapter. Venlafaxine is not approved by regulatory authorities for pain treatment.

4.4 Dosing Recommendations

Duloxetine is manufactured in 20, 30, and 60 mg capsules. The typical starting dose is 30 mg per day, and its approved maximum dose is 120 mg per day for MDD and generalized anxiety disorder. Sixty mg per day is the maximum recommended dosing for diabetic neuropathic pain, fibromyalgia, and musculoskeletal pain, although clinical observation suggests that higher doses may be more effective than 60 mg. The approved doses for generalized anxiety disorder in children are the same as adults.

5 Milnacipran

5.1 Chemistry, Pharmacology, and Metabolism

Milnacipran (also earlier called midalcipran) is a cyclopropane derivative, 1-phenyl-1-diethyl-aminocarbonyl-cyclopropane (z) hydrochloride. It is a racemic mixture composed of two enantiomers which are both active based on preclinical pharmacology (Deprez et al. 1998). Milnacipran is marketed in France, Japan, and a few other countries for the treatment of depression (Tajima 2002). It entered development for MDD in the USA in the late 1980s through the early 1990s, but that development was discontinued. It was subsequently approved by the US FDA for the treatment of fibromyalgia (Kyle et al. 2010).

Milnacipran is a moderately potent 5-HT and NE reuptake inhibitor and thus is in the same class as the antidepressants venlafaxine, desvenlafaxine, duloxetine, and levomilnacipran as well as the anti-obesity drug sibutramine. It is a relatively potent inhibitor of both 5-HT and NE transporters (Ki = 8.4 and 22, respectively), with a binding ratio of about 2.6. It produces several-fold and long-lasting elevations in the extracellular levels of monoamines in mammalian brains and is active in animal models of depression (Briley et al. 1996; Delini-Stula 2000). It has no direct effect on DA. Other than its 5-HT and NE transporter binding, milnacipran has low affinity for receptors binding acetylcholine, DA, histamine NE, and 5-HT and does not affect ion channels, nor does it inhibit monoamine oxidase (Briley et al. 1996).

In rat brains, specific binding of milnacipran has been found in structures dense in 5-HT innervation including the dorsal raphe, basal ganglia, colliculi, and cerebral cortex (Barone et al. 1994). Selective lesioning of 5-HT neurons caused large decreases in milnacipran binding in septal nuclei, caudate, hippocampus, thalamus, and ventral and dorsal hypothalamus, but in other brain regions had only partial (putamen) or no effect (amygdala, lateral hypothalamus). Milnacipran was differentially displaceable in these various areas by SSRIs (e.g., paroxetine) and NRIs (e.g., desipramine). These binding data are consistent with milnacipran binding to both the 5-HT and NE transporters.

Consistent with its in vitro profile and its anatomical distribution, local administration of milnacipran increased 5-HT output in the rat frontal cortex and the dorsal raphe by sevenfold and tenfold, respectively, via a calcium- and tetrodotoxin-

dependent mechanism (Bel and Artigas 1999). A smaller magnitude increase was seen in these regions following systemic administration and was modestly potentiated by co-administration of the 5-HT1A antagonist WAY 100635, consistent with the inhibition of the 5-HT1A autoreceptor regulating synaptic 5-HT concentration. Systemic administration of milnacipran for 2 days in rats reduced the firing rate of both NE neurons in the locus ceruleus and 5-HT neurons in the dorsal raphe (Mongeau et al. 1998). The reduction in NE but not 5-HT neuronal firing persisted following 14 days of continuous milnacipran administration. Fourteen days of continuous administration of milnacipran substantially attenuated the ability of the a2-adrenergic agonist clonidine to suppress both NE and 5-HT neuronal firing but had no effect on the ability of the 5-HT1A agonist to suppress 5-HT neuronal firing (Mongeau et al. 1998). Finally, milnacipran was able to suppress 5-HT neuronal firing in intact but not in NE-denervated rats. Taken together, this set of studies confirms that milnacipran has acute effects on both 5-HT and NE uptake inhibition but differential long-term effects on a2-adrenergic and 5-HT1A autoreceptors and suggests the possibility that the mechanism by which 5-HT neurons regain their normal firing during chronic milnacipran treatment may be mediated through its effects on the NE system, specifically the a2-adrenergic heteroreceptor. These results were consistent with findings in several behavioral studies in rats, including its effects on the forced swimming test, clonidine-induced aggression, and methoxamine-induced exploratory hyperactivity (Maj et al. 2000; Reneric et al. 2002).

Despite these results, milnacipran differs from a number of (but not all) established antidepressants in that chronic administration, including osmotic minipump infusion for 27 days, did not downregulate NE β-adrenergic receptors or β-adrenergic-stimulated adenylate cyclase activity (i.e., b-adrenergic second messenger function) in rats (Assie et al. 1992; Neliat et al. 1996). Such dosing also did not alter NE α1or a2-adrenergic, or 5-HT1 or 5-HT2 receptors, and did not modify the uptake or accumulation of 5-HT or NE. In contrast to citalopram, chronic administration of milnacipran also did not downregulate 5-HT autoreceptors, which is the apparent mechanism permitting an increase in 5-HT neurotransmission with SSRIs (Moret and Briley 1994). However, other work suggests that chronic administration of milnacipran desensitizes somatodendritic but not postsynaptic 5-HT1A receptors in rats (Mochizuki et al. 2002a). Like the results for duloxetine reviewed earlier, chronic administration of milnacipran may affect DA neurotransmission in the brain as witnessed by an increased density of DA D2 (but not D1 or D3) receptors in the striatum, but not the limbic forebrain (Rogoz et al. 2000).

Milnacipran is active in several animal models of depression, including the forced swim test in both mice and rats, learned helplessness in rats, conditioned fear stress test, and the olfactory bulbectomized rat (Mochizuki et al. 2002b; Reneric et al. 2002; Rogoz et al. 1999, 2000). Milnacipran also antagonized the depressant effect of tetrabenazine, yohimbine-induced mortality, and p-chloroamphetamine-induced hyperthermia in mice and enhanced l-tryptophan-induced behavioral changes in rats, consistent with NE reuptake blockade, but produced no anticholinergic, sedative, or

stimulant effects (Stenger et al. 1987). These latter results are consistent with its in vitro pharmacological profile: 5-HT and NE uptake inhibition without effects on receptors.

In anesthetized guinea pigs, intravenous milnacipran caused ventricular arrhythmias and cardiac arrests. However, milnacipran had a 22 times wider therapeutic index compared with imipramine.

A human study in 12 healthy volunteers demonstrated that milnacipran at clinically used doses produced concentrations which are capable ex vivo of inhibiting 5-HT and NE uptake into human platelets and rat hypothalamic homogenates, respectively (Palmier et al. 1989). These results support its ability to inhibit the transporters for both 5-HT and NE with similar potency and under clinically used dosing conditions. Also consistent with its in vitro and preclinical pharmacology, milnacipran in comparison to placebo and amitriptyline had a benign effect profile on cognitive function in both young and elderly (>65 years) volunteers as measured by a psychometric test battery consisting of critical flicker fusion, choice reaction time, compensatory tracking, short-term memory, and subjective sedation and sleep (Hindmarch et al. 2000). Intravenous infusion of milnacipran to normal volunteers at doses up to 0.8 mg/kg produced an average 18% increase in heart rate, 22% increase in systolic blood pressure, and decreases in the functional refractory period of the atrium and atrioventricular node and in the effective refractory period of the right ventricle, as well as transient nausea in 50% of these volunteers (Caron et al. 1993).

Milnacipran demonstrates linear pharmacokinetics over a dose range of 25–200 mg per day, is rapidly and extensively absorbed (>85%), and has a half-life of 8–12 h (Delini-Stula 2000). Because of its shorter half-life, it should be dosed twice per day. Its metabolism does not require CYP enzyme-mediated biotransformation. Milnacipran is principally eliminated by renal excretion. Consistent with that fact, the clearance of milnacipran was significantly prolonged in patients with renal failure (creatinine clearance = 9–84.5 mL/min) with its half-life being three times longer in renal failure vs normal volunteers (Puozzo et al. 1998b). Conversely, its pharmacokinetics was essentially unchanged in volunteers with even severe liver impairment (Puozzo et al. 1998a).

The mechanisms for the pain benefits with milnacipran are likely to be similar to those described for duloxetine above. One exception is that it does not have sodium channel blocking effects.

5.2 Safety and Adverse Effects

5.2.1 Drug–Drug Interactions

Milnacipran would be predicted to be susceptible to the same pharmacodynamic drug–drug interactions as other 5-HT and NE uptake inhibitors, described earlier. It undergoes minimal CYP metabolism and it is largely excreted unchanged in the urine. It does not inhibit CYP enzymes. It also has low protein binding at 13%. Therefore, it should have minimal drug–drug interactions, with the exception of MAOIs, including linezolid and methylene blue, which are also MAOIs (Spina et al.

2012). Case reports of serotonin syndrome when milnacipran is combined with tramadol have been reported, as with other 5-HT uptake inhibitors (Park et al. 2014).

5.2.2 Adverse Effects

Consistent with its absence of effects on muscarinic, adrenergic, and histamine receptors, milnacipran at doses of 50–200 mg per day has a favorable adverse effect profile when compared with tertiary amine TCAs such as amitriptyline and imipramine, including a lower incidence of abnormal liver function tests based on analysis of a database of over 3,300 patients (Montgomery et al. 1996; Puech et al. 1997). Milnacipran at doses of 50 or 100 mg twice a day but not 100 mg once a day caused a lower incidence of nausea and anxiety but a higher incidence of headache, dry mouth, and dysuria than did fluoxetine, 20 mg per day, or fluvoxamine, 100 mg twice a day, in 4–12-week trials (Lopez-Ibor et al. 1996). As with other drugs in this class, dysuria is the most (Delini-Stula 2000) common and dose dependent adverse effect of milnacipran occurring in up to 7% of patients (Spencer and Wilde 1998). In placebo-controlled trials in patients with fibromyalgia, a relatively high rate of patients discontinued due to side effects at both 100 and 200 mg per day (23% and 26% respectively, versus 12% on placebo) (Allergan Plc 2016). The most common side effects include nausea, constipation, headache, dizziness, insomnia, and flushing.

Consistent with its NE uptake inhibition, high-dose milnacipran has been reported to cause occasional mild blood pressure elevation (Yoshida et al. 2002). An unpublished double-blind, placebo-controlled ambulatory blood pressure monitoring study was conducted to evaluate the effects of milnacipran on blood pressure in 321 fibromyalgia patients (Allergan Plc 2016). Hypertension was defined in this study as mean systolic blood pressure of $\geq$140 mmHg, change from baseline in mean SBP $\geq$10 mmHg or mean diastolic blood pressure $\geq$90 mmHg, and change from baseline in mean DBP $\geq$5 mmHg. The blood pressure findings in previously normotensive patients showed a higher proportion of milnacipran-treated patients had hypertensive blood pressure readings. At week 4, 50 mg given twice per day had a rate of mild hypertension of 17.7% versus 3.7% for placebo. At week 7, 100 mg twice per day produced hypertension in 14.3%, versus 0% for placebo. The mean change in both diastolic and systolic blood pressure was 5 mmHg. In phase 3 clinical trials, milnacipran 50 mg twice per day or 100 mg twice per day produced hypertension in 20% and 17% respectively (Allergan Plc 2016). The mean increase in pulse rate was 13 bpm; 8% of patients experienced an increase in pulse rate of $\geq$20 bpm (Allergan Plc 2016). These findings are consistent with significant norepinephrine reuptake inhibition.

Risks of teratogenicity with intrauterine exposure are unknown. Intrauterine exposure in rodents resulted in higher rates of fetal and perinatal lethality when milnacipran was given at a very high dose (Allergan Plc 2016). Milnacipran is listed as a category C medication. There is an online pregnancy registry (https://savellapregnancyregistry.com/).

5.2.3 Overdose

Milnacipran has produced rare deaths due to overdose as a single agent (Allergan Plc 2016). Deaths have occurred more commonly associated with multiple drug ingestions that include milnacipran.

5.3 Clinical Use/Therapeutic Indications

5.3.1 Major Depression

The development of milnacipran for depression was mostly outside of the U.S. and the bulk of trials were active medication controlled but not placebo controlled (Spencer and Wilde 1998), and therefore do not represent optimal rigor. A meta-analysis of three multicenter, double-blind, placebo-controlled 4–8-week acute efficacy trials in inpatients and outpatients with moderate to severe depression found milnacipran produced a superior antidepressant response compared with placebo at doses of 50 and 100 mg twice a day but not at a dose of 25 mg twice a day (Lecrubier et al. 1996; Macher et al. 1989). Another meta-analysis of seven randomized, double-blind studies of milnacipran, 50 mg twice a day, found comparable antidepressant efficacy to imipramine, clomipramine, and amitriptyline, 150 mg per day (Ansseau et al. 1989; Kasper et al. 1996). However, one randomized, double-blind, parallel-group study found milnacipran at a dose of 200 mg per day produced superior antidepressant response compared to milnacipran 50 and 100 mg per day and a comparable antidepressant response in reference to amitriptyline 150 mg per day (von Frenckell et al. 1990). In an 8-week, double-blind, random assignment trial involving 219 depressed elderly patients, milnacipran and imipramine at doses of 50 mg twice a day had comparable antidepressant efficacy but imipramine produced a greater number of adverse effects, particularly those attributable to muscarinic acetylcholine receptor blockade (Tignol et al. 1998). In a 6-week, double-blind, random assignment study involving treatment-refractory patients, milnacipran, 200 mg per day, and clomipramine, 150 mg per day, produced comparable but low antidepressant response rates (Steen and Den Boer 1997). In 4–12-week acute efficacy trials, milnacipran at doses of 50 or 100 mg twice a day but not 100 mg once a day was as effective as fluoxetine, 20 mg per day, and possibly more effective than fluvoxamine, 100 mg twice a day, particularly in patients with higher depression rating scale scores. Two separate meta-analyses of trials comparing milnacipran to other antidepressants concluded that milnacipran was neither superior nor inferior to other medications (Nakagawa et al. 2008; Papakostas and Fava 2007).

Milnacipran has been shown in prior continuation trials to be superior to placebo in relapse prevention (Preskorn 2004b). In a 4-month continuation study, relapse rates were 16% for patients treated with milnacipran (50 mg twice a day) vs 24% for placebo ($p < 0.05$) (Rouillon et al. 2000). A 6-month continuation study in which there was not only a lower relapse rate in patients treated with milnacipran compared with those receiving placebo but also the patients treated with milnacipran had higher quality of life scores at the end of the continuation phase (Rouillon et al.

2000). However, clomipramine (75–150 mg per day) in a 6-month continuation study produced a statistically significant lower relapse rate than did milnacipran (100–200 mg per day) at 63% vs 45%, respectively (Leinonen et al. 1997).

5.3.2 Other Indications

Milnacipran is approved in the U.S. and elsewhere for the treatment of fibromyalgia pain (Derry et al. 2012; Hauser et al. 2011; Kyle et al. 2010). A meta-analysis of clinical trials concluded that milnacipran was not as effective as amitriptyline for pain, sleep disturbance, and health related quality of life (HRQOL) and was less effective than duloxetine for improving pain, sleep disturbances and HRQOL, although milnacipran was superior to duloxetine for fatigue (Hauser et al. 2011).

5.4 Dosing Recommendations

As reviewed above, milnacipran has been tested at doses of 50–200 mg per day, given on a twice-a-day schedule. In general, doses of 100 mg per day or higher produced effects that were superior to 50 mg per day. Higher doses have also been required to achieve efficacy comparable to tricyclics and fluoxetine. There is some evidence that 200 mg per day may produce superior response compared to 100 mg per day. Twice per day dosing is recommended because of the relatively short half-life.

6 Levomilnacipran

6.1 Chemistry, Pharmacology, and Metabolism

Levomilnacipran is the levorotary enantiomer of racemic milnacipran (Zadka et al. 2016) called (1*S*,2*R*)-2-(aminomethyl)-*N*,*N*-diethyl-1-phenylcyclopropane-1-carboxamide (Ragguett et al. 2017). The levorotary enantiomer has higher potency for 5-HT and NE transporters than the dextrorotary form (Auclair et al. 2013). It has a higher ratio of binding NE to 5-HT transporters; the 5-HT to NE ratio is about 1.2:1. However, racemic milnacipran contains levomilnacipran and, therefore, the pharmacology of the two compounds is very similar, and it will not be reviewed extensively here. Like racemic milnacipran, there is minimal off-target receptor binding (Sansone and Sansone 2014).

In rodent models, intraperitoneal levomilnacipran increased cortical extracellular levels of 5-HT and NE, as would be expected for an SNRI. In behavioral tests of antidepressant action, levomilnacipran decreased immobility time in both the tail suspension and forced swim tests, along with ultrasonic vocalizations, a non-specific measure of distress (Sansone and Sansone 2014).

The half-life of levomilnacipran is 12 h. However, it is marketed as an extended release and can therefore be dosed once per day.

Like the racemic mixture, it undergoes limited CYP metabolism (primarily via CYP3A4) and it is largely excreted unchanged in the urine (58%) (Allergan Plc 2017). Levels are increased in the face of significant renal but not hepatic impairment. Recommended dosage adjustments are to limit the dose to 80 mg daily for moderate impairment and 40 mg daily for severe renal insufficiency (Allergan Plc 2017).

6.2 Safety and Adverse Effects

6.2.1 Drug–Drug Interactions

Levomilnacipran would be predicted to be susceptible to the same pharmacodynamic drug–drug interactions as other 5-HT and NE uptake inhibitors, described earlier. It does not inhibit CYP enzymes. It also has low protein binding at 22%. Therefore, it should have minimal drug–drug interactions. Like other 5-HT uptake inhibitors, it should be avoided with MAOIs including linezolid and methylene blue (Spina et al. 2012).

Other drugs have very limited effects on levomilnacipran. Co-administration with strong CYP3A4 inhibitors (e.g., ketoconazole) will increase levomilnacipran, and a maximal dose of 80 mg per day is recommended unless side effects emerge. There are minimal effects of CYP3A4 inducers, and no dosage adjustment is needed unless there is re-emergence of symptoms.

6.2.2 Adverse Effects

The side effect profile of levomilnacipran is very similar to racemic milnacipran, although somewhat milder in its typical dosing range of 20–120 mg per day. Common side effects include nausea, constipation, diaphoresis, urinary hesitancy (especially in men), and erectile dysfunction.

Levomilnacipran produces only modest increases in blood pressure. In clinical trials, the mean increase in systolic blood pressure was 3 mmHg and in diastolic was 3.2 mmHg (Allergan Plc 2017). Similar results were found in both short- and long-term studies. Only 1.8% of normotensive patients treated with 40–120 mg per day met criteria for hypertension during levomilnacipran treatment, compared with 1.2% of placebo patients (Allergan Plc 2017). The mean change in heart rate was 7.4 bpm, and 40, 80, and 120 mg per day doses changed pulse 7.2, 7.2, and 9.1 bpm. These results suggest that levomilnacipran has a better cardiac safety profile than milnacipran in recommended doses. Milnacipran produced greater effects on both blood pressure and pulse rate. In contrast to the results with levomilnacipran, the mean change in pulse rate with milnacipran was 13 bpm, and 8% of patients experienced an increase in pulse rate of $\geq$20 bpm (Allergan Plc 2016). However, these results may also indicate that within the recommended dosing range milnacipran may be a more potent norepinephrine reuptake inhibitor.

As with other potent serotonin reuptake inhibitors, discontinuation reactions may occur on abrupt discontinuation or rapid reduction of levomilnacipran. Therefore, as with other SRIs, tapering should be slow.

No teratogenic effects were observed when levomilnacipran was administered to pregnant rats or rabbits during pregnancy in oral doses of up to 100 mg/kg/day. However, fetal body weights were reduced in rats, and skeletal ossification was delayed in both species. At 60 mg/kg/day there was an increase in early postnatal mortality. However, these effects were not observed at lower doses that are more comparable to those used in humans (Allergan Plc 2017). There is very limited pregnancy exposure data with levomilnacipran; however, it is not expected to be different than milnacipran. It is pregnancy category C. Excretion in breast milk is unknown, but again, it is unlikely to be different than milnacipran.

6.2.3 Overdose

There are no published reports of levomilnacipran overdose. However, it is expected to be similar to milnacipran and, therefore, relatively safe.

6.3 Clinical Use/Therapeutic Indications

6.3.1 Major Depression

There were two early phase 2 trials of levomilnacipran. The first was a 10-week comparison of levomilnacipran 75 or 100 mg per day versus placebo. Levomilnacipran produced a robust antidepressant effect relative to placebo (LS mean difference −4.2 points on the MADRS) and positive results on multiple secondary endpoints (e.g., HAM-D, Sheehan Disability Scale, CGI, response and remission) (Montgomery et al. 2013; Ragguett et al. 2017). In this study, remission rate was relatively high (46.4% versus 26% for placebo). There were multiple phase 3 trials of levomilnacipran (Asnis et al. 2013; Bakish et al. 2014; Kornstein et al. 2016; Montgomery et al. 2013, 2014; Sambunaris et al. 2014; Wesnes et al. 2017). Montgomery et al. (2015) conducted a post hoc pooled analysis of five levomilnacipran extended-release (ER) trials in MDD. Efficacy was evaluated by LS mean change in MADRS score along with both response (MADRS improvement $\geq$ 50%), and remission (MADRS $\leq$ 10). Levomilnacipran produced a greater improvement in MADRS score than placebo, with a LS mean difference of 2.9, along with higher response rates (44.7% versus 34.5% for placebo) and remission rates (27.7% versus 21.5% for placebo). These differences overall were modest for levomilnacipran but sufficient to achieve regulatory approval. A network meta-analysis compared levomilnacipran with so-called second-generation antidepressants (i.e., SSRIs, SNRIs, and serotonin receptor modulators) and found no differences in outcome for levomilnacipran or other newer antidepressants (vilazodone and vortioxetine) (Wagner et al. 2017). There are no published studies in children or adolescents.

There was also a published 48-week open-label extension study with levomilnacipran in people with MDD who had participated in prior acute treatment trials. The rate of completion was 47%; 13% discontinued due to adverse effects. There were no significant laboratory changes including liver enzymes. The mean increase in pulse rate was 9.1 bpm, and there were modest changes in diastolic and

systolic blood pressure (3.3 and 3.9 mmHg). Unfortunately, relapse rates were not reported. A second 24-week study (Shiovitz et al. 2014) compared levomilnacipran and placebo for relapse prevention in patients who had responded to an initial 12-week trial of levomilnacipran. In that study, mean time to relapse was greater than placebo, but this was not statistically significant. However, the relapse rates for both levomilnacipran and placebo were low (13.9% and 20.5%, respectively) (Shiovitz et al. 2014).

6.3.2 Other Indications

Levomilnacipran is not approved for use in any other indications. There are no published studies in fibromyalgia or other pain syndromes.

6.4 Dosing Recommendations

Levomilnacipran is manufactured in 20, 40, 80, and 120 mg capsules. The recommended starting dose is 20 mg for 2 days, then increasing the dose to 40 mg. However, many patients can start at 40 mg per day. The maximum approved dose is 120 mg per day. Levomilnacipran is a CYP3A4 substrate and is subject to effects of inhibitors (e.g., ketoconazole) and inducers (e.g., carbamazepine). Dosage adjustment may be needed with concomitant administration.

7 Conclusion

Tables 2 and 3 in the Appendix to this volume present comparisons of the placebo-subtracted incidence rate (percentage) of frequent adverse effects for a number of commonly used antidepressants based on data from the double-blind trials presented to the FDA for drug approval, which can be helpful in choosing medications of comparable efficacy. The placebo-subtracted incidence can assist with attributing adverse events to the specific effects of a drug, as opposed to other factors such as the underlying illness (e.g., major depressive disorder). The data in this table are a function of the average dose used in the clinical trials program that led to the drug's approval. Unlike the SSRIs, the adverse effect profiles of the SNRI class tend to be dose-dependent, with side effects related to binding to the 5-HT transporter occurring at lower doses and those related to NE uptake inhibition at higher doses. In some instances, particularly with desvenlafaxine, this is somewhat less significant because of the very narrow dosing range of 50–100 mg per day. By contrast, it is more significant with venlafaxine.

In addition to MDD, duloxetine and milnacipran are approved for pain syndromes (which is limited to fibromyalgia with milnacipran). There is limited evidence for pain benefit for venlafaxine, but the evidence is not as robust as for milnacipran and duloxetine. Venlafaxine is also approved for generalized anxiety disorder, social anxiety disorder, and panic disorder.

Selecting between SNRIs is difficult and the data are somewhat inconsistent with the pharmacology. For example, there is evidence that venlafaxine, the weakest 5-HT and NE uptake inhibitor of the group, may have superior antidepressant actions, at least at higher doses (Ferrier 2001). Alternatively, duloxetine, which is a much more potent and balanced 5-HT and NE reuptake inhibitor, was shown to be less effective in one network meta-analysis (Cipriani et al. 2012). Whether this relates to true effectiveness or just the limitations of meta-analysis is unclear. It does seem clear that the data on milnacipran (for fibromyalgia) and duloxetine (for fibromyalgia, diabetic neuropathy, and musculoskeletal) have relatively robust pain benefits. It is unclear whether there are true differences between those two medications, or whether the data are just limited with other medications.

There was sufficient justification for the development of SNRIs as a class. Some SNRIs have been shown to be beneficial in situations in which SSRIs have failed (Lenox-Smith and Jiang 2008; Rosso et al. 2012; Rush et al. 2006). In addition, certain SNRIs have shown benefit for pain syndromes and painful physical symptoms associated with MDD that appear to be comparable (or almost so) to tricyclic antidepressants but with fewer side effects. Further, milnacipran and duloxetine appear to have greater benefits on pain than SSRIs (although the data are limited). For these reasons, SNRIs fill an important niche in antidepressant therapy.

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Neurostimulation Therapies

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Abstract

Depression is one of the most disabling conditions in the world. In many cases patients continue to suffer with depressive disorders despite a series of adequate trials of medication and psychotherapy. Neuromodulation treatments offer a qualitatively different modality of treatment that can frequently prove efficacious in these treatment-refractory patients. The field of neuromodulation focuses on the use of electrical/electromagnetic energy, both invasively and noninvasively, to interface with and ultimately alter activity within the human brain for therapeutic purposes. These treatments provide another set of options to offer patients when clinically indicated, and knowledge of their safety, risks and benefits, and appropriate clinical application is essential for modern psychiatrists and other mental health professionals. Although neuromodulation techniques hold tremendous promise, only three such treatments are currently approved by the United States Food and Drug Administration (FDA) for the treatment of major depressive disorder: electroconvulsive therapy (ECT), vagus nerve stimulation (VNS), and repetitive transcranial magnetic stimulation (rTMS). Additionally, numerous other neurostimulation modalities (deep brain stimulation [DBS], magnetic seizure therapy [MST], transcranial electric stimulation [tES], and trigeminal nerve stimulation [TNS]), though currently experimental, show considerable therapeutic promise. Researchers are actively looking for ways to optimize outcomes and clinical benefits by making neuromodulation treatments safer, more efficacious, and more durable.

Keywords

Brain stimulation · Electroconvulsive therapy · Neuromodulation · Neurostimulation · Repetitive transcranial magnetic stimulation · Treatment-resistant depression · Treatment-resistant mood disorders

Abbreviations

BDNF	Brain-derived neurotrophic factor
ECT	Electroconvulsive therapy
EEG	Electroencephalography

MRI	Magnetic resonance imaging
MST	Magnetic seizure therapy
PET	Positron emission tomography
rTMS	Repetitive transcranial magnetic stimulation
SPECT	Single positron emission computed tomography
tACS	Transcranial alternating current stimulation
tDCS	Transcranial direct current stimulation
TMS	Transcranial magnetic stimulation
tRNS	Transcranial random noise stimulation

Depression is one of the most disabling conditions in the world today, both on an individual patient level and a global scale. Since the advent of antidepressant medications in the late 1950s, progress toward newer and more effective treatments has been challenging. With the possible exception of electroconvulsive therapy (ECT), pharmacotherapies targeting neurotransmitter systems have been the staple depression treatment for the past 60 years. For the most part, attempts to improve upon earlier generations of antidepressant drugs have struggled to demonstrate significantly greater benefits or novel mechanisms of action. Further, the challenge of managing treatment-refractory depression reaches an additional level of complexity, as many of these patients will not respond to a series of antidepressant trials and continue to suffer for years, even decades, with debilitating depression.

Neurostimulation therapies offer a unique approach for effecting change within the brain and nervous system. Focusing primarily on the use of electrical and magnetic forces, this category of therapeutics has ushered in a new and different way of not only thinking about studying mental illness and neuropsychiatric pathology in the brain but also an alternate strategy for modulating the brain and its neural elements to benefit patients struggling with depression and various other disorders of the brain. Encompassing older methods such as electroconvulsive therapy and newer technologies such as transcranial magnetic stimulation and vagus nerve stimulation, neurostimulation therapies have proven efficacious and exciting options for clinicians and researchers to utilize and explore. This chapter focuses on neurostimulation therapies and the role they play in the treatment of depression and other illnesses, with a focus on clinical methodology and use.

1 Electroconvulsive Therapy

1.1 Introduction

Electroconvulsive therapy (ECT) is one of the oldest and most effective psychiatric treatments still in regular use today. Despite repeated demonstrations of ECT's efficacy in depression and other psychiatric conditions, it remains controversial due to apprehensions over adverse effects and misunderstandings about the treatment itself. Modern techniques have minimized prior safety concerns, and continued

research and methodological advances have led to a renewed interest in ECT in recent decades.

1.2 Historical Background

The use of chemically induced seizures dates to the 1930s, when the Hungarian neuropsychiatrist Meduna hypothesized a "biological antagonism" between schizophrenia and epilepsy in patients, such that having seizures was "protective" against psychosis (Coffey and Weiner 1990). Despite Meduna's success in treating patients with schizophrenia with camphor-induced seizures, the use of this modality was painful and unreliable. In 1938, the Italian physicians Cerletti and Bini successfully administered the first electrically induced therapeutic seizure on a patient (Coffey and Weiner 1990). Subsequently, the practice of convulsive therapy rapidly spread throughout Europe and the United States and became a dominant form of somatic therapy for psychiatric disorders.

The use of ECT waned in the 1950s with the development of antipsychotic and antidepressant drugs. Misconceptions promulgated by sensationalized depictions of ECT, such as portrayed in the film *One Flew Over the Cuckoo's Nest*, and negative media portrayals led to further public disinterest (Jenkusky 1991). Although early attempts at treatment were riddled with injuries and complications, techniques have dramatically evolved with the routine use of anesthetics, muscle relaxants, oxygenation, and seizure monitoring. In recent decades, ECT has experienced a resurgence, partly in light of a growing recognition of its benefits and safety profile and partly due to the limitations of existing pharmacologic modalities (Lisanby 2007).

1.3 Mechanisms of Action

Despite decades of research and experience, the exact mechanism underlying ECT's benefits has yet to be elucidated. The possibility of a placebo or psychological effect was eliminated by multiple trials demonstrating significant efficacy of ECT over sham ECT (Janicak et al. 1985; UK ECT Review Group 2003; Tharyan and Adams 2005). Sackeim (1994) has described over 100 other theories, including alterations in neurotransmitters, the hypothalamic-pituitary-adrenal axis, neuroendocrine pathways, neurophysiological changes, and synaptic plasticity. The role of the electrical seizure itself has been a research subject of much interest. Cronholm and Ottosson (1996) classic research demonstrated that ECT is ineffective when the seizure is pharmacologically blocked by lidocaine. However, although the presence of a seizure is necessary, it is not sufficient for clinical efficacy: studies have established a lack of efficacy from marginally suprathreshold yet seizure-inducing treatments. Further, the dose of electrical charge relative to seizure threshold used to trigger generalized seizures appears to play a critical role in determining efficacy

depending on electrode placement (i.e., unilateral vs. bilateral vs. bifrontal lead placement) (Sackeim et al. 1993, 2000).

1.4 Indications (Table 1)

1.4.1 Unipolar Depression

ECT is well-established as the most effective treatment for major depressive episodes, with response rates of 70–90% and remission rates well over 40–50%, even in treatment-resistant patients (Prudic et al. 1996; UK ECT Review Group 2003; Kellner et al. 2006). However, ECT is largely utilized as a secondary treatment in patients who have failed to respond to a series of adequate antidepressant trials. Given that an "adequate" trial generally refers to 4–6 weeks of a medication at a therapeutic dose, this entire process of titration, waiting, and switching may span months and even years, leaving the patient with prolonged and unnecessary suffering (Beale and Kellner 2000).

According to practice guidelines from the American Psychiatric Association, ECT should be considered as first-line treatment for major depression with high symptom severity, such as concurrent psychosis or catatonia, and urgent cases necessitating a rapid symptomatic response (American Psychiatric Association 2010). This includes patients who are at high suicide risk, nutritional compromise (e.g., food refusal, dehydration or failure to thrive from loss of appetite), and severely ill inpatients. There is greater consensus on initiating ECT for such emergently ill cases than for medication-resistant depression. ECT is also indicated

Table 1 Indications for electroconvulsive therapy

Principal indications by diagnosis
• Major depressive disorder
• Bipolar disorder
• Catatonia
• Schizophrenia
Other indications by diagnosis
• Parkinson's disease
• Intractable epilepsy
• Neuroleptic malignant disorder
Primary clinical indications
• Need for a rapid, definitive response due to emergent psychiatric or medical condition
• History of poor response to pharmacotherapy
• History of good ECT response
• Patient's preference
Secondary clinical indications
• Treatment resistance
• Intolerance to pharmacotherapy
• Need for a rapid, definitive response due to deterioration in psychiatric or medical condition

as first-line treatment for patients who have previously shown a positive ECT response or patients who self-request (American Psychiatric Association 2010).

1.4.2 Bipolar Disorder

ECT has been less extensively studied for bipolar depression. Several older, controlled studies have found ECT to be as or more effective than MAOIs, tricyclics, and placebo (Zornberg and Pope 1993). As with unipolar depression, ECT is a reasonable treatment in bipolar depression associated with life-threatening conditions, psychotic or catatonic features, affective symptoms occurring during pregnancy, as well as treatment-resistant cases (American Psychiatric Association 2002). ECT is also efficacious for acute mania, with marked improvements in approximately 80% of patients (Mukherjee et al. 1994). In small prospective comparison studies, ECT was superior in efficacy to lithium and the combination of lithium and haloperidol (Small et al. 1988; Mukherjee et al. 1994). ECT may play a role in the treatment of delirious mania, rapid-cycling mania, treatment-refractory cases (Perugi et al. 2017), as well as emergent situations (e.g., mania leading to physical exhaustion) and pregnant patients with severe mania (American Psychiatric Association 2002).

Mixed episodes in bipolar disorder are notoriously difficult to treat with conventional pharmacologic modalities (Kruger et al. 2005). In a prior trial of ECT for patients with mania, the strongest predictor of clinical response was baseline depressive symptoms, suggesting ECT's possible benefits in mixed episodes (Small et al. 1988). Case reports have also proposed that ECT can successfully treat mixed states, but no prospective, randomized controlled studies have been completed (Devanand et al. 2000; Gruber et al. 2000; Ciapparelli et al. 2001).

1.4.3 Catatonia

Catatonia may develop in up to one third of patients during mania and is associated with increased episode severity and poor short-term outcomes (Braunig et al. 1998). Antipsychotic medications have had relatively poor utility in treating catatonia. Typically, benzodiazepines are the drugs of choice in catatonia; however, their use is based largely on anecdotal cases or small studies with deficiencies in methodology or reporting of findings, as was recently summarized in a Cochrane review (Hawkins et al. 1995; Gibson and Walcott 2008). ECT should be considered if benzodiazepines do not improve symptoms or if immediate resolution is necessary (e.g., malignant catatonia).

1.4.4 Schizophrenia

Several trials have found ECT to be less effective than antipsychotic medications, particularly clozapine, as first-line treatment in patients with schizophrenia (Small 1985; Tharyan and Adams 2005). However, ECT has shown therapeutic benefit when given together with antipsychotics, particularly if rapid symptomatic improvement is desired (Tharyan and Adams 2005). Patients with catatonia or prominent affective symptoms may be more likely to respond to treatment (Konig and Glatter-Gotz 1990). ECT is recommended by the APA for psychosis resistant to

antipsychotics, particularly failure of clozapine, as well as catatonia and emergent cases (American Psychiatric Association 2004). Although only 5–10% of ECT courses in the United States are given for patients with schizophrenia, many developing countries continue to use ECT for this indication, as the treatment is relatively available, effective, and inexpensive (Leiknes et al. 2012).

1.4.5 Other Conditions

ECT may be the treatment of choice in cases that preclude the use of medications, particularly due to safety concerns; this includes geriatric patients, the medically ill, and even pregnant patients who wish to avoid the potential teratogenic side effects of psychotropics. ECT also has potential benefits in the on-off phenomenon of Parkinson's disease, intractable epilepsy, and neuroleptic malignant syndrome (Faber and Trimble 1991; Trollor and Sachdev 1999; Lisanby et al. 2001). ECT is not effective for treating personality disorders, and, in fact, comorbid personality disorders have been associated with decreased efficacy (Prudic et al. 2004).

1.5 Contraindications

While there are no absolute contraindications to ECT, certain patients are at increased risk for complications. These include individuals with recent myocardial infarction, unstable symptomatic cardiac disease (e.g., arrhythmias, severe hypertension, unstable angina), decompensated congestive heart failure, and increased intracranial pressure (e.g., space-occupying brain lesions) and those at increased risk for cerebral bleeding (e.g., recent hemorrhage, unstable aneurysms (Lisanby 2007)). Some patient populations may also be deemed to be of higher anesthesia risk due to underlying medical or surgical conditions and will require closer anesthesia monitoring. ECT has been shown to be safe in pregnancy, the elderly, and persons with cardiac pacemakers or implantable cardioverter-defibrillators (Dolenc et al. 2004a).

1.6 Administration of ECT

1.6.1 Pre-treatment Evaluation

A thorough pre-ECT work-up should be conducted to detect the aforementioned conditions, which may increase a patient's risk of ECT-related adverse events. This entails a detailed medical and psychiatric history, physical and neurological exam, pre-anesthesia exam conducted by the anesthesia team, basic lab work (i.e., complete blood count, serum electrolytes), and an electrocardiogram (EKG). Other imaging is typically indicated only on an as-needed basis, for example, a chest x-ray for suspected acute pulmonary disease, a spinal x-ray in cases of severe osteoarthritis/osteoporosis, and brain imaging if specific concerns for neurological condition arise (e.g., concerns about stroke, previous history of head trauma or skull fracture). Patients with histories of skull fracture should have careful identification of the

location of the healed sutures, so lead placement is distant from these sites to prevent electricity from directly entering the brain.

1.6.2 Preparation for Treatment

All of the patient's medications must be carefully reviewed for potential adverse effects or interactions. Benzodiazepines are typically reduced or withdrawn due to their anticonvulsant activity and potential for increasing postictal confusion. Antiepileptics also raise seizure threshold and are often decreased or discontinued, though patients with comorbid depression and epilepsy may require these medication to avoid spontaneous or prolonged seizures, in which case minimizing the antiepileptic dose becomes the goal. Concurrent administration of lithium may increase the risk for cognitive disturbances, delirium, and spontaneous seizures, although recent case reviews and prospective studies have challenged this (Dolenc and Rasmussen 2005; Thirthalli et al. 2011); clinicians should weight the risks of neurotoxicity against relapse of symptoms on a case-by-case basis. MAOIs were historically recommended to be discontinued prior to ECT, but the current literature suggests that they are safe to continue (Dolenc et al. 2004b; Horn et al. 2010). Non-psychotropic medications that should be avoided include theophylline, which increases seizure duration, lidocaine, which increases seizure threshold, and reserpine, which compromises the cardiorespiratory system.

As with any procedure requiring general anesthesia, patients must not have anything to eat or drink for 6–8 h prior to treatment. Routine, medications needed for significant underlying medical illnesses can be administered by mouth, however, with minimal amounts of water. The patient's mouth should be checked for foreign bodies or loose teeth, and dentures should be removed. Fake nails or nail polish that could interfere with pulse oximetry should also be avoided.

1.6.3 Anesthesia

ECT is performed under general anesthesia in order to prevent injuries and control the pronounced sympathetic response and subsequent hemodynamic changes associated with seizure activity. The procedure is typically administered in a specialized suite in some centers and in a standard operating or recovery room in others. A peripheral intravenous catheter is inserted to administer medications, and a bite block inserted in the mouth just prior to electrical stimulation to protect the teeth and tongue. The patient's blood pressure, pulse rate, EKG, and oxygen saturation are carefully monitored throughout treatment.

The patient is pre-oxygenated with 100% oxygen by mask and is continued on mask ventilation until the procedure ends and the patient resumes normal respiration. Neuromuscular blocking agents are administered to prevent skeletal muscle contractions and injuries during tonic-clonic convulsions. Succinylcholine is the paralytic agent of choice for nearly all individuals but may lead to prolonged paralysis in those with pseudocholinesterase deficiencies; non-depolarizing muscle relaxants are used in these cases instead. Muscarinic anticholinergics (e.g., glycopyrrolate, atropine) are given on a case-by-case basis to minimize salivation and bradycardia. A short-acting anesthetic, typically low-dose etomidate,

methohexital, or propofol, is used for anesthesia. Despite propofol producing shorter duration seizures than methohexital, seizure quality and therapeutic outcomes of the two agents have been comparable (Mårtensson et al. 1994; Geretsegger et al. 2007).

1.6.4 Electrode Placement

Three electrode arrangements are commonly used in practice today: bilateral, right unilateral (RUL), and bifrontal. Bilateral placement offers more predictable efficacy and speed of response than RUL, but this placement is associated with considerably greater cognitive side effects. Sackeim et al. (2000) found that RUL ECT treatment, with an electrical stimulus 500% above the seizure threshold, produces therapeutic effects comparable to that seen with bilateral ECT with less cognitive dysfunction. A common treatment strategy is to start with a course of RUL and then switch to bilateral placement if the patient does not respond after adjustments in stimulus dosing (Mankad et al. 2010) (Fig. 1).

Bifrontal lead placement is not as well studied as bilateral and unilateral placements. It was initially believed to be as efficacious as bilateral placement, but with less cognitive side effects (Letemendia et al. 1993; Bailine et al. 2000). However, recent studies have failed to confirm these advantages, with the majority of research indicating that bifrontral lead placement has efficacy and cognitive side effects comparable to RUL placement (Eschweiler et al. 2007; Bjølseth et al. 2015; Dybedal et al. 2016). Further studies are still needed to clarify its place among the other treatment techniques.

1.6.5 Electrical Stimulus

Stimulus dosing should be adjusted on an individual basis to induce an adequate generalized seizure. A dosage titration technique is commonly employed as follows: (1) the approximate seizure threshold is determined during the initial ECT session by a method of limits approach; (2) once the seizure threshold is determined, subsequent sessions are performed at a factor of the threshold (6× seizure threshold for right unilateral treatment; 1.5–2× seizure threshold for bilateral (Coffey et al. 1995; Mankad et al. 2010)). Stimulus dosing can also be established via an

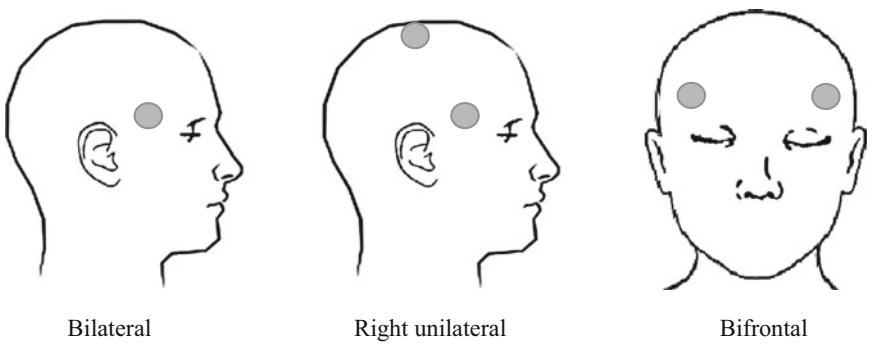

Fig. 1 Electroconvulsive therapy electrode placements

age-based dosing algorithm, but this method is limited by the fact that age alone does not adequately account for the variance in individual seizure thresholds (Coffey et al. 1995). Of note, existing dosing research has been performed only for bilateral and RUL placement, while little is known regarding optimal dosing for bifrontal placement.

Originally, ECT was delivered via a sinusoidal electrical waveform, which was physiologically inefficient and resulted in significant cognitive side effects (Peterchev et al. 2010). Present ECT machines use constant-current brief (0.5–2.0 ms) or ultrabrief ($\leq$0.5; typically 0.5 or 0.3 ms) rectangular pulses. Compared to sine wave generators, seizures can now be induced at significantly lower charges, with less adverse effects and equivalent efficacy (Peterchev et al. 2010).

1.6.6 Seizure Monitoring

The optimal ECT seizure lasts at least 20 s in motor duration and 30 s in electroencephalogram (EEG) duration (American Psychiatric Association 2001). Because treatments are performed under muscle relaxation, motor duration should be assessed by occluding flow of the muscle relaxant into the right ankle with an inflated blood pressure cuff. One can then observe the unmodified seizure in the foot and count how many seconds the seizure episode lasts. The ankle ipsilateral to the side of stimulation in unilateral treatments is used to ensure generalization of the seizure.

1.6.7 Treatment Course

A typical ECT course consists of 6–12 treatments administered 2–3 times/week, with the actual number of treatments dependent on the patient's clinical response and side effects. Given a significant risk of symptom relapse, all patients must receive maintenance treatment, either pharmacologic, continued ECT, or both (American Psychiatric Association 2001). If offered as maintenance, ECT treatments may be gradually decreased in frequency to monthly visits eventually. This process remains highly empirical due to a paucity of data on the optimal maintenance interval. Even with vigorous maintenance therapy, the relapse rate remains substantial at an estimated 40–50% at 6 months (Sackeim et al. 2001; Kellner et al. 2006); without effective maintenance treatment (e.g., placebo), relapse rates exceed 80%. Furthermore, Prudic et al. (2004) noted high relapse rates in community settings compared to clinical trials, possibly secondary to less aggressive maintenance treatment or premature discontinuation of ECT.

1.7 Side Effects

ECT-associated cognitive effects have been the subject of intense investigation. Patients commonly experience a brief period of disorientation and even delirium following the seizure and emergence from anesthesia (Lisanby 2007). ECT can cause anterograde amnesia, or inability to recall newly learned information, which is short-lived and resolves after ECT is terminated (Lisanby 2007). Patients may also

experience retrograde amnesia, or the forgetting of information learned before treatment, extending back months or years. This retrograde memory loss improves in the first few months after completing ECT in some individuals, but may be prolonged in others (Lisanby 2007). In addition, ECT may affect memory of prior personal events – that is, autobiographical memory – predominantly those occurring within 6 months of treatment, although some subjective accounts have reported this amnesia to be persistent as well (Fraser et al. 2008).

The cognitive deficits from ECT are related to specific factors, including bilateral electrode placement, higher stimulus dosages, and longer pulse waveforms (Sackeim et al. 2008). Older age, baseline cognitive status, and co-administration of medications such as anticholinergics may also be contributing factors. Because psychiatric disorders, particularly depression, are associated with deficits in concentration and executive functioning, some patients report an improvement in memory, as well as quality of life, following ECT (Prudic et al. 2000; McCall et al. 2006). A meta-analysis also showed that multiple cognitive measures, including processing speed, anterograde memory, and executive function, improved beyond baseline levels after 15 days (Semkovska and McLoughlin 2010).

Other side effects experienced by patients receiving ECT include muscle soreness, jaw pain, headaches, and nausea. In most instances, these lesser side effects can be resolved with analgesics (e.g., intravenous NSAIDs) and antiemetics given during the treatment. Rarely, episodes of hypotension, hypertension, tachycardia, and transient arrhythmias may occur with seizure activity; such cases require optimizing blood pressure pre-treatment and administering antihypertensives or antiarrhythmics as needed (American Psychiatric Association 2001). Prolonged seizures of greater than 120 s during ECT are also extremely rare and can be terminated via intravenous administration of either a repeat anesthetic dose or a short-acting benzodiazepine (e.g., midazolam 1–2 mg); this should be repeated after 2 min if the seizure is still not aborted (Greenberg 1985; Mankad et al. 2010). The overall mortality rate of ECT is estimated to be 1 per 10,000 patients or 1 per 80,000 treatments, which is no greater than the risk associated with general anesthesia alone and notably less than the mortality rate of inadequately treated depressed patients (Avery and Winokur 1976; American Psychiatric Association 2001).

2 Summary

ECT is backed by an extensive evidence base supporting its use and remains a standard psychiatric treatment around the world. Despite the extensive knowledge base regarding various aspects of treatment, much is left to be discovered, particularly in relation to how ECT works mechanistically and how to further reduce cognitive effects. It is crucial for clinicians to be aware of recent advances in technique that have allowed ECT to be even more effective and better tolerated than ever before, as well as to educate patients and counter the stigma surrounding this well-established treatment.

3 Repetitive Transcranial Magnetic Stimulation (rTMS)

3.1 Introduction

Transcranial magnetic stimulation is a unique tool that can be used to noninvasively induce an electrical current in the brain. This electrical current is induced via the creation of a temporary magnetic field that can pass unimpeded into the brain tissue and depolarize neurons, primarily in the cortex. As a magnetic field is not shunted or deflected by the human skull in the same way that an electrical current is (e.g., as in ECT), this allows TMS to be utilized in a manner that is safe and well-tolerated by patients while they are awake and alert. Transcranial magnetic stimulation administers brief "pulses" of electromagnetic energy that stimulate a small area (~2 cm) of the cortex of brain (Thielscher and Kammer 2002; Deng et al. 2013).

In addition to the potential clinical uses of TMS, researchers have used this modality to probe different areas of the brain and look for perceptual, behavioral, or motor changes to assess for cortical integrity. For example, a stimulation applied over the primary motor cortex of the brain will induce a motor-evoked potential (i.e., a small muscle twitch) in the region of the body controlled by the population of neurons in the cortex being stimulated. Hence, assuming the motor pathway is intact, stimulating the hand representation region in the motor cortex results in a muscle twitch in the hand.

Repetitive TMS (abbreviated rTMS) is a process of repeatedly pulsing electromagnetic stimuli into certain regions of the brain with specific parameters. Studies have shown that rTMS can induce long-lasting functional changes, which can then be used for therapeutic purposes. For this reason, rTMS is being explored for a host of different neuropsychiatric conditions. Although rTMS is a promising new tool for clinicians and researchers in neurology, neurorehabilitation, psychiatry, and neuroscience, there remains a great deal to be learned about the mechanism of action and how to optimize the treatment to interface with the brain in a therapeutic manner.

3.2 Brief History and Physics

A TMS device is a large capacitor that simply produces and stores an electrical charge. This device is attached to a "wand" that rests upon the patient's scalp. The wand contains a copper coil through which the electrical charge from the capacitor flows. Electrical current passing through a coil induces a magnetic field. This magnetic field can pass right through the scalp and skull. Since the brain uses electrical energy as a method for transmitting signals between neurons and down nerves to other areas of the body, it can "translate" this magnetic field back into electrical energy, thus inducing an action potential in the neurons under the coil in the wand (Fig. 2) (Frye et al. 2013).

The shape of the magnetic field determines how large an area of cortex is affected; hence, different magnetic coils can create different magnetic fields in the brain (Deng et al. 2013). The shape of the field, in addition to several other parameters,

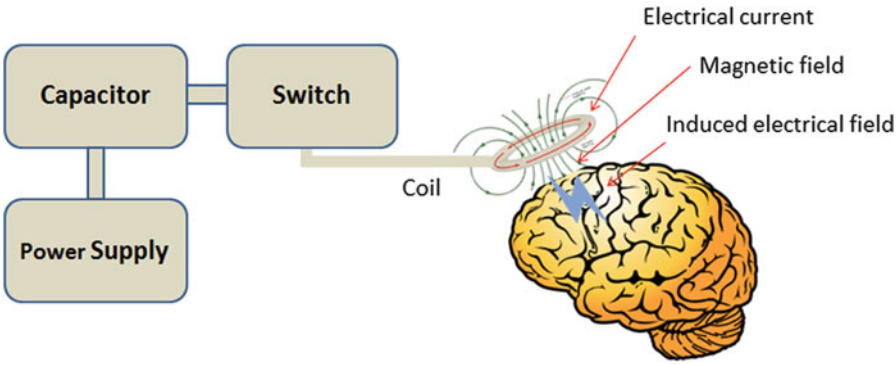

Fig. 2 Creation of a magnetic field (Adapted from Frye et al. (2013))

determines how deep the field will penetrate as well as how diffusely across the cortex the field will spread. There will be considerably different effects created by stimulating a small focal area versus a large swath of brain tissue, and researchers are actively investigating the best way to shape magnetic fields to address different research questions/disease conditions. Additionally, different TMS device manufacturers produce different coil shapes with different magnetic fields. It is important for TMS clinical practitioners to understand the properties of different magnetic fields so as to best understand how the rTMS treatment they are administering is interacting with cortical neurons.

Although achieving more popularity and attention in the modern era, the notion of using electromagnetic energy to induce changes in the brain is not a new one. The concept of electromagnetic induction was first described by Michael Faraday in 1831, and since then researchers have been attempting various forms of transcranial magnetic stimulation. D'Arsonval (Vidal-Dourado et al. 2014) first produced phosphenes by placing a volunteer's head into a magnetic coil in the late 1800s; this was later confirmed by the work of Silvanus Thompson in 1910 (Thompson 1910). The modern TMS device and coil was developed by Anthony Barker and colleagues in 1974, and the first stimulation of the human motor cortex took place in 1985 (Vidal-Dourado et al. 2014). Since then, there has been a very large expansion of TMS uses, both investigative and clinical.

3.3 How Does TMS Work?

It has been clearly demonstrated that a TMS pulse will induce an electrical current in the effected neuronal elements. The most dramatic forms of this occur with TMS of the primary motor cortex, which can produce a visible muscle twitch, and TMS of the primary visual cortex, which can lead to a patient experiencing phosphenes in their visual field. Critically, TMS pulses can travel "transynaptically," meaning that

a pulse can cross neuronal synapses and effect neurons further downstream from the stimulated neuron. This ability provides the rationale for how TMS can act both locally and across different brain networks to induce effects. This is important to recognize because the astute TMS practitioner can take advantage of "connectivity pathways" in the brain by applying current to specific cortical "nodes" in an effort to induce downstream (perhaps subcortical) effects on networks thought to be pathological; hence, TMS may be able to noninvasively influence deeper brain regions (Fox et al. 2014). Although single TMS pulses do not seem to have any durable effects, repetitive TMS has been shown to induce longer-lasting changes in brain regions and corresponding networks.

The exact effects of repetitive TMS are less well understood. Some evidence suggests that rTMS is capable of inducing long-term potentiation and long-term depression-like effects in targeted brain regions or networks, although this is admittedly a simplified and inexact description of the underlying processes, which are more complex (Cirillo et al. 2017). The general nomenclature suggests that "low frequency rTMS" (defined as pulses delivered at a frequency of 1 Hz or less) are inhibitory in the underlying neurons, whereas "high frequency rTMS" (defined as pulses delivered at a frequency greater than 1 Hz and usually greater than 5 Hz) is excitatory. Most of the evidence for these hypotheses comes from work done with repetitive stimulation of the primary motor cortex (motor-evoked potentials). If a high-frequency rTMS paradigm reduced the amount of energy required to produce a motor-evoked potential, that paradigm was thought to be excitatory and vice versa for low-frequency rTMS (Chen et al. 1997; Wu et al. 2000).

Research now demonstrates this conceptualization is an oversimplification; many factors will determine whether a stimulation protocol is excitatory or inhibitory, or has any effect at all, including the following:

1. Duration since the previous pulse sequence (Julkunen et al. 2012)
2. Ongoing tasks or cognitive processes occurring during stimulation time (Suzuki et al. 2014)
3. Orientation of the magnetic coil in reference to the neuronal elements being stimulated (Thomson et al. 2013)
4. Orientation of the neuronal elements themselves (e.g., operating in parallel or perpendicular to the induced current, often determined by the location of the gyri and sulci)
5. Any underlying pathologic process in the brain
6. Medication changes, sleep changes, caffeine or alcohol intake changes
7. Likely numerous other factors yet to be identified (Fitzgerald and Daskalakis 2013)

Several of these factors can also play a role in the size and quality of the motor-evoked potential obtained with stimulation of the primary cortex (see "motor threshold" below).

In addition, rTMS has been associated with brain changes identified using various research modalities, including changes in motor cortical excitability and plasticity,

EEG signaling, PET imaging, functional connectivity MRI, MR spectroscopy, SPECT imaging, brain-derived neurotrophic factor (BDNF), genetic transcription factor activity, dopamine levels or dopamine-binding activity, and functional near-infrared spectroscopy, among others (Fitzgerald and Daskalakis 2013). Details of the myriad identified changes are beyond the scope of this chapter but strongly suggest that rTMS is having a significant impact on brain neurochemistry and neurophysiology that lasts well beyond the duration of the stimulation.

3.4 Clinical Indications and Clinical Utility

Although it is being studied for almost every neuropsychiatric illness, there are only a few conditions for which TMS and rTMS are currently FDA-approved for clinical use in the United States. These are as follows (For a summary of clinical and experimental indications for rTMS, see Table 2):

1. The use of high-frequency rTMS of the left prefrontal cortex for major depressive disorder that has failed to respond to at least one medication
2. The use of TMS for motor and speech mapping for presurgical planning in neurosurgery, often for epilepsy or brain tumor resections
3. The use of single-pulse TMS to the occiput for the abortion of migraine headache with aura

The use of rTMS for major depressive disorder (MDD) is the focus of this chapter, after which we will briefly discuss its experimental use for other neuropsychiatric indications.

Table 2 Current and experimental indications for transcranial magnetic stimulation therapy

Diagnostic indications (FDA-approved as of 2017)
• Major depressive disorder (repetitive TMS)
• Migraine with aura abortive therapy (single-pulse TMS)
• Presurgical motor and speech mapping (single-pulse and repetitive TMS, respectively)
Experimental (CE marking in Europe, *not* FDA-approved in the United States as of 2017)
• Alzheimer's disease
• Autism
• Bipolar disorder
• Epilepsy
• Chronic pain
• Parkinson's disease
• Post-traumatic stress disorder
Primary clinical indications for depression rTMS protocol
• Failure of at least one antidepressant medication
• Intolerance to antidepressant medications

The use of repetitive transcranial magnetic stimulation for unipolar major depressive disorder has been an FDA-approved indication for rTMS since 2007. The first device to be approved for rTMS in depression was the Neuronetics device. Neuronetics sponsored the pivotal trial that demonstrated efficacy of the rTMS treatment (compared to sham treatment) in major depressive disorder. Since then, several other rTMS devices have been approved. Notably, although the FDA's medical device approval was for a specific indication, the device can be used for off-label purposes, as deemed appropriate by the physician. Thus, although a specific protocol was utilized in the pivotal Neuronetics trial, the FDA approval indicated use of high-frequency rTMS to the left prefrontal cortex (no specific parameters required).

In general, "high-frequency" TMS refers to any frequency >1 Hz, although most studied high-frequency protocols utilize 5 Hz or greater. The frequency used in the Neuronetics trial was 10 Hz (10 pulses/s). In addition to frequency, there are several other parameters of the TMS stimulus which can be adjusted to alter the treatment and its effects on the brain. These include changing the percentage of machine output (total stimulus charge), the length of each "train" of pulses, the duration of time between pulse trains (the "inter-train interval"), and the total number of trains and pulses delivered. Although some research suggests that longer courses of treatment with more total pulses may lead to additional benefit for patients with depression (Perera et al. 2016), the optimal parameters are still being studied.

3.5 Dosing of rTMS

The current method used to "dose" rTMS is based on the patient's "motor threshold." By delivering a single TMS pulse over the primary cortex, the stimulation intensity required to induce a muscle twitch in the hand can be determined. The exact "dose" of stimulation is variable and is determined by several factors. The "motor threshold" is defined as the minimum stimulus intensity at which a muscle twitch is elicited in the contralateral hand muscles in at least five of ten successive single-pulse stimulation trials. The treatment stimulation dose is then set based on a percentage above or below the motor threshold. For example, in the Neuronetics trial, treatments were delivered over the prefrontal cortex at a stimulus intensity 120% of the patient's individual motor threshold.

3.5.1 Treatment Parameters

For the Neuronetics trial, which led to the FDA approval of rTMS for depression, treatments were delivered at 120% of the motor threshold, over the left dorsolateral prefrontal cortex, which was defined as a target 5 cm anterior to the motor threshold target of the primary motor cortex. A frequency of 10 Hz was used, and pulses were clustered into 4 s trains (10 pulses/s $\times$ 4 s = 40 pulses/train), for a total of 3,000 pulses per session. There was a 26 s break in between each "train" of pulses. Sessions were performed daily, 5 days/week, for 4–6 weeks (Perera et al. 2016).

Significant changes in a standardized depression scale (Hamilton Depression Rating Scale – 24 items) were identified at the 4-week and 6-week time points for a subcategory of patients who had failed one antidepressant medication, leading to the initial FDA approval. As several additional subsequent confirmatory studies have emerged, the FDA approval has been expanded to allow for treatment of patients with major depressive disorder who have failed *at least one* antidepressant medication of adequate dose and duration in the current depressive episode. Although some physicians may adjust the parameters of the treatments, the vast majority of rTMS practitioners in MDD use the parameters employed in the Neuronetics trial.

3.6 Clinical Indications in MDD

When is it clinically appropriate/therapeutic to use rTMS for MDD? The answer may vary from practitioner to practitioner depending on several factors, including access to an rTMS device/provider, as well as access to other treatment options (e.g., ECT). Generally speaking, rTMS is often considered for patients who have failed several medication trials or who cannot tolerate side effects of medications. It is often considered prior to a trial of ECT for patients with treatment-resistant MDD. Many times patients who suffer from treatment-resistant depression (TRD) will come seeking rTMS due to fears of undergoing a course of ECT or having previously experienced intolerable side effects to ECT. Finally, rTMS is often considered in severely medically ill patients (if there are concerns over medical tolerability of ECT). For a summary of clinical and experimental indications for rTMS, please see Table 2.

3.7 ECT vs. rTMS

Although studies in the literature are mixed about whether rTMS is as efficacious as ECT, the general consensus among experts is that ECT is a more effective treatment for treatment-refractory depression as of the time of this writing and should still be considered as an option even if a patient fails a course of rTMS (Fitzgerald and Daskalakis 2013). If a patient is suffering from bipolar depression, bipolar mania, or any type of psychotic illness, ECT or pharmacotherapy would be the treatment of choice, as there is insufficient evidence to suggest that rTMS is an effective therapy in these populations.

3.8 rTMS in Other Clinical Populations

TMS is being explored as a therapy for specific populations of depressed patients, as well as for other neuropsychiatric indications. Ongoing research looking at subpopulations of depressed patients, such as the use of rTMS in child and adolescent depression, geriatric depression, depression secondary to traumatic brain injury,

bipolar depression, and postpartum depression, is ongoing and promising (Fitzgerald and Daskalakis 2013).

In terms of other neuropsychiatric indications, rTMS of various brain regions, using various treatment parameters, is being studied for obsessive compulsive disorder, Tourette's and tic disorders, post-traumatic stress disorder, cravings associated with substance use disorders, auditory hallucinations in schizophrenia, negative symptoms of schizophrenia, cognitive enhancement in Alzheimer's dementia, poststroke recovery, epilepsy, Parkinson's disease, autism, tinnitus, ADHD, chronic pain, headache, and other disorders (Wassermann and Lisanby 2001; Kobayashi and Pascual-Leone 2003).

3.9 Practical Considerations and Patient Selection

rTMS is considered a safe and well-tolerated procedure, which is a significant factor leading to its popularity as a novel therapy for depression. Unlike ECT, rTMS requires no general anesthesia or induction of a seizure. It can be performed on an outpatient basis, and patients have no restrictions on diet or activities before or after treatment. Nonetheless, there are some practical considerations the rTMS specialist must address when consulting on a patient considered for rTMS therapy.

3.9.1 Patient Evaluation

Usually a patient will be referred to an rTMS practitioner for a psychiatric diagnostic evaluation to consider rTMS treatment. This evaluation serves two primary purposes – to confirm the MDD diagnosis and to ensure the patient is appropriately medically stable. In addition to the confirmation of MDD, it is important to note any comorbid psychiatric illnesses, which can significantly contribute to likelihood of response. For example, comorbid anxiety has been identified as a poor predictor of rTMS response (Lisanby et al. 2009). In contrast, more recent work has suggested rTMS that targets the dorsolateral prefrontal cortex may address psychiatric symptoms that span several diagnostic categories, perhaps by addressing underlying transdiagnostic problems influenced by cognitive control networks in the brain (Taylor et al. 2014).

In terms of medical safety, a practitioner's main concern should be evaluating for risk of inducing a generalized seizure, the most dangerous risk of rTMS application. Hence, medical conditions/circumstances that increase the patient's risk for a seizure need to be determined. Along these lines, the practitioner should inquire about any history of head injuries, concussions, neurological surgery, epilepsy, or seizures. As rTMS induces a brief magnetic field in the area around the coil, the practitioner also needs to query about implanted devices near the coil, including devices such as deep brain stimulators, vagal nerve stimulators, or cochlear implants. Further, patients should be asked about other implanted devices within the body, specifically those which are ferromagnetic. Sometimes treatment parameters can be adjusted to accommodate such patients, but these adjustments are patient-specific and will not be discussed here.

As a practical matter, rTMS is a time- and resource-intensive process. Patients need to be able to come in for treatments 5 days/week for 4–6 weeks. This requires reliable transportation to and from the hospital and a flexible daily schedule that allows the patient access to treatment. This logistical matter is very important to discuss in advance with new patients considering rTMS therapy, so that commitment expectations are clear.

3.9.2 Pre-treatment Work-Up

There is little recommended or required in the way of blood tests, imaging, or diagnostic tests prior to pursuing rTMS therapy for a healthy individual. If a patient has a history of head trauma or has had a surgical procedure on the head or neck, obtaining previously performed imaging or ordering new imaging might be worthwhile. The goal of reviewing this imaging would be to ensure there is no ferromagnetic material in the scalp or head and to ensure that there is no evidence of visible neurologic damage that could place the patient at higher risk for a seizure. Other work-up should be obtained only as clinically indicated for special circumstances – for example, a urine drug screen in a patient with a history of substance abuse if there is concern for active use, as use of certain substances, may alter seizure threshold. Obtaining metabolic blood samples in a patient with chronic medical problems such as hypernatremia may also help to evaluate for seizure risk.

If a patient has a history of seizures, inquiring further about the nature of these seizures and ensuring a proper work-up has been conducted by a neurologist is important. If the seizure was provoked by fever, medications, or illicit drugs, and there is no concern for continued seizure risk, it may not result in an absolute contraindication for treatment; again, this is something that must be evaluated on a case-by-case basis, and discussion with the patient and other physicians involved in the patient's care is important for adequate determination of risks and benefits of rTMS therapy.

3.9.3 Medication Adjustments

Some practitioners may consider making medication adjustments based on the premise that certain medications may inhibit neuroplasticity (thus decreasing potential response to rTMS therapy), while others may lower seizure threshold (placing the patient at higher risk with treatment). The general practice is to continue psychiatric medication management with rTMS therapy augmentation. Although some medications (e.g., lamotrigine (Manganotti et al. 1999)) have clearly been shown to alter cortical excitability, and others (e.g., bupropion) are known to alter/lower seizure threshold, there are no clinical guidelines at this time to suggest that removing or adjusting doses of certain medications is necessary to achieve an rTMS response. Altering medication doses is often left to the best judgment of the rTMS practitioner in collaboration with the patient's primary psychiatrist. Indeed, ensuring a patient is not in active withdrawal (e.g., from benzodiazepines or antiepileptic mood stabilizers) during the administration of rTMS, therapy is important to minimize seizure risk. In general, avoidance of drastic medication changes prior to adding rTMS may be the safest course.

3.9.4 The Treatment Course

rTMS is usually administered by an rTMS-certified technician. This can be the physician with special rTMS training, but oftentimes it will be a nurse practitioner, physician's assistant, nurse, behavioral health expert, or a trained technician. It is usually recommended that the technician have basic life support training and rTMS training with a focus on how to be a first responder in the case of seizure or behavioral emergency (Perera et al. 2016).

The rTMS course usually lasts 4–6 weeks. Some research suggests that patients will continue to respond with longer courses even if they do not respond in the first 4–6 weeks (Perera et al. 2016); however, practically speaking, this is difficult unless the patient is motivated and has an insurance environment that will continue to reimburse for the continued provision of treatments (typically infrequent in the United States beyond 6 weeks). If a patient fails to respond to rTMS therapy, referral to ECT is commonly a consideration. Other patients will return to their primary provider to consider other pharmacotherapeutic options.

As with most therapy for major depression, a higher level of treatment resistance is a poor prognostic factor for rTMS response (Lisanby et al. 2009). However, several studies have now demonstrated that even in patients who have failed several medications, TMS can be a viable and effective alternative (Fitzgerald and Daskalakis 2013; Perera et al. 2016). Although some rTMS practitioners may try to augment or alter the treatment protocol to address issues of treatment resistance or nonresponse, the evidence for doing such is mixed (Blumberger et al. 2016).

Durability of rTMS is a subject of active research. There are no well-accepted practice guidelines for rTMS discontinuation/taper in MDD treatment. There is also no clear indication regarding whether or how to offer maintenance rTMS therapies after a successful rTMS course. Some data suggests rTMS may be more durable than ECT; however, a large proportion of patients will still relapse within 6–12 months of discontinuing a course (Perera et al. 2016). The current common practice is to taper the patient off rTMS (a common taper used in studies is the 3-2-1 taper – three times per week for a week, two times per week for a week, one time per week for a week, and then stop) and then discuss pharmacologic maintenance therapies. Although one study suggested that monthly rTMS maintenance could offer a mild benefit over no treatment at all (Philip et al. 2016), the current consensus is that a more aggressive frequency maintenance strategy would likely be required to keep a higher percentage of patients from relapsing. At this time, rTMS continuation or maintenance is not common practice.

3.10 Adverse Effects of rTMS

As mentioned previously, the most serious adverse effect associated with rTMS treatment is seizure induction. All seizures induced with rTMS therapy have been self-limited. There are no cases of patients developing epilepsy, or any type of seizure disorder, after a course of rTMS. The risk of seizure is minimal, estimated to be approximately 1 in 30,000 treatments (Perera et al. 2016). Usually with

appropriate precautions, this risk can be minimized and is negligible. There are several ways to evaluate and minimize seizure risk:

1. Ensure the patient is taking their medication reliably and regularly – A patient who misses a dose of an antiepileptic or benzodiazepine that was not appropriately tapered could be at higher risk for a seizure. Be aware of any medication changes that are made during the course of the treatment.
2. Evaluate for any medications or illicit drug use that may lower seizure threshold, either in the intoxicated state (stimulants) or in the withdrawal state (barbiturates, alcohol, benzodiazepines).
3. Ensure your patient is attempting to get an adequate amount of sleep and is maintaining good sleep hygiene, as sleep deprivation will lower seizure threshold.
4. Be sure to stay within the safety guidelines for rTMS stimulation parameters. Seizures are shown to occur more commonly with primary motor cortex stimulation and high-frequency stimulation protocols.

Other potential-related adverse effects are syncope, dizziness, scalp irritation, headaches, muscle twitching, and scalp burns (if the coil malfunctions and overheats).

There are strategies for minimizing or mitigating these side effects:

1. Slowly increase a patient's dose over the course of a single treatment or several treatments to the 120% motor threshold dose. Sometimes side effects can be minimized or eliminated by increasing the dose rather than subjecting patients to the full dose at the start of session one.
2. Keep the treatment coil in proper working order, and maintain a good relationship with the device manufacturer so any problems can be addressed expeditiously.
3. Be aware of warning signs of syncope or seizure and terminate or pause a session early if needed to ensure safety.
    (a) Warning signs for syncope – Dizziness, diaphoresis, lightheadedness, increased heart rate, tunneling vision.
    (b) Warning signs for seizure – Purposeless or stereotyped movements, unresponsiveness to commands or questions, contralateral motor movements during the prefrontal stimulation trains (especially if the movements continue beyond the end of the train; if motor movement is occurring during a prefrontal stimulation, strongly consider repositioning the coil or troubleshooting to ensure your target location is correct, as this could be a harbinger of impending seizure).
4. Recommend over-the-counter analgesic medications such as acetaminophen or ibuprofen to manage headaches or scalp irritation. Patients can be reassured that the irritation rarely lasts longer than a week of treatment – Studies replicate that scalp pain rapidly dissipates with repeated stimulation.

3.11 Future Directions

The use of transcranial magnetic stimulation in its various forms for clinical and experimental neuropsychiatric applications is a rapidly evolving and exciting field. Briefly we will discuss some of the areas of active and promising research:

3.11.1 Targeting Treatments

Considerable recent research has focused on finding better ways to target rTMS treatments to specific regions in the brain. Research groups are now looking at using personalized head measurements or neuroimaging to target treatments more precisely and reliably.

3.11.2 State-Dependent Treatment

The notion that brain state plays an important role in the efficacy of treatment is gaining ground. Research is ongoing in linking EEG readings with TMS stimulation to allow for parameter adjustments based on a patient's personal EEG output. Other ongoing work is combining rTMS with psychotherapy (Donse et al. 2018), mindfulness, and other activities that might place the brain into a "state" that is more receptive to beneficial neuroplasticity changes.

3.11.3 Maximizing Neuroplasticity

The concept of neuroplasticity, or the brain's ability to adapt and change its function and structure over time, is an exciting discovery. Researchers are trying to find ways to enhance neuroplasticity using novel rTMS protocols and other augmenting agents. This includes the use of specialized rTMS protocols, such as "priming" rTMS or "theta burst" rTMS, to more effectively and efficiently enhance the neuroplasticity of the brain.

3.11.4 Coil Variation

The electrical field induced by an rTMS pulse is dependent on the shape and physical properties of the magnetic coil being used. Coils are being developed that allow for varying levels of brain coverage and depth of penetration. In 2013 a "deep TMS" device was approved for use in major depressive disorder, which provides much deeper and broader brain stimulation, allowing modulation of deeper brain structures (Perera et al. 2016). This device has shown similar efficacy in achieving response and remission for major depressive disorder when compared to more superficially stimulating coils. Newer coils are being developed with the intent to target much smaller cortical areas or to simultaneously stimulate multiple cortical targets.

3.11.5 Parameter Space

As one can imagine, a dizzying amount of parameter changes can be made, such as altering frequency, number of pulses, number of treatment sessions per day, time between treatment sessions or pulse trains. Studies looking at "high-dose" rTMS protocols or unique treatment targets are underway for almost every neuropsychiatric known psychiatric condition.

3.12 Conclusion

Repetitive transcranial magnetic stimulation is an exciting new technology that affords physicians and researchers a new method for modulating and probing the human brain. It offers several practical advantages over the more cumbersome and invasive ECT treatment in the management of MDD, although currently rTMS does not rival ECT in antidepressant effectiveness, especially in highly refractory MDD. As more research is conducted, and we learn better ways to optimize this versatile treatment, it is likely that treatment success rates will improve, methods to sustain the effects will emerge, and new neuropsychiatric indications will arise.

4 Vagal Nerve Stimulation

4.1 Background

The concept that stimulation of the left cervical vagus could lead to an antidepressant response emerged from the epilepsy literature. Vagus nerve stimulation (VNS) has demonstrated efficacy in the treatment of certain forms of refractory epilepsy (Morris and Mueller 1999; Food and Drug Administration 2005); during these trials, it was anecdotally reported that epileptic patients suffering from comorbid depression experienced depressive symptom improvement. Subsequently, two studies (Elger et al. 2000; Harden et al. 2000) assessed for the reduction in depressive symptomology in refractory epileptic patients receiving VNS, and both studies found a trend toward depression reduction in those patients receiving VNS, *independent of reduction in seizure frequency.* This exciting finding prompted the study of VNS in treatment-refractory major depression (TRD) without concomitant epilepsy.

In 2005, in response to two large clinical trials that demonstrated antidepressant efficacy (Rush et al. 2000, 2005a, b), the US Food and Drug Administration (US-FDA) approved the use of adjunctive VNS for the treatment of major depressive disorder in patients not responding to four or more antidepressant courses. Despite this FDA approval, in 2007 the United States Committee on Medicare and Medicaid Services (CMS) elected not to reimburse VNS for TRD, contending that the treatment was experimental/unproven. Since that time, most private insurers have fallen in line with this decision, leading to very limited availability of VNS to TRD patients. Currently, there are ongoing efforts to further study/understand how VNS works in TRD with the eventual goal of making it available to individuals with severe, refractory depression.

4.2 Surgery and Stimulus Delivery

The primary means of VNS delivery in the United States and Europe is via the Neurocybernetic Prosthesis™ system (NCP; Cyberonics, Houston, TX; Fig. 3). The

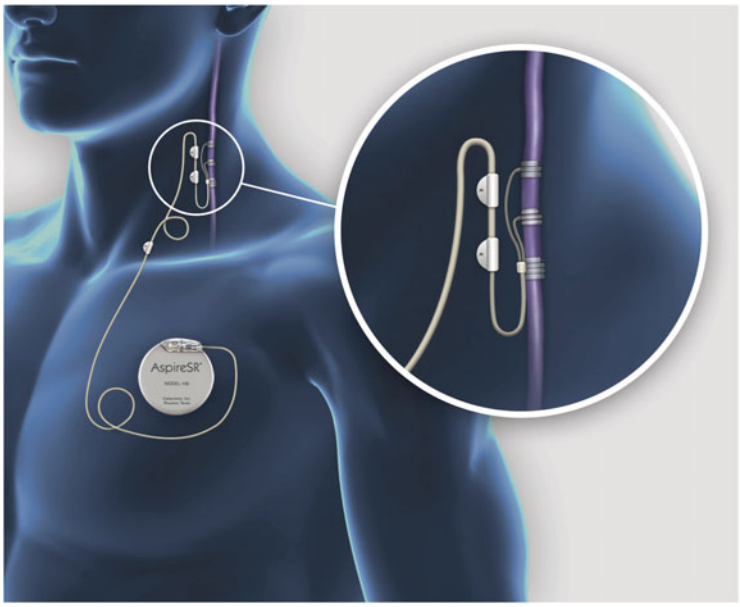

Fig. 3 The implanted VNS generator device (Neurocybernetic Prosthesis™ system (NCP; Cyberonics, Houston, TX). The VNS generator is subcutaneously implanted beneath the left clavicle, with the emerging lead subcutaneously tunneled in the skin over the clavicle. A second incision is made in the mid-neck region to expose the vagus nerve. The leads (see enlargement) are then attached at three points, a cathode, anode, and ground. Source: Reproduced with permission of LivaNova

VNS device is an implantable, multi-programmable, battery-operated current generator, which is typically implanted under the skin below the clavicle (typically the surgeon will access this area via the axilla). The lead from the device is then run under the skin into the neck region, where a second incision is made to expose the left cervical vagus. The bipolar lead is typically attached above the cardiac branch of the vagus.

Once turned on, the device delivers around-the-clock vagal stimulation. Table 3 describes the modifiable electrical stimulation parameters used in VNS and the standard ranges allowable for these parameters.

Animal studies, and experience in human studies, demonstrate that at current clinical levels of stimulus delivery (0.25–3.5 mA), the vast majority of the electrical stimulus is directed afferently (toward the brain). Hence, the thoracic (lung and heart) as well as the abdominal organs (gastrointestinal tract) supplied by the vagus are minimally affected by VNS. The more proximal/afferently located recurrent laryngeal nerve (supplies the larynx) does frequently receive afferent stimulus; hence, approximately two thirds of patients experience hoarseness/stridor during VNS stimulation for TRMD.

Table 3 Modifiable electrical parameters of VNS

Parameter	Standard range for VNS in TRMD	Device range	Comments
Current (milliamps, mA)	0.25–2.0	0.25 increments; 0.25–3.5 mA	Evidence suggests that maximizing electrical current may provide better sustained antidepressant benefit (Aaronson et al. 2013)
Pulse width (micrometers, μm)	130–300	140–500	Clinical experience suggests that elevated pulse width is associated with throat discomfort
Frequency (hertz, Hz)	20, 30	1–30	Clinical experience suggests higher frequency associated with greater throat discomfort
Duty cycle (time "on" [delivering stimulus] vs. time "off" [not delivering stimulus])	Typical starting cycle = 30 s on, 5 min off, or ~14% duty cycle	Not to exceed 50% "on" time	Longer duty or more rapid duty cycles may be more effective but use up battery life faster

4.3 Clinical Studies of TRMD

To date, there have been six clinical trials to test the antidepressant efficacy of VNS in TRMD summarized in Table 4 (Rush et al. 2000, 2005a; Marangell et al. 2002; Nahas et al. 2005; Schlaepfer et al. 2008a; Bajbouj et al. 2010; Aaronson et al. 2013, 2017). Only one of these (Rush et al. 2005b) had a double-blind, placebo arm (all subjects implanted, only 50% had devices turned on). The most recently published trial, described below, was an FDA-mandated, open-label registry of patients with TRMD (Aaronson et al. 2017) that spanned a 5-year period. With exception of the 2013 dose-finding study (Aaronson et al. 2013), all of the studies had similar initial dosing patterns.

The single double-blind, placebo-controlled study came close to but did not achieve statistical significance after 10 weeks of stimulation; however, importantly, it has since been determined that the majority of VNS patients require sustained VNS, typically in the range of 6–12 months, before achieving maximal antidepressant response.

Notably, all VNS TRMD studies to date demonstrate antidepressant efficacy with response rates ranging from 30 to 53% (see Table 4). A vexing problem of TRMD treatment is *maintaining* efficacy. Studies assessing existing treatments (including electroconvulsive therapy [ECT]) demonstrate that the typical 1-year response rate in TRMD is abysmal (~10% (Dunner et al. 2006)). In contrast, studies of VNS in TRMD demonstrate that the majority of patients achieving antidepressant response maintain this response at 1 (Marangell et al. 2002) and 2 years (Nahas et al. 2005); hence, there is emerging evidence that VNS has sustained efficacy in TRMD. In fact,

Table 4 Summary of clinical trials of VNS in adults with treatment-resistant depression

	Sample size	Age (mean)	% MDD	% Bipolar	Duration	TRD definition (# of failed DT)	Study design	Results
Rush et al. (2000)	60	46.8	70	30	12 weeks	2	Open, acute-phase, pilot, multisite	Different stimulation parameters (low, medium, high). Response rate of 40% by HRDS-28 and CGI, 50% by MADRS, 17% remission rate
Marangell et al. (2002)	30	46.8	70	30	12 months	2	Open, naturalistic, follow-up	Response rate sustained (40–46%) and remission rate significantly increased (17–29%) $p = 0.045$
Nahas et al. (2005)	59	46.8	73	27	24 months	2	Open, naturalistic, follow-up	Response rate 42% after 2 years; remission rate 22% after 2 years
Rush et al. (2005a)	222	46.5	90	10	10 weeks	2; ≤6	Double-blind, controlled, American multisite	No statistically significant difference in response rate active vs. sham VNS (15.2% vs. 10%) at 10 weeks
Rush et al. (2005b)	205	46.3	90	10	12 months	2; ≤6	Open-label follow-up after 12 weeks	Cumulative increase observed in MDD response rates (HRDS-24) over sustained stimulation, up to 30% response at 1 year
Schlaepfer et al. (2008a)	74	47.4	73	27	12 months	2; ≤6	Open-label, uncontrolled, European multisite	Response rate 53% after 1 year; remission rate 33% after 1 year
Bajbouj et al. (2010)	74	47.4	73	27	24 months	2; ≤6	Open, naturalistic, follow-up	Response rate 53% and remission rate 38.9% sustained at 2 years
Aaronson et al. (2013)	331	47.9	78	22	50 weeks	≥4	Double-blind, randomized dose-finding, multisite	Higher dosing predicted a greater *sustained* antidepressant effect at 1 year. Amount of charge delivered

								over time correlated with degree of AD response
Christmas et al. (2013)[a]	13	47.3	100	0	12 months	≥4	Open, uncontrolled	Response rate of 30.8% in chronic, unipolar severe TRD subgroup
Aaronson et al. (2017)	795	49.4	74	26	1–5 years	≥4	Prospective, open-label, non-randomized, naturalistic, multisite	335 patients with no prior VNS treatment; 159 patients from Aaronson et al. (2013). VNS group had higher 5-year cumulative response (67.6%) and higher first-time remission (43.3%) cumulative rates versus TAU (40.9% and 25.7%, respectively)

HRDS Hamilton rating scale for depression, *CGI* clinical global impression, *MADRS* Montgomery-Åsberg depression rating scale, *VNS* vagus nerve stimulation, *MDD* major depressive disorder, *DT* depression treatment, *TRD* treatment-resistant depression

[a]Refers to new subgroup not included elsewhere

a recent published case series described six TRMD patients with 15–33 years of preimplantation depression, who have maintained antidepressant remission post-VNS treatment for a mean of 9.2 years (Salloum et al. 2017).

As part of an FDA-mandated registry, Aaronson et al. (2017) followed a collection of 795 TRMD patients in the largest and longest study comparing VNS against treatment as usual (TAU). The TAU cohort was able to receive any treatment for the study duration ($n = 301$) and were compared to TAU plus adjunctive VNS (VNS + TAU, $n = 494$). After 5 years of follow-up, VNS + TAU had higher cumulative response rates (67.6% vs. 40.9%, $p < 0.001$) and remission rates (cumulative first-time remitters, 43.3% vs. 25.7%, $p < 0.001$). Further analyses demonstrated VNS + TAU had a more rapid response to treatment and had a slower relapse rate. Additionally, when comparing antidepressant response rates between patients who had not responded to ECT across both cohorts, VNS + TAU demonstrated greater antidepressant efficacy (59.6% vs. 34.1%, $p < 0.001$), demonstrating that failing a course of ECT does not necessarily predict failing VNS.

Aaronson et al. (2013) attempted to compare efficacy of VNS in TRMD using a "dosing study" of three different electrical parameters: a "low," "medium," and "high." The doses differed in pulse width and current; however, the groups held constant the duty cycles (30 s "on," 5 min "off") and pulse frequencies (20 Hz). This trial had an acute phase (first 22 weeks) and a long-term phase (subsequent 28 weeks). The acute phase had "fixed" (unchangeable) parameters; however, the long-term phase allowed for upward dose titration. During the acute phase of the trial, the higher current and pulse width groups ("medium" and "high") demonstrated numerically higher response rates (than the low-dose group) at 22 weeks, although these groups did not achieve statistical significance. However, at the end of the long-term phase, the "medium-" and "high"-dose cohorts were less likely to have a depressive relapse, suggesting that a higher VNS treatment initiation dose may help maintain antidepressant response.

4.4 Surgical Procedure

In general, the implantation procedure is done on an outpatient basis. The entire procedure (including VNS therapy generator implantation and attachment of the lead to left vagus nerve) takes about 1.5–2 h. The procedure is typically very well-tolerated and has low rates of complication (~1% infection rate).

4.5 Delivery of VNS in TRMD

Typically, due to postoperative swelling and pain, it is advisable to allow a period of 2 weeks of postoperative surgical recovery before initiation of stimulation. During each of the "titration visits," the electrical current is gradually increased (typically over two to three visits separated by 5–7 days).

In light of the research that supports that higher electrical current likely provides better sustained antidepressant effects (Aaronson et al. 2013), the current standard practice (subject to change with further research findings) is to attempt to push the treatment to the patient's "highest tolerable" current level. In general, our experience is that TRMD patients may not tolerate aggressive ramping up of the electrical current (less so than refractory epileptic VNS patients). Additionally, there is considerable between-patients tolerability of VNS: some patients develop discomfort at very low levels of current (e.g., 0.5 mA), while others tolerate very high currents (2.5 mA). In general, we recommend attempting to achieve an initial treatment current in the 1.5–2.0 mA range. Further, experience suggests that TRMD patients slowly acclimate to the upward titration of current, so the "start low, go slow" process is advisable to insure that patients achieve higher current. In general, this is best achieved over two to three visits during which the current increases are 0.25 mA/current increase, allowing the patient to experience several "firing cycles" at this dose before titrating further upward.

Additionally, experience has also demonstrated that certain stimulation parameters are more frequently associated with pain or discomfort. In particular, frequencies above 20 Hz and pulse widths greater than 250 μs are avoided during initial titrations, as we have found these to be more frequently associated with patient discomfort.

In summary, our experience, and that of many users of VNS in TRMD, is to start with low frequency (20 Hz), low pulse width (250 μs), and a "standard" duty cycle of 30 s "on" and 5 min "off." We typically use the first two to three office visits to titrate up to a tolerable dose with a period of observation of 15–20 min between upward output current titrations.

4.6 Programming the VNS Device

Similar to the method employed with programming a cardiac pacemaker, a handheld programming computer is attached to a "wand" that allows the programmer to check device integrity and modify electrical parameters (Fig. 4). The modifiable electrical parameters involved in VNS include output current (milliamps, mA), current frequency (Hertz, Hz), pulse width (microseconds, μs), and duty cycle (time "on" vs. time "off"). For titrating VNS in TRD, the clinician must first take into account patient comfort.

4.6.1 Example Titration

Based on our experience with VNS in TRMD, we present the following example titration:

Office Visit #1: Stimulation is initiated with the following parameters:

Frequency:	20 Hz
Pulse width:	250 μs
Duty cycle:	30 s "on" and 5 min "off"
Output current:	0.25 mA

Fig. 4 The VNS device programming wand. This instrument is held against the skin directly over the implanted VNS generator. The wand is attached to a handheld computer, similar to a smartphone, which allows for modification of electrical parameters changes and is used for assessments of circuit integrity (successful transmission of current to the vagus nerve), as well as programming the electrical parameters being delivered during VNS. Source: Reproduced with permission of LivaNova

Starting with an output current of 0.25 mA, have the patient sit in the waiting room for 20–25 min to allow the device to cycle three to four times to assess tolerability. If the patient tolerates these settings without pain/discomfort/side effects, increase the output current by another 0.25 mA (to 0.50 mA), followed by another 20–25 min observation. This is repeated a third time on the first office visit with a final first visit output current (assuming patient tolerability) of 0.75 mA. If at any time during the upward titration the patient experiences pain/discomfort/side effects, we decrease the output current by 0.25 mA to the previously tolerated level. We then have the patient return in 1 week and reattempt to increase the output current by at least 0.25 mA.

Office Visit #2:

Frequency:	20 Hz
Pulse width:	250 μs
Duty cycle:	30 s “on” and 5 min “off”
Output current:	0.75 mA

Similar to Visit #1, we increase the output current by 0.25–1.0 mA and observe the patient while the device cycles, three to four times; during this process, we ask the patient if they are experiencing any pain/discomfort/side effects. This is repeated one to two more times during this visit. Some clinicians will be more aggressive with their upward titration (increasing by current output increments >0.25 mA); however, we have observed that a more gradual titration allows for both greater final output currents and greater patient comfort.

Once you have achieved the patient's maximal tolerable current, we recommend holding this dose for a sustained period, typically 9–12 months.

4.6.2 When Should You Make Further Parameter Adjustments?

Evidence from clinical and neuroimaging studies (Rush et al. 2005b; Nahas et al. 2007; Conway et al. 2013) strongly suggest that response to VNS in TRD typically develops longer term. Response rates (i.e., a 50% drop in standard MDD measures) appear to increase most precipitously at 6–12 months. For this reason, we believe that once the maximally tolerated output current (during original titration) is achieved, it is wise to maintain these parameters for at least 12 months. If the patient is having partial or no response to treatment, our experience suggests that increasing the amount of charge delivered over time has the greatest influence on antidepressant outcome. This can be achieved by either increasing the amount of "on" time or decreasing the amount of "off" time between charge deliveries. The VNS therapy user guide, which accompanies the VNS programming system, details the allowable percentage on time/duty cycle. A duty cycle in excess of 50% "on" time equal to or greater than "off" time is not recommended. It should be noted that increasing the amount of charge delivered in a given time span will also more rapidly decrease battery life; therefore, this step should be reserved for situations in which standard parameter settings have not proven successful.

4.6.3 What Constitutes a VNS Antidepressant Response in TRMD?

Several key points about VNS response in TRD:

1. Though there are some TRD patients who respond quickly to VNS, clinical studies and brain imaging studies suggest that the majority of TRD patients take 6–12 months of VNS before exhibiting a response.
2. From experience, the antidepressant response tends to be very subtle at first, and then increases with time, typically over many weeks.
3. If a TRMD patient does not have a response after 8–10 months of stimulation at his or her "maximal tolerated dose," we recommend increasing the charge/time delivered using the method described above.
4. Unpublished data (as of this writing) suggests that many patients who fail to fall below the 50% drop in standard antidepressant rating scales (classic antidepressant response and remission) still report significant improvements in quality of life which is not directly captured on these scales. In general, with careful patient selection, our experience suggests that approximately two out of three patients

experience a clinically meaningful improvement in quality of life, such that they do not desire to have the device removed/turned off.

5 Other Evolving Neurostimulation Treatments

5.1 Deep Brain Stimulation (DBS) for Treatment-Resistant Major Depression

Deep brain stimulation involves the placement of a lead into specific, targeted brain regions. The use of DBS for TRMD emerged from the highly successful use of DBS in movement disorders. More recently, DBS has been successfully employed in obsessive compulsive disorder (OCD).

Currently, there are studies/reports showing the successful use of DBS on six different brain regions: the nucleus accumbens (NAcc), ventral capsule/ventral striatum (VC/VS), Brodmann area 25 or subgenual cingulate cortex (SCC), lateral habenula, inferior thalamic peduncle, and medial forebrain bundle.

Most of the DBS studies published to date do not employ placebo/sham groups; to date only four (Mayberg et al. 2005; Schlaepfer et al. 2008b; Holtzheimer et al. 2012) are controlled trials with sham stimulation periods.

Though research is proceeding in all the abovementioned regions, the three regions currently with the most active research include the NAcc, VC/VS, and SCC. Early open-label studies of the NAcc showed great promise, with early studies demonstrating antidepressant benefits early [6 months (Schlaepfer et al. 2008b)]. Larger sample studies from the same group over a longer period (Bewernick et al. 2010, 2012) demonstrated approximately 50% response rates.

Based on several studies demonstrating that targeting the VC/VS in OCD patients led to improvement in concomitant depressive symptoms (Greenberg et al. 2006, 2010; Goodman et al. 2010), researchers now study this region as a target for TRMD. The term VC/VS includes the NAcc and the ventral aspect of the anterior limb of the internal capsule (ALIC). In contrast to the NAcc DBS studies, the VC/VS trials used larger electrodes. Malone et al. (2009, 2010) reported on a series of 17 TRMD patients receiving VC/VS DBS from several sites. This group reported a 53% response rate at 12 months and a 71% response rate at the last follow-up (14–67 months, average stimulation duration 37.4 months). Of note, two patients receiving VC/VS DBS (one with bipolar disorder) reported symptoms of mania (Malone et al. 2009); whether this is a relevant consideration regarding future use of VC/VS DBS in bipolar disorder is yet to be determined. Dougherty et al. (2015) also conducted a study of VC/VS DBS in 30 TRD patients. Half of the TRD patients were randomized to active treatment for 16 weeks, and half to sham. There was no difference in response rate observed between active treatment and sham at study conclusion, though an open-label extension of the trial suggested some longer term response (20–27% response rate over 2 years extension). Finally, a recent multicenter, prospective trial of VC/VS DBS (sponsored by Medtronic) failed to show significant antidepressant improvement after 16 weeks of stimulation and was discontinued due to the design which predicted futility (Underwood 2013).

Researchers in this subtype of VC/VS DBS remain hopeful that modifications of technique and patient selection may enhance outcomes in larger multicenter trials.

Another well-studied, DBS-targeted region is Brodmann's area 25 or the SCC. Mayberg et al. (2005) reported that four of six patients responded to SCC stimulation at 6 months. Subsequently, larger studies with longer stimulation durations found similar significant response rates (Kennedy et al. 2011): mean response rates for years 1, 2, and 3 of 63%, 46%, and 75%, respectively (Kennedy et al. 2011). Similarly, another large sample ($N = 21$) open-label, longitudinal study demonstrated antidepressant efficacy, though it did not achieve statistical significance (29% response rate at 12 months; mean drop of 41% on depression scale, with 62% of patients having a greater than 40% improvement (Lozano et al. 2012)). In a single-blinded study of SCC DBS, Holtzheimer et al. (2012) reported a very high response rate in a population of TRMD patients (unipolar and bipolar). Remission and response rates increased with time: 18% remission and 41% response at 24 weeks ($n = 17$) up to 58% remission and 92% response at 2 years ($n = 12$). Notably, this study used higher current DBS (highest of the current SCC DBS studies), ranging from 6.0 to 10 mA. The bipolar TRMD patients responded with equal frequency as unipolar TRMD patients, and there were no reported cases of manic emergence. Despite these very impressive early studies, a large multicenter, prospective trial of SCC DBS for TRMD (the BROADEN study, sponsored by St. Jude Medical) had to be discontinued due to futility analysis at 6 months of stimulation (statistical probability of response determined to be less than 17.2%; letter from St. Jude Medical Clinical Study Management). Very active work on SCC DBS in TRMD remains, with researchers remaining hopeful that perhaps more precise localization of lead placement, as well as more precise patient selection, can lead to improved outcomes.

There are other regions targeted for DBS in TRMD, including the lateral habenula, inferior thalamic peduncle, and medial forebrain bundle, but the results of these are beyond the scope of this section. For a nice summary of DBS findings in TRMD, please see Morishita et al. (2014).

5.2 Magnetic Seizure Therapy (MST)

Magnetic seizure therapy involves the use of an electromagnetic transcranial magnetic stimulation device to purposefully induce a generalized seizure under anesthesia. This is utilized in a manner similar to electroconvulsive therapy (ECT), although is capable of inducing a seizure with a less intense and more focal electric field than ECT (Lee et al. 2016). This increased focality allows for MST to initiate a seizure with primarily superficial cortical stimulation of the brain. The premise for MST is based on the theory that by sparing deeper brain structures from passage of electrical current, as occurs with ECT, some of the negative sequelae, especially cognitive, of ECT can be avoided. Early studies seem to suggest that magnetic seizure therapy may have fewer cognitive side effects when compared to ECT, as demonstrated by a

faster post-procedure reorientation time and better acute cognitive performance following treatments (Lisanby et al. 2003; Cretaz et al. 2015).

Despite theoretical promise, thus far studies have not reliably demonstrated that MST can achieve the same antidepressant efficacy in major depressive disorder as ECT. MST response and remission rates in MDD have been highly variable, ranging anywhere from 38 to 69% and 15 to 46%, respectively. One systematic review of MST therapy suggested that these levels of therapeutic efficacy were still significantly lower than those achieved in most studies of right unilateral ECT at six times seizure threshold, the standard treatment delivered in many ECT practice settings (Cretaz et al. 2015). Despite this, MST is in its infancy as a tool for treating mood disorders and continues to be refined and improved in the hope of developing a new technology with similar efficacy to ECT and potentially fewer side effects (Radman and Lisanby 2017).

5.3 Transcranial Electrical Stimulation (tES)

Transcranial electrical stimulation is an umbrella term that encompasses various forms of noninvasive, subconvulsive electrical stimulation applied to the human head, with the intent of altering cortical excitability to achieve therapeutic goals. As compared to ECT, which also involves application of an electrical stimulus, tES therapies do not require anesthesia due to low-intensity stimulation that is attributable to few side effects and minimal discomfort. The current is administered via conducting pads applied to the scalp. Unlike rTMS therapy, which delivers a relatively focal stimulation in a repetitive fashion, tES therapies have a broader area of stimulation and constant current delivery. Additionally, unlike rTMS, tES stimulation intensity is usually not strong enough to induce depolarization of neurons. The type of current delivered defines the specific tES nomenclature; for example, under the tES umbrella, there exist transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial random noise stimulation (tRNS), among others.

Due to the relative affordability, simplicity, tolerability, safety, and durability of these devices, they have been studied for numerous neuropsychiatric applications, with varying degrees of success. Indeed, outside the realm of medicine, many of these devices are currently being marketed and sold as nonclinical agents for improving video game skills, cognitive ability, sleep, and energy, frequently resting on the basis of questionable and unreplicated data.

Within the realm of medicine, to date the modality with the biggest body of research underneath the tES umbrella is tDCS, with studies primarily looking at its uses for cognitive enhancement, depression, poststroke rehabilitation, and pain (Fregni et al. 2006; Zimerman et al. 2012; Marlow et al. 2013; Tremblay et al. 2014; de Aguiar et al. 2015). Mechanistic studies have supported evidence that tDCS has some effect on cortical excitability, as measured by induced changes in the amplitude of evoked potentials in the underlying cortical regions [usually motor cortex (Ammann et al. 2017)]. Additionally, some studies suggest that the effects of

tDCS may be neurotransmitter-mediated. For example, studies of neuropharmacologic agents that act on various neurotransmitter systems including NMDA, serotonin, and dopamine demonstrate the ability to enhance or suppress tDCS-mediated effects on cortical excitability (Liebetanz et al. 2002; Nitsche et al. 2004, 2009; Kuo et al. 2008).

In terms of tDCS's practical application, the general notion is that a battery generated electrical current and conducting pads of positive (anode) and negative (cathode) charge are applied to the scalp to incorporate brain tissue into the electrical circuit. Thus, the standard practice is to apply a pad delivering anodal stimulation at one scalp location and a second pad delivering cathodal stimulation at a second scalp location. Early evidence suggested that the anodal stimulation site would increase cortical excitability in the underlying neural elements, and cathodal stimulation would decrease cortical excitability (Nitsche et al. 2003). This phenomenon occurred via alterations in the membrane potentials of underlying neurons, thus increasing or decreasing the likelihood that they would fire an action potential.

The primary brain regions tDCS targets in the treatment of MDD are typically the left dorsolateral prefrontal cortex (anodal stimulation site) and the right dorsolateral prefrontal cortex (often cathodal stimulation site), based upon data demonstrating mood effects during rTMS stimulation of these regions and their presumptive involvement in mood regulation networks in the brain. The most common side effects of treatment include scalp tenderness, headache, fatigue, and, in rare instances, scalp burns. There have been no serious adverse events causally related to tDCS stimulation, with the biggest risk being the induction of mania in some bipolar patients (Antal et al. 2017).

Although tDCS is remarkably safe and well-tolerated, many researchers have questioned whether such a low-intensity stimulus could be inducing meaningful changes in the brain (Horvath et al. 2015). To date, the studies of its use in depression have been mixed and difficult to interpret. Although some early studies indicated a potential benefit for treating depressive symptoms when anodal tDCS was applied daily to the left DLPFC for several weeks at a time (Boggio et al. 2008; Loo et al. 2012; Brunoni et al. 2013), this has more recently been contradicted by a large, multisite, randomized controlled trial which showed no benefit (Loo et al. 2018). Ultimately, tDCS faces many of the same challenges identified to optimize rTMS treatments for MDD, that is, an almost-infinite parameter space in which to work, complicated by underpowered, poorly designed, or unblinded trials with conflicting results.

5.4 Trigeminal Nerve Stimulation (TNS)

Trigeminal nerve stimulation is a novel neuromodulation treatment that uses mild electrical signals to stimulate branches of the trigeminal nerve, also known as cranial nerve V (CN V). Similar to the vagus nerve, CN V is thought to have effects on mood regulation (DeGiorgio et al. 2011). However, unlike CN X, CN V is superficially located and has three branches traversing beneath the skin of the face, allowing

for transcutaneous stimulation and obviating the need for an implanted device (DeGiorgio et al. 2011). Additionally, unlike CN X, CN V contains no autonomic outflow fibers to pose any cardiac risks (DeGiorgio et al. 2011). After demonstrating some success in decreasing seizure frequency in adults with drug-resistant epilepsy, TNS was then applied to depression research (DeGiorgio et al. 2003, 2006, 2009).

In an 8-week, open-label, pilot trial, Cook et al. (2013) demonstrated that TNS resulted in significant improvements in depression and quality-of-life measures in 11 adults with treatment-resistant major depressive disorder. Another 8-week study of 12 adults with comorbid MDD and post-traumatic stress disorder (PTSD) demonstrated significant improvements in both depression and PTSD severity from TNS (Cook et al. 2016). Finally, a recent study of the antiepileptic effects of TNS in 50 epilepsy patients also found significant improvements in mood independent of antiepileptic response as a secondary outcome (DeGiorgio et al. 2013).

Currently, the only commercially available TNS device is NeuroSigma's Monarch™ external trigeminal nerve stimulation (eTNS™) delivery system in the European Union and Canada, where it has been approved for both depression and epilepsy (NeuroSigma 2012). The eTNS™ system is also approved in the European Union for attention-deficit/hyperactivity disorder (ADHD) after one promising pilot study (McGough et al. 2015). Notably, patients are able to use the physician-prescribed device in the comfort of their own homes. The device is approximately the size of a smartphone, with a wire connecting to a patch that adheres to the patient's forehead. A minimally invasive subcutaneous trigeminal nerve stimulation (sTNS™) system is also under development by the same company. Further research efforts are required for FDA approval of TNS modalities in the United States. Replication of aforementioned studies with double-blinded conditions, as well as investigation of the durability of antidepressant efficacy following an acute treatment course, is all needed at this time.

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Current Role of Herbal and Natural Preparations

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Abstract

Depression remains difficult to manage, despite the many registered treatments available. For many depressed individuals, particularly those who have not responded to and/or had adverse effects from standard therapies, herbal and natural medications represent a potentially valuable alternative. This chapter will review several natural remedies used in the treatment of depression. Specific remedies covered include St. John's wort (SJW), S-adenosyl-L-methionine (SAMe), omega-3 fatty acids, rhodiola, and others. We will begin by providing some historical and social context about these remedies. Then we will review efficacy and safety data, as well as biological mechanisms of action of these therapies. Finally, we will discuss the limitations of the current state of knowledge and provide suggestions for a productive research agenda focused on natural remedies. While many questions about these treatments remain unanswered and much work needs to be done before we determine their place in the psychiatric armamentarium, we believe that this chapter will give psychiatrists a good perspective on the pros and cons of herbal and natural antidepressants as part of the pharmacological armamentarium and sensible guidelines on how and when they should be used.

Keywords

5-Hydroxy tryptophan · 5-MTHF · Acetyl-L-carnitine · Alpha lipoic acid · Complementary and alternative medicine · Deplin · Folate · Hypericum · Inositol · N-acetyl cysteine · Natural remedies · Nutraceuticals · Omega-3 · Rhodiola · S-adenosyl methionine · SAMe · St. John's wort

1 General Introduction: Prevalence of Depressive Disorders and Limitations of Current Therapies

Major depressive disorder (MDD) is common and disabling, with a lifetime prevalence of 16.2% (Kessler et al. 2003). From 2000 to 2010, the annual cost of depression in the USA increased by 21.5%, to a total of $210.5 billion (Greenberg et al. 2015), exceeding that of many other diseases. Despite the many antidepressants available, their use is limited by delays in clinical improvement, relatively low rates of response and remission, significant residual symptoms, and high relapse and recurrence rates (Kennedy 2013; Safer 2017). Medication-related side effects may also represent a substantial obstacle to successful pharmacological treatment of depression (Cassano and Fava 2004).

For the significant proportion of patients who are non-responsive and/or intolerant to standard antidepressants, alternative and natural therapies may be compelling. A 2007 National Health Interview Survey reported that in the past year, 38% of adults and 12% of children had used CAM therapies, to an out-of-pocket cost of about $33.9 billion (National Institutes of Health 2010). Many individuals, particularly those with psychiatric disorders, choose to reject US Food and Drug

Administration (FDA)-sanctioned medications in favor of natural products, given the above-mentioned limitations of registered medications or because of personal preferences (Mischoulon 2004; Kessler et al. 2001).

Given the limitations of established therapies, and the growing interest in CAM, there is a need for further research to identify and characterize novel therapies that work via different mechanisms of action, in the hopes of finding an agent that may work faster, better, and with fewer side effects than the current armamentarium of biological therapies. Complementary and natural remedies may represent a potential family of treatments to fill this gap.

2 Natural Products: Introduction

2.1 Common Source of Refined Medications and Challenges with Formulations of Natural Products

Natural and herbal remedies have been used for medical and psychiatric indications for millennia. These products are found in nature and are harvested, processed, and purified to differing degrees depending on the particular standards of each manufacturer and what the local/national regulations may require and allow (Mischoulon 2004). Herbal remedies such as St. John's wort (SJW) may contain hundreds of potentially active chemicals, of which some may be the key psychotropic components (Nierenberg et al. 2008). Other natural remedies, such as SAMe or omega-3 fatty acids, are limited to one or a few chemical components and may therefore be easier to obtain and standardize (Mischoulon 2009). Omega-3 fatty acids, for example, can be readily obtained from fish oil or algae and contain fewer variants.

Consideration of the quality and preparation of different natural remedies is important. For example, SAMe was historically subject to degradation on the shelf, until more stable forms such as tosylated SAMe were developed (Mischoulon et al. 2012a). Without head-to-head comparisons between different preparations, it is difficult to make recommendations about which brand of a particular natural product a patient should or should not use, and the wide variety of options can make product selection complicated and confusing for both doctor and patient.

2.2 Importance of Healing Traditions vs Allopathic Medicine

Natural therapies have historically been widely used throughout Europe and Asia but are relative newcomers to the USA, gaining increased prominence and visibility since the 1990s (Mischoulon and Rosenbaum 1999). Asia in particular has a long tradition of healing and prevention of illness through natural remedies as well as other disciplines such as acupuncture and Traditional Chinese Medicine (TCM) (Kleinman 1975). In South America there is also a tradition of alternative healing, as in the form of curanderos and other types of healers (Risser and Mazur 1995). In

Europe, natural remedies are more strongly integrated into general medical practice, and many licensed physicians use natural products routinely (Fürst and Zündorf 2015).

In the USA, however, there has been more resistance to the adoption of natural remedies, partly due to skepticism on the part of practitioners (Asher et al. 2017), who are trained in the Western model of medicine that historically has emphasized acute treatment rather than prevention of illness and has not included complementary medicine as part of medical school and residency program curricula, though this has been changing with the growing prominence of complementary and alternative medicine. Allopathic medicine also places a great deal of weight on the "gold standard" of randomized controlled clinical trials as the test for whether a treatment is adequate. This "high bar" is especially problematic when dealing with alternative therapies, since many may be harder to blind (e.g., acupuncture and massage) or to deliver in a consistent, generalizable manner (Yeung et al. 2007). For example, therapies such as acupuncture and homeopathy are typically administered in highly individualized regimens for each patient based on the diagnostic tenets of the discipline. In cases where two patients may have the same "Western diagnosis," the TCM diagnosis may differ between both patients, and this could impact the clinician's choice of treatment (Mischoulon et al. 2012b). This makes the development of rigorous double-blind controlled trials difficult and leads to continued reluctance on the part of US physicians to recommend these therapies.

Despite this skepticism, natural remedies are becoming an ever-growing component of health care, and psychiatric conditions are among the most common reasons for which people seek out alternative therapies. Reasons for their popularity include reported effectiveness, easy access without a physician's prescription, and generally superior tolerability compared to standard medications (Mischoulon 2009).

Several caveats need to be considered, however. Natural remedies are not as tightly regulated as drugs registered with the FDA (Mischoulon 2004). The law permits manufacturers to word claims about natural remedies in such a way that does not suggest their product can prevent or cure an illness. For example, antidepressants such as St. John's wort may be marketed as "mood enhancers" or "well-being boosters," claims which do not require FDA oversight or approval. Likewise, unregulated or under-regulated treatments may present certain risks that are not well characterized, since there is no need to obtain approval from the FDA with regard to safety. Economic considerations are also important. Medical insurance plans, whether state-supported or private, generally do not cover herbal and natural remedies, because they have not been approved by the FDA. Consequently, patients who want to use these therapies have to pay out of pocket for them, and many can be quite costly, at times prohibitively expensive with patients of limited means. The costs, risks, and benefits of natural remedies therefore need to be carefully considered by both the practitioner and the patient (Mischoulon 2004).

2.3 The Importance of Research

Given the growing popularity of natural remedies, along with the aforementioned limitations of current registered antidepressant therapies, research on clinical efficacy, safety, mechanisms of action, and cost-effectiveness of natural therapies represents an important scientific endeavor. A better understanding of these remedies could guide physicians about when and when not to recommend them and may help insurance carriers decide whether to cover their costs, as a potential means of reducing more expensive health care utilization, such as inpatient hospitalizations (Ostermann et al. 2017). As it stands, there are relatively few rigorous large-scale RCTs of natural remedies. Most manufacturers of natural remedies do not have the requisite funds to sponsor large studies, which limits their contributions to donating their products for government funded research or at times sponsoring small pilot trials (Mischoulon 2004).

One particularly important reason for continued research is the emergence of serious adverse effects, albeit rare, that have been reported. Notable examples include liver failure associated with the herbal anxiolytic kava (Sarris and Kavanagh 2009), transplant rejection and failure of anti-HIV agents from interactions with SJW (Baede-van Dijk et al. 2000; Markowitz et al. 2003), and sudden death secondary to use of ephedra (Wallace 2003). Continued research on natural remedies is therefore critical from a public health standpoint. An improved understanding of the efficacy and safety of natural products represents an impactful endeavor that could have significant benefits for society.

3 Natural Products Commonly Used for Depression

3.1 St. John's Wort (SJW)

3.1.1 Overview and Efficacy

St. John's wort (SJW; *Hypericum perforatum* L.) is an herbal remedy for depression, studied in over 40 clinical trials (Apaydin et al. 2016), including comparisons against tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) (Apaydin et al. 2016; Linde et al. 2008). The data support SJW as more effective than placebo and being comparable to low-dose TCAs and to standard doses of SSRIs. Tolerability and adherence appear better than for registered antidepressants (Apaydin et al. 2016). However, the published studies are limited by recruitment of patients with milder depression, underreported adverse effects, and often shorter than optimal treatment periods.

3.1.2 Mechanisms

The key psychotropic ingredients of SJW appear to be hypericin, pseudohypericin, and hyperforin (Brockmöller et al. 1997; Seifritz et al. 2016). These chemicals are believed to interact with the hypothalamic-pituitary-adrenal axis to reduce cytokine production, suggesting an anti-inflammatory mechanism of action for SJW.

Likewise, SJW's antidepressant effect may only be partly due to serotonergic activity. SJW also has some mild monoamine oxidase inhibitor (MAOI) activity (Gnerre et al. 2001), but it is thought too modest to contribute to SJW's antidepressant effect.

3.1.3 Dosing

Recommended doses of SJW range from 300 to 1,800 mg/day, usually divided in a twice or three times daily dosing regimen. Different preparations may vary with regard to the amount of active ingredients present, and different brands may therefore differ in efficacy. Commercial preparations are typically standardized based on their hypericin or hyperforin levels (Mischoulon 2009).

3.1.4 Adverse Effects

SJW is generally safe and well tolerated. The most common side effects include dry mouth, dizziness, and constipation (Rodríguez-Landa and Contreras 2003). Increased sensitivity to sunlight (phototoxicity) may occur, which can be prevented by using protection such as sunscreen and hats on occasions where significant exposure to the sun is expected (Clauson et al. 2008). In view of SJW's MAOI activity, there is a concern about serotonin syndrome (hypertension, hyperthermia, flushing, hyperreflexia, dizziness, disorientation, and myoclonus) when combined with other serotonergic drugs (Baede-van Dijk et al. 2000). Combinations with SSRIs are strongly discouraged, though it may be a common practice. Given how frequently SSRIs are prescribed, the risk of this interaction is unknown.

SJW induces the enzyme cytochrome P450 (CYP-450)-3A4, which can reduce clinical effects of warfarin, cyclosporin, oral contraceptives, theophylline, fenprocoumon, digoxin, indinavir, zolpidem, irinotecan, olanzapine, and probably others (Rodríguez-Landa and Contreras 2003). Severe adverse reactions, such as transplant rejection, reduced efficacy of anticancer drugs, and development of resistant HIV strains, have been documented. Cycling to mania may occur in bipolar disorder patients who take SJW when depressed (Nierenberg et al. 2008), so in cases of bipolar depression, SJW should be taken with a mood stabilizer and preferably under clinician supervision. Preliminary evidence suggests that SJW is safe in pregnancy, but in the absence of more conclusive data, pregnant women should probably avoid SJW in favor of antidepressants with more established safety records (Gregoretti et al. 2004).

3.1.5 Conclusion

SJW appears to be a promising natural antidepressant. There are ample small trials and a few larger-scale trials with generally supportive, though mixed evidence. The logical next step would be the continued development of larger-scale trials and more comparisons with standard antidepressants.

3.2 S-Adenosyl-L-Methionine (SAMe)

3.2.1 Overview and Efficacy

S-adenosyl-L-methionine (SAMe) has been used extensively in Europe for decades but arrived in the USA only in the late 1990s (Hardy et al. 2003; Sharma et al. 2017). SAMe is produced by all living beings and functions as a methyl donor in many important physiologic reactions, most notably neurotransmitter synthesis. There are about 50 published clinical trials of SAMe, with administration via oral, intramuscular, and intravenous routes (Galizia et al. 2016; Hardy et al. 2003; Sharma et al. 2017).

SAMe has been successfully combined with TCAs, SSRIs, and SNRIs. Alpert et al. (2004) examined SAMe augmentation in 30 SSRI nonresponders who received open-label therapy with SAMe 800–1,600 mg/day with good results. Papakostas et al. (2010) carried out a double-blind placebo-controlled study of SAMe augmentation in SSRI and SNRI nonresponders. After 6 weeks of treatment with SAMe 800 mg twice daily or placebo, SAMe resulted in significantly greater improvement and response and remission rates than placebo.

A meta-analysis by Hardy et al. (2003) supported SAMe as more effective than placebo and equivalent to tricyclic antidepressants. A more recent meta-analysis of various adjunctive therapies, including SAMe, also supported the use of SAMe in depression (Turner et al. 2014). A recent systematic review (Sharma et al. 2017) also supports SAMe's efficacy but noted that few SAMe studies have emerged in the past 15 years since the Hardy et al.'s meta-analysis. Only one placebo-controlled RCT to date has compared SAMe against an SSRI (escitalopram 20 mg daily) (Mischoulon et al. 2014). This 12-week three-armed study with 189 subjects with MDD used the highest dose of SAMe in a clinical trial (up to 3,200 mg/day). The high placebo response rate resulted in equivalence between the three treatment arms, despite significant improvement for the active treatment arms. Ancillary analyses suggest a gender-related effect favoring men (Sarris et al. 2015), and other investigations suggest that SAMe may help reduce sexual dysfunction in men (Dording et al. 2012).

3.2.2 Mechanisms

SAMe is an intermediate in the one-carbon metabolic cycle, which also involves folic acid and vitamin B12 (Alpert et al. 2008). SAMe formation depends on the enzyme methylene tetrahydrofolate reductase (MTHFR). Genetic polymorphisms can render MTHFR thermolabile, making it less functional and thus unbalancing the one-carbon cycle (Mischoulon et al. 2012c), which may contribute to depression via reduced synthesis of neurotransmitters. SAMe supplements could therefore bypass the MTHFR polymorphism and stimulate neurotransmitter synthesis of serotonin, dopamine, and norepinephrine.

3.2.3 Dosing

The literature on SAMe reports doses ranging from 200 to 3,200 mg/day (Sharma et al. 2017), typically on a twice daily basis. In clinical practice, we have observed

that some patients may require even higher doses to obtain an optimal antidepressant effect.

3.2.4 Adverse Effects

SAMe is well tolerated and safe. Preparations that come in blister packs are preferred, since those have longer shelf lives (Appleton et al. 2016). Gastrointestinal upset appears to be the most common side effect reported (Mischoulon et al. 2014; Papakostas et al. 2010). Other side effects include insomnia, anorexia, dry mouth, sweating, dizziness, and anxiety. Mania and hypomania have been reported in patients with bipolar depression who take SAMe (Mischoulon and Fava 2002; Papakostas 2009). SAMe has few if any interactions with other drugs and is often combined with standard antidepressants and other medications. Pregnancy may result in decreased SAMe and methylation activity. A meta-analysis examining studies of pregnant women with intrahepatic cholestasis found benefit and safety for SAMe (Zhang et al. 2016). Pregnant women with depression may therefore benefit from supplementation, but caution is advised in the absence of more systematic investigations.

3.2.5 Conclusion

SAMe is a promising natural antidepressant. One particular concern that needs to be kept in mind is SAMe is expensive, costing from $0.75 to 1.25 for a 400 mg tablet. Cost-benefit issues therefore need to be considered carefully and discussed between the doctor and patient.

3.3 Omega-3 Fatty Acids

3.3.1 Overview and Efficacy

The omega-3s are long-chain polyunsaturated fatty acids (PUFA) found primarily in fish oil and other marine sources (Appleton et al. 2016). Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are considered to be the primary psychotropic fatty acids in this family (Appleton et al. 2016).

More than 30 clinical trials have tested omega-3 preparations in depressed populations, as adjunctive therapy in subjects with inadequate response to standard antidepressants and also as monotherapy (Appleton et al. 2016; Grosso et al. 2014a; Sublette et al. 2011). Most studies use either EPA or a combination of EPA plus DHA. Doses vary widely, as do the compositions of the preparations. A recent meta-analysis by Sublette et al. (2011) reported that the most effective preparations appear to be those with at least 60% EPA relative to DHA. The various meta-analyses of omega-3s in depressive disorders have shown generally positive but mixed results, which is not surprising, in view of the wide heterogeneity of omega-3 ratios, doses, and study designs (Appleton et al. 2016; Bloch and Hannestad 2012; Grosso et al. 2014b; Lin and Su 2007; Mocking et al. 2016; Sarris et al. 2012; Sublette et al. 2011).

DHA therapy for depression is less well studied (Lewis et al. 2011; Marangell et al. 2003; Mischoulon et al. 2008, 2015). Mischoulon and colleagues found benefit in a double-blind dose-finding study of DHA monotherapy, with a reversed dose-response curve favoring 1 g/day over 2 g/day and 4 g/day. This study was limited by a lack of a placebo arm. Marangell et al. (2003) found no benefit for DHA at 2 g/day, which appears consistent with Mischoulon et al.'s study that found less benefit at 2 g/day or higher (Mischoulon et al. 2008). A more recent double-blind controlled comparison of EPA versus DHA found less benefit for DHA, while EPA appeared more effective in overweight subjects with elevated levels of inflammation (Mischoulon et al. 2015; Rapaport et al. 2016).

Omega-3s have been studied in different forms of depression. Some preliminary evidence suggests benefit in postpartum depression (Freeman et al. 2006; Marangell et al. 2004). In bipolar disorder (Keck et al. 2006; Stoll et al. 1999), the depressive phase of the illness may be more responsive than the manic phase (Sarris et al. 2012). Children and adolescents with depression may also benefit (Trebatická et al. 2017). A large study examining preventive effects of omega-3 and vitamin D for depression in older individuals is underway (Okereke et al. 2018).

3.3.2 Mechanisms

The omega-3s are thought to function in various ways including G-protein signaling inhibition, neuronal membrane stabilization, anti-inflammatory effects, modulation of calcium transport, and possibly others (Stoll 2008; Grosso et al. 2014a). Similarities with lithium's mechanism of action have been proposed (Stoll 2008).

3.3.3 Dosing

Published doses for depression range from as little as <1 g/day to as much as 10 g/day, but most reported doses typically are between 1 and 2 g/day. In unipolar depression, 1–2 g/day of EPA/DHA combination, with $\geq 60\%$ EPA may be a good starting point (Sublette et al. 2011). Studies for bipolar disorder have used between 6 and 10 g/day (Sarris et al. 2012), but caution should be taken with higher doses (see below).

3.3.4 Adverse Effects

Omega-3s are generally well tolerated. Common side effects include stomach upset and fishy taste, which are less frequent now than previously thanks to improved manufacturing standards that reduce impurities. Previous concerns about increased risk of bleeding have been disproven to some degree (Begtrup et al. 2017), though caution is still advised (Gross et al. 2017). Despite their apparent efficacy in the treatment of bipolar illness, cycling has been reported (Stoll 2008), so caution is recommended with this population. Omega-3s are important to the development of the infant brain and pregnancy depletes omega-3 in the mother (Ostadrahimi et al. 2017). Therefore omega-3 supplementation should benefit expectant mothers and their children. Along these lines, fish consumption in pregnancy is supported (U.S. Food and Drug Administration n.d.). However, because we do not have

long-term data on safety or the safest upper limits of omega-3 in pregnancy, caution is advised with pregnant women.

3.3.5 Conclusion

Omega-3 fatty acids are among the more promising natural treatments for depression. Larger-scale studies, dose-finding studies, and mechanistic studies are called for.

3.4 *Rhodiola rosea*

3.4.1 Overview and Efficacy

Rhodiola rosea grows in the mountains of Europe and Asia (Iovieno et al. 2011) and has been used for centuries as an herbal remedy in Asia, Scandinavia, and Eastern Europe. Rhodiola has been studied mostly in Russia and Scandinavia for more than 40 years, though relatively few of these studies have been translated into English. At least four controlled trials support antidepressant effects, anxiolytic effects, and cognitive benefits (Iovieno et al. 2011; Hung et al. 2011), but others have not been so encouraging regarding depression, anxiety, stress, and cognition, though tolerability for rhodiola was good and in one study superior to sertraline's (Cropley et al. 2015).

3.4.2 Mechanisms

Rhodiola's mechanism of action is not well understood. It is proposed to work as an "adaptogen," increasing the body's resistance to external and internal stress and stimulating nervous system activity to improve physical and mental performance. Symptoms that seem particularly good targets for rhodiola include fatigue, stress, depression, and sexual dysfunction (Iovieno et al. 2011).

Rhodiola's "adaptogenic" chemicals include rosavins, salidroside, and p-tyrosol (Ming et al. 2005), as well as antioxidant flavonoids and organic acids. Rhodiola also may modulate monoamines and catecholamines by inhibiting the enzymes MAO-A and MAO-B (Kelly 2001; van Diermen et al. 2009). It may stimulate opioid synthesis and activate central and peripheral opioid receptors (Lishmanov et al. 1997). Finally, rhodiola may reduce secretion of corticotropin-releasing factor (CRF) (Lishmanov et al. 1987; Maslova et al. 1994).

3.4.3 Dosing

Recommended doses range from 100 to 680 mg/day. Rhodiola formulations are usually standardized to a minimum 3% rosavins and 0.8% salidroside (Iovieno et al. 2011).

3.4.4 Adverse Effects

Rhodiola has few side effects, and most are mild and dose-related. These include allergy, irritability, insomnia (including vivid dreams) if taken at night, fatigue, and unpleasant sensations (Iovieno et al. 2011). Rhodiola has few known interactions

and has been combined with TCAs with resultant dampening of TCA side effects (Iovieno et al. 2011). However, mild serotonin syndrome was reported with the combination of rhodiola and paroxetine (Maniscalco et al. 2015). One mouse study supports safety in pregnancy and lactation (Lewicki et al. 2017), but there are no equivalent human studies. While there are no reports of bipolar cycling, rhodiola should probably be used with caution in this population.

3.4.5 Conclusion

Overall, rhodiola appears promising for treating mood disorders. Its clearest indication may be asthenic or lethargic conditions associated with physical or mental strain (Iovieno et al. 2011). Whether rhodiola should be combined with standard antidepressants remains unclear. Combining rhodiola with TCAs, SSRIs, or SNRIs might theoretically diminish their common side effects such as poor memory, sexual dysfunction, and weight gain, but the possibility of serotonin syndrome (Maniscalco et al. 2015) requires caution with such combinations. More controlled studies are warranted.

3.5 Folic Acid

3.5.1 Overview and Efficacy

Folic acid deficiency has been long associated with depression. A few studies of folate supplementation for depression have supported efficacy (Almeida et al. 2015), though the findings are limited by small sample sizes and heterogeneity of folate preparations. L-methylfolate (5-methyltetrahydrofolate; 5-MTHF; Deplin) is approved by the FDA as a medical food to supplement or prevent of vitamin deficiency but has also shown promise as an antidepressant. In a multicenter, randomized, double-blind study (Papakostas et al. 2012), adults 18–65 years of age with MDD and limited response to SSRIs were randomized to augmentation with L-methylfolate 15 mg/day or placebo. The resulting mean change in depression measures from baseline was significantly greater for L-methylfolate than for placebo.

Other L-methylfolate preparations include Cerefolin, which contains 5.6 mg L-methylfolate (Metafolin), 1 mg of vitamin B12 (cyanocobalamin), 50 mg of vitamin B2 (riboflavin), and 5 mg of vitamin B6 (pyridoxine). Its variant, Cerefolin NAC, includes methylcobalamin 2 mg and N-acetylcysteine (NAC) 600 mg (NAC is discussed later in this chapter). Like Deplin, Cerefolin and Cerefolin NAC are approved for the treatment or prevention of vitamin deficiencies and are available by prescription. They are often used off-label for psychiatric indications, including depression, and there is growing evidence of efficacy at slowing down the progression of dementia (Shankle et al. 2016; Hara et al. 2016; Spence et al. 2017). The role of these folate preparations in psychiatric conditions merits further investigation.

3.5.2 Mechanisms

Folic acid is critical in the synthesis of various neurotransmitters and is a key participant in the one-carbon methylation cycle (Alpert et al. 2008). Like SAMe, it is affected by MTHFR polymorphisms that can reduce folate's conversion to 5-MTHF, which is its most active form. Supplementation with Deplin can therefore bypass this polymorphism and also crosses the blood-brain barrier directly to provide needed benefit to the brain.

3.5.3 Dosing

Recommended doses of Deplin are between 7.5 and 15 mg daily (Papakostas et al. 2012). Reported doses of other folate preparations have ranged from 50 to 500 μg/day of folic acid (Mischoulon and Raab 2007) and 15 to 30 mg/day of leucovorin (Alpert et al. 2008).

3.5.4 Adverse Effects

Deplin is very safe and well tolerated with minimal complaints about side effects (Papakostas et al. 2012). Other folate preparations are also considered very safe and well tolerated (Alpert et al. 2008). Concerns have been raised, however, about potential risks associated with folate supplementation, including masking of B12-deficiency anemia, and promotion of cancer (Frankenburg 2009). While the masking of B12 deficiency anemia with folate supplementation is an established risk, newer folate forms such as L-methylfolate (Deplin) are less likely to mask a B12 deficiency anemia and are recommended as the preferred folate form in cases where B12 deficiency may be suspected or under management (Mischoulon et al. 2009). Regarding tumor promotion, evidence for such a role for folate has been mixed (Mischoulon et al. 2009). In the USA, Canada, and Chile, colorectal cancer rates have increased since the introduction of folate fortification (Hirsch et al. 2009), but other investigations have suggested potential benefits and risk reduction (Mischoulon et al. 2009). An extended follow-up of a sample of 6,837 Norwegian ischemic heart disease patients found that supplementation with folic acid plus B12 was associated with increased risk of cancer and cancer deaths, but these results were driven mostly by lung cancer (Ebbing et al. 2009). A recent case-control study suggested an increased risk of prostate cancer associated with higher plasma levels of folate and B12 (Collin et al. 2010). Breast cancer in postmenopausal women has also been linked to high folate intake (Stolzenberg-Solomon et al. 2006). On the other hand, in a recent meta-analysis including almost 50,000 individuals, folic acid supplementation for 5 years resulted in no significant impact on incidence of various cancers (Vollset et al. 2013), and it is worth remembering that folinic acid (leucovorin) is a folate form that has long been used for folate rescue during cancer chemotherapy (Cohen 2017). At this time it is difficult to draw clear conclusions from the literature. We therefore suggest that physicians who are treating patients with a high risk or history of cancer should carefully weigh the risks and benefits of folate supplementation in these individuals.

3.5.5 Conclusion

Folic acid preparations, particularly Deplin, appear as promising augmentative therapies for resistant depression. Large controlled studies are needed in order to provide clearer recommendations about preparation types and dosing.

3.6 5-Hydroxy Tryptophan (5-HTP)

3.6.1 Overview and Efficacy

The amino acid 5-hydroxytryptophan (5-HTP), a serotonin precursor, is obtained commercially as an extract from the African plant *Griffonia simplicifolia* (Iovieno et al. 2011). Most clinical trials of 5-HTP – about 27 in all, including 4 that used active comparators – were conducted in the 1970s and 1980s, based on the serotonin hypothesis of depression (Iovieno et al. 2011). Studies examined combinations of 5-HTP with nialamide, clomipramine, dopamine agonists, or L-tryptophan (L-TRP), and one crossover trial investigated relapse prevention. While 5-HTP outperformed placebo in most trials, often with rapid improvement, the results are limited by small samples, with only six studies showing a statistically significant advantage for 5-HTP. A Cochrane review suggested most of these studies, except for one or two, did not meet criteria for a meta-analysis (Shaw et al. 2002), which does not represent a strong endorsement of the body of work thus far.

3.6.2 Mechanisms

5-HTP is produced chemically from L-tryptophan (L-TRP). The latter can also boost serotonin production, but 5-HTP bypasses conversion of L-TRP into 5-HTP by tryptophan (TRP) hydroxylase, which is the rate-limiting step of serotonin synthesis (Iovieno et al. 2011). TRP hydroxylase may be inhibited by various illnesses and physical or psychological stress, decreasing L-TRP availability. 5-HTP can cross the blood-brain barrier (BBB) for conversion to serotonin (Green et al. 1980; Maes et al. 1990) and may also stimulate synthesis of melatonin, dopamine, norepinephrine, and beta-endorphin.

3.6.3 Dosing

Recommended doses of 5-HTP range from 20 to 3,250 mg/day. 5-HTP is typically started at 50 mg three times daily with meals and titrated upward gradually. Doses are administered on a 2–4×/day schedule, because 5-HTP has a short half-life of about 4 h (Iovieno et al. 2011).

3.6.4 Adverse Effects

The most common adverse effects from 5-HTP are gastrointestinal (nausea, vomiting, and diarrhea) (Iovieno et al. 2011). Gijsman and colleagues recommend combining 5-HTP with a peripheral decarboxylase inhibitor (PDI) that blocks peripheral conversion of 5-HTP to serotonin and decreases GI upset (Gijsman et al. 2002). Less common side effects include headaches, insomnia, and palpitations. Serotonin syndrome has been reported when 5-HTP is combined with

fluoxetine or MAOIs (Lane and Baldwin 1997). However, in one study where single 200 mg doses of 5-HTP were administered to 26 patients taking fluoxetine, none developed serotonin syndrome (Meltzer et al. 1997). Nonetheless, 5-HTP should be used with caution in patients taking antidepressants. There is limited information regarding safety in pregnancy or in patients with bipolar disorder, and caution is therefore advised.

In the 1990s, research on 5-HTP was for the most part discontinued, partly because of the emergence of selective serotonin reuptake inhibitors (SSRIs), and because of outbreaks of eosinophilia-myalgia syndrome (EMS) in 1989 and 1990, which resulted in many fatalities. Despite an FDA ban, it was eventually determined that EMS was the result of bacterial contamination and fermentation and not 5-HTP itself. 5-HTP has since been reinstated on the market, and current data support safety (Iovieno et al. 2011).

3.6.5 Conclusions

After being mostly ignored for almost three decades, 5-HTP deserves reconsideration as a potential antidepressant, and clinical research on this agent should be resumed.

3.7 Inositol

3.7.1 Overview and Efficacy

Inositol is a structural isomer of glucose found primarily in cell membranes as myoinositol. It can be obtained in the diet by eating beans, grains, nuts, and fruits (Moore et al. 1999). There are six small clinical trials of inositol, primarily as augmentation for antidepressants and mood stabilizers in unipolar and bipolar depression (Belmaker and Levine 2008). Inositol outperformed placebo in three controlled studies, and two studies on unipolar depression were negative. Most comparisons in depression, however, did not produce significant differences, likely because of small samples (Iovieno et al. 2011; Mukai et al. 2014).

3.7.2 Mechanisms

Inositol participates in the synthesis of membrane phospholipids and is a precursor in the phosphatidylinositol (PI) cycle, producing inositol triphosphate (IP3) and diacylglycerol (DAG), both second messengers that interact with neurotransmitter receptors (Baraban et al. 1989). Mechanistic similarities to lithium have been proposed to account for inositol's mood-enhancing effects (Belmaker and Levine 2008).

3.7.3 Dosing

Recommended doses range from 6 to 20 g/day, depending on the indication. For depression, doses are typically 12 g/day divided on a two to four times a day basis (Belmaker and Levine 2008; Iovieno et al. 2011).

3.7.4 Adverse Effects

Reported side effects of inositol include mild plasma glucose elevation, gas, nausea, sleepiness, insomnia, dizziness, and headaches (Iovieno et al. 2011). There are no serious toxicities or interactions. Cycling has been reported in bipolar patients, so inositol should be used in combination with a mood stabilizer in bipolar patients (Belmaker and Levine 2008; Iovieno et al. 2011). It not recommended for pregnant women, because it may induce premature uterine contractions (Iovieno et al. 2011).

3.7.5 Conclusion

Inositol appears safe and may alleviate mood disorders, as well as some anxiety disorders, but studies so far are limited by small sample sizes, and larger controlled studies are needed.

3.8 Acetyl-L-Carnitine (ALCAR)

3.8.1 Overview and Efficacy

Acetyl-L-carnitine (ALCAR) belongs to a group of natural products termed "mitochondrial modulators," which are thought to modulate activity of mitochondria and the electron transport chain. Nierenberg and colleagues suggested mitochondrial modulation disruption as a potential factor in bipolar illness (Nierenberg et al. 2013). Placebo-controlled studies of ALCAR in elderly patients with dysthymia or depression have supported efficacy and showed a particularly rapid response (Bersani et al. 2013; Tempesta et al. 1987). A meta-analysis of 12 studies (Veronese et al. 2017) and a systematic review (Wang et al. 2014) have supported ALCAR as more effective than placebo and better tolerated than antidepressants. A study comparing intravenous (IV) and oral ALCAR in alcoholic patients found an advantage for IV ALCAR regarding depressive symptoms such as anhedonia and melancholic and negative symptoms (Martinotti et al. 2011). Not all studies are supportive, however. An RCT in dysthymic patients (Zanardi and Smeraldi 2006) and one in bipolar depression were both negative (Brennan et al. 2013).

3.8.2 Mechanisms

Carnitines are fatty acids that enter the mitochondria as acyl-carnitines and are oxidized to release energy and form acetyl coenzyme A, a factor in the citric acid cycle. ALCAR may protect brain cells by scavenging reactive oxygen species, decreasing oxidative stress, and promoting reactivity to a hostile environment (Nierenberg et al. 2013; Bersani et al. 2013).

3.8.3 Dosing

ALCAR is usually dosed between 1,000 and 3,000 mg/day.

3.8.4 Adverse Effects

ALCAR appears safe and well tolerated. There is one case report of psychosis (Evcimen et al. 2007) and one of mania recurrence associated with ALCAR (Goodison et al. 2017).

3.8.5 Conclusions

Overall, ALCAR appears safe, and there is promising early evidence of efficacy. It is difficult to make recommendations at this time, but further research should be undertaken.

3.9 N-Acetyl Cysteine (NAC)

3.9.1 Overview and Efficacy

N-acetyl cysteine (NAC) is another "mitochondrial modulator," mostly studied in bipolar disorder, but there is some evidence in unipolar depression as well. In a double-blind placebo-controlled trial, 76 subjects with bipolar disorder undergoing treatment as usual (TAU) were randomized for 6 months to augmentation with 2,000 mg/day NAC or placebo, with an advantage for NAC (Berk et al. 2008). A follow-up open trial treated 149 bipolar disorder patients for 8 weeks of NAC 2,000 mg/day and then randomized them to maintenance with NAC or placebo + TAU. There was improvement in the open phase but minimal additional change during double-blind maintenance (Berk et al. 2011). In a 6-month double-blind placebo-controlled trial with 15 bipolar subjects, NAC produced greater improvement in manic symptoms, and depressive symptoms worsened in the placebo group (Magalhães et al. 2013). A study in unipolar MDD found greater remission and response rates in the NAC group after 16 weeks of treatment (Berk et al. 2014).

3.9.2 Mechanisms

N-acetyl cysteine (NAC) increases synthesis of glutathione (GSH), which in turn reduces oxidative stress. It thus prevents oxidative damage in the mitochondrial electron transport chain and protects brain cells. Effects similar to those of lithium and valproate have also been proposed (Data-Franco et al. 2017).

3.9.3 Dosing

Recommended doses of NAC are typically about 2,000 mg/day (Fernandes et al. 2016).

3.9.4 Adverse Effects

Gastrointestinal and musculoskeletal side effects are the most common ones reported with NAC (Kennedy 2013).

3.9.5 Conclusions

Evidence for NAC's benefit in mood disorders is currently very preliminary, and more trials need to be conducted.

3.10 Alpha Lipoic Acid (ALA)

3.10.1 Overview and Efficacy

Studies of alpha lipoic acid (ALA) in animals suggest possible antidepressant effects (Silva et al. 2013, 2016), particularly if BDNF deficiency is involved (de Sousa et al. 2015). A 2-week controlled study of intravenous ALA (600 mg/day) versus mexidol (300 mg/day) in diabetic patients compared effects on affective status, cognitive function, glycemic control, and quality of life. ALA decreased feelings of guilt and increased attention in subjects (Volchegorskiĭ et al. 2011). A combination of ALCAR and ALA in bipolar depression was not encouraging, however (Brennan et al. 2013).

3.10.2 Mechanisms

Alpha lipoic acid (ALA) is a cofactor for the pyruvate dehydrogenase (PDH) complex. It scavenges reactive oxygen species (free radicals) and increases cellular glucose via stimulation of insulin sensitivity. Because insulin activity increases tryptophan influx into the brain (and hence serotonin), insulin sensitivity secondary to ALA supplementation could potentially alleviate depression (Salazar 2000).

3.10.3 Dosing

Typical doses of ALA are about 600 mg/day.

3.10.4 Adverse Effects

Side effects of ALA appear uncommon and include allergic reactions, nausea, and hypoglycemia (Volchegorskiĭ et al. 2011).

3.10.5 Conclusion

ALA appears well tolerated and safe, but evidence thus far is very preliminary, and more systematic human studies in depressed populations are needed to help guide treatment recommendations.

4 The Limitations of Our Current Knowledge and How It Establishes Our Research Agenda

There are scientific as well as safety challenges associated with the use of natural products, either as a monotherapy or as part of combination therapy. At least in the USA, natural products are considered food rather than pharmaceuticals by the FDA, and so they do not undergo the same rigorous preclinical and clinical review as pharmaceuticals (Mischoulon 2004). This limits our knowledge of

pharmacodynamics, pharmacokinetics, animal studies, Phase I–III studies, good manufacturing standards, and post-marketing surveillance of natural products. The paucity of information poses a significant challenge to thoughtful practitioners who want to prescribe natural products as part of a treatment regimen.

One of the greatest fallacies regarding natural products is naïve assumption that "natural" somehow equates with "safe" (Mischoulon and Rosenbaum 1999). Since we frequently do not fully appreciate the mechanisms of action, pharmacodynamics, and pharmacokinetics of even the purported primary active ingredient in a natural product, let alone metabolites or secondary compounds in the product, employing those products either as a monotherapy or in combination with other agents may subject patients to significant unanticipated risks. Even in cases like St. John's wort (SJW; see also Sect. 3.1), where we do have a fair amount of pharmacokinetic data, patients may be subjected to unanticipated drug interactions. In an analysis of the National Ambulatory Medical Care Survey (NAMS) data between 1993 and 2010, SJW was listed 2,300,000 times in the medical record, and 28% of the time a concomitant medication was prescribed that was contraindicated while a patient was taking SJW (Davis et al. 2014).

In a study of 1,466 patients treated in six mental health clinics in Edmonton, Alberta, Canada, 19% of patients were concomitantly taking prescription psychotropic medications and natural products. These patients were 2.8 times more likely to experience a medication-related adverse event when compared with patients who only used prescription psychotropic medications (Necyk et al. 2016). Thus it is incumbent on the practitioner to review the known interactions of a natural product prior to prescribing it and to caution the patient about potential risks.

There is a growing body of evidence about the pharmacokinetic effects of at least the purported key ingredient in some natural products (Hu et al. 2012). A great deal of effort has been spent characterizing the impact of psychotropic medications on the hepatic microsomal systems, since cytochrome P450 enzymes are responsible for over 90% of the oxidative metabolism of most drugs (Na et al. 2011). However, as highlighted by Hu and colleagues in their review of natural products and theranostics, there are other important pharmacokinetic considerations. These include the impact of the compound on the cytochrome P450 (CYP) enzymes in the small intestine as well as the liver (Hu et al. 2012). CYP3A, which is potently induced by SJW, accounts for 70% of the intestinal CYP activity and 30% of hepatic CYP activity (Pal and Mitra 2006). One must also consider the impact of natural products on Phase II conjugation reactions such as glucuronidation or sulfaction, which facilitate biliary and renal excretion. Unfortunately, there are scant data available about the in vivo and in vitro actions of most natural products on these important Phase II reactions (Hu et al. 2012; Mohamed and Frye 2011).

Another important area of pharmacokinetic investigation that requires consideration is the role that transport systems such as the ATP-binding cassette (ABC) and solute carrier (SLC) superfamilies play on the absorption, distribution, and elimination of natural products. Not surprisingly, SJW is the most thoroughly investigated of the natural products with antidepressant properties. SJW is not only a potent inducer of CYP3A4 in the intestine and the liver but is also a potent inducer of the

ABC efflux transporter P-glycoprotein (P-gp). P-gp is extensively expressed and pumps xenobiotics back into the bile duct for excretion and from the proximal tubule of the kidney into urine (Schwarz et al. 2007; Turkanovic et al. 2017). In summary, studies of the pharmacokinetic properties of natural products should investigate their impact not only on protein distribution but also Phase I and Phase II enzymes as well as membrane influx and efflux transporter proteins.

A second area where more extensive investigation is warranted is the study of the pharmacodynamic properties of natural products and their metabolites. Unlike traditional pharmaceutical development, little is known about the binding properties of most natural products. Even less is known about the mechanisms of action of these compounds. This can lead to serious and potentially life-threatening interactions. For example, hyperforin, one of the compounds of St. John's wort, may inhibit the reuptake of serotonin, dopamine, and norepinephrine, and so coadministration with an SSRI or a monamine oxidase inhibitor can potentially have life-threatening consequences (Fasinu et al. 2012). There is even less information available investigating the effects of natural products and their metabolites on second messenger systems of gene expression changes (Hu et al. 2012). There has been one study employing interactive pathway analysis of RNA microarray expression data from neuroglial cell lines to investigate the mechanism of action of *Rhodiola* extract and three of its active constituents (salidroside, tyrosal, and triandrin). Rhodiola and its three active principal constituents altered regulation of 1,062, 1,052, 1,062, and 1,057 genes, respectively, in neuroglial cell lines. The most significant effects of *Rhodiola* were on pathways involved in immune function and modulation, glutamate transmission, G-protein-coupled receptor signaling, c-AMP signaling, and atherosclerosis (Panossian et al. 2014). Again, this work highlights the complexity but also the potential benefit of more detailed study of the impact of natural products at the level of the genome. At this time no one has systematically investigated the effect that natural products might play at modulating the interactions that occur between neurons and glial cells.

An additional area of investigation that might prove fruitful is the interplay between natural products and the human gut microbiome. There are at least three ways one could conceptualize interactions between the gut microbiome and natural products that have antidepressant properties. The natural product could influence the microbiome by changing the makeup of the gut microbiome. This could be accomplished either directly by the bactericidal activity of the product or its metabolites or by introducing exogenous bacteria through probiotics to influence the gut microbiome. Such changes could impact gut permeability as well as the mucus immune and systemic immune systems. A third interaction between the gut microbiome and a natural product involves the metabolism of the natural product into active metabolites that can be absorbed into the portal circulation (Chen et al. 2016).

In summary, there is an exciting opportunity for many further studies of pharmacokinetic, pharmacodynamic, pharmacogenetic, and systems biology approaches to the investigation of natural products with antidepressant effects. These studies are necessary not only to better understand the mechanisms of actions of natural

products and their metabolites but also to ensure the safety of patients employing these therapies.

5 Conclusions

Natural remedies show varying degrees of promise in mood disorders. With continued emergence of quality research studies on efficacy and safety, it is reasonable to expect that some remedies will attain status comparable to standard antidepressants, while others will remain as second-tier agents, and others may be discarded altogether, at least as potential psychotropics. Given the limitations of registered antidepressants, continued research into these agents is warranted so as to determine a place for each in the psychiatric armamentarium.

The best candidates for natural remedies are patients with mild illness who have a strong interest in trying a natural product or are reluctant about registered antidepressants. These individuals are unlikely to suffer from trying a natural agent and can later decide to try a standard agent if the natural remedy proves ineffective. There are also patients who have tried many or most registered antidepressants without benefit, often finding them ineffective or the side effects intolerable. These individuals may also want to try natural remedies, in combination with or as an alternative to standard agents. But these patients are generally more difficult to treat and may not be the optimal candidates for relatively unproven therapies, in view of the risks of untreated or undertreated depression. Clinicians whose patients are considering natural antidepressants should discuss them in depth with their patients and review the pros and cons, particularly efficacy and safety as well as cost-effectiveness.

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Role of Inflammation in Depression and Treatment Implications

Jennifer C. Felger

Contents

Abstract

Approximately one third of depressed patients fail to respond to currently available antidepressant therapies. Therefore, new conceptual frameworks are needed to identify pathophysiologic pathways and neurobiological targets for the development of novel treatment strategies. In this regard, recent evidence suggests that inflammation may contribute to symptoms relevant to a number of psychiatric disorders and particularly depression. Numerous studies (including meta-analyses) have found elevated peripheral and central inflammatory cytokines

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and acute phase proteins in depression. Chronic exposure to increased inflammation is thought to drive changes in neurotransmitters and neurocircuits that lead to depressive symptoms and that may also interfere with or circumvent the efficacy of antidepressants. Indeed, patients with high inflammation have been shown to exhibit poor response to conventional antidepressant therapies. Recent developments in our ability to understand and measure the effects of inflammation on the brain in patients have opened new doors for the testing of novel treatment strategies that target the immune system or its consequences on neurotransmitter systems. Such recent developments in the field of behavioral immunology and their translational implications for the treatment of depression are discussed herein.

Keywords
Anhedonia · Anti-inflammatories · Anxiety · Cytokines · Depression · Dopamine · Glutamate · Inflammation · Motor slowing · Neuroimaging

1 Introduction

A growing body of evidence suggests that inflammation plays a role in psychiatric illnesses and especially major depressive disorder (MDD) (Howren et al. 2009; Miller et al. 2017). Inflammatory markers, including cytokines, chemokines, and acute phase reactants like C-reactive protein (CRP), are reliably increased in a number of depressed patients with respect to controls (Howren et al. 2009; Maes et al. 1997; Haapakoski et al. 2015). Furthermore, elevated CRP and other peripheral blood markers of inflammation have been found to predict future development of depression (Wium-Andersen et al. 2013; Gimeno et al. 2009; Au et al. 2015). Although not every patient with MDD has increased inflammation, it is thought that elevated levels of inflammation may contribute to the disease process and to specific symptoms in a subgroup of patients within this complex and heterogeneous disease.

Recent data indicate that increasing plasma CRP (as well as cytokines and their soluble receptors) is associated with decreased functional connectivity within corticostriatal reward and motor circuitry and with increased central nervous system (CNS) glutamate in patients with MDD, which correlates with symptoms of anhedonia and motor slowing (Felger et al. 2016; Haroon et al. 2016). These findings in depressed patients with elevated levels of inflammation are strikingly similar to the effects of peripheral administration of inflammatory stimuli on neural activity in reward and motor circuitry, as well as the effects of exogenously administered inflammatory stimuli on CNS neurotransmitters such as glutamate and dopamine (DA) (Felger et al. 2013a; Capuron et al. 2012; Eisenberger et al. 2010; Harrison et al. 2015a; Haroon et al. 2015). Therefore, elevated levels of inflammation in the blood of patients with MDD may reflect increased inflammatory activity in the CNS and its effects on neural systems and neurotransmitters (Felger et al. 2018). Interestingly in this regard, MDD patients with high levels of CRP and other markers of

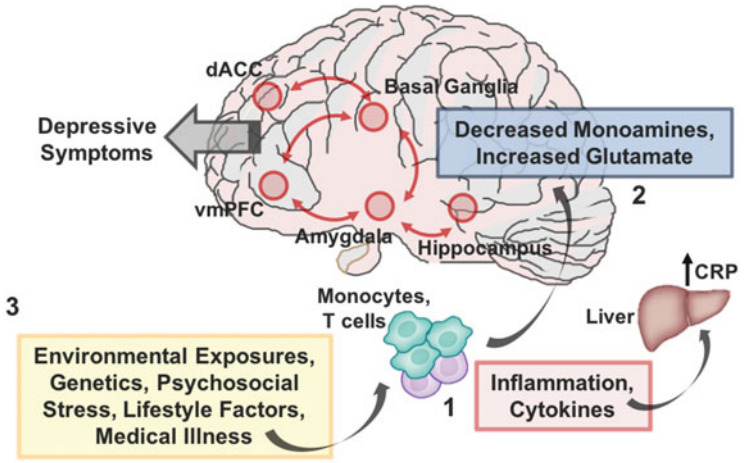

Fig. 1 Mechanisms of inflammation effects on the brain and behavior and targets for intervention in depression. Inflammation is increased in patients with major depressive disorder (MDD) due to environmental exposures, genetics, psychosocial stressors, diet, and other lifestyle factors (i.e., smoking) and medical illnesses. Innate immune cell activation and the release of inflammatory cytokines cause both increased CRP production from the liver and effects on brain neurotransmitters and circuits to drive relevant behavioral changes. Evidence indicates that inflammation and cytokines may preferentially affect dopamine and glutamate systems to disrupt circuits involved in reward and motor activity, as well as those involved anxiety and emotional regulation. In terms of potential novel therapies that may target inflammation or its effects on the brain, there is current interest in treatment strategies that affect the immune system to decrease inflammation (**1**), drugs that increase dopamine synthesis or synaptic availability or that decrease glutamate signaling (**2**), and lifestyle changes or alternative therapies that modify the sources of inflammation in MDD patients (**3**). *CRP* C-reactive protein, *dACC* dorsal anterior cingulate cortex, *vmPFC* ventromedial prefrontal cortex

peripheral inflammation have been found to exhibit resistance to conventional antidepressant therapies (Strawbridge et al. 2015; Cattaneo et al. 2013, 2016). This chapter will review the sources of inflammation in depression, its consequences on the brain, and how it has led to trials of novel immune-based therapies and treatments that reverse the effects of inflammation on neurotransmitter systems (Fig. 1).

2 Evidence of Increased Inflammation in Depression and Treatment Implications

2.1 Increased Peripheral and Central Inflammation

Numerous studies have reported increased circulating inflammatory cytokines, such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF), their soluble receptors, and acute phase reactants, like C-reactive protein (CRP), in patients with MDD (Maes 1999; Maes et al. 1992; Sluzewska 1999). These findings have been

corroborated by meta-analyses (Howren et al. 2009; Dowlati et al. 2010). The American Heart Association considers peripheral CRP >3 mg/L, e.g., "high CRP," to be associated with the greatest risk for development of cardiovascular disease relative to concentrations considered low (<1 mg/L) and moderate (1–3 mg/L) (Ridker 2003). These guidelines for risk of heart disease are consistent with emerging evidence that inflammation serves as a common mechanism of disease affecting multiple bodily systems, including the brain (Couzin-Frankel 2010). Not every MDD patient exhibits high concentrations of inflammatory markers or CRP, yet "high" CRP >3 mg/L is detected in a substantial proportion of patients, 20–50% depending on the sample. Even higher CRP concentrations are observed in patients who are resistant to standard antidepressant therapies (Felger et al. 2016; Haroon et al. 2016; Rapaport et al. 2016; Raison et al. 2013a; Uher et al. 2014). CRP, an acute phase reactant produced by the liver in response to innate immune cytokines, notably IL-6 and TNF, is used in clinical practice as a biomarker of systemic inflammation. Although CRP does play a role in activating the complement system (Rhodes et al. 2011; Devaraj et al. 2009), it is not thought to be a primary driver of inflammation effects on the brain. Rather, cytokines and downstream inflammatory mediators are known to exert effects on neurons and glia, which then drive changes in brain function. Nevertheless, CRP is associated with the activity of other inflammatory molecules, is routinely measured across medical centers and research laboratories (Aziz et al. 2003; Coventry et al. 2009), and is being used in clinical trials in MDD to target anti-cytokine therapies in patients with elevated levels of inflammation (Miller et al. 2017; Raison et al. 2013a).

With such strong evidence for increased inflammatory markers in the periphery of patients with psychiatric illness, there has been growing interest in finding ways to more directly measure the activation of inflammatory processes in the brain. Increased inflammatory cytokine concentrations in the cerebrospinal fluid (CSF) of patients with MDD have been observed (Levine et al. 1999; Schwieler et al. 2015; Garver et al. 2003; Soderlund et al. 2009, 2011). Additionally, increased CSF cytokines have been associated with the severity of depression and with improvement in symptoms in response to successful treatment (Levine et al. 1999; Lindqvist et al. 2009; Martinez et al. 2012). Despite intense efforts to measure inflammation in the brain by neuroimaging, positron emission tomography (PET) for imaging upregulation of the translocator protein (TSPO) on activated microglia and macrophages using ligands such as [^{11}C]PK 11195 (Venneti et al. 2007; Cagnin et al. 2007), [^{11}C]PBR28 (Imaizumi et al. 2007), and [^{18}F]FEPPA (Wilson et al. 2008) in MDD patients has yielded mixed results. For example, in a sample of patients with mild to moderate MDD using [^{11}C]PBR28, no differences were found between patients and controls, though the sample was small and the depression severity was relatively low (Hannestad et al. 2012a). In contrast, the use of [^{18}F]FEPPA in a more severely depressed sample showed significantly increased binding in the striatum, hippocampus, insula, and prefrontal cortex (Setiawan et al. 2015), yet no significant relationship was found between peripheral inflammatory markers and central TSPO binding. These findings are in contrast to studies in nonhuman primates (NHP) and in healthy humans where peripheral inflammatory cytokines

were increased in response to a peripheral inflammatory challenge in association with increased [^{11}C]PBR28 (Hannestad et al. 2012a; Sandiego et al. 2015), which was found primarily in microglia (Hannestad et al. 2012a). These data raise questions regarding what specifically TSPO binding is measuring in patients. More studies are likely needed prior to the use of such techniques in clinical trials exploring novel anti-inflammatory therapies.

2.2 Sources of Innate Immune Activation and Inflammation

Depressed patients who are otherwise medically healthy may experience chronic levels of increased innate immune system activation and inflammation due to a variety of environmental exposures including psychosocial stress (and particularly early life stress and trauma), sleep disturbance, inflammatory diet, gastrointestinal permeability, obesity, and other lifestyle factors such as smoking (Berk et al. 2013). History of childhood trauma is often associated with elevated inflammatory biomarkers and higher rates of depression as adults (Danese et al. 2008). Thus a "biological embedding" or imprinting of stress through inflammatory processes in childhood has been described (Danese et al. 2011). MDD patients with a history of early life stress have been shown to respond to psychological stress (the Trier Social Stress Test) with exaggerated circulating IL-6 production and increased DNA binding of nuclear factor (NF)-kB in peripheral blood mononuclear cells compared to non-depressed controls (Pace et al. 2006). In adolescents with a history of childhood adversity, high IL-6 production has been shown to precede subsequent development of depression 6 months later (Miller and Cole 2012), indicating causal relationships between early life stress, increased inflammation, and depression. Regarding mechanisms, recent work has demonstrated that stress can activate the inflammatory response through sterile inflammatory processes using signals called damage-associated molecular patterns (DAMPs), as well as by bacteria and bacterial products such as microbial-associated molecular patterns (MAMPs) leaked from the gut (Wong et al. 2016; Fleshner 2011, 2013). DAMPS refer to molecules produced as a function of cellular stress and accelerated metabolism, such as uric acid, adenosine triphosphate (ATP), glucose, and heat shock proteins (Fleshner 2013; Maslanik et al. 2012). DAMPS and MAMPS can then lead to stimulation of the NLRP3 inflammasome and NF-kB in monocytes, ultimately leading to the production of inflammatory cytokines including IL-1, IL-18, IL-6, and TNF (Maslanik et al. 2012; Iwata et al. 2013).

Additional environmental and lifestyle factors such as sleep disturbance may also contribute to increased inflammation in depression (Opp et al. 2007; Suarez 2008). Disturbed sleep increases circulating IL-6, TNF, and CRP (Meier-Ewert et al. 2004; Vgontzas et al. 2004), and sleep impairments in psychiatric illnesses such as depression have been associated with increased inflammation (Opp et al. 2007; Motivala et al. 2005). Furthermore, inflammatory diets that promote gut permeability and changes in the microbiota, smoking, and increased body mass index (BMI) all contribute to increased inflammation and may interact with genetics and stress to

contribute to behavioral symptoms and poor overall health outcomes in patients with psychiatric illness (Berk et al. 2013; Jamal et al. 2014). For example, obesity from consumption of a high-fat diet in rodents induces changes in the gut microbiota and increases ileal inflammation and permeability (de La Serre et al. 2010). Obesity and high BMI are associated with increased concentrations of IL-6 and other inflammatory markers in humans (Khaodhiar et al. 2004; Lim et al. 2005) thought to be the result of macrophage accumulation in adipose tissue, and especially visceral adiposity, which can release cytokines into the portal circulation (Weisberg et al. 2003; Suganami and Ogawa 2010; Park et al. 2005).

2.3 Gene Expression and Genetic Predisposition

Several functional allelic variants and single-nucleotide polymorphisms (SNPs) of genes encoding immune and inflammatory molecules have been associated with depression, including those encoding expression of inflammatory cytokines, major histocompatibility complex proteins, B and T cells, and inflammatory mediators like cyclooxygenase-2 (Bosker et al. 2011; Raison and Miller 2013; Bufalino et al. 2012). These findings have engendered speculation as to whether alleles that promote enhanced inflammatory cytokine secretion were evolutionarily advantageous and thus conserved (Raison and Miller 2013). Indeed, heightened inflammatory responses to environmental stimuli may have improved survival by conferring greater protection from bacterial and viral infection (Raison and Miller 2013). Further, genetic priming to respond to stress and the environment with increased inflammatory and antiviral responses could contribute to the high prevalence of psychiatric disorders comorbid with medical illnesses that are associated with inflammation (e.g., cardiovascular disease, metabolic disorders, and autoimmune disorders) (Yirmiya et al. 1999, 2000; Raison and Miller 2003; Evans et al. 1999; Pollak and Yirmiya 2002; Shelton and Miller 2010). In addition to genetic polymorphisms, increased inflammatory gene expression has been found in circulating immune cells[80] as well as in brains of patients with MDD (Shelton et al. 2011).

2.4 Influence of High Inflammation on Antidepressant Treatment Response

Current antidepressant therapies are effective for many patients with MDD. However, up to 30% fail to achieve remission, and even antidepressant responders often exhibit significant residual symptoms consistent with many of those caused by exposure to cytokines and inflammation, such as anhedonia, fatigue, and psychomotor retardation (Targum and Fava 2011; Rush 2007; Dunlop and Nemeroff 2007; Trivedi et al. 2008; Nierenberg 2015). Nonresponsiveness of inflammation-related symptoms to standard antidepressant therapies has been exemplified in cancer patients and in those patients receiving IFN-α therapy treated with SSRIs to alleviate

inflammation-related depression and fatigue (Bower et al. 2002; Miller et al. 2008; Ahles et al. 2002). SSRIs alleviated cancer-related or IFN-α-induced anxiety and some depressive symptoms, but not those of fatigue or psychomotor retardation (Capuron et al. 2002a; Raison et al. 2005a; Morrow et al. 2003). A similar lack of response to SSRIs in patients with increased inflammation has also been observed in MDD. For instance, patients with higher levels of CRP (>1 mg/L) have been found to demonstrate worse response to the SSRI escitalopram but to have more favorable responses to the noradrenergic antidepressant nortriptyline (Uher et al. 2014; Jha et al. 2017). Measurement of inflammatory cytokine mRNA expression in peripheral immune cells was even more predictive than CRP of this effect (Cattaneo et al. 2013, 2016). Additionally, MDD patients with high inflammation have been shown to respond better to adjuvant or novel therapies that boost monoamine availability or that target glutamate (Jha et al. 2017; Yang et al. 2015; Shelton et al. 2015). Therefore, it is important to better understand the mechanisms by which inflammation affects the brain in order to develop novel therapies or to appropriately target existing therapies to patients with elevated levels of inflammation.

3 Inflammation Effects on the Brain and Behavior

3.1 Immunologic Mechanisms

Immune Signaling in the Brain Peripheral inflammation and cytokines may signal the CNS to initiate local immune activation by several mechanisms, including (1) passage of cytokines through leaky regions in the blood-brain barrier at circumventricular organs (Katsuura et al. 1990; Pan and Kastin 2003), (2) active uptake mechanisms of cytokines across the blood-brain barrier (Banks and Erickson 2010; Banks et al. 1995, 2002), and (3) local actions at peripheral vagal nerve afferents that relay inflammatory signals to relevant brain regions, including the nucleus of the solitary tract and hypothalamus (the so-called neural route) (Bluthe et al. 1994; Ericsson et al. 1994; Watkins et al. 1994, 1995). However, recent translational data indicate that during peripheral inflammation, activated monocytes/macrophages traffic to the brain in response to monocyte chemoattractant protein (MCP-1), a chemokine produced by activated microglial cells in response to cytokine signaling from the periphery (D'Mello et al. 2009, 2015). These monocytes/macrophages traffic primarily to perivascular and meningeal spaces and have been shown to contribute to behavioral changes in rodent models of stress-induced depressive and anxiety behaviors (Wohleb et al. 2012, 2014; Hodes et al. 2014). Interestingly, patterns of gene expression in the peripheral blood of patients with psychiatric disorders exhibit increased signatures consistent with pro-inflammatory "M1" activation of monocyte/macrophages (Mostafavi et al. 2014; Brambilla et al. 2014; Drago et al. 2015). Furthermore, recruitment of activated peripheral macrophages to perivascular spaces, as well as localized activation of microglia neighboring these blood vessels and increased expression of MCP-1, has been observed in the dorsal anterior cingulate cortex (dACC) of

postmortem tissue from patients with depression (MDD or bipolar disorder) who completed suicide (Steiner et al. 2011; Torres-Platas et al. 2014). These findings indicate that accumulation of peripheral immune cells in vascular compartments in association with restricted and/or regionally specific activation of microglia may be characteristic of patients with depression who exhibit elevated levels of inflammation.

T Cells and Cytokines Promote Cognition and Plasticity A large body of work has found that CD4 T effector cells that traffic to the brain vasculature have beneficial effects on brain function by promoting tissue repair processes after injury, boosting cognitive function, reducing depressive or anxiety behaviors, and increasing neurogenesis (Derecki et al. 2010; Wolf et al. 2009; Schwartz and Shechter 2010; Lewitus et al. 2008). Relevant to depression and behavior, T cells traffic to the brain to reduce stress-induced anxiety-like behavior and reverse stress-induced decreases in brain-derived neurotrophic factor (BDNF), which is known to stimulate neurogenesis and possess antidepressant effects (Lewitus et al. 2008). T cells may also be required for normal cognitive function considering that T cell-deficient animals exhibit impaired learning and memory in water tests and mazes that can be reversed by the adoptive transfer of T cells (Kipnis et al. 2004; Ziv et al. 2006). T cells trafficking to the brain vasculature and meningeal space can produce IL-4 which stimulates astrocytes to produce growth factors including BDNF while also leading to the skewing of meningeal macrophages from a pro-inflammatory M1 phenotype to an anti-inflammatory, neuroprotective M2 phenotype (Derecki et al. 2010). A rich literature has also described the impact of a cytokines, including TNF and IL-1, on synaptic plasticity and learning and memory (del Rey et al. 2013). For example, mice depleted of the IL-1 type 1 receptor exhibit significant decreases in learning and memory and impaired long-term potentiation (LTP) (Yirmiya and Goshen 2011). Similar to IL-1, deletion of TNF receptors 1 and 2 has been associated with cognitive deficits (Naude et al. 2014), which may be due to their role in strengthening of excitatory synapses and plasticity by induction of surface expression of AMPA receptors (Stellwagen and Malenka 2006; Beattie et al. 2002) and stimulation of synaptic scaling (Stellwagen and Malenka 2006).

3.2 Neurobiological Mechanisms: Inflammation Effects on Circuits

A wealth of clinical and translational work has demonstrated that peripheral inflammation impacts brain regions relevant to both reward and threat sensitivity. PET and fMRI neuroimaging studies in humans have involved either the acute administration of inflammatory stimuli, such as endotoxin or vaccination, or chronic exposure to inflammatory cytokines, such as interferon [IFN]-α, as therapy for cancers and infectious diseases like hepatitis C virus (Capuron et al. 2007, 2012). Inflammation has consistently been found to affect both corticostriatal reward and motor circuits to drive reduced motivation and motor activity, as well as anxiety-related brain regions

including the amygdala, insula, and ACC, which may result from cytokine effects on monoamines and glutamate (Fig. 1). Recent work has aimed to translate these findings to the investigation of relationships between increased inflammation and altered neurocircuits in patients with MDD.

Reward and Motor Circuits Findings from numerous laboratories have consistently indicated that innate immune activation and the release of inflammatory cytokines preferentially affect reward and motor circuits and DA in the basal ganglia to contribute to reduced motivation and motor slowing (Capuron et al. 2007, 2012; Eisenberger et al. 2010; Harrison et al. 2015a; Felger and Miller 2012; Brydon et al. 2008; Majer et al. 2008; Goldsmith et al. 2016). Much of this work has stemmed from patients administered with IFN-α, up to 50% of whom met symptom criteria for major depression (depending on the dosing) and up to 80% of whom experienced significant fatigue, lack of energy, and motor slowing during treatment (Capuron et al. 2002a, b, 2003; Donnelly 1998; Musselman et al. 2001; Raison et al. 2005b, 2009, 2010a). Reduced motivation and anhedonia were also frequently reported in IFN-α-treated patients (Capuron et al. 2002a, 2012; Majer et al. 2008). Indeed, the Snaith-Hamilton Pleasure Scale (SHAPS) and the Reduced Motivation subscale of the Multidimensional Fatigue Inventory (MFI) yielded comparable effect sizes (all $r = 0.47–0.49$) for increases in self-reported depression or fatigue scores after chronic IFN-α treatment (Capuron et al. 2012; Majer et al. 2008). In IFN-α-treated patients, whole-brain analysis of fluorine-18-labeled fluorodeoxyglucose (FDG) PET found that, in addition to decreased metabolism in PFC, increased glucose metabolism was found in the basal ganglia and particularly the DA-rich putamen (Capuron et al. 2007; Juengling et al. 2000). Increased glucose metabolism in the left putamen and left nucleus accumbens (NAcc) correlated with fatigue in these patients, as assessed by the "energy" subscale of the Visual Analog Scale of Fatigue (VAS-F) (Capuron et al. 2007). This pattern of increased glucose metabolism in the basal ganglia is similar to that seen in Parkinson's disease (PD) (Spetsieris et al. 1995; Eidelberg et al. 1994; Mentis et al. 2002), where it is thought to reflect increased oscillatory burst activity in relevant nuclei secondary to loss of inhibitory nigral DA input (Wichmann and DeLong 1999, 2003). Interestingly, this pattern of increased metabolism in the striatum is also similar to the effects of transient catecholamine depletion in patients with MDD, which correlated with anhedonic symptoms (Hasler et al. 2008). Functional magnetic resonance imaging (fMRI) has also demonstrated decreased neural activation in the basal ganglia, including ventral striatum, with unexpected delivery of reward (winning in a gambling task) (Reuter et al. 2005) in patients undergoing IFN-α administration, which correlated with reduced motivation (Capuron et al. 2012). Acute administration of IFN-α has also been shown to induce a change in striatal microstructure, as measured by quantitative magnetization transfer (qMT) imaging that predicted development of fatigue symptoms during treatment (Dowell et al. 2016).

Administration of the cytokine inducers endotoxin and typhoid vaccination to healthy volunteers produces similar effects on the ventral striatum in response to

rewarding stimuli, suggesting that findings from IFN-α generalize to other inflammatory stimuli (Eisenberger et al. 2010; Harrison et al. 2015a). Indeed, endotoxin administration led to reduced activation of the ventral striatum to reward-predicting cues during a monetary incentive delay task (MIDT), which was associated with increases in self-reported depressed mood as measured by the Profile of Mood States (POMS) depression subscale (Eisenberger et al. 2010). Similar blunting of neural responses to reward anticipation has been observed following dietary depletion of precursors for DA synthesis (Bjork et al. 2014). Moreover, typhoid vaccination was found to cause a shift in reward versus punishment sensitivity in a probabilistic instrumental learning task combined with fMRI (Harrison et al. 2015a). Compared to saline control, typhoid vaccination reduced the behavioral attractiveness of rewards while making punishments more aversive, effects that were related to decreased neural activation of the ventral striatum to reward prediction errors and increased activation of the anterior insula to punishment prediction errors (Harrison et al. 2015a). Of relevance to the potential effects of inflammation on DA, the magnitude of response to prediction error signaling is fundamentally modulated by DA-dependent striatal activity as determined by the administration of drugs that enhance (L-DOPA) or inhibit (haloperidol) DAergic function (Pessiglione et al. 2006). Additionally, typhoid vaccination compared with saline has been shown to affect activity in the substantia nigra, including increased activation during a cognitive Stroop task and decreased activation in response to visual or novel stimuli, which correlated with both psychomotor slowing and increased peripheral blood concentrations of IL-6 (Brydon et al. 2008; Harrison et al. 2015b).

In medically stable patients with MDD, a relationship was observed between increased inflammation and decreased functional connectivity within reward-related corticostriatal neurocircuitry (Felger et al. 2016). Indeed, increased inflammation (plasma concentrations of CRP as well as cytokines and their soluble receptors) was associated with decreased functional connectivity between the ventral striatum and vmPFC and decreased connectivity between the dorsal striatum and the vmPFC and pre-supplementary motor area (pre-SMA), which correlated with self-reported symptoms of anhedonia and objective measures of psychomotor slowing, respectively (Felger et al. 2016). Interestingly, dorsal striatum and pre-SMA/SMA are key components of corticostriatal circuitry involved in linking motivation to motor output (Haber and Knutson 2010; Samanez-Larkin and Knutson 2015). Like the ventral striatum, vmPFC is part of the classic reward circuitry that receives significant mesocorticolimbic DA innervation (Russo and Nestler 2013; Diekhof et al. 2012).

Fear and Anxiety Circuits A number of studies have examined the effects of inflammation on the activation of brain regions that contribute to fear, anxiety, and emotional processing, such as the amygdala, insula, or dorsal anterior cingulate cortex (dACC). In addition, other studies have examined changes in the function of circuitry involving these regions. Inflammation has been shown to not only increase amygdala activity but to also increase amygdala responsiveness to stress that drives increased production of inflammatory cytokines (Harrison et al. 2009a; Inagaki et al.

2012; Muscatell et al. 2015). Increased IL-6 and TNF after administration of endotoxin to healthy subjects has been shown to increase amygdala activity in response to socially threatening images, which was associated with enhanced feelings of social disconnection (Inagaki et al. 2012). Administration of typhoid vaccination, which increases IL-6 and induces behavioral changes including cognitive disturbances and fatigue, also increased activation of the amygdala during presentation of congruent and incongruent stimuli (Harrison et al. 2009b). In terms of stress sensitivity and neural pathways involved in the inflammatory response to stress, heightened neural activity in the amygdala in response to a psychosocial laboratory stressor was associated with greater stress-induced increases in IL-6 (Muscatell et al. 2015).

Several studies have also reported relationships between peripheral inflammatory cytokines and activity of medial prefrontal cortical regions, including the subgenual ACC, either in individuals undergoing stress or following administration of cytokine inducers (Harrison et al. 2009a; O'Connor et al. 2009c). Indeed, administration of typhoid vaccination to healthy controls induced mood changes that correlated with enhanced activity within the subgenual ACC during an implicit emotional face perception task. Typhoid vaccination also reduced task-related functional connectivity of the subgenual ACC to the amygdala and other medial prefrontal cortical regions, as well as the NAcc and superior temporal sulcus, which correlated with peripheral blood IL-6 (Harrison et al. 2009a). As mentioned above, heightened neural activity in the amygdala was associated with increased IL-6 responses to a psychosocial laboratory stressor. Functional connectivity analyses also indicated that individuals who showed a heightened inflammatory response to the stressor exhibited stronger coupling between the amygdala and the dorsomedial prefrontal cortex (Muscatell et al. 2015). In addition to activation of the amygdala, administration of typhoid vaccination increased activation of the insula during presentation of congruent and incongruent stimuli (Harrison et al. 2009b). Among females but not males administered endotoxin, increases in IL-6 were associated with increases in neural activity in brain regions including the anterior insula in response to social exclusion during a virtual ball-tossing game (Eisenberger et al. 2009). Endotoxin administration has also been shown to increase cerebral glucose metabolism in the insula as measured by PET (Hannestad et al. 2012b). Therefore, heightened sensitivity of the insula to inflammatory cytokines in the periphery, particularly in the presence of emotional stimuli, may contribute to altered neural circuitry involving the amygdala, medial prefrontal cortex, and ACC to precipitate symptoms of anxiety and emotional disturbance that contribute to MDD.

3.3 Neurobiological Mechanisms: Inflammation Effects on Neurotransmitters

Inflammation Effects on Monoamine Metabolism and Neurotransmission Although most recent studies examining the effect of cytokines or inflammatory stimuli on

monoamine release, tissue content, or turnover in animal studies have focused on DA, some studies have observed changes in the other monoamines, especially serotonin (5-HT). Acutely, monoamines are released in the hypothalamus and other limbic structures to mediate fever and early behavioral changes associated with sickness behavior (Dunn et al. 2005; O'Connor et al. 2009a). Administration of inflammatory cytokines also increase early 5-HT turnover in the cortex and NAcc (Song et al. 1999; De La Garza and Asnis 2003) in association with later, more persistent depressive-like behaviors (O'Connor et al. 2009a; Frenois et al. 2007). Additionally, both chronic administration of cytokines and chronic low-grade inflammation in humans have been shown to increase indoleamine-2,3-dioxygenase (IDO) activity and the metabolisms of tryptophan, the primary amino acid precursor of serotonin, to kynurenine (KYN) in the periphery (Capuron et al. 2003, 2011; Raison et al. 2010b). In patients treated with IFN-α for hepatitis C virus, CSF concentrations of IL-6 negatively correlated with 5-hydroxyindoleacetic acid (5-HIAA) concentrations, which in turn negatively correlated with IFN-α-induced depression severity (Raison et al. 2009). However, in a separate study, increased CSF KYN and QUIN concentrations were observed to correlate with depressive symptoms and with CSF cytokines, yet tryptophan concentrations were not decreased in the CSF despite decreased blood tryptophan concentrations (Raison et al. 2010b). These findings are consistent with recent work in rodents indicating that KYN administration alone was sufficient to induce depressive-like behavior and pharmacological inhibition of IDO with 1-methyl-tryptophan prevented lipopolysaccharide (LPS/endotoxin)-induced depressive-like behavior but did not prevent changes in 5-HT turnover (O'Connor et al. 2009a, b; Salazar et al. 2012). These findings suggest that neuroactive KYN metabolite effects on glutamate signaling are likely responsible for the behavioral changes associated with cytokine-induced IDO activity.

With regard to DA, some studies reported increases (Kumai et al. 2000; Sato et al. 2006), while others have reported decreases (Kamata et al. 2000; Kitagami et al. 2003; Shuto et al. 1997) in brain DA and/or metabolites following acute or sub-chronic IFN-α administration, which has been reviewed elsewhere (Felger and Miller 2012; Felger and Treadway 2017). These discrepancies were likely due to differences in dosing, length of exposure, and, most importantly, the fact that species-specific IFN-α was variably used and rodents do not respond to human IFN-α with activation of classic type I IFN receptor signaling (Loftis et al. 2006a, b; Wang et al. 2008). However, in monkeys chronically administered IFN-α, which causes similar behavioral responses as in humans, stimulated DA release was decreased in the striatum and correlated with reduced effort-based sucrose consumption (Felger et al. 2013a). Furthermore, IFN-α-induced decreases in striatal DA release were reversed by the DA precursor levodopa (L-DOPA) administered via reverse in vivo microdialysis (Felger et al. 2015). These findings were consistent with results from PET imaging with [F^{18}]Fluorodopa in IFN-α-treated patients indicating that cytokines reduce DA synthesis and availability (Felger et al. 2015).

Indeed, inflammation and cytokines may decrease DA (and 5-HT) availability and release by decreasing tetrahydrobiopterin (BH4), an inflammation and oxidative stress-sensitive enzyme cofactor required for conversion of phenylalanine (Phe) to tyrosine (Tyr) by Phe hydroxylase and Tyr to L-DOPA by Tyr hydroxylase (as well as tryptophan to 5-HT) (Neurauter et al. 2008; Cunnington and Channon 2010). We and others have examined biomarkers of the DA synthetic pathway in IFN-α-treated patients, including the plasma Phe/Tyr ratio, which goes up when BH4 is low. We observed increased plasma Phe/Tyr and evidence of reduced cerebrospinal fluid (CSF) BH4 activity in IFN-α-treated patients (Kitagami et al. 2003; Felger et al. 2013b; Zoller et al. 2012), which correlated with decreased CSF DA and its major metabolite homovanillic acid (HVA) and with IFN-α-induced depressive symptoms (Felger et al. 2013b). Similarly, intramuscular injection of rats with IFN-α has been shown to decrease CNS concentrations of BH4 through inflammation-related stimulation of nitric oxide, whereas inhibition of nitric oxide synthase (which usurps BH4 during inflammation) was found to reverse IFN-α's inhibitory effects on brain concentrations of both BH4 and DA (Kitagami et al. 2003). Moreover, in a study of healthy elderly persons with low-grade inflammation, peripheral blood concentrations of Phe and Tyr and an increased Phe/Tyr ratio were associated with neuropsychiatric symptoms including anhedonia and altered sleep (Capuron et al. 2011).

Finally, attention has been paid to the effects of cytokines and inflammatory signaling pathways on monoamine reuptake mechanisms and particularly the 5-HT transporter (Moron et al. 2003; Zhu et al. 2005, 2006, 2010). Both in vitro and in vivo data have established that stimulation of p38 mitogen-activated protein kinase (MAPK), a primary signaling pathway activated by IFN-α and other cytokines, can increase the expression and function of the serotonin transporter, leading to increased serotonin reuptake (Zhu et al. 2005, 2006, 2010). MAPK pathways have also been found to influence DAT. For example, DAT-expressing cells transfected with constitutively activate MAPK kinase (MEK) show increased DA reuptake (Vmax), whereas treatment of rat striatal synaptosomes with MEK inhibitors decreased DA reuptake in a concentration- and time-dependent manner (Moron et al. 2003). Therefore, reduced synaptic monoamines following chronic exposure to inflammatory cytokines may be mediated, in part, by increased transporter expression or function.

Inflammation Effects on Glutamate Another mechanism by which cytokines may influence behavior is through stimulation of IDO and downstream KYN pathway metabolites on glutamate neurotransmission in the brain (Dantzer and Walker 2014; Dantzer et al. 2011). Immune-mediated activation of IDO catabolizes tryptophan, the primary amino acid precursor of serotonin, to KYN. KYN is further catabolized into the neuroactive metabolites kynurenic acid (KA) (in astrocytes) and quinolinic acid (QUIN) (in microglia), both of which have been found to be increased in the plasma and CSF of IFN-α-treated patients (Capuron et al. 2003; Raison et al. 2010b; Schwarcz and Pellicciari 2002; Bonaccorso et al. 2002). Of note, CSF QUIN significantly correlated with depressive symptoms during IFN-α administration, as

measured by MADRS (Raison et al. 2010b). In addition to increasing oxidative stress (Santamaria et al. 2003; Behan et al. 1999), the neurotoxic metabolite QUIN can also directly activate the n-methyl-d-aspartate (NMDA) receptor to further induce the release of glutamate to lead to excitotoxicity in the brain (Schwarcz and Pellicciari 2002; Tavares et al. 2005). In contrast to QUIN, KA reduces glutamate release and has been shown to be an antagonist of NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Stone 2000). DA release is in part under glutamatergic control, and thereby KA may exert downstream effects that further decrease DA to contribute to inflammation-induced depressive behavior (Schwarcz and Pellicciari 2002). Indeed, intrastriatal administration of KA to rodents leads to marked reductions in extracellular DA concentrations, as determined by in vivo microdialysis (Wu et al. 2007).

Finally, cytokines and inflammation have been shown to increase glutamate by effects on microglia and astrocytes (Haroon et al. 2017). A rich literature has shown that cytokines can decrease the astrocytic expression of glutamate transporters and increase release of glutamate from astrocytes and activated microglia in vitro (Dantzer and Walker 2014; Tilleux and Hermans 2007; Ida et al. 2008; Takaki et al. 2012). Of note, glutamate released from glia may have preferential access to extrasynaptic NMDA receptors, which lead to decreased production of trophic factors including brain-derived neurotrophic factor (BDNF) (Hardingham et al. 2002; Haydon and Carmignoto 2006). Increased glutamate, as measured by magnetic resonance spectroscopy (MRS), has been observed in patients chronically administered INF-α, which correlated with symptoms of reduced motivation and psychomotor slowing (Haroon et al. 2014, 2015). Likewise, increased glutamate was also observed in MDD patients with increased inflammation that correlated with anhedonia and psychomotor slowing (Haroon et al. 2016).

4 Potential Treatment Targets for Depressed Patients with Increased Inflammation

As described above, the neurobiological effects of inflammation on the brain, particularly via decreased monoamine synthesis and availability or increased reuptake, may circumvent or interfere with standard antidepressant therapies such as SSRIs. Therefore, there is a need to consider new therapies or a combination of treatments that reduce inflammation or that target its sources or consequences on the brain (Fig. 1). Indeed, the preferential effects of inflammation on DA and glutamate in reward and motor circuits and related behaviors indicate that patients with increased inflammation may respond better to DA- and glutamate-relevant therapies (Fig. 1). Reviewed below is current information regarding the clinical and/or translational use of relevant pharmacological strategies to reduce inflammation or its effects on the brain, as well as results from trials in MDD, if available (Table 1). Many potential new therapies exist, and results to date are encouraging; however additional studies using better trial design (i.e., targeting of therapies to patients with high inflammation) are warranted.

Table 1 Pharmacologic targets for blocking inflammation or reversing its effects on the brain and results of trials in MDD that considered antidepressant response in association with increased inflammation

Pharmacological target	Previous trials (results, +, −)	Example compounds
Immune function		
Inflammatory cytokines	+	TNF/IL-6 antagonists
COX-2/prostaglandins	+	Celecoxib, aspirin
Immune modulators	n.a.	Helminths, MSCs
Monoamines		
Synthesis		
Tetrahydrobiopterin	n.a.	Sapropterin (Kuvan)
L-methylfolate	+	Levomefolic acid (Metafolin)
SAMe	n.a.	Ademetionine
L-DOPA	n.a.	Levodopa/carbidopa (Sinemet)
Release/reuptake		
NE/DA reuptake inhibitors	+	Bupropion
Stimulants	n.a.	Methylphenidate, modafinil
Agonists		
DA receptor agonists	n.a.	Pramipexole
Adenosine A2A antagonists	n.a.	ADORA2A
Glutamate		
Reuptake enhancers	n.a.	Riluzole
Antagonists	+/−	Memantine, ketamine
Kynurenine modulators	n.a.	IDO (e.g., 1-MT) or KMO inhibitors
Supplements		
Omega-3 fatty acid	+	Eicosapentaenoic acid
Antioxidants	n.a.	*N*-acetyl-cysteine

+ increased, **+/−** mixed results, *n.a.* not available, *ADORA2A* adenosine a2a receptor, *COX* cyclooxygenase, *DA* dopamine, *IDO* indoleamine-2,3-dioxygenase, *IL* interleukin, *KMO* kynurenine 3-monooxygenase, *L-DOPA* levodopa, *MSC* mesenchymal stem cell, *MT* methyl-tryptophan, *NE* norepinephrine, *SAMe* s-adenosyl-l-methionine, *TNF* tumor necrosis factor

4.1 Therapies That Affect the Immune System

Anti-inflammatories A number of recent studies have begun to test the potential of anti-inflammatory compounds as possible antidepressant therapies (Target 1, Fig. 1). Most studies to date have focused on compounds such as cyclooxygenase (COX)-2 inhibitors that block the production of prostaglandins, which are the primary downstream mediators of the inflammatory response that are increased in the peripheral blood of patients with depression (Lieb et al. 1983). Recent meta-analyses have reported modest effect sizes indicating a benefit of COX-2 inhibitors in reducing symptom severity. However, there was high heterogeneity across studies and mostly small sample sizes (Na et al. 2014; Kohler et al. 2014; Faridhosseini et al. 2014). Of the included studies, only a handful assessed the efficacy of nonsteroidal anti-

inflammatories (NSAIDs) compared to placebo, whereas the majority used celecoxib or acetylsalicylic acid (aspirin) as adjuvants to conventional antidepressant therapies. Moreover, these studies did not select patients based on increased inflammation, and only a few measured peripheral inflammatory markers to establish the anti-inflammatory activity of the treatments. It should also be noted that these NSAID therapies convey relatively mild anti-inflammatory activity and numerous "off-target" effects that may confound data interpretation (Miller et al. 2017; Miller and Raison 2015).

More specific therapies inhibiting cytokine activity that are used to treat inflammatory illnesses have shown efficacy for reducing depressive symptoms in medically ill patients or in medically stable persons with MDD (Miller et al. 2017; Kohler et al. 2014). For example, a recent study tested the efficacy of infliximab, a highly selective TNF antagonist, in treatment-resistant patients with MDD as a function of peripheral inflammation. Treatment with infliximab was associated with robust decreases in plasma CRP concentrations, as well as a strong antidepressant effect, but only in patients with elevated CRP at baseline (Raison et al. 2013a). Moreover, the greatest area of symptom improvement was related to motivation (Raison et al. 2013a), which is consistent with the hypothesis that inflammation affects corticostriatal reward circuits as described elsewhere in this chapter. An ongoing clinical trial is examining the efficacy of infliximab in patients with bipolar depression and a CRP >5 mg/L (NCT02363738), and a Phase II trial of an anti-IL-6 mAb (sirukumab) is being run in patients with depression and a CRP >3 mg/L (NCT02473289).

Lastly, strategies aim to stimulate the production of IL-4-producing T cells, which has been accomplished in animal studies by administration of organisms such as helminths or cell therapies such as mesenchymal stem cells (MSCs), both of which have been shown to promote tolerant and anti-inflammatory responses. Helminths have been shown to stimulate IL-4 and regulatory "M2" macrophages in the gut via effects on the microbiome in a mouse model of inflammatory bowel disease (Ramanan et al. 2016). In an emerging field of immunomodulatory treatments involving stem cell therapies, MSCs have been shown to promote the development and differentiation of regulatory T cells and production of immunomodulatory and anti-inflammatory molecules such as TGF-beta, IL-10, and IL-1ra (Shi et al. 2011; Francois et al. 2012). Ongoing trials are testing the efficacy of MSC therapy in inflammatory and autoimmune disorders, and one study is examining the impact of a single infusion of allogeneic human MSCs for patients with treatment-resistant depression and increased inflammation (CRP >3 mg/L) (NCT02675556).

4.2 Compounds That Improve DA Synthesis, Availability, or Signaling

Considering the strong evidence presented above indicating that inflammation can inhibit key components of DA synthesis and availability, pharmacologic strategies

that increase DA availability or signaling may effectively treat MDD in patients with high inflammation (Target 2, Fig. 1). Relevant pharmacologic agents include DA agonists, stimulants, bupropion, adenosine A2A receptor antagonists, and drugs that support DA synthesis through stimulation of BH4 activity. Such therapies that increase BH4 include saproterin and folic acid, L-methylfolate, and S-adenosylmethionine (SAMe) (Table 1), many of which help convert inactive BH2 to BH4. Of relevance to low BH4 activity in MDD, low serum folate has been associated with increased risk of depression as well as nonresponse to antidepressant treatment and an increased likelihood of depression relapse (Papakostas et al. 2004). Clinical trials have been conducted using L-methylfolate (marketed as Deplin and Zervalx) and SAMe in depression with mixed results (Papakostas et al. 2012; Sarris et al. 2015). Interestingly, however, a post hoc analysis of two parallel-sequential adjuvant trials of L-methylfolate in patients with MDD (Papakostas et al. 2012) was conducted while considering the influence of inflammatory markers. It was found that BMI >30 as well as increased concentrations of TNF, IL-8, CRP, and leptin over the median, alone or in combination with each other or with IL-6, predicted greater symptom improvement (Shelton et al. 2015). Stratified analyses based on inflammatory biomarkers have not been conducted with SAMe, yet these findings with L-methylfolate support the value of targeting such therapies to MDD patients with high inflammation. Furthermore, whether strategies that augment BH4 restore DA function or improve inflammation-related symptoms of reduced motivation or motor slowing remain to be determined. Replacement of DA with the precursor L-DOPA is known to improve motor function and has also been shown to increase motivation in patients with PD (Czernecki et al. 2002). An ongoing trial will determine whether L-DOPA administration has an antidepressant effect in aged persons with motor slowing (NCT02744391).

Although classical stimulant medications that increase DA release and/or block DA reuptake increase motivation in rodent models (Yohn et al. 2015; Randall et al. 2015), they have demonstrated only limited efficacy in chronically treating fatigue and other DA-related symptoms in trials for patients with cancer and other medical illnesses that are associated with inflammation (Mar Fan et al. 2008; Moraska et al. 2010; Butler et al. 2007; Sugawara et al. 2002; Pucci et al. 2007; Stankoff et al. 2005; Bruera et al. 2013; Ruddy et al. 2014; Escalante et al. 2014; Gong et al. 2014). Since stimulants act to increase DA release and block DAT function to increase synaptic levels of available DA, these drugs may not provide long-term efficacy in the context of inflammation during medical illness. However, new evidence indicates that in MDD patients with high inflammation (as measured by CRP) exhibit a greater antidepressant response to SSRIs used in combination with the DAT blocker bupropion compared to SSRI monotherapy (Jha et al. 2017). Although no data exists in humans, adenosine A2A receptor antagonists (which facilitate DA receptor signaling) reverse the effects of IL-1beta on effort-based sucrose preference (Nunes et al. 2014). Furthermore, DA agonists, such as pramipexole, have demonstrated efficacy in patients with treatment-resistant depression (Cassano et al. 2004; Cusin et al. 2013; Franco-Chaves et al. 2013). Although it is unknown whether this effect is specific to high inflammation in MDD patients, it has been shown to block

endotoxin-induced degeneration of nigrostriatal DA cells in rodents (Iravani et al. 2008).

4.3 Therapies That Target Glutamate

Inhibition of glutamate signaling may be an important target in reversing the impact of inflammation in the brain (Target 2, Fig. 1). With regard to preventing activation of the KYN pathway, the IDO antagonist, 1-methyl-tryptophan (1-MT), has been shown to abrogate the impact of LPS, as well as an attenuated form of *Mycobacterium bovis*, on depressive-like behavior (O'Connor et al. 2009a, b). Given that inflammation can cause neurotoxic effects via increased QUIN and excessive glutamate (Schwarcz and Pellicciari 2002; Tavares et al. 2002, 2005), glutamate receptor antagonists may be useful in preventing excitotoxicity and oxidative stress and may reverse or prevent inflammation-related behavioral change. Indeed, one study in rodents demonstrated that the NMDA antagonist ketamine was able to reverse LPS-induced depressive-like behavior including sucrose preference, a measure of anhedonia (Walker et al. 2013). Ketamine had no effect on LPS-induced inflammation in the brain or CNS activation of IDO or decreases in BDNF expression. Moreover, blockade of AMPA receptors was able to reverse ketamine's effects on LPS-induced depressive-like behavior, indicating that the effects of ketamine were specific to its impact on glutamate signaling. In humans, administration of the NMDA antagonist ketamine has potent antidepressant effects in MDD patients who are resistant to standard therapies and who often exhibit increased inflammation (aan het Rot et al. 2010; Price et al. 2009; Raison et al. 2013b). Interestingly, a recent study in treatment-resistant depression found that patients who were most responsive to ketamine were those with the highest concentrations of serum IL-6 (Yang et al. 2015). However, another study found that although treatment-resistant depressed patients exhibited increased IL-6 compared to controls, IL-6 and other inflammatory cytokines were not associated with treatment response to ketamine (Kiraly et al. 2017). There are also drugs available or in development that influence glutamate reuptake (e.g., riluzole); however there have been no studies examining their ability to reverse the effects of inflammation in patients with MDD. In sum, future therapies that block KYN pathways or modulate glutamate may confer protection against inflammation and/or IDO-mediated behavioral symptoms in patients with MDD.

4.4 Diet, Supplements, and Alternative Strategies

In terms of modifying the environmental exposures and lifestyle factors that contribute to inflammation in depression (Target 3, Fig. 1), studies have investigated the efficacy of exercise, weight reduction, certain diets, as well as supplements such as omega-3 fatty acids, yoga, massage, tai chi, cognitive behavioral therapy, and meditation to reduce psychiatric symptoms such as depression and anxiety. Many

of these interventions have been shown to induce a variety of immune changes including a reduction in inflammation (Bower and Irwin 2016). For example, mindfulness meditation has been shown to increase functional connectivity between the posterior cingulate cortex and the left dorsolateral prefrontal cortex, which in turn was associated with decreases in IL-6 over a 4-month period (Creswell et al. 2016). In addition, both cognitive behavioral therapy and tai chi were associated with reduced levels of CRP, monocyte production of inflammatory cytokines, and inflammatory gene expression in elderly patients with insomnia (Irwin et al. 2015). Both diet and exercise programs have been shown to have antidepressant and antianxiety effects (Schuch et al. 2016; Fabricatore et al. 2011) and to reduce a variety of inflammatory markers in longitudinal studies (Forsythe et al. 2008; Woods et al. 2009). A hatha yoga program was also shown to reduce LPS-induced peripheral blood mononuclear cell production of TNF, IL-6, and IL-1beta as well as fatigue at 3 months in breast cancer survivors (Kiecolt-Glaser et al. 2014). These studies have, however, failed to determine whether changes in inflammation or immune function are required for the efficacy of these interventions (Miller et al. 2017).

The impact of the vast array of dietary supplements including curcumin, resveratrol, and ginger supplementation on the immune system and inflammation has been studied, yet the most common supplements studied in MDD patients involve omega-3 fatty acids. Meta-analyses have shown significant antidepressant efficacy especially for eicosapentaenoic acid (EPA) (Mocking et al. 2016). A recent study demonstrated that patients with a compilation of inflammatory markers including increased CRP and IL-1ra had a greater antidepressant response to EPA, whereas individuals with increased CRP and IL-6 were less responsive to placebo (Rapaport et al. 2016). Although there is some in vitro and in vivo data supporting anti-inflammatory effects of omega-3 fatty acids in humans (Rangel-Huerta et al. 2012), data linking these effects to their impact on behavior including depression is warranted. Therefore, an ongoing trial is currently investigating links between the antidepressant effects of omega-3 fatty acids and anti-inflammatory responses (NCT02553915). Antioxidant supplements such as *N*-acetyl-D-cysteine have also been included in meta-analyses of the antidepressant efficacy of anti-inflammatory drugs (Rosenblat et al. 2016), even though ability to specifically modulate inflammation has yet to be determined.

5 Summary and Conclusions

This chapter has presented evidence that inflammation is increased in a subset of patients with MDD and that it may play a role in depressive symptoms and influence response to antidepressants in these patients. In addition to observations regarding lack of response to conventional antidepressants in patients with increased peripheral blood markers of inflammation, such as CRP, a vast literature has described the effects that inflammation and cytokines have on neurotransmitters and circuits in the brain. These findings stem largely from over a decade of clinical and translational neuroimaging studies examining the effects of the acute and chronic administration

of inflammatory stimuli on the brain. Results have indicated that inflammation affects brain regions relevant to reward, motor activity, and threat sensitivity to lead to symptoms of reduced motivation, motor slowing, and anxiety and these changes are largely driven by effects on monoamines, like DA, and glutamate. These findings are now being translated to better understand the role of inflammation in behavioral symptoms in patients with psychiatric illness and especially MDD.

The current data indicate that novel strategies to block inflammation or reverse its effects on the brain are promising, yet incomplete, and much additional work is needed in the area to move treatment development forward. More informed trials using drugs with known targets and selecting patients based on peripheral inflammation levels using markers such as CRP will contribute to progress in this regard. Another challenge in this area is the ability to image the effects of such treatments on the brain. Although attempts have been made to image local activation of CNS immune cells in these patients, evidence described herein of the functional and neurotransmitter effects of increased inflammation on the brain as measured by fMRI, PET, and MRS have most consistently been associated with increased peripheral inflammatory markers as well as behavior and may be best suited for use in future treatment trials. Coupling measures of target engagement in the brain – for both pharmacological and behavioral intervention studies – with outcome variables based on behaviors that are known to be impacted by inflammation (e.g., motivation, motor activity, or anxiety), will significantly strengthen the interpretation of future results. A number of trials that embrace at least some of these features are under way and may reveal additional information regarding novel therapies for patients with a wide variety of psychiatric disorders and evidence of increased inflammation.

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NMDA Antagonists for Treatment-Resistant Depression

Nuri B. Farber

Contents

Abstract

Fifteen to thirty percent of patients with major depressive disorder do not respond to antidepressants that target the monoaminergic systems. NMDA antagonists are currently being actively investigated as a treatment for these patients. Ketamine is the most widely studied of the compounds. A brief infusion of a low dose of this agent produces rapid improvement in depressive symptoms that lasts for several

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days. The improvement occurs after the agent has produced its well characterized psychotomimetic and cognitive side effects. Multiple infusions of the agent (e.g., 2–3× per week for several weeks) provide relief from depressive symptoms, but the symptoms reoccur once the treatment has been stopped. A 96-h infusion of a higher dose using add-on clonidine to mitigate the psychotomimetic effects appears to also provide relief and resulted in about 40% of the subjects still having a good response 8 weeks after the infusion. As this was a pilot study, additional work is needed to confirm and extend this finding. Nitrous oxide also has had positive results. Of the other investigational agents, CERC-301 and rapastinel remain in clinical development. When careful monitoring of neuropsychiatric symptoms has been conducted, these agents all produce similar side effects in the same dose range, indicating that NMDA receptor blockade produces both the wanted and unwanted effects. Research is still needed to determine the appropriate dose, schedule, and ways to mitigate against unwanted side effects of NMDA receptor blockade. These hurdles need to be overcome before ketamine and similar agents can be prescribed routinely to patients.

Keywords
CERC-301 · Ketamine · Major depressive disorder · Memantine · Nitrous oxide · NMDA antagonists · Rapastinel · Treatment-resistant depression

1 Introduction

All currently approved antidepressant medications interact with brain monoamine systems – serotonin, norepinephrine, and dopamine (see Chockalingam et al. 2018; Lochmann and Richardson 2018; Shelton 2018; Schwasinger-Schmidt and Macaluso 2018). While they have had a significant impact on improving the lives of people suffering from major depressive disorder, approximately 15–30% of individuals with depression have a severe form that is resistant to standard antidepressant treatments (Trevino et al. 2014; John Rush and Jain 2018), leading to extended suffering, excess healthcare costs, and elevated risk of suicide (Petersen et al. 2004; Mrazek et al. 2014). Treatment approaches that do not directly target the monoaminergic systems offer the theoretical potential of providing relief to those individuals suffering from treatment-resistant depression (TRD).

Glutamate (Glu) is an amino acid and is the major excitatory neurotransmitter in the brain, estimated to be present in over 50% of the synapses. In the adult human brain, the *N*-methyl-D-aspartate (NMDA) Glu transmitter system is thought to play an important role in memory and cognition and in sensory information processing to name but a few of its many functions. NMDA antagonists by blocking NMDA receptors produce a NMDA receptor hypofunction (NRHypo) state, which is associated with psychiatric symptoms. PCP and ketamine, two NMDA antagonists, are classified as dissociative anesthetics. Early studies found that with this type of anesthesia, adult patients exhibited psychiatric symptoms (referred to as an "emergence reaction") including maniacal excitation, catatonic signs, euphoria,

hallucinations, delusions, and agitation (White et al. 1982; Reich and Silvay 1989). More recent studies employing ketamine in subanesthetic doses have confirmed some of these initial findings, but the symptoms produced were milder and not as extensive (Krystal et al. 1994; Malhotra et al. 1996; Newcomer et al. 1999). In these carefully controlled later studies, very low doses of ketamine produced selective impairments in explicit/declarative memory in the absence of psychosis. Higher subanesthetic doses of ketamine produced positive symptoms (delusions and hallucinations) and still higher subanesthetic doses produced thought disorder. Because these later studies were appropriately concerned with minimizing symptom severity and protecting human subjects from unpleasant experiences, they did not produce the full range of symptoms seen in the earlier studies using anesthetic doses of PCP and ketamine. However, the dose dependence of ketamine-induced core schizophrenia-like symptoms suggests that if higher doses of ketamine had been used in the later studies, the full variety and severity of effects seen in earlier studies probably would have been produced. The ability of competitive NMDA antagonists, which are structurally dissimilar from PCP and ketamine and block the NMDA receptor at a completely different site, to produce similar neuropsychiatric sequelae (Kristensen et al. 1992; Herrling 1994; Grotta et al. 1995) indicate that producing a NRHypo state is the likely mechanism via which ketamine and PCP produce their psychotomimetic effects. Such effects would be expected to accompany any treatment that substantially produced a NRHypo state unless these effects were mitigated.

2 Ketamine

2.1 Initial Studies with Ketamine as an Antidepressant

Soon after the initial studies examining the psychotomimetic effects of ketamine in humans, Berman et al. (2000) made the initial observation that ketamine had antidepressant activity in a group of nine individuals. This initial crossover study utilized a brief 40-min infusion of ketamine (0.5 mg/kg) which was the same dose used by Krystal et al. (1994) to describe some of the cognitive and behavioral effects of ketamine. With this dose of ketamine, Berman and colleagues noted a significant reduction in depressive symptoms. This observation was notable for two key reasons. First the improvement in depressive symptoms was not seen during the 40-min infusion or soon thereafter, indicating that it was not a reflection of the psychotomimetic effects (i.e., an intoxication syndrome) but rather was detectable initially at 240 min–over 3 h after drug exposure had stopped and when emergence phenomena were no longer present. The antidepressant response continued to increase over the next several days. This time course indicates that the antidepressant response is not due directly to the intoxication syndrome itself but rather is the result of having been in a NRHypo state. Second compared to the days to weeks that are required for monoaminergic agents to have an effect, the response was rapid (hours), indicating that it is possible to reverse the depressive state more rapidly than previously imagined.

Subsequent studies have confirmed these initial observations, lending hope that NMDA antagonism might provide a novel antidepressant mechanism (Li et al. 2010; Williams and Schatzberg 2016). Including the initial Berman et al. report, research groups have tested the antidepressant effects of a brief infusion of ketamine in 162 individuals with either unipolar (Berman et al. 2000; Zarate et al. 2006a; Sos et al. 2013; Murrough et al. 2013) or bipolar depression (Diazgranados et al. 2010) and found a significant reduction in depressive symptoms lasting approximately 1 week using 0.5 mg/kg ketamine infused over a 40-min period (Xu et al. 2016). This infusion rate of ketamine typically produces peak serum total (R + S) ketamine levels of approximately 180 ng/mL (Zhao et al. 2012). Such a level of ketamine would be expected to block approximately 30% of NMDA receptor activity (Emnett et al. 2013) (Table 1). However, this calculation is based upon the assumption that serum levels are the same as CNS levels, which might not be the case as there is some evidence that CNS levels could be up to twofold to fivefold higher (Pedraz et al. 1991) and does not factor the impact of physiological magnesium as the Emnett et al. study was done in the absence of magnesium.

Having an antidepressant effect at a serum concentration in the range of its NMDA receptor affinity indicates that this site could be responsible for its antidepressant effect. One of ketamine's metabolites, 2*R*,6*R*-hydroxynorketamine, has agonist activity at the AMPA receptor and has been found to have antidepressant actions in a rodent model (Zanos et al. 2016), suggesting that the AMPA receptor could also be a potential site. However, the ability of nitrous oxide (as well as

Table 1 Ketamine concentrations and % inhibition of NMDA receptors

[Ketamine] in ng/mL	[Ketamine] in μM	% NMDA receptor blockade[a]
25	0.10	5
50	0.21	10
100	0.42	20
150	0.63	28
200	0.84	35
250	1.0	40
300	1.3	45
350	1.5	49
400	1.7	53
450	1.9	56
500	2.1	59
600	2.5	64
700	2.9	68
1,000	4.2	76
1,500	6.3	83
2,000	8.4	87
3,000	12	91
5,000	21	95

[a]Calculated from Emnett et al. (2013)

other NMDA antagonists), which does not have any metabolites but does have either no or even mild AMPA antagonistic activity (Jevtovic-Todorovic et al. 1998a; Mennerick et al. 1998), to treat TRD indicates the NMDA receptor blockade must be responsible for some of ketamine's activity. 2*R*,6*R*-hydroxynorketamine's activity at the AMPA site might produce additional benefit based upon the basic science understanding of ketamine's effects (see below).

While ketamine appears to have an ameliorative effect in both unipolar and bipolar depression, the effect appears to be weaker in the bipolar variant with the effect lasting approximately 3 days in people with bipolar depression compared to 5–7 days in unipolar depression (Xu et al. 2016). Evolving evidence about other predictors of response suggests that those patients with an anxious phenotype (Ionescu et al. 2014, 2015) or with a family history of alcohol use disorder (Phelps et al. 2009; Luckenbaugh et al. 2012; Niciu et al. 2014; Pennybaker et al. 2017) have a preferential positive response to ketamine. Imaging has shown that people who respond to ketamine had increased elicited activity in the anterior cingulate cortex prior to ketamine (Salvadore et al. 2009) and larger fractional anisotropy in the cingulum and forceps minor (Vasavada et al. 2016).

This focus on brief, low-dose infusions (Lai et al. 2014) stems from ketamine's propensity to have significant neuropsychiatric side effects, including impaired declarative memory, dissociation, confusion, and even overt psychosis (Newcomer et al. 1999; Morgan et al. 2004). These neuropsychiatric effects are highly correlated with plasma ketamine concentrations (Bowdle et al. 1998; Newcomer et al. 1999). For example, Newcomer et al. (1999) showed that impairment in verbal declarative memory performance occurs at very low ketamine levels (<10 ng/mL) while there is no effect on BPRS positive symptoms. BPRS positive symptoms begin to appear at a steady-state ketamine level of 20 ng/mL (about 5% blockade; Table 1), and these symptoms are even greater at 90 ng/mL (approximately 18% blockade; Table 1). While the change in positive symptoms was significant, it should be pointed out that the effects were subtle and mild; rarely did subjects reach a full psychotic state. This was by design as the subjects were normal volunteers, and for safety reasons the study was designed to not produce clinically significant symptoms. It is not likely that such mild and subtle changes in BPRS positive symptoms would be detected if standardized scales sensitive to such changes are not used. In addition to psychotomimetic side effects, another safety concern with ketamine is sympathomimetic effects, including increased blood pressure and elevated pulse (Luckenbaugh et al. 2014).

While NMDA antagonists produced a dose-dependent increase in psychotomimetic effects, the important question is whether significant and clinically useful antidepressant effects of ketamine can be seen at levels lower than that for these unwanted side effects. To evaluate this question, even lower doses of ketamine in the treatment of depression have been explored (Lai et al. 2014; Lapidus et al. 2014; Loo et al. 2016). While these lower doses do ameliorate depressive symptoms, they are less effective both in degree of symptom relief and duration of symptom relief (Xu et al. 2016). Thus, while lower doses might be better tolerated, the clinical utility of this approach is unclear.

This dose response nature of the antidepressant response suggests that doses higher than 0.5 mg/kg over 40 min could produce a more robust antidepressant response. However, because the neuropsychiatric side effects of ketamine occur at serum levels below that obtained with this dose of ketamine, attempts at increasing ketamine serum levels will likely result in even greater side effects and the inability of subjects to tolerate the higher levels desired for a more robust antidepressant response. Thus, attempts at producing a more robust clinical response with higher doses of ketamine require a mitigation of ketamine's side effects. Basic science research has improved our understanding of how to mitigate these effects.

2.2 The NRHypo State Is a Disinhibition Syndrome

Preclinical research on ketamine and other NMDA antagonists (Farber et al. 2003) has found that these agents produce a disinhibitory syndrome in which cholinergic pathways arising out of the basal forebrain, as well as glutamatergic pathways arising out of the thalamus, become hyperactive via loss of GABAergic inhibition (see Fig. 1 for depiction of the neurocircuitry underlying the NRHypo state). These two disinhibited excitatory pathways converge on the same downstream corticolimbic neurons, thus hyperactivating them and leading to cognitive deficits, complex behavioral, as well as histopathological effects (Newcomer et al. 1999; Farber 2003). Several pharmacological approaches (Table 2) can restore control over the disinhibited pathways in animals and prevent these side effects in humans (Farber 2003). While any of these agents could be used to prevent the unwanted neuropsychiatric effects, thought needs to be given to whether these same protective agents (safeners) would interfere with ketamine's antidepressant effect.

2.3 Downstream Activation of AMPA Receptors Could Be Responsible for Ketamine's Antidepressant Effects

Activation of AMPA receptors (and its downstream consequences) by NMDA antagonists is necessary for the antidepressant effects to be seen in rodent models of depression (Maeng et al. 2008; Li et al. 2010; Autry et al. 2011; Koike et al. 2011). The downstream consequences of NMDA receptor blockade and AMPA receptor activation are multiple and include increased brain-derived neurotrophic factor (BDNF), activation of mammalian target of rapamycin (mTOR), increased protein synthesis, and synaptogenesis. Whether a similar mechanism is involved in ketamine's clinical action in TRD is unclear, but studies in humans have shown that ketamine leads to increased levels of Glu and glutamine (Milak et al. 2016) and increased glucose metabolism (Li et al. 2016) and that increased evoked cortical excitability, possibly via non-NMDA receptors, correlates with antidepressant response (Cornwell et al. 2012). The hypothesized activation of AMPA receptors could be a consequence of the disinhibited glutamatergic projection arising from the thalamus that is involved in the psychotomimetic effects of the NRHypo state

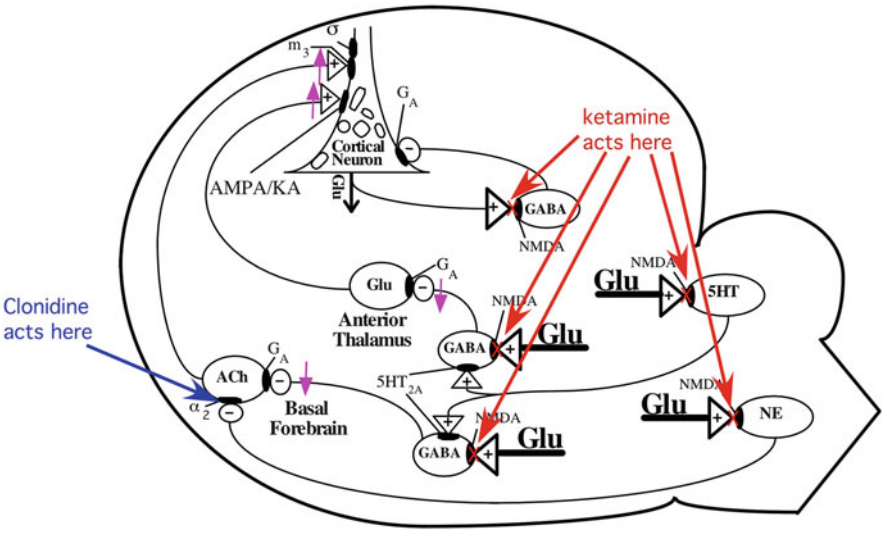

Fig. 1 NRHypo disinhibition circuit. In certain circuits in normal brain tonic Glu release acts at NMDA receptors to stimulate GABAergic inhibitory neurons. These GABAergic neurons inhibit two key stimulatory pathways – a cholinergic pathway that arises from the basal forebrain and a glutamatergic pathway that arises from the thalamus. These two pathways stimulate downstream cortical pyramidal neurons. NMDA antagonists like ketamine block NMDA receptors throughout the brain but by blocking the NMDA receptors in the NRHypo circuit they prevent stimulation of these key GABAergic neurons. This lack of stimulation results in the loss of GABAergic inhibition (down purple arrows) causing the two excitatory pathways to become disinhibited and to fire excessively (up purple arrows). This combined disinhibited firing results in the histological, cognitive, and psychotomimetic side effects of ketamine. The excessive stimulation of the downstream AMPA/KA receptor also could be responsible for the antidepressant effects of NMDA antagonists. There are additional serotonergic and adrenergic control elements. The adrenergic control element is of import as it appears to provide additional control only over the cholinergic arm. Clonidine by stimulating an α-2 adrenergic receptor on the cholinergic neuron inhibits this neuron and decreases the amount of excessive release of ACh in the cortex during NMDA antagonist exposure. Published with the kind permission of Farber (2017). All rights reserved

Table 2 Agents that prevent NRHypo effects in animals and psychosis in humans

Agent	Animals	Humans
GABAergic agents	Olney et al. (1991), Ishimaru et al. (1995), and Jevtovic-Todorovic et al. (1997)	Magbagbeola and Thomas (1974) and Reich and Silvay (1989)
α-2 adrenergic agonists	Farber et al. (1995, 2002b)	Levanen et al. (1995), Newcomer et al. (1998), and Handa et al. (2000)
Clozapine	Farber et al. (1996)	Malhotra et al. (1997)
Lamotrigine	Farber et al. (2002a)	Anand et al. (2000)

(Fig. 1). If the activation of AMPA receptors were due to disinhibition of the thalamic glutamatergic pathway, then the use of agents that restore control over this arm of the circuit (e.g., GABAergic agents, anticonvulsants) would be predicted to ameliorate ketamine's side effect profile but also to prevent its antidepressant effects.

For that reason α-2 adrenergic agonists might be the class of agents that would be ideal safeners. The basis for α-2 agonist co-administration stems from preclinical research on NMDA antagonists (Farber et al. 1995) showing that α-2 agonist co-administration dampens the cholinergic pathway (Farber et al. 2002b), relieving some of the excessive stimulation of the downstream corticolimbic neurons (Fig. 1), thereby reducing pathologic effects of NMDA antagonists (Newcomer et al. 1998; Jevtovic-Todorovic et al. 1998b). These agents are not known to interact with the glutamatergic arm of the circuit. However, they do ameliorate the psychotomimetic effects of ketamine (Levanen et al. 1995; Newcomer et al. 1998; Handa et al. 2000; Sigtermans et al. 2009; Schwartzman et al. 2009; Nitta et al. 2013). Thus, the co-administration of an α-2 agonist may allow for higher dosing of ketamine for treatment-resistant depression without producing intolerable side effects.

2.4 Extending Duration of Response

While the totality of studies looking at ketamine infusions supports the conclusion that blocking NMDA receptors can provide significant antidepressant effects to those with TRD, the response is short-lived, lasting only up to maybe a week (Xu et al. 2016). Thus, an important issue facing the field is how to turn this observation into a treatment that people with TRD can use on a long-term basis. Initial forays with serial brief low-dose infusions (e.g., 0.5 mg/kg over 40 min three times per week) have been explored (Liebrenz et al. 2009; Rasmussen and Lineberry 2013; Singh et al. 2016). While improvement in depression occurs over the approximately first week of treatment, the improvement then reaches a plateau, and, potentially more importantly, the symptoms appear to quickly return once the infusions are stopped (Liebrenz et al. 2009; Murrough et al. 2012; Rasmussen and Lineberry 2013; Cusin et al. 2017). These early findings suggest that low-dose serial infusions need to be continued in order to maintain the observed response. Chronically giving ketamine to patients with TRD likely is not feasible for the vast majority of people as ketamine must be given either intravenously or intramuscularly because of the poor bioavailability of oral ketamine. To address the bioavailability issue, Janssen has developed an intranasal preparation of s-ketamine, which is the optical isomer, which has the stronger NMDA binding affinity (Zeilhofer et al. 1992; Ebert et al. 1997). As the two optical isomers have similar neuropsychiatric side effects once the doses are adjusted for their differences in binding affinity (Niesters and Dahan 2012), the neuropsychiatric side effects would still likely be present and need to be minimized so that patients could continue to function in their normal daily life in a reasonable fashion.

In a report on a recently completed Phase II trial, subjects, who had failed to respond to at least two or more antidepressants, received either 1 or 2 weeks of twice-a-week placebo, 28, 56, and 84 mg of s-ketamine in a randomized double-blind fashion (Daly et al. 2018). After the conclusion of the double-blind phase, subjects could enter a 59-day open-label phase during which s-ketamine was continued but at a decreased frequency (twice weekly × 2 weeks, weekly × 3 weeks, and then every other week thereafter). During the double-blind phase, s-ketamine produced a rapid response compared to placebo as measured by the MADRS, and the effect was dose dependent. In those subjects, who had received s-ketamine for 2 weeks, 38% (28 mg), 36% (56 mg), and 50% (84 mg) had a greater than 50% decrease in their MADRS score (vs. 10% for placebo). Improvement was maintained during the open-label decreasing frequency maintenance phase as well as during a subsequent 8-week follow-up phase when no s-ketamine was given. Neuropsychiatric symptoms while frequent were mainly mild to moderate in severity and transient. The most common effect was dizziness (39%), dissociative symptoms (25%), and dysgeusia (23%). Consistent with the experience with i.v. ketamine transient increases in both BP (mean increase of 19/10 mmHg) and pulse (mean increase of 9 beats per minute) were also seen. While such a formulation could conceivably be used by patients on a chronic basis at home, the trial required dosing of the agent at a treatment center.

Another potential dosing approach to ketamine is suggested by work with this agent in the treatment of neuropathic pain. In order to obviate a need for long-term daily blockade of NMDA receptors, groups studying ketamine for chronic pain have tested prolonged, moderately high-dose ketamine infusions of 4–14 days to provide sustained pain relief (Dahanl et al. 2011; Niesters et al. 2014). The rationale is that a prolonged blockade of NMDA receptors causes long-term changes in signal transduction leading to sustained clinical improvement (Sigtermans et al. 2009). Results of these studies have been promising with subjects obtaining relief for up to 77 days after the termination of the infusion (Sigtermans et al. 2009; Dahanl et al. 2011).

Based on these results in patients with pain, a 4-day infusion of moderate-dose ketamine has been explored for patients with TRD (Lenze et al. 2016) in the hope that such an approach would provide for a more sustained antidepressant response after the infusion ended. In this feasibility study, 96-h moderate-dose ketamine infusions (up to 0.6 mg/kg h) in people with TRD ($n = 10$) were compared to the more frequently studied brief 40-min exposure ($n = 10$). Clonidine (up to 0.3 mg po bid) was used to diminish the neuropsychiatric and cardiovascular side effects. Subjects undergoing the 96-h infusion developed 2.7-fold higher ketamine concentrations than the 40-min group (424 ng/mL vs. 156 ng/mL) but had similar degrees of neuropsychiatric and cardiovascular side effects. While the study was not designed to demonstrate that clonidine has an ameliorative effect on these symptoms, the results are suggestive that clonidine was effective in mitigating these side effects and resulted in subjects being able to tolerate higher ketamine serum levels. Such a conclusion is consistent with other findings that demonstrate such an ability of α-2 adrenergic agonists (Levanen et al. 1995; Newcomer et al. 1998; Handa et al. 2000; Sigtermans et al. 2009; Schwartzman et al. 2009;

Nitta et al. 2013). Both treatment groups demonstrated rapid antidepressant effects, as measured by the CGI-I on post-infusion day 1: 7/10 in each arm had had a score in the "much" or "very much improved" range. Additionally, both arms showed sustained reduction in depressive symptoms in some subjects compared to baseline: 4/10 having a CGI-I of 1–2 at week 8 in the 96-h arm vs. 2/10 in the 40-min arm. While the 96-h arm numerically had a twofold increase in the number of subjects who maintained a prolonged response, the study was not powered to determine whether the two groups had a differential outcome. Exploratory analyses examining the relationship of ketamine exposure with sustained antidepressant effects and psychotomimetic side effects found that higher ketamine concentrations were associated with better sustained antidepressant response, but not higher side effects, in the 96-h arm. This finding is consistent with the position that higher doses are more efficacious and that clonidine would alleviate unwanted side effects. The results of this pilot work indicate the feasibility of using α-2 agonists to improve the tolerability of ketamine such that higher doses can be used for longer periods of time and support the notion that such an approach could result in more sustained benefit. Additional work is needed to confirm these tentative conclusions and to develop a treatment approach that could be used in routine clinical practice.

2.5 Ketamine: Conclusion

In conclusion, multiple groups have found that ketamine produces a rapid antidepressant response in individuals who have been resistant to antidepressants that target different monoaminergic sites. Several hurdles need to be overcome before this observation can be turned into a useful clinical treatment that can be routinely given to patients. Hurdles include determining the optimal dose and scheduling such that the response can be maintained on a chronic basis and diminishing side effects to make the treatment more tolerable.

3 Non-ketamine NMDA Antagonists

Based on this initial experience with ketamine, multiple groups have been developing and/or exploring other NMDA antagonists for their utility as novel antidepressants.

3.1 Nitrous Oxide

Nitrous oxide is a volatile anesthetic. Its mechanism of action remained a mystery until it was shown to have mixed competitive and noncompetitive NMDA antagonist properties (Jevtovic-Todorovic et al. 1998a; Mennerick et al. 1998; Nagele et al. 2004). Nagele et al. (2015) in a double-blind placebo-controlled crossover trial with 20 patients suffering from TRD found that 50% nitrous oxide over 60 min produced

a significant improvement in depression as judged by the HDRS-21 at both 2- and 24-h postexposure. Twenty percent of subjects ($n = 4$) had a $\geq$50% reduction in their severity, and of that group three had a complete remission of symptoms (HDRS $\leq$ 7). Consistent with results from studies using a single exposure to ketamine, by 1-week postexposure, the effects of nitrous oxide on depression were no longer apparent. Given its relatively selective NMDA activity (Jevtovic-Todorovic et al. 1998a; Mennerick et al. 1998) and its unique chemical structure, the ability of nitrous oxide to improve TRD confirms that ketamine exerts it antidepressant activity at least in part by blocking NMDA receptors.

The treatment was relatively well tolerated. No clinically apparent psychosis was reported. However, structured scales were not used, and thus subtle effects might have been missed. Consistent with this conclusion, anxiety-like effects, which could be subtle psychotomimetic effects, were experienced by 15% of the subjects. Overall 25% of the subjects had the treatment interrupted or discontinued because of side effects.

3.2 Traxoprodil (CP-101,606)

Traxoprodil is a selective antagonist of the NR2B subunit of the NMDA receptor. In a double-blind placebo control trial (Preskorn et al. 2008), it was added onto paroxetine (40 mg) in patients with MDD who had failed to respond to at least one SSRI. Traxoprodil was given as either an 8-h (0.75 mg/kg h $\times$ 1.5 h + 0.15 mg/kg h $\times$ 6.5 h) or 1.5-h (0.5 mg/kg h) infusion, and the change in severity of depression was determined 4 days after drug exposure. The agent ($n = 15$ subjects) produced a statistically significant improvement in depression scores 4 days after its infusion as judged by the MADRS and HDRS. Sixty percent of the subjects had a 50% decrease in depression severity, and 33% had remission of their symptoms. While the medication was tolerated with there being no dropouts, 40% had CNS symptoms associated with NMDA exposure in humans (impaired attention, impaired memory, disturbance of time, body, and/or environmental perception, stilted speech, emotional withdrawal, impaired coordination, emotional blunting, intense emotional reaction, anxiety, feelings of unreality and loss of control over thought processes, concrete thinking, bizarre reasoning, illusory experiences, out-of-body experience, tunnel vision, derealization, depersonalization, suspiciousness, ideas of reference, paranoid thoughts, loosening of association, thought derailment, conceptual disorganization, confusion). These results confirm the results seen with ketamine that brief blockade of the NMDA receptor produces a quick and robust antidepressant response. Furthermore, the results argue that both the antidepressant and psychotomimetic effects are a consequence of blockade of NMDA receptors containing the NR2B subunit. Because the drug was found to also prolong the QT interval, it was dropped from further development (https://en.wikipedia.org/wiki/Traxoprodil; accessed 8/11/2017).

3.3 MK-0657 (CERC-301)

MK-0657 is another selective NR2B antagonist. In a double-blind placebo-controlled, crossover pilot study (Ibrahim et al. 2012), five individuals with TRD who received MK-0657 (4–8 mg, po qDay) for 12 days showed significant improvement in depression as judged by the HDRS and BDI but showed no significant improvement with the MADRS. The study was terminated early because the compound, which was being developed for the treatment of Parkinson's disease, was dropped from development by the manufacturer. Rights to the compound were obtained by Cerecor, who initiated two Phase II trials of compound, renamed CERC-301. While no peer-reviewed results have been published, the first study apparently showed that CERC-301 (8 mg/day) did not improve depressive symptoms as judged by the HDRS in 135 patients with TRD. A second Phase II study (NCT02459236), recently completed, is evaluating the efficacy of 12 and 20 mg in patients with TRD. The study completed enrollment in late 2016. While no published results exist, reports suggest the compound failed to demonstrate efficacy on its primary endpoints, though subanalyses did suggest some efficacy (https://www.streetinsider.com/Corporate+News/Cerecor+(CERC)+Announces+CERC-301+Phase+2+Missed+Primary+Endpoint+in+MDD/12292976.html; accessed 8/11/2017). It is unclear whether psychotomimetic effects were seen at these doses. In addition, it is unclear to what extent the different dosing schedule – chronic daily dosing of the NMDA antagonist vs. intermittent dosing – has in altering the ability to detect and/or produce an antidepressant response. The drug remains in development.

3.4 Memantine

In an early, open-label, flexible dosing (20–40 mg/day) explorative study (Ferguson and Shingleton 2007), memantine showed early evidence for efficacy in seven individuals with depression who completed the 8-week study. However, subsequent more rigorous studies have not found any effect of memantine on depression. Zarate et al. (2006b) found no effect on major depression with memantine (5–20 mg/day) when it was given in a blinded fashion ($n = 16$ memantine; $n = 16$ placebo) at 8 weeks with the MADRS as a primary endpoint. Memantine (5–20 mg/day; $n = 15$) also failed to separate from placebo ($n = 16$) in an 8-week trial when it was added onto the current antidepressant regimen in subjects with major depression who were nonresponsive or partially responsive to their current medication (Smith et al. 2013). Similarly, memantine (20 mg; $n = 14$) compared to placebo ($n = 15$) has also not been found to be effective as an augmenting agent in subjects with a bipolar depressive episode who were on a stable dose of lamotrigine (100 mg or more) and who were treated in a double-blind fashion for 8 weeks (Anand et al. 2012). Negative CNS effects associated with NMDA receptor blockade were either not reported or were not significantly different from placebo in these studies. As memantine has been shown to have the electrophysiological, histopathological, behavioral, and cognitive side effects associated with the NRHypo state in animals

(Creeley et al. 2006; Emnett et al. 2013), the lack of CNS side effects in humans in these antidepressant studies suggests that 20 mg/day of memantine probably is not sufficient to adequately block the NMDA receptor and at this dose memantine is likely interacting with some other neurotransmitter site (Creeley et al. 2006). Whether higher doses of the drug will have antidepressant activity remains to be determined.

3.5 Lanicemine (AZD6765)

Two separate reports exist on the effectiveness of lanicemine (AZD6765), an NMDA antagonist, in patients with TRD. In the first report (Zarate et al. 2013), subjects ($n = 22$) received an infusion of either placebo or lanicemine (150 mg) over 1 h in a double-blind fashion and 1 week later were crossed over to receive an infusion of the other agent. Some improvement was seen in depression as judged by the MADRS and HRDS at 80 and 110 min, but the effect was not seen at subsequent time points over the next week. No psychotomimetic effects were seen with the BPRS at any time point. The second report (Sanacora et al. 2014) consisted of several studies (preclinical rodent, Phase I, Phase IIa, Phase IIb). The Phase IIa study evaluated the utility of lanicemine (100 mg IV over 60 min) compared to placebo in subjects with TRD in a double-blind and random fashion. MADRS score at 24 h was the primary endpoint. No effect was seen at this time point. However, exploratory analyses found an effect at the 1- and 72-h time points. There were no psychotomimetic effects detected with the BPRS or CADSS. A follow-up double-blind, randomized, Phase IIb study was conducted subsequently to evaluate the effectiveness of lanicemine (100 [$n = 51$] or 150 mg [$n = 51$]) compared to placebo ($n = 50$) as an adjunct to ongoing antidepressant treatment in subjects with TRD. Agents were administered three times per week for 3 weeks. After 3 weeks subjects treated with either dose of the active compound displayed significantly greater improvement in the MADRS compared to those receiving placebo. Lanicemine was well tolerated by the subjects, and mild psychotomimetic-like effects were seen in some subjects in the two lanicemine groups based on BPRS ratings. No differences in the CADSS occurred. Lanicemine has been dropped from further clinical development (https://en.wikipedia.org/wiki/Lanicemine; accessed 8/11/2017).

3.6 Rapastinel (Glyx-13)

Given the ability of a variety of NMDA antagonists to treat major depression, Preskorn et al. (2015) evaluated the efficacy of rapastinel (Glyx-13) in the treatment of TRD. Rapastinel is a partial agonist at the glycine site of the NMDA receptor. Glycine is an obligate co-agonist that must be bound to the receptor in order for glutamate to gate the receptor (Mayer and Westbrook 1987; McBain and Mayer 1994). It is estimated that the concentration of glycine in the NMDA synapse is such that it is bound to greater than 80% of the NMDA receptors (Mayer and Westbrook

1987; McBain and Mayer 1994). Being a partial agonist, rapastinel should lower the amount of agonist binding to the glycine site and thus lower the amount of NMDA receptor activity, producing partial blockade of the NMDA receptor system. In this double-blind placebo-controlled pilot study, two separate cohorts were dosed with the drug. In cohort 1, study subjects with TRD received a brief IV infusion of either placebo or one of four doses of rapastinel (1, 5, or 10 mg; $n = 20$ in each arm). In study 2, subjects received either placebo ($n = 14$) or 30 mg of rapastinel ($n = 21$). An inverted "u-shaped" dose response was found. Subjects receiving either 5 or 10 mg had an antidepressant response as judged by the HDRS for up to 1 week after the infusion. No effect was seen with either the 1 or 30 mg dose. A high placebo response rate was seen in the study (64% response rate, 42% remission rate), and it was not significantly different than that seen with rapastinel (70% response rate, 53% remission rate). The drug was well tolerated, and the BPRS did not detect any psychotomimetic-like effects. The compound is currently in Phase III clinical trials.

3.7 D-Cycloserine

D-Cycloserine is another partial agonist at the glycine site of the NMDA receptor that should also produce inhibition of the receptor. Heresco-Levy and colleagues studied the effect of D-cycloserine (1,000 mg po, daily) as an add-on medication in a double-blind, placebo-controlled 6-week trial in 26 individuals with treatment-resistant depression (Heresco-Levy et al. 2013). Approximately 50% of the patients had a greater than 50% improvement in depressive symptoms as measured by the HDRS compared to 15% of subjects in the placebo arm having a similar drop.

4 Conclusion

Experience to date with a variety of NMDA antagonists has shown that a single dose of these drugs produces a rapid antidepressant response that last for several days in people who have been resistant to other antidepressants. When careful monitoring of neuropsychiatric symptoms has been conducted, these agents produce similar side effects in the same dose range. Based on an analysis of receptor binding, these effects are likely due to antagonism of the NR2B subtype of the NMDA receptor. The ability of a metabolite of ketamine to be an agonist of the AMPA receptor might play an additional role in that compound's antidepressant response. The failure of certain agents appears to be due to either underdosing of the compound or unwanted side effects. These results indicate that further research into the clinical utility of NMDA antagonists might lead to the subsequent successful development of this category of agents for the treatment of TRD. However, significant work remains to be done to determine appropriate dosing, dose schedules, and side effect mitigation before these agents enter the routine clinical armamentarium (Newport et al. 2015; Sanacora et al. 2017; Zorumski and Conway 2017).

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Drug Development in Psychiatry: The Long and Winding Road from Chance Discovery to Rational Development

Sheldon H. Preskorn

Contents

Abstract

Based extensively on tables and figures, this chapter reviews drug development in psychiatry with an emphasis on antidepressants from 1950s to the present and then looks forward to the future. It begins with the chance discovery drugs and then moves to through their rational refinement using structure activity relationships to narrow the pharmacological actions of the drugs to those mediating their antidepressant effects and eliminating the effects on targets that mediate adverse effects. This approach yielded newer antidepressants which compared to older antidepressants are safer and better tolerated but nevertheless do still not treat the approximately 40% of patients with major depression (MD) which is unresponsive to biogenic amine mechanisms of action. This form of MD is commonly referred to as treatment resistant depression. Esketamine is an investigational antidepressant which has a novel mechanism of action: blockade of the glutamate NMDA receptor. Positive trials reported this year for esketamine make it likely this drug will be approved next year in the USA. These studies coupled with earlier studies with other NMDA drugs suggest approximately 60%

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of patient with TRD are rapidly and robustly responsive to this mechanism of action. Thus, there appears to be three forms of MD based on pharmacological responsiveness: (a) 60% responsive to biogenic amine mechanisms of action, (b) 24% (i.e., 40 × 60%) responsive to NMDA but not to biogenic amine mechanisms of action, and (c) 16% (i.e., 40 − 24%) not responsive to either of these mechanisms of action. Scientific investigation of these three groups may yield important information about the pathophysiology and/or pathoetiology of these different forms of MD. This information coupled with studies into the neurobiology (e.g., imaging studies, connectomes to name a few approaches being used) and genetics of MD should provide the fundamental knowledge which will permit a rational search for and discovery of newer antidepressant drugs and other somatic and psychotherapeutic approaches to the treatment of patients with different forms of MD based on pathophysiology and pathoetiology. Examples are given of how such discovery and development has occurred in other areas of medicine and even in central nervous system (CNS) space including six novel mechanisms of action CNS drugs which have been successfully developed and marketed over the last 25 years.

Keywords

Antidepressants · Central nervous system biogenic amines · Drug development · Esketamine · Major depression · Mechanism(s) of action · Psychiatric diagnosis · Relative receptor binding · Structure-activity relationships

> [For] knowledge of mental diseases . . .one must have: (a) knowledge of the physical changes in the cerebral cortex, and (b) [knowledge of] the mental symptoms associated with them.
>
> Until this is known, we cannot hope to understand the relationship between. . .symptoms of disease and the. . .physical processes underlying them. . .—Emil Kraepelin (1915), Father of modern psychiatry

> Symptoms and behaviors are the output of brain function whereas syndromes are man-made constructions.—Sheldon Preskorn (2015)

This chapter in the book, "Antidepressants: From Biogenic Amines to New Mechanisms of Action," will discuss the history of antidepressant drug development and put it into the broader context of psychiatric drug development. This chapter will focus on the history of and current status of antidepressant drug development but will also incorporate other concepts relevant to future antidepressants and other central nervous system (CNS) drug development. It will be heavily dependent on the writings of the author on these topics over the last 30 years. The chapter will be primarily focused on illustrative figures and tables with the minimum amount of text needed to explain the figures and tables, put them in context, and then transition to the next topic. All the articles in which figures and tables originally appeared are cited in the reference list. The reader who wants additional text and references on a given topic can do so by referring to the specific cited article of interest.

1 Current Status of Psychiatric Diagnosis as a Rate-Limiting Step in Rational Psychiatric Drug Development

In all of medicine, there are four levels of increasing sophistication of diagnosis as illustrated in Fig. 1 (Preskorn and Baker 2002).

The first level is symptomatic diagnosis which is generally the presenting complaint of the patient to the treatment provider. For patients suffering from major depressive disorder (MDD), that presenting complaint may be feeling tired, absence of enjoyment, insomnia, or even headache to name but a few.

In general, the psychiatrist is then taught to advance to a second level of diagnostic sophistication which is the syndromic level. The result may be that the patient presenting with these initial complaints may meet criteria for major depressive disorder or perhaps acquired immunodeficiency disorder (AIDS) if the patient also has Kaposi's sarcoma, an opportunistic infection, and generalized wasting.

To reach the third level of diagnostic sophistication illustrated in Fig. 1 requires testing for pathophysiological findings. In the case of AIDS, that would be a lowering of the CD 4 count or a positive Western blot test or a high HIV titer. In the case of MDD, there is no generally established testing, but some practitioners might test for cortisol nonsuppression or REM latency which have both been proposed as biochemical test for "endogenous major depression."

To reach the fourth level of diagnostic sophistication illustrated in Fig. 1 requires the establishment of a test for the etiological agent or a neurobiological condition which is not established for most psychiatric disorders with the possible exception being testing for the presence of autoantibodies against the NMDA receptor for patients suffering from NMDA receptor-mediated neuroencephalitis. In the case of AIDS, it would be to test for the presence of the etiological agent the HIV virus.

The above illustrates the basic problem with psychiatric drug development: The field is currently principally stuck at the syndromic diagnosis and has not been able – in general – to advance to the pathophysiological or to the even higher etiological level. However, that is not completely true. In the early 1900s, approximately 20% of admission to psychiatric hospitalization no longer exist. Those conditions were pellagra and general paresis of the insane. The former was due to vitamin D deficiency and the latter to tertiary syphilis. Once those etiological causes were

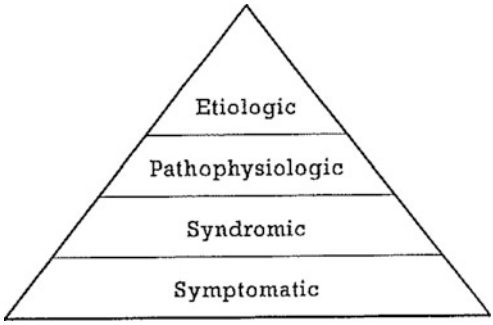

Fig. 1 Diagnostic criteria pyramid – the four levels of increasing diagnostic sophistication. Reproduced with permission from Preskorn and Baker (2002). © Preskorn, 2002

identified and specific treatments identified, those conditions essentially no longer exist in the modern age and instead are consigned to being historical footnotes. In the future, the same will likely be true for major depressive disorder and other similar currently syndromic psychiatric diagnoses.

2 What Possible Changes Lie Ahead for Psychiatric Diagnoses?

Considering the philosophy expressed in my quote at the beginning of this paper, the National Institute of Mental Health (NIMH) in 2008 began to develop for research purposes new ways of classifying mental disorders based on behavioral dimensions and neurobiological measures. The goal being to move from the relatively primitive level of syndromic diagnoses to the next level pathophysiological diagnoses (Fig. 1).

The author proposed a similar approach in a paper published 34 years earlier and illustrated in Fig. 2 (Preskorn 1990). The concept expressed in this figure is that there may be both syndromes which have an underlying biology and dimensional aspects of traits such as impulsivity, IQ, and introversion to extroversion which are independently, biologically, and environmentally determined which can modify the expression of the syndromic cluster such as agitated versus psychomotor retard MDD. Treatments addressing both the pathophysiology or even better – perhaps – the pathoetiology of the syndromic diagnosis (MDD) and the pathophysiology of the modifying dimension (e.g., impulsivity) might be the ideal way to approach a given patient.

3 The History of Current Psychiatric Drug Development: Chance Discovery and Rationale Refinement

The current treatment armamentarium for major depressive disorder (and psychotic disorders for that matter) owes their existence to two factors: first, chance discovery and then rationale refinement (Table 1) (Preskorn 2010a, b, 2011). That is particularly true for the treatments aimed at the two of the most major syndromic diagnoses: affective and psychotic disorders.

Chlorpromazine can be viewed as the "Adam" or "Eve" (whichever the reader prefers) to both the family of modern antipsychotics and modern antidepressants as illustrated in Fig. 3 (Preskorn 2010a, b, 2011). Since the book in which this chapter occurs is devoted to antidepressants, this text will not cover the antipsychotic line of the family of drugs while acknowledging that the first widely used class of antidepressants [i.e., tricyclic antidepressants (TCAs)] resulted from a failed medicinal chemistry attempts to develop better antipsychotics. The interested reader can review the primary papers cited in the reference list for details on the antipsychotic lineage if they wish.

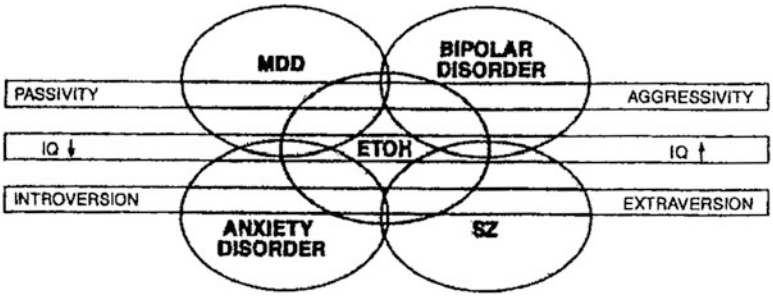

Fig. 2 Future of psychopharmacology. Interaction among syndromic diagnoses and between such diagnoses and dimensional aspects of personality. Space and the constraints of being a two-dimensional drawing of three-dimensional phenomena place limitations on this figure. In a three-dimensional figure, it would be clear that there is the potential for overlap between any two syndromic diagnoses and that the syndromic diagnoses are not on a personality trait continuum with respect to each other but rather that such traits are dimensionally present in all diagnoses and influence their expression. This figure also is not meant to imply that there are only three personality traits nor that the three depicted here are necessarily the most important (*MDD* major depressive disorders, *ETOH* alcoholism, *SZ* schizophrenia). Reproduced with permission from Preskorn 1990. © Preskorn 1990

Table 1 Early drugs that targeted the central nervous system

Drug	Class	Decade of discovery
Amphetamine	Stimulant	1880s
Cocaine	Analgesic/stimulant	1850s
Chlorpromazine	Antipsychotic	1950s
Diazepam	Anti-anxiety	1950s
Imipramine	Antidepressant	1950s
Isocarboxazid	Antidepressant	1950s
Lithium	Mood stabilizer	1940s
Morphine	Analgesic	2100 BC
Phenobarbital	Anticonvulsant	1930s
Reserpine	Antipsychotic	1950s

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Briefly, chlorpromazine begat imipramine as a failed attempt by relatively blind medicinal chemistry to develop a better antipsychotic. The structural change leads to the loss of antipsychotic efficacy (i.e., no to weak D-2 receptor blockade) but the emergence of antidepressant efficacy (due to most likely the ability to inhibit the neuronal uptake of either norepinephrine or serotonin uptake).

About the same time, there was a failed attempt to develop better antitubercular drugs based on the structure of isoniazid produced effective antidepressants. These drugs are called monoamine oxidase inhibitors (i.e., MAOIs) because they presumably work via their ability to inhibit monoamine oxidase, the rate-limiting enzyme in the degradation of three biogenic amine neurotransmitters: dopamine (DA),

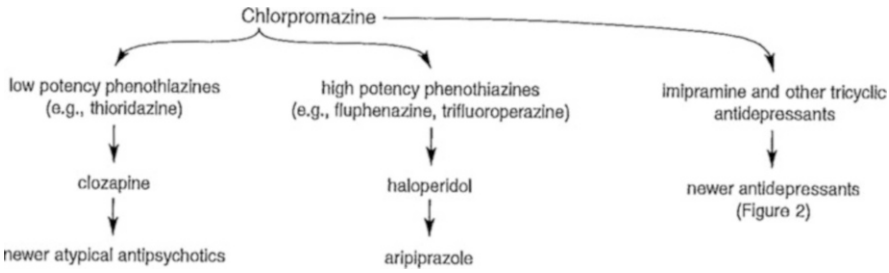

Fig. 3 Drug development based on chlorpromazine. Reproduced with permission from Preskorn 2010b. © Preskorn 2010

epinephrine (E), norepinephrine (NE), and serotonin (SE). The antidepressant activity of the MAOIs coupled with the antidepressant efficacy of the TCAs reinforced the idea that deficiency in either SE or NE neurotransmission was responsible for the depressive symptoms seen in patients with MDD.

Armed with the knowledge of the antidepressant activity of TCAs and MAOIs in the 1970s coupled with the ability to use structure-activity relationships and in vitro methods to examine in vitro receptor binding lead to the development via medicinal chemistry to new compounds which were capable of blocking either SE or NE transporters either selectively or in a sequential manner to develop molecules (i.e., ten times more potent at one than the other or both sequentially over less than a tenfold concentration range). The former were SE or NE selective reuptake inhibitors, whereas the latter were combined SE and NE reuptake inhibitors over their dosing range (i.e., generally capable of blocking SE reuptake at low concentrations and NE uptake inhibition at higher concentrations) (Fig. 4) (Preskorn 2010a, b, 2011). In the case of bupropion, the goal was to develop a molecule capable of blocking NE and dopamine (DA) reuptake pumps, but the concept is otherwise the same.

The "pharmacological refinement approach" allowed the development of drugs capable of affecting the desirable target (e.g., the SE transporter) at concentrations low enough to not engage from other targets which produce undesirable effects (e.g., acetylcholine muscarinic receptors). Importantly, this approach meant that the new drug did not have a novel mechanism of action different from the earlier antidepressants but instead had a more limited range of pharmacologic actions making it more focused and with a more limited adverse effect profile by eliminating effects on targets capable of mediating adverse effects which were off target.

This strategy has led to the development of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) which are the latest, generally accepted antidepressants.

The consequence of this iterative step without knowledge of the fundamental biology underlying the disorder has led to a plethora of drugs capable of treating

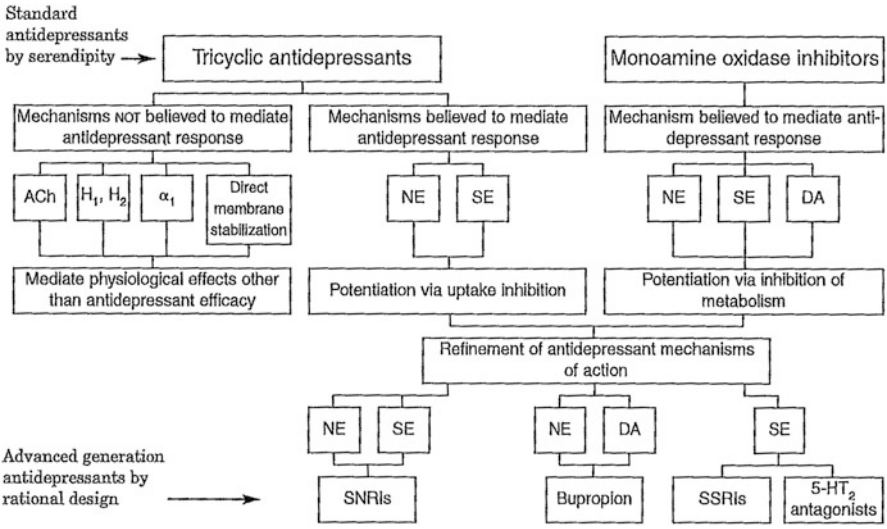

Fig. 4 Evolution of antidepressants. *ACh* acetylcholine, *H* histamine, α_1 alpha adrenergic, *NE* norepinephrine, *SE* serotonin, *DA* dopamine, *SNRI* serotonin-norepinephrine reuptake inhibitor, *SSRI* selective serotonin reuptake inhibitor. Reproduced with permission from Preskorn 2010a. © Preskorn 1996

patient suffering from a form of the illness which is responsive to their mechanism of action. Table 2 shows the relative receptor binding of most currently marketed antidepressants relative to the receptors currently known to be clinically relevant in terms of either producing antidepressant efficacy or "off-target" adverse effects (Preskorn 2018).

All the drugs shown in Table 3 (Preskorn 2017a) are essentially a "rehash" or a realignment of the mechanisms previously suggested to play a role in producing an antidepressant response. The question is: Do they offer anything which is meaningfully new in terms of additional efficacy. In general, the answer is no based on the results of the largest sequential trial of currently marketed antidepressants ever funded by the NIMH, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D). That study showed that perhaps 40% of patients with MDD have a form of the illness which is not responsive to multiple trials of antidepressants which work via effects on biogenic amine antidepressants (i.e., SE, NE, or DA).

That finding is the reason for the interest in antidepressants which work via non-biogenic amine antidepressants such as ketamine and related drugs (see the chapter in this book by Nuri Farber).

Table 2 Antidepressants' relative receptor binding affinity[a]

Generic name	Branded name	hSET	hNET	hDAT	5-HT_{1A}	5-HT_{1B}	5-HT_{1D}	5-HT_{2A}
Serotonin and norepinephrine reuptake inhibitors and antagonists at various neuroreceptors and ion channels								
Amitriptyline	Elavil	4	34	>1,000				
Imipramine	Tofranil	1	26	>5,000				
Nortriptyline	Pamelor	4	1	261				
Selective serotonin reuptake inhibitors								
Citalopram	Celexa	1	>1,000	>10,000				
Escitalopram	Lexapro	1	>1,000	>10,000				
Fluoxetine	Prozac	1	545	>1,000				
Fluvoxamine	Luvox	1	620	>1,000				
Paroxetine	Paxil	1	450	>1,000				
Sertraline	Zoloft	1	>1,000	220				
Selective norepinephrine reuptake inhibitors								
Desipramine[b]	Norpramin	21	1	>1,000				
Reboxetine	Vestra	8	1	>1,000				
Dual serotonin and norepinephrine (SE≥NE) reuptake inhibitors								
Desvenlafaxine	Pristiq	1	27	>1,000				
Duloxetine	Cymbalta	1	7.5	504				
Levomilnacipran	Fetzima	1	8	>1,000				
Milnacipran	Savella	1	8	>1,000				
Venlafaxine	Effexor	1	16	>10,000				
5-HT_{2A} antagonist and weak serotonin reuptake inhibitors								
Flibanserin	Addyi				1	>1,000	>1,000	49
Nefazodone	Serzone	9	18	17				1
Trazodone	Oleptro	21	>1,000	929				1
Specific histamine, serotonin, and norepinephrine receptor antagonist								
Mirtazapine	Remeron	>100,000	>10,000	>100,000				

Dopamine and norepinephrine (weak) reuptake inhibitor								
Bupropion	Wellbutrin	17	95	1				
SSRIs + specific SE receptor activity								
Vilazodone	Viibryd	1	>500	370	21			
Vortioxetine	Brintellix	1	71	>1,000	9	33	21	
Generic name	p5-HT_{2C}	5-HT_3	5-HT_7	h alpha1	hM_1	gpH_1	D3	D4
Serotonin and norepinephrine reuptake inhibitors and antagonists at various neuroreceptors and ion channels								
Amitriptyline	–			25	16	1		
Imipramine	–			65	65	8		
Nortriptyline	–			148	34	1		
Selective serotonin reuptake inhibitors								
Citalopram	>1,000			757	894	179		
Escitalopram	>1,000			>1,000	>1,000	257		
Fluoxetine	65			>1,000	638	>1,000		
Fluvoxamine	>1,000			560	>5,000	>5,000		
Paroxetine	>10,000			>10,000	720	>100,000		
Sertraline	>10,000			>1,000	>1,000	>100,000		
Selective norepinephrine reuptake inhibitors								
Desipramine[b]	–			156	235	132		
Reboxetine	875			>1,000	933	44		
Dual serotonin and norepinephrine (SE≥NE) reuptake inhibitors								
Desvenlafaxine	>1,000			>1,000	>1,000	>1,000		
Duloxetine	>1,000			>1,000	>1,000	>1,000		
Levomilnacipran								
Milnacipran	917			>1,000	>1,000	>1,000		

(continued)

Table 2 (continued)

Generic name	p5-HT_{2C}	5-HT_3	5-HT_7	h alpha1	hM_1	gpH_1	D3	D4
Venlafaxine	>1,000			>1,000	>1,000	>1,000		
5-HT_{2A} antagonist and weak serotonin reuptake inhibitors								
Flibanserin		>10,000	990				>100	>10,000
Nefazodone	–			1.2	522	1		
Trazodone	1			5	>1,000	45		
Specific histamine, serotonin, and norepinephrine receptor antagonist								
Mirtazapine	–			>1,000	>1,000	1		
Dopamine and norepinephrine (weak) reuptake inhibitor								
Bupropion	–			10	95	10		
SSRIs + specific SE receptor activity								
Vilazodone								
Vortioxetine		2	12					

Key: *h* human, *SET* serotonin transporter, *NET* norepinephrine transporter, *DAT* dopamine transporter, *p* porcine, *5-HT* serotonin, *gp* guinea pig, *H* histamine, *M* muscarinic, *D* dopamine, *SE* serotonin, *NE* norepinephrine, *SSRIs* selective serotonin reuptake inhibitors

[a]Relative binding affinity (RRB) is the binding affinity of the drug for every receptor reported in the package insert in relationship to the drug's highest affinity site. To calculate the relative binding affinity for each drug, its Ki for its highest affinity site is divided by itself, yielding 1, and next the Ki for the highest affinity site (which is the smallest concentration of drug needed to bind to any site) is divided into all its Ki's for lower affinity sites (which is hence a higher concentration needed to bind to a lower affinity site), the result then is a number greater than 1. The larger that number, the higher the concentration needed to bind to the next potential target for the drug

[b]This drug is also a selective norepinephrine reuptake inhibitor

For each drug in this table, its highest affinity and its affinity expressed in nanomolar concentration are as follows: amitriptyline, H_1 (1); bupropion, DAT (526); citalopram, SET (1.6); desipramine, NET (0.83); desvenlafaxine, SET (115); duloxetine, SET (1); flibanserin, 5-HT_{1A} (1); fluoxetine, SET (1.1); fluvoxamine, SET (2.3); imipramine, SET (1.41); levomilnacipran, SET (11.2); milnacipran, SET (9); mirtazapine, Hr (0.14), nafazodone, H1 (6); nortriptyline, NET or H_1 (4.35); paroxetine, SET (0.1); reboxetine, NET (7); sertraline, SET (0.3); trazodone, 5-HT_{2A} (7.7); venlafaxine, SET (102); vilazodone, SET (0.1); vortloxetine, SET (1.6). Flibanserin and milnacipran are not labeled for antidepressant activity. They were initially developed and tested for this indication but clinical trials were not supportive. In the case of milnacipran, its active enationer, levomilnacipran, was successfully developed for an antidepressant indication[2,14]

Table 3 Psychiatric and selected CNS drugs approved 2009 to 2016

Year	Total drugs approved	CNS drugs	Psychiatric and selected CNS drugs	Specific psychiatric or CNS drugs generic/brand name (manufacturer)[a,b,c]	Labeled indication	Mechanism of action[d]	Substrate for drug transporter	Substrate for drug metabolizing enzymes
2009	26	4	3	Iloperidone/Fanapt (Vanda)[b]	Schizophrenia	5-HT2A > alpha-1 > D_2 (1:2:17)	Not P-gp; otherwise	CYP3A4 > CYP 2D6 = carbonyl reductase
							NA	
				Asenapine/Saphris (Allergan)[b]	Schizophrenia and manic or mixed episodes of bipolar I disorder	5-HT2C > 5-HT2A > alpha-1 > D_2 (1:3:4:7)	NA	CYP1A2
				Milnacipran/ Savella (Allergan)[c]	Fibromyalgia	SET > NET (1:8)	NA	Mainly excreted unchanged with little to no drug metabolism
2010	21	1	1	Lurasidone/Latuda (Sunovion)[b]	Schizophrenia and depressed phase of bipolar I disorder	5-HT2A = 5-HT7 > D_2 (1:1:2)	NA	CYP3A4
2011	28	5	1	Vilazodone/ Viibryd (Allergan)[b]	Major depressive disorder	SET > 5-HT1A (1:21)	NA	CYP3A4 > > 2C19 = 2D6
2012	39	3	1	Locaserin.Belviq [Arena Pharm (US distributor: Eisai)][c]	Weight management/ obesity	5-HT 2C > 5-HT2A > 5-HT2B receptors (1:7:11)	NA	Multiple CYP and non-CYP pathways
2013	27	4	2	Vortioxetine/ Brintellix (Takeda)[b]	Major depressive disorder	SET > multiple 5-HT receptors (1 ≥ 10)	NA	CYP2D6 > > CYP3A4/5, CYP2C19, CYP2C9, CYP2A6, CYP2C8, and CYP2B6

(continued)

Table 3 (continued)

Year	Total drugs approved	CNS drugs	Psychiatric and selected CNS drugs	Specific psychiatric or CNS drugs generic/brand name (manufacturer)[a,b,c]	Labeled indication	Mechanism of action[d]	Substrate for drug transporter	Substrate for drug metabolizing enzymes
				Levomilnacipran/ Fetzima (Allergan)[b]	Major depressive disorder	SET > NET (1:8)	NA	Mainly excreted unchanged
2014	42	4	3	Suvorexant/ Belsomra (Merck)[c]	Onset and maintenance of sleep	Orexin 1 and 2 receptors	NA	CYP3A4
				Tasimelteon/ Hetlioz (Vanda)[c]	Non-24-hour sleep-wake disorder	MT-1 and -2 receptors	NA	CYP1A2, 3A4, and phenolic glucuronidation
				Bupropion plus naltrexone/ Contrave (Orexigen)[a]	Weight management in obesity	Bupropion: DAT > SET > NET (1:17:95); for naltrexone, see note below[e]	NA	CYP2B6 (bupropion); non-CYP enzyme (naltrexone)
2015	45	4	4	Proaripiprazole/ Aristada (Alkermes)[a]	Schizophrenia	D_2 > 5-HT1A > 5-HT2A (1:5:10)	NA	Same as aripiprazole (i.e., CYP3A4 and 2D6)
				Cariprazine/ Vraylar (Allergan)[b]	Schizophrenia and manic or mixed episodes of bipolar I disorder	D3 > D2 = 5-HT2B (1:6-8)	Not a substrate for multiple transporters	CYP3A4 > > 2D6
				Flibanserin/Addy (Sprout)[c]	Hypoactive sexual desire in premenopausal females	5-HT1A	NA	CYP3A4 > 2C19
				Brexpiprazole/ Rexulti (Otsuka)[b]	Schizophrenia and as an adjunct to antidepressants in	5-HT1A > D_2 > 5-HT2A > alpha; 2C (1:3:4:5)	NA	CYP2D6 and 3A4

					major depressive disorder			
2016	26	2	1	Pimavanaserin/ Nuplazid (Acadia)[b]	Psychosis in Parkinson disease	5-HT2A > 5-HT2C (1:5)	Not a substrate for multiple transporters	CYP3A4 and 3A5 > 2J2, 2D6, and various other CYP and FMO enzymes
Total	254	27	16					

Of these 16 drugs:

[a]One was a combination of two existing drugs (bupropion+naltrexone); one was a prodrug of an existing molecule (proaripiprazole)

[b]Nine were NMEs approved for a psychiatric indication

[c]Five were NMEs approved for nonpsychiatric indications but which nevertheless targeted brain dysfunction (i.e., sleep, weight, or pain) with mechanisms of action that worked via the brain

[d]Numbers in parentheses in the mechanism of action column represent the relative binding affinity of the drug for these respective targets, with 1 being the highest binding affinity for the drug and the larger numbers being how much the concentration of the drug has to increase to affect the next target (with the general rule in pharmacology being that a drug is selective for a target if its next binding requires more than a tenfold increase in concentration). For more details, see Preskorn et al.[4]

Most of the drugs listed in the table are full antagonists at their respective receptors. The few exceptions are aripiprazole, brexipiprazole, and cariprazine, which are partial agonists at the D_2 receptor, and pimavanserin, which is an inverse agonist and antagonist at the 5-HT2A and 5-HT2C receptors (five times higher affinity for the 5-HT2A receptor than the 5-HT2C receptor)

[e]Naltrexone and its active metabolite 6β-naltrexol are antagonists at the MOR, to a lesser extent at the KOR, and to a far lesser and possibly insignificant extent, at the DOR. The K_i affinity values of naltrexone at the MOR, KOR, and DOR have been reported as 0.0825, 0.509, and 8.02 nM, respectively, demonstrating a MOR/KOR binding ratio of 6.17 and a MOR/DOR binding ratio of 97.2[5,6]

CNS indicates central nervous system, *CYP* cytochrome P-450 enzyme, *D* dopamine, *DAT* dopamine transporter, *DOR* δ-opioid receptor, *FMO* flavin-containing monooxygenase, *gp* guinea pig, *H* histamine, *KOR* κ-opioid receptor, *M* muscarinic, *MOR* μ-opioid receptor, *MT* melatonin, *NA* not available, *NE* norepinephrine, *NET* norepinephrine transporter, *NME* new molecular entity, *P* porcine, *SET* serotonin transporter, *5-HT* serotonin

4 The Future or Where to Go from Here?

On the downside, one could look at the last 50 years of psychiatric drug development particularly regarding antidepressants and antipsychotics as an era in which the same mechanisms were rehashed repeatedly. That is simply because these mechanisms were known to work and not enough was known about the biology of the illness to take many chances on speculative targets. Admittedly, some development work was tried on speculative targets but failed which is the reason why it is not being discussed here. That is the reason why most of the psychiatric drugs approved from 2009 to 2016 (Table 3) had the same well-established mechanisms of action (Preskorn 2017a).

With that said, there have been six novel mechanisms of action drugs developed and approved over the last 25 years (Table 4) (Preskorn 2014). These drugs may point the way to the future because of common features in their development. First, they were directed at a single behavior of symptom rather than a syndrome or cluster of behaviors and symptoms which may have different mechanisms mediating them. Second, the circuitry underlying the disturbance was relatively simple and well established. Third, the outcome variable was relatively dichotomous (e.g., smoke, don't smoke) rather than a reduction in a rating scale based on a compilation of the various disparate symptoms of a syndromic diagnosis such as MDD (e.g., the Hamilton Depression Rating Scale or the Montgomery-Asberg Depression Rating Scale). As knowledge of the biology underlying MDD continues to improve, it will guide the development of mechanistically new antidepressants.

The other plus is that high-throughput screening can make new medications highly selective for their desired target. That is illustrated by the development done with tasimelteon and suvorexant which were screened against 200 targets which were not desired targets of the drug Table 5 (Preskorn 2017b). The molecules, tasimelteon and suvorexant, were taken forward both because they affected their desired target at nanomolar concentrations and did not affect any of these other non-desired targets even at micromolar concentrations (i.e., 1,000 times greater than the concentration needed to bind to their desired target).

5 The Immediate Future and It Is Upbeat

Between that development and the near future, ketamine and related drugs are the first legitimate hope for a new approach to treating patients with the form of MDD which is not responsive to biogenic amine antidepressants. While the antidepressant activity of ketamine and related drugs was initially discovered by chance as was the case with TCAs and MAOIs, it appears nevertheless to be robustly and rapidly effective in approximately 60% of patients whose depressive disorder is not responsive to biogenic amine antidepressants. Based on the early readouts of the Janssen

Table 4 Six central nervous system drugs with novel mechanisms of action developed in the past 25 years

Generic name	Brand name	Originator	Approval date	Latest PI revision	Indication(s)	Mechanism	Generic available
Ondansetron	Zofran	Glaxo	1/4/1991	9/18/2014	Chemotherapy-induced nausea and vomiting (CINV)	Serotonin 5-HT_3 receptor antagonism	7/2/2010
Aprepitant	Emend	Merck	3/27/2003	8/12/2014	CINV	Neurokinin (substance P)-1 receptor antagnoism	7/24/2012
Ramelteon	Rozerem	Takeda	7/22/2005	3/1/2012	Insomnia[a]	Melatonin (MT_1, MT_2) receptor agonism	7/26/2013
Varenicline	Chantix	Pfizer	5/10/2006	10/15/2014	Smoking cessation	Acetylcholine nicotinic receptor alpha-4 beta-2 partial agonism	No
Lorcaserin	Belviq	Arena[b]	6/27/2012	6/27/2012	Weight loss	5-HT_{2c} agonism	No
Suvorexant	Belsomra	Merck	8/13/2014	N/A	Insomnia[c]	Dual orexin 1 and 2 receptor antagonism	No

PI package insert
[a]Difficulty with sleep onset
[b]Marketed by Eisai
[c]Difficulties with sleep onset and/or sleep maintenance
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Table 5 Receptors for which tasimelteon (10 μm) did not inhibit or stimulate binding by >50%[a]

Adenosine A_1	Dopamine D_1	Melanocortin MC1	Rolipram
Adenosine A_{2A}	Dopamine D_{2L}	Melanocortin MC_3	Ryanodine RyR3
Adenosine A_3	Dopamine D_{2S}	Melanocortin MC_4	Serotonin 5-HT_1
Adrenergic α_{1A}	Dopamine D_3	Melanocortin MC_5	Serotonin 5-HT_{1A}
Adrenergic α_{1B}	Dopamine $D_{4.2}$	Motilin	Serotonin 5-HT_{1B}
Adrenergic α_{1D}	Dopamine D_5	Muscarinic M_1	Serotonin 5-HT_2
Adrenergic α_2	Endothelin ET_A	Muscarinic M_2	Serotonin 5-HT_{2A}
Adrenergic α_{2A}	Endothelin ET_B	Muscarinic M_3	Serotonin 5-HT_{2B}
Adrenergic α_{2C}	Epidermal growth factor	Muscarinic M_4	Serotonin 5-HT_{2C}
Adrenergic β_1	Erythropoietin EPOR	Muscarinic M_5	Serotonin 5-HT_3
Adrenergic β_2	Estrogen Erα	N-formyl peptide receptor FPR1	Serotonin 5-HT_4
Adrenergic β_3	Estrogen Erβ	N-formyl peptide receptor-like FPRL1	Serotonin 5-HT_{5A}
Adrenomedullin AM_1	G Protein-coupled receptor GPR103	Neurokinin NK_1	Serotonin 5-HT_6
Adrenomedullin AM_2	G Protein-coupled receptor GPR8	Neuromedin U NMU_1	Sigma σ1
Aldosterone	$GABA_B$	Neuromedin U NMU_2	Sigma σ2
Anaphylatoxin C5a	$GABA_{B1A}$	Neuropeptide Y, Y_1	Sodium channel, site 2
Androgen	$GABA_{B1B}$	Neuropeptide Y, Y_2	Somatostatin sst1
Angiotensin AT_1	Gabapentin	Neurotensin NT_1	Somatostatin sst2
Angiotensin AT_2	Galanin GAL1	Nicotinic acetylcholine	Somatostatin sst3
Apelin (APJ)	Galanin GAL2	Nicotinic acetylcholine α1	Somatostatin sst4
Atrial natriuretic factor	Glucocorticoid	Nicotinic acetylcholine α7	Somatostatin sst5
Bombesin BB1	Glutamate, AMPA	Opiate δ (OP1, DOP)	Tachykinin NK_1
Bombesin BB2	Glutamate, Kainate	Opiate κ (OP2, KOP)	Tachykinin NK_2
Bombesin BB3	Glutamate, NMDA	Opiate μ (OP3, MOP)	Tachykinin NK_3
Bradykinin B_1	Glycine, strychnine-sensitive	Orphanin ORL_1	Thromboxane A_2
Bradykinin B_2	Growth hormone secretagogue	Phorbol ester	Thyroid hormone
Calcitonin	Histamine H_1, central	Platelet activating factor	Thyrotropin releasing hormone
Calcitonin gene-related peptide $CGRP_1$	Histamine H_2	Platelet-derived growth factor	Transforming growth factor-β
Calcium channel L-type	Histamine H_3	Potassium channel [K_A]	Transporter, adenosine
Calcium channel N-type	Histamine H_4	Potassium channel [K_{ATP}]	Transporter, choline

(continued)

Table 5 (continued)

Cannabinoid CB_1	Hypocretin (orexin) receptor 1	Potassium channel [SK_{CA}]	Transporter, dopamine
Cannabinoid CB_2	Hypocretin (orexin) receptor 2	Potassium channel HERG	Transporter, GABA
Chemokine CCR1	Imidazoline I_2, central	Progesterone	Transporter, monoamine
Chemokine CCR2B	Inositol trisphosphate IP_3	Progesterone PR-B	Transporter, norepinephrine
Chemokine CCR4	Insulin	Prostanoid CRTH2	Transporter, serotonin
Chemokine CCR5	Interleukin IL-1	Prostanoid DP	Tumor necrosis factor
Chemokine CX3CR1	Interleukin IL-2	Prostanoid EP_2	Urotensin II
Chemokine CXCR2 (IL-$8R_B$)	Interleukin IL-6	Prostanoid EP_4	Vanilloid
Cholecystokinin CCK_1 (CCK_A)	Leptin	Prostanoid, thromboxane A_2	Vascular endothelial growth factor
Cholecystokinin CCK_2 (CCK_B)	Leukotriene (LTB_4)	Purinergic P_{2X}	Vasoactive intestinal peptide
Colchicine	Leukotriene, cysteinyl $CysLT_1$	Purinergic P_{2Y}	Vasoactive intestinal peptide 1
Corticotropin releasing factor CRF_1	Leukotriene, cysteinyl $CysLT_2$	Retinoid X receptor RXRα	Vasopressin V_{1A}
			Vasopressin V_{1B}
			Vasopressin V_2
			Vitamin D_3

Standard radioligand binding and enzyme inhibition assays were performed on receptors, binding sites, or enzyme systems obtained from various sources, including human, rat, mouse, guinea pig, rabbit, hamster, and bovine tissues (see Lavedan et al. 2015, Supplemental Information), using the profiling screen and discovery screen panels (Panlabs) which consisted of 56 radioligand binding assays and 7 enzyme assays, respectively, and the SpectrumScreen panel (MDS Pharma Services) that included 170 pharmacological relevant targets (see Lavedan et al. 2015, Supplemental Information). In addition, the $GABA_A$ benzodiazepine and $GABA_B$ binding sites were also tested independently (Panlabs biochemical pharmacology assays). Tasimelteon was used at a concentration of 10 μm except for two enzyme assays (protein kinases C: PKCα and PKCβ) where it was used at 100 μm and for the melatonin receptors in the SpectrumScreen panel where four concentrations (10 nm, 0.1 μm, 1 μm, and 10 μm) were tested. A response was considered significant if there was ≥50% inhibition or stimulation for the assays

The affinity of tasimelteon (10 μm) for the human hypocretin (orexin) receptor 1 expressed in transfected CHO cells and for the human hypocretin (orexin) receptor 2 expressed in transfected HEK-293 cells was determined in radioligand binding assays (Eurofins Cerep SA, Celle l'Evescault, France)

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studies of esketamine this year, this new treatment may be on the market by 2019 and will have thousands of patients who have been long suffering waiting for it.

This new era will not simply hold the promise for treating those patients but also provide biological insights into these different forms of the major depression: (a) those responsive to biogenic amine antidepressants, (b) those not responsive to biogenic amine antidepressants but to glutaminergic antidepressants such as esketamine, and (c) those not responsive to either of these forms of treatment. The ability to divide patients with the syndrome of major depression into these three categories has the potential to permit understanding the biological reasons for why they fall into those three groups. The knowledge gained from that and from the mechanisms underlying the response to esketamine will in turn lead to new developments just as was true the development of SSRIs and SNRIs from the knowledge gained from studies of TCAS and MAOIs.

The figures and tables in this chapter come from the articles below. Each of these articles has its own reference list which the interested reader can access either through PubMed or on the Lippincott Williams & Wilkins website.

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Other Antidepressants

T. E. Schwasinger-Schmidt and M. Macaluso

Contents

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Abstract

This chapter addresses the following FDA-approved medications for the treatment of major depressive disorder available for use in the United States including bupropion, mirtazapine, trazodone, vortioxetine, and vilazodone. These medications do not belong to one of the previously featured classes of antidepressants discussed in the preceding chapters. Each medication featured in this chapter has a unique structure and properties that target diverse receptors in the central nervous system. These diverse targets are distinct from other classes of medications used to treat major depressive disorder. This chapter will provide an overview of each medication's indication for use, history of development, pharmacology, metabolism, dosing recommendations, onset of action, use in special populations, safety and tolerability, adverse effects, potential interactions with additional medications, and data regarding possible overdose with available treatments.

Bupropion was initially developed for its combined effects on the norepinephrine and dopamine neurotransmitters. Currently, bupropion is the only antidepressant on the market in the United States with no appreciable activity on serotonin concentrations in the central nervous system. Bupropion is extensively metabolized in humans into three active metabolites including hydroxybupropion, threohydrobupropion, and erythrohydrobuproprion each with substantial antidepressant activity. The most serious side effect of bupropion is the development of

seizures, so the dose must be gradually titrated to a maximum dose of 450 mg per day of the immediate-release formulation and 400 mg per day of the sustained-release formulation. Additional adverse effects include agitation, dry mouth, insomnia, headaches, migraines, nausea, vomiting, constipation, and tremor. The onset of action of bupropion is 2 weeks with full efficacy attained at 4 weeks of treatment. Bupropion produced similar depression remission rates when compared to SSRIs with a median time to relapse of 44 weeks. Bupropion has additionally been approved for smoking cessation and may have a combined role in treating nicotine cravings and depression.

Mirtazapine has a unique method of action by enhancing norepinephrine and serotonin neurotransmission by blocking the alpha-2 presynaptic adrenoceptors resulting in increased release of serotonin at the nerve terminals. Mirtazapine additionally binds to the 5-HT_2, 5-HT_3, and H_1 receptors resulting in increased sedation, which is the most common side effect. Additional side effects include increased appetite and weight gain, dizziness, and transient elevations in cholesterol levels and liver function tests. Mirtazapine is unlike any other antidepressant in that it also has a hormonal effect that reduces cortisol levels within the body. Patients on mirtazapine showed significant improvement in symptoms of major depressive disorder within the first 1–2 weeks of treatment with long-term studies at 40 weeks showing continued improvements in response rates in addition to lower relapse rates. Mirtazapine has an antagonistic effect at the central presynaptic 5-HT_2 receptors and alpha-2 adrenergic inhibitory autoreceptors and heteroreceptors resulting in increased norepinephrine release with an indirect release of serotonin due to increased noradrenergic input to the raphe nucleus. Mirtazapine has an effective dose range from 15 to 45 mg once daily with a long half-life preventing dose adjustments more often than every 1–2 weeks.

Trazadone is a 5-HT_{2A} and 5-HT_{2C} receptor antagonist and selective serotonin reuptake inhibitor. While trazodone has only been FDA approved for use in the treatment of major depressive disorder, it has been used off label for numerous conditions including insomnia, anxiety, dementia, Alzheimer's disease, substance abuse, schizophrenia, bulimia, and fibromyalgia. The most common adverse reaction is drowsiness, followed by dizziness, dry mouth, and nervousness. In the United States, trazadone is the second most commonly prescribed agent used to treat insomnia. The hypnotic action of this medication at lower doses is attributed primarily to the antagonism of the 5-HT_{2A} receptors, H_1 receptors, and alpha-1 adrenergic receptors. The most active metabolite is m-chlorophenylpiperazine produced by the CYP_{3A4} enzyme, which is a more profound inhibitor of serotonin reuptake as compared to the parent molecule of trazadone. The maximum outpatient dose should not exceed 400 mg per day in divided doses, but in hospitalized patients, the dose may be increased to a maximum dose of 600 mg daily in divided doses while the patient is being actively monitored for side effects. One third of inpatients and one half of outpatients had a significant therapeutic response to trazadone by the end of the first week with the remainder of patients responding in 2–4 weeks of therapy.

Vortioxetine is a novel antidepressant classified by the World Health Organization as a N06AX antidepressant that was derived from studies targeting the combination of direct serotonin transporter inhibition and 5-HT_{1A} receptor modulation leading to rapid desensitization of the somatodendritic 5-HT_{1A} autoreceptors and activation of the postsynaptic 5-HT_{1A} receptors. This medication is an antagonist at 5-HT_3, 5-HT_{1D}, and 5-HT_7 receptors, an agonist at 5-HT_{1A} receptors, and a partial agonist at 5-HT_{1B} receptors. Blockade of the 5-HT_3 receptor was noted to produce increased levels of serotonin, dopamine, norepinephrine, acetylcholine, and histamine in the prefrontal cortex and hippocampus, which are known to be associated with the development of depression. The most common adverse effect is nausea followed by sexual dysfunction, constipation, and vomiting. The maximum dose of vortioxetine is 20 mg daily with improvement in symptoms of depression noted at 2 weeks with a full therapeutic effect observed at 4–6 weeks.

Vilazodone is a selective serotonin reuptake inhibitor and 5-HT_{1A} receptor partial agonist. This medication works by enhancing serotonergic activity in the central nervous system through selective inhibition of serotonin reuptake with no significant effects noted on norepinephrine or dopamine uptake. Vilazodone additionally binds with high affinity to the 5-HT_{1A} receptors as a partial agonist resulting in faster onset of action, greater efficacy, and better tolerability with reduced sexual side effects when compared to other SSRIs. The most common adverse effects were diarrhea, nausea, vomiting, and insomnia. Additional reported adverse effects included dizziness, dry mouth, fatigue, abnormal dreams, decreased libido, arthralgias, and palpitations which were self-limited with resolution in 4–5 days after starting the medication. The recommended therapeutic dose of vilazodone is 40 mg daily with improvement noted in depressive symptoms within 1 week of initiating therapy with increased remission rates noted at 6 weeks of therapy.

The medications featured in this chapter do not fall within the major categories of antidepressant classes but add additional unique mechanisms for the treatment of major depressive disorder. Each medication targets different receptors in the central nervous system involved in the development of depression. Resolution of depressive symptoms and response rates of these medications are similar to SSRIs with reduced side effects that can often lead to discontinuation of therapy. Use of these unique medications allows clinicians to target specific symptoms and comorbidities often associated with depression resulting in improved symptom resolution and long-term maintenance of remission.

Keywords

Bupropion · Mirtazapine · Trazadone · Vilazodone · Vortioxetine

1 Introduction

This chapter focuses on a series of antidepressant medications that do not belong to the major classes of antidepressants that were previously described in the preceding chapters. The medications featured in this section are bupropion, mirtazapine, trazadone, vortioxetine, and vilazodone. The pharmacokinetic and pharmacodynamic activity of these medications differs substantially from the other classes of antidepressants including tricyclic antidepressants (TCA), monoamine oxidase inhibitors (MAOI), selective serotonin inhibitors (SSRI), and selective norepinephrine inhibitors (SNRI).

The activity of each of the following medications on receptors in the central nervous system is unique in targeting different areas of the brain known to be involved with the development of major depressive disorder. Bupropion was initially developed due to its combined effects on norepinephrine and dopamine neurotransmitters and is the only medication on the market that has no effect on serotonin concentrations (GlaxoSmithKline 2017; Fava et al. 2005). Mirtazapine has a unique method of action by enhancing norepinephrine and serotonin neurotransmission by blocking the alpha-2 presynaptic adrenoceptors resulting in increased release of serotonin at the nerve terminals (Lavergne et al. 2005; Preskorn and Ross 2004; De Boer and Ruigt 1995; Haddjeri et al. 1995). Mirtazapine is unlike any other antidepressant in that it additionally reduces the release of cortisol (Lavergne et al. 2005; Schüle et al. 2002; Laakmann et al. 2000). Trazadone is a $5HT_{2A}$ and $5\text{-}HT_{2C}$ receptor antagonist and selective serotonin reuptake inhibitor that has only been FDA approved for use in the treatment of major depressive disorder but has been used off label for numerous conditions due to its varied receptor activity (Georgotas et al. 1982; Fagiolini et al. 2012). Vortioxetine is a novel antidepressant that was derived from studies targeting the combination of direct serotonin transporter inhibition and $5\text{-}HT_{1A}$ receptor modulation (Sanchez et al. 2015). Blockade of the $5\text{-}HT_3$ receptor with vortioxetine was noted to produce increased levels of serotonin, dopamine, norepinephrine, acetylcholine, and histamine in the prefrontal cortex and hippocampus (Sanchez et al. 2015; D'Agostino et al. 2015). Vilazodone is a selective serotonin reuptake inhibitor and $5\text{-}HT_{1A}$ receptor partial agonist. This medication works by enhancing serotonergic activity in the central nervous system through selective inhibition of serotonin reuptake with no significant effects noted on norepinephrine or dopamine uptake (Cruz 2012). Vilazodone additionally binds with high affinity to the $5\text{-}HT_{1A}$ receptors as a partial agonist resulting in a faster onset of action, greater efficacy, and better tolerability with reduced sexual side effects when compared to other SSRIs (Cruz 2012; Sahli et al. 2016; Wang et al. 2016).

The unique features of these novel antidepressants allow clinicians to target specific symptoms and comorbidities often associated with depression resulting in improved symptom resolution and long-term maintenance of remission. Gaining an understanding of the mechanisms of action of antidepressants by knowing the different receptor-binding properties of the medications and anticipating potential adverse effects can help develop individualized targeted therapy for patients with major depressive disorder.

2 Bupropion

2.1 Indications for Use and Medication History

Bupropion hydrochloride is an aminoketone antidepressant that is indicated for the treatment of major depressive disorder (GlaxoSmithKline 2017). This medication was initially developed due to its unique pharmacological profile with combined effects on the norepinephrine and dopamine neurotransmitters, which is different from all previous antidepressant classes including the tricyclic antidepressants, selective serotonin reuptake inhibitors, and selective norepinephrine reuptake inhibitors (GlaxoSmithKline 2017; Fava et al. 2005). To date, bupropion is the only antidepressant on the market in the United States with no appreciable activity on serotonin concentrations in the brain (Fava et al. 2005). Clinical trials for bupropion started in the 1970s, and the medication received FDA approval as an immediate-release product in 1989 for the treatment of major depressive disorder (Fava et al. 2005; Preskorn and Ross 2004). The sustained-release version of the medication that allowed for reduced daily dosing to twice daily was FDA approved and available on the market in 1996 (Fava et al. 2005). The once-daily dosing formulation known as bupropion XL was approved in 2003 by the FDA (Fava et al. 2005).

The efficacy of bupropion has been previously established in multiple placebo-controlled clinical trials with both inpatients and outpatients (GlaxoSmithKline 2009; Fava et al. 2005). Seven additional studies have been conducted that showed that bupropion produced similar depression remission rates when compared to SSRIs (Fava et al. 2005; Thase et al. 2005). Long-term efficacy for depression relapse rates has additionally been studied following 1 year of therapy with a median time to relapse of 44 weeks for bupropion compared to 24 weeks with placebo (Fava et al. 2005; Weihs et al. 2002).

Bupropion has been approved for smoking cessation and may play a dual role in treating nicotine cravings and depression, which commonly co-occur in patients who use tobacco products (GlaxoSmithKline 2017; Preskorn and Ross 2004. The use of bupropion for smoking cessation in clinical trials has shown increased likelihood of abstinence from tobacco products for up to 6 months compared with placebo (GlaxoSmithKline 2017).

2.2 Pharmacology and Metabolism

The exact neurological and chemical mechanism of action of bupropion is not fully understood; however, the medication is known to be a relatively week inhibitor of norepinephrine and dopamine uptake with no observed effects on the reuptake of serotonin or monoamine oxidase (GlaxoSmithKline 2009, 2017; Fava et al. 2005; Preskorn and Ross 2004). Studies conducted with bupropion showed reduced firing of neurons that respond to norepinephrine and dopamine in the brain stem with

additional reductions in firing rates of norepinephrine-responsive neurons in the locus coeruleus (Fava et al. 2005). Additionally, animal models of depression that were given norepinephrine- or dopamine-blocking medications showed reductions in the efficacy of bupropion and hydroxybupropion, which is one of the active metabolites of the medication (Fava et al. 2005; Cooper et al. 1980). Animal studies conducted with bupropion showed stimulant effects with observed increased locomotor activities, increased operant behavioral activities, and mild stereotyped behaviors at large doses, which is due in part to its chemical structure that is similar to phenylethylamines (GlaxoSmithKline 2009; Preskorn and Ross 2004).

The peak plasma concentration of bupropion is observed within 2 h with an average half-life of 14 h that ranges from 8 to 24 h (GlaxoSmithKline 2009). The average elimination half-life after chronic dosing is 21(±9) hours with a steady-state plasma concentration attained in 8 days (GlaxoSmithKline 2009, 2017). Bupropion is extensively metabolized in humans into three active metabolites (hydroxybupropion, threohydrobupropion, and erythrohydrobuproprion) with antidepressant activity (Fava et al. 2005; Preskorn and Ross 2004; GlaxoSmithKline 2009). CYP_{2B6} is the enzyme responsible for the conversion of bupropion into hydroxybupropion, and clinical studies have shown that hydroxybupropion is half as potent as bupropion in its antidepressant effects (GlaxoSmithKline 2009, 2017; Preskorn and Ross 2004). Peak concentrations of this metabolite have been observed 3 h after administration and are at least ten times the peak level of bupropion at steady state (GlaxoSmithKline 2009, 2017). The enzymes responsible for the conversion of bupropion to threohydrobupropion and erythrohydrobuproprion have not been fully characterized, but studies have shown that the antidepressant effects of these two metabolites are fivefold less than bupropion (GlaxoSmithKline 2009, 2017; Preskorn and Ross 2004). Peak concentrations of threohydrobupropion and erythrohydrobuproprion are similar to hydroxybupropion with a longer elimination half-life (GlaxoSmithKline 2009, 2017). Elimination of the medication is primarily through the urine at 87% with 10% eliminated through the feces (GlaxoSmithKline 2009, 2017).

2.3 Dosing Recommendations

The dosing of bupropion should be given as an upward titration that will minimize the risk of seizures (GlaxoSmithKline 2009, 2017). Additionally, gradual dose escalations help minimize symptoms of agitation, restlessness, and insomnia, which are often present in the initial treatment stages (GlaxoSmithKline 2009). The recommended starting dose of bupropion is 100 mg twice daily, which may be increased over time to a total daily dose of 300 mg given with at least 6 h between dosages (GlaxoSmithKline 2009, 2017). Increases in dose should not exceed 100 mg per day within a 3-day period to prevent the development of seizure activity that has been observed with a rapid up-titration (GlaxoSmithKline 2009, 2017). A maximum dose of 450 mg daily may be given in divided doses not to exceed 150 mg per dose. This dose escalation is indicated for patients who show no clinical improvement in

depression after several weeks of 300 mg daily dosing (GlaxoSmithKline 2009, 2017). The immediate-release formulation should be given three times daily with doses at least 4 h apart, with the sustained-release formulation given twice a day with doses given at least 4 h apart (Preskorn and Ross 2004). Similar to other antidepressants, the lowest dose of the medication that maintains remission should be administered with periodic reassessment of symptoms for possible cessation of the medication after the resolution of the acute depressive episode (GlaxoSmithKline 2009, 2017).

Bupropion should be used with caution in patients with hepatic cirrhosis with a maximum dose of 75 mg daily. Patients with mild to moderate cirrhosis as indicated by a Child-Pugh score of 5–6 should be used with caution at a reduced frequency and dose (GlaxoSmithKline 2009, 2017). Bupropion is extensively metabolized in the liver to the active components and in patients with hepatic impairment may result in elevated levels of the medication resulting in significant side effects (GlaxoSmithKline 2009). Patients must be closely monitored with reductions in dose or cessation of the medication if side effects are noted. Animal studies additionally showed the potential for hepatocellular injury including increased incidence of hyperplastic nodules and hepatocellular hypertrophy with high doses of the medication chronically (GlaxoSmithKline 2009).

Bupropion should be used with caution in patients with renal impairment at a reduced frequency and dose (GlaxoSmithKline 2009, 2017). Metabolites of bupropion may accumulate in patients with renal impairment due to elimination of the medication primarily through the urine which may result in increased adverse effects in this patient population (GlaxoSmithKline 2009).

2.4 Onset of Action

Double-blinded clinical trials have indicated the onset of action of bupropion to be approximately 2 weeks with full efficacy realized at approximately 4 weeks of treatment or longer (Preskorn and Ross 2004; GlaxoSmithKline 2009).

2.5 Use in Special Populations

Bupropion is contraindicated in several patient populations due to its potential to invoke seizures, which occurs in a dose-related response. The incidence of seizures with bupropion use is 0.4% in patients on doses of 450 mg daily. The risk of seizures increases tenfold in patients on doses of up to 600 mg daily (GlaxoSmithKline 2017). Patients with a known seizure disorder and patients with a current or prior diagnosis of anorexia nervosa or bulimia are not indicated for treatment with bupropion as it lowers the seizure threshold (GlaxoSmithKline 2009, 2017). Bupropion is additionally contraindicated in patients undergoing alcohol cessation or when weaning off benzodiazepines, barbiturates, or anti-epileptic medications. Conditions that increase the risk of seizures including severe head trauma;

arteriovenous malformations; central nervous system tumors or infections; severe stroke; use of tricyclic antidepressants, theophylline, and chronic systemic corticosteroids; hypoglycemia; hyponatremia; hypoxia; severe hepatic impairment; use of illicit drugs including cocaine; use of central nervous system stimulants; diabetes mellitus on insulin; use of anorectic medications; and use of sedative hypnotics or opiates can result in increased seizure activity preventing the use of bupropion for antidepressant therapy (GlaxoSmithKline 2017).

Bupropion treatment can result in hypertension and is contraindicated in patients on MAOIs and other medications that increase dopaminergic or noradrenergic activity (GlaxoSmithKline 2017). Due to the increased risk of hypertensive urgency, bupropion may not be used within 14 days of stopping MOAIs to allow for a washout period of the medication. Bupropion is contraindicated in patients on linezolid or IV methylene blue as interactions with these medications can additionally result in hypertensive urgency requiring hospitalization (GlaxoSmithKline 2017). Treatment with bupropion may be resumed in patients 24 h after the last dose of linezolid or IV methylene blue (GlaxoSmithKline 2017) if the patient was previously on the medication.

Bupropion was classified a pregnancy category C under the old system for classifying teratogenic risk. This was because epidemiological studies of women on the medication during the first trimester indicate no increased risk of congenital malformations. Animal studies showed no clear evidence of teratogenicity (GlaxoSmithKline 2009, 2017). Bupropion and its metabolites are excreted in breast milk with the average daily infant exposure of 2% of the material weight-adjusted dose (GlaxoSmithKline 2017). Based on this data, bupropion should be used with caution in lactating mothers. Safety and efficacy of bupropion have not been clearly established in the pediatric population (GlaxoSmithKline 2009, 2017).

2.6 Drug Interactions

Bupropion is metabolized by the cytochrome P450 enzymes and as such may interact with other medications that are metabolized by this system (Preskorn and Ross 2004; GlaxoSmithKline 2009, 2017; Fava et al. 2005). Bupropion is metabolized to hydroxybupropion by CYP_{2B6}, and administration of inhibitors of this system including ticlopidine and clopidogrel can increase levels of bupropion and its metabolites (GlaxoSmithKline 2017). Inducers of CYP_{2B6} used for HARRT therapy in HIV including ritonavir, lopinavir, and efavirenz can decrease the effective doses of bupropion. It is important to note that despite the decreased available dose of the medication, doses exceeding the maximum doses should not be used as it can increase the risk of seizures (GlaxoSmithKline 2009, 2017).

Bupropion and its metabolites are inhibitors of the CYP_{2D6} enzymes and can result in increased levels of medications including SNRIs, SSRIs, TCAs, antipsychotics, beta blockers, and type IC antiarrhythmics including propafenone and flecainide. Additionally, medications that require activation of CYP_{2D6} for effectiveness including tamoxifen can result in reduced efficacy when administered

with bupropion (GlaxoSmithKline 2017). Administration of bupropion with digoxin can reduce digoxin levels and will require close monitoring to ensure therapeutic levels of digoxin (GlaxoSmithKline 2017).

Bupropion has been shown to result in central nervous system toxicity in patients that are on levodopa and amantadine due to additive dopamine agonist effects of the medications. Most adverse reactions between the medications have resulted in restlessness, agitation, tremor, ataxia, gait disturbances, vertigo, and dizziness (GlaxoSmithKline 2017).

Bupropion has additionally been noted to interact with laboratory testing including urine drug screens. Patients on bupropion have been noted to have false-positive results for amphetamine on urine drug screens due to a lack of specificity of some screening tests (GlaxoSmithKline 2017). False-positive test results may be seen in patients even after discontinuation of therapy, and patients will need to have confirmatory testing with gas chromatography or mass spectrometry to distinguish between the use of bupropion and amphetamines (GlaxoSmithKline 2017).

2.7 Adverse Reactions

The adverse reactions that are commonly associated with bupropion use include agitation, dry mouth, insomnia, headaches, migraines, nausea, vomiting, constipation, and tremor (GlaxoSmithKline 2009). These adverse effects were noted in 5% of the 40 million clinical trial participants administered bupropion (Fava et al. 2005). In clinical trials, approximately 10% of patients experienced a significant adverse reaction that resulted in discontinuation of therapy with most of these events occurring in patients that were on doses that exceed the maximum recommended dose. The most common reason to stop therapy was neuropsychiatric conditions occurring in 3% of patients with the primary symptoms consisting of agitation and abnormalities in mental status (GlaxoSmithKline 2009, 2017). The second most common adverse effects were GI disturbances consisting of nausea and vomiting at 2.1%, followed by neurological events consisting of seizures, headaches, and sleep disturbances occurring in 1.7% of patients (GlaxoSmithKline 2009).

Additional adverse reactions noted on bupropion include the worsening of suicidal thoughts and behaviors that are most pronounced in adolescents and young adults. The development of acute angle-closure glaucoma and hypersensitivity reactions was also noted (GlaxoSmithKline 2009, 2017). Activation of mania or hypomania with or without psychosis was also noted most commonly in patients with bipolar I disorder (GlaxoSmithKline 2009, 2017). Long-term use data obtained from the 52-week relapse prevention study indicated a reduction in adverse events with continued treatment with the medication (Fava et al. 2005; Weihs et al. 2002).

2.8 Overdose

The potential for overdose with bupropion is present with case reports of patients ingesting up to 30 g of bupropion (GlaxoSmithKline 2009, 2017). Seizures are the most common side effect of overdose and have been reported in one third of all cases (GlaxoSmithKline 2009, 2017). Other noted reactions to the medication in high doses include hallucinations, loss of consciousness, sinus tachycardia, QRS prolongation, and arrhythmias. Multiple drug overdoses with bupropion and other substances have resulted in fever, muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure (GlaxoSmithKline 2009, 2017). Most patients have recovered with supportive care, but a few deaths have been reported with bupropion overdose due to uncontrolled seizures, bradycardia, and cardiac arrest (GlaxoSmithKline 2009, 2017).

3 Mirtazapine

3.1 Indications for Use and Medication History

Mirtazapine is a tetracyclic compound used to treat major depressive disorder that was first synthesized in the Netherlands in 1987 (Alam et al. 2013; Merck 2012). This medication was FDA approved in the United States in 1996 and has a unique method of action by enhancing noradrenaline and serotonin neurotransmission through direct actions on alpha-adrenergic and serotonergic receptors (Lavergne 2005; Preskorn and Ross 2004). Mirtazapine increases the release of norepinephrine through blocking the alpha-2 presynaptic adrenoceptors that in turn activate the alpha-1 adrenoreceptors on the serotonergic neurons resulting in increased firing and release of serotonin at the nerve terminals (Lavergne et al. 2005; De Boer and Ruigt 1995; Haddjeri et al. 1995). Mirtazapine additionally binds to the 5-HT_2, 5-HT_3, and H_1 receptors preventing overexcitation to the serotonergic neurons resulting in a sedative action of the medication (Lavergne et al. 2005). Mirtazapine is unlike any other antidepressant on the market in that it additionally has a hormonal component that reduces the release of corticotrophin resulting in reduced cortisol levels within the body (Lavergne et al. 2005; Schüle et al. 2002; Laakmann 2000).

The efficacy for mirtazapine has been shown in four placebo-controlled 6-week trials in adult outpatients with major depressive disorder (Merck 2012). Within these studies, patients showed significant improvement in depressive symptoms within the first week of treatment with minimal anticholinergic- or serotonergic-related side effects that are often observed with other antidepressant therapies (Lavergne et al. 2005; Alam et al. 2013). Studies that compared the efficacy of mirtazapine with additional available antidepressants including amitriptyline, clomipramine, doxepin, fluoxetine, citalopram, paroxetine, sertraline, and venlafaxine showed similar efficacy among medications (Alam et al. 2013). Comparison studies between mirtazapine and SSRIs showed an increased onset of action in the early phases of treatment with higher efficacy of mirtazapine at week 1 compared to paroxetine,

weeks 1–2 compared with sertraline, week 2 compared with citalopram, and weeks 3–4 compared with fluoxetine (Lavergne et al. 2005; Alam et al. 2013). Long-term data on the efficacy of mirtazapine with studies of medication use for up to 40 weeks show continued improvements in response rates and lower relapse rates compared to placebo (Merck 2012, 2017). Of note, the effectiveness of mirtazapine in hospitalized patients with depression has not been adequately studied to draw significant conclusions regarding this patient population (Merck 2012, 2017).

3.2 Pharmacology and Metabolism

The exact mechanism of action of mirtazapine in the treatment of major depressive disorder is unknown, which is similar to many other antidepressants (Merck 2012, 2017). Information obtained from preclinical data in trials indicates that mirtazapine has an antagonistic effect at the central presynaptic 5-HT_2 receptors and alpha-2 adrenergic inhibitory autoreceptors and heteroreceptors. This results in increased norepinephrine release with an indirect release of serotonin due to increased noradrenergic input to the raphe nucleus (Merck 2012, 2017; Preskorn and Ross 2004). Mirtazapine is additionally a potent antagonist of the 5-HT_2 and 5-HT_3 receptors with no significant effects on the 5-HT_{1A} and 5-HT_{1B} receptors. The binding of mirtazapine to these receptors with resulting antagonistic effects is what produces the antidepressive effects of this medication (Preskorn and Ross 2004).

In addition to the antidepressive effects of mirtazapine, this medication has several additional effects on neurons through the body, which explains some of the more prominent side effects of the medication. Mirtazapine is a potent antagonist of the H_1 receptor resulting in the observed sedative effects of the medication (Merck 2012, 2017; Preskorn and Ross 2004). In the periphery, mirtazapine works as a moderate alpha-1 adrenergic antagonist resulting in vasodilation producing intermittent orthostatic hypotension (Merck 2012, 2017). Actions of the medication as a moderate antagonist at the muscarinic receptors explain the low incidence of anticholinergic side effects with mirtazapine that can often be observed with other antidepressants (Merck 2012, 2017; Preskorn and Ross 2004). Mirtazapine has no affinity for dopamine receptors and no effect on monoamine reuptake (Alam et al. 2013; Preskorn and Ross 2004).

Mirtazapine is quickly absorbed with a half-life of 20–40 h allowing for once-daily dosing at bedtime with peak plasma concentrations observed within 2 h of ingestion (Merck 2012, 2017; Alam et al. 2013). The rate and extent of absorption are not affected by food (Merck 2012, 2017). Mirtazapine is extensively metabolized in the liver with the formation of the 8-hydroxy metabolite by CYP_{2D6} and CYP_{1A2} enzymes with the formation of the N-desmethyl and N-oxide metabolites formed by the CYP_{3A} enzymes (Merck 2012, 2017; Alam et al. 2013; Preskorn and Ross 2004). The absolute bioavailability of the medication is 50% with the metabolites eliminated primarily in the urine (75%) with a small proportion (15%) eliminated in the feces (Merck 2012, 2017).

Plasma levels of mirtazapine have a linear relationship with the dose administered over a range of 15–80 mg daily (Merck 2012, 2017; Preskorn and Ross 2004). Studies have shown that females have longer elimination half-lives with 37 h compared to 26 h in males (Merck 2012, 2017). Steady-state plasma levels of mirtazapine are achieved within 5 days of starting the medication with a 50% accumulation of the medication in circulation that is 85% bound to plasma proteins (Merck 2012, 2017).

3.3 Dosing Recommendations

The initial recommended starting dose for mirtazapine is 15 mg daily given in the evening to help promote sleep (Merck 2012, 2017). Results obtained from clinical trials indicate that the effective dose range was from 15 to 45 mg once daily (Merck 2012, 2017). Since mirtazapine has a long elimination half-life of 20–40 h, dose adjustments should only be made every 1–2 weeks to allow for evaluation of the therapeutic response to the adjusted dose (Merck 2012, 2017). Long-term studies on mirtazapine have shown that the efficacy of the medication in treating major depressive disorder is maintained for up to 40 weeks after an initial 8–12 weeks in the suggested dose range (Merck 2012, 2017). As with all antidepressants, patients should be periodically assessed to determine the need for the medication, and dose adjustments should be made if indicated (Merck 2017).

Mirtazapine should be used with caution in elderly patients and at reduced doses in patients with hepatic or renal impairment. Studies have shown a 40% reduced clearance in elderly males with only a 10% reduction noted in females (Merck 2017). Elimination of mirtazapine is reduced by 30% in patients with moderate renal insufficiency with a creatinine clearance of 11–39 mL/min/1.73 m^2 and 50% in patients with severe renal impairment with a creatinine clearance of less than 10 mL/min/1.73 m^2 (Merck 2012, 2017; Preskorn and Ross 2004). Due to extensive hepatic metabolism, clearance of mirtazapine is decreased by approximately 30% in patients with hepatic impairment (Merck 2017; Preskorn and Ross 2004).

3.4 Onset of Action

Results obtained from double-blinded clinical trials indicate that the time to therapeutic efficacy for major depressive disorder is approximately 2 weeks, which is comparable with other antidepressants (Preskorn and Ross 2004; Lavergne et al. 2005).

3.5 Use in Special Populations

The use of mirtazapine is contraindicated in patients with a known hypersensitivity to the medication or its components and patients on MAOIs. Patients on MAOIs,

linezolid, or IV methylene blue must have a 14-day washout period prior to starting mirtazapine due to increased risk of serotonin syndrome (Merck 2012, 2017). Additional risks for the development of serotonin syndrome include the combination of mirtazapine with triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, and St. John's wort with the greatest risk of interactions at medication initiation and during dose adjustments (Merck 2017).

The use of mirtazapine has been associated with the development of acute angle-closure glaucoma and QT prolongation that can lead to torsades de pointes and sudden cardiac death. Given this finding, mirtazapine should not be used or used with extreme caution in patients with known cardiovascular disease, in patients with a family history of QT prolongation, or in patients on additional medications known to prolong QT intervals (Merck 2012, 2017).

Mirtazapine was rated as pregnancy category C under the old system of classifying teratogenic risk with animal studies revealing no evidence of teratogenicity (Merck 2012). To date, there are no adequate controlled studies in pregnant women to determine the risk to the fetus (Merck 2017). It is currently unknown if mirtazapine is excreted in human breast milk so caution should be used in nursing mothers (Merck 2012, 2017). Safety and efficacy studies of mirtazapine in pediatric patients have not been determined (Merck 2012, 2017).

3.6 Drug Interactions

Mirtazapine is extensively processed by the liver and as such is affected by medications that induce or inhibit the cytochrome enzymes (Merck 2017). Phenytoin has been shown to increase the clearance of mirtazapine twofold resulting in a 45% reduction in plasma concentrations of the medication. Carbamazepine has a similar effect resulting in a 60% reduction in plasma mirtazapine concentrations (Merck 2012, 2017). Cytochrome enzyme inhibitors including cimetidine and ketoconazole resulted in increased areas under the curve of mirtazapine by 50% and 40–50%, respectively, resulting in increased doses of the medications in circulating plasma (Merck 2017). Of note, caution should be used when administering mirtazapine with potent CYP_{3A4} inhibitors including HIV protease inhibitors, azole antifungal medications, erythromycin, or nefazodone (Merck 2012, 2017). Mirtazapine has been noted to result in an increased INR in patients on warfarin requiring close monitoring of anticoagulation (Merck 2017). Co-administration of mirtazapine and alcohol or diazepam has shown increased impairments in cognition and motor skills that are additive with increasing doses (Merck 2012, 2017).

3.7 Adverse Reactions

Approximately 16% of the 453 patients enrolled in clinical trials in the United States discontinued therapy with mirtazapine due to adverse reactions (Merck 2012, 2017). The most commonly reported side effect noted on the medication included somnolence that resulted in 10% of patients discontinuing the medication (Preskorn and

Ross 2004). It is unclear based on trial results if a tolerance develops for the sedating aspects of the medication over time (Merck 2012, 2017; Alam et al. 2013). Increased appetite and weight gain were reported as the second most common side effect occurring in 17% of patients results in a weight gain of greater than 7% of body weight in 7.5% of patients treated with mirtazapine (Merck 2017). Dizziness was reported in 7% of patients, and transient elevations in cholesterol and liver function tests were noted on the medication (Merck 2012, 2017).

Results obtained from clinical trial data showed an association of treatment with mirtazapine with development of agranulocytosis resulting in neutropenia and increased risk of infections (Merck 2012, 2017). Discontinuation of the medication resulted in resolution of the reduction in blood counts and risk for neutropenic fever (Merck 2017). Discontinuation of mirtazapine should occur with a gradual reduction over serval weeks rather than abrupt discontinuation of the medication (Merck 2012, 2017).

3.8 Overdose

Review of the literature shows that there are very few examples of overdose with mirtazapine, with only eight reported cases to date (Merck 2012, 2017). The only reported death associated with mirtazapine occurred in a patient with toxic levels of amitriptyline and chlorprothixene (Merck 2017). Signs of overdose include increased disorientation, somnolence, impaired memory, and tachycardia. Treatment consists of supportive care and managing the toxicities of additional medications that may have been ingested along with mirtazapine (Merck 2012, 2017).

4 Trazadone

4.1 Indications for Use and Medication History

Trazadone is a triazolopyridine derivative that was initially synthesized by the Angelini Francesco Pharmaceutical Laboratories in Rome, Italy (Georgotas et al. 1982; Fagiolini et al. 2012). The medication is a 5-HT_2 receptor antagonist and selective serotonin reuptake inhibitor that are indicated to treat major depressive disorder. This medication became available as an immediate-release formulation in the United States in the 1970s with a prolonged-release formulation of the medication developed in the 1980s with approval in the United States in 2010 for treatment of major depressive disorder (Georgotas et al. 1982; Pragma Pharmaceuticals 2017; Preskorn and Ross 2004; Fagiolini et al. 2012; Feighner and Boyer 1988).

Clinical trials have demonstrated the efficacy and safety of trazodone for use in both inpatient and outpatient settings for the immediate-release formulation with comparable antidepressant activity noted between trazodone and tricyclic antidepressants including amitriptyline and imipramine; selective serotonin reuptake inhibitors including fluoxetine, paroxetine, sertraline, citalopram, and escitalopram;

bupropion; and selective norepinephrine reuptake inhibitors including venlafaxine and mirtazapine (Fagiolini et al. 2012). The efficacy and safety profile of this medication allow for it to be administered as both monotherapy and in combination with additional antidepressants (Fagiolini et al. 2012).

Due to trazodone's unique mechanism of action, the medication has several benefits in treating associated comorbidities with major depression including anxiety and insomnia (Fagiolini et al. 2012; Stahl 2009). While trazodone has only been FDA approved for use in the treatment of major depressive disorder, it has been used off label for insomnia, anxiety, dementia, Alzheimer's disease, substance abuse, schizophrenia, bulimia, and fibromyalgia with most of the trials for these indications conducted in the 1980s (Georgotas et al. 1982; Fagiolini et al. 2012). Trazadone has been extensively used for the treatment of insomnia due to its anxiolytic actions and ability to normalize sleep patterns (Fagiolini et al. 2012). In the United States, trazadone is most frequently prescribed for insomnia, rather than depression, and is the second most commonly prescribed agent to treat insomnia. The hypnotic action of this medication when used at lower doses than indicated for depression treatment is attributed primarily to the antagonism of the 5-HT_{2A} receptors, H_1 receptors, and alpha-1 adrenergic receptors (Fagiolini et al. 2012).

4.2 Pharmacology and Metabolism

The exact mechanism of action for trazadone on depressive symptoms is not fully understood but is likely related to the effects of the medication on serotonergic activity in the central nervous system (Fagiolini et al. 2012; Pragma Pharmaceuticals 2017). Evidence obtained from clinical trials and preclinical data indicate that the effect of trazadone on depressive symptoms can be attributed to the simultaneous inhibition of the serotonin transporter and antagonism of the 5-HT_{2A} and 5-HT_{2C} receptors (Fagiolini et al. 2012). The synergistic actions of trazodone on these receptors are suggested to potentiate the antidepressant activity of the medication and improve tolerance of the medication due to reduced side effects seen in other antidepressants including SSRIs (Fagiolini et al. 2012). Trazadone additionally has antagonistic properties against the alpha-1 and alpha-2 adrenergic receptors in addition to antagonistic effects on the H_1 receptors. Trazadone is noted to have minimal anticholinergic effects (Fagiolini et al. 2012; Pragma Pharmaceuticals 2017).

Investigations of low-dose administration of trazadone in the 25–100 mg dose range have been shown to have hypnotic activity that can help promote sleep (Fagiolini et al. 2012). The efficacy of trazadone in sleep enhancement is secondary to its antagonistic effects on the H_1 receptors that are additionally enhanced by the additional antagonism of the 5-HT_{2A} and alpha-adrenergic receptors (Fagiolini et al. 2012; Preskorn and Ross 2004). While not FDA approved for this indication, this property of trazadone has been extensively used in clinical practice.

Trazadone is well absorbed after ingestion with food without selective localization in any tissues within the body (Mead Johnson 2017). Peak plasma levels are

noted 1 h after ingestion if the medication is taken on an empty stomach and 2 h after dosing if taken with food (Pragma Pharmaceuticals 2017; Georgotas et al. 1982; Mead Johnson 2017). Elimination of the medication from the body occurs in a biphasic pattern with a half-life in the initial phase of 3–6 h and a slower phase noted to have a half-life consisting of 5–9 h that is unaffected by the presence or absence of food (Mead Johnson 2017).

Trazadone is extensively metabolized in the liver by oxidative cleavage with less than 1% excreted unchanged in the urine (Pragma 2017). The most active metabolite is m-chlorophenylpiperazine produced by the CYP_{3A4} enzyme. This molecule is a greater inhibitor of serotonin reuptake as compared to the parent molecule of trazadone (Pragma Pharmaceuticals 2017; Georgotas et al. 1982). Trazodone is 89–95% protein bound with a half-life of approximately 7 h for the immediate-release formulation and 10 h in the extended-release formulation (Pragma Pharmaceuticals 2017; Georgotas et al. 1982; Fagiolini et al. 2012). The main route of elimination of the medication is through the urine at 70–75% with approximately 20% eliminated in the feces (Brogden et al. 1981).

4.3 Dosing Recommendations

The initial dose recommendation for trazadone by the manufacturer is 75–150 mg daily starting at bedtime due to the known sedative effects of the medication (Pragma Pharmaceuticals 2017; Mead Johnson 2017). Initial dosing should start low with a gradual up-titration relating to depressive symptom response and monitoring of intolerance of the medication (Pragma Pharmaceuticals 2017). The dose of trazadone can be increased by 50 mg per day every 3 days for a total dose of 300 mg given after meals for the immediate-release formulation and one to two times daily for the sustained-release formulation (Fagiolini et al. 2012; Mead Johnson 2017; Pragma Pharmaceuticals 2017). The maximum outpatient dose should not exceed 400 mg per day in divided doses (Mead Johnson 2017; Pragma Pharmaceuticals 2017). In hospitalized patients, the dose may be increased to a maximum dose of 600 mg daily in divided doses while the patient is being actively monitored for side effects (Fagiolini et al. 2012; Mead Johnson 2017; Pragma Pharmaceuticals 2017). In elderly patients, the initiation dose should be kept low at 75–100 mg daily at bedtime to prevent significant side effects (Fagiolini et al. 2012). Once a therapeutic dose has been established, the patient should continue to undergo active monitoring with reductions in dose gradually as tolerated and guided by therapeutic response (Pragma Pharmaceuticals 2017; Mead Johnson 2017).

Trazodone is contraindicated in patients taking or within 14 days of stopping MAOIs, linezolid, and IV methylene blue due to an increased risk of serotonin syndrome (Pragma Pharmaceuticals 2017; Mead Johnson 2017). The risk of developing serotonin syndrome is increased with co-administration of trazodone with other serotonergic medications including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, and St. John's wort (Mead Johnson 2017). Additionally, this medication should not be administered to patients

with a hypersensitivity to the medication or its metabolites (Pragma Pharmaceuticals 2017; Mead Johnson 2017).

Results obtained from clinical trials indicate that trazodone has been associated with the development of arrhythmias in patients with pre-existing cardiac disease. The most common arrhythmias identified included premature ventricular contractions, ventricular couplets, tachycardia with syncope, and torsades de pointes (Pragma 2017; Mead Johnson 2017). Due to this information, trazadone should not be prescribed to patients with a history of cardiac arrhythmias, symptomatic bradycardia, hypokalemia, hypomagnesemia, and conditions or medications that prolong QT intervals including quinidine, procainamide, amiodarone, sotalol, ziprasidone, chlorpromazine, thioridazine, or fluoroquinolones (Pragma 2017; Mead Johnson 2017). Trazadone should additionally not be administered with CYP_{3A4} inhibitors including itraconazole, clarithromycin, and voriconazole due to QT prolongation and the potential to develop torsades de pointes (Pragma Pharmaceuticals 2017).

Trazadone has been indicated to cause numerous blood-related conditions including orthostatic hypotension with syncope, increased risk of bleeding, and priapism. Co-administration with aspirin, NSAIDs, antiplatelet medications, warfarin, or additional anticoagulants has been shown to increase the risk of bleeding, most notably in the GI tract (Pragma Pharmaceuticals 2017). Cases of priapism have been reported in the literature and require prompt treatment to prevent irreversible damage to the erectile tissue (Pragma Pharmaceuticals 2017; Mead Johnson 2017). Patients at highest risk for this condition include males with sickle cell anemia, multiple myeloma, and leukemia or men with anatomical deformities including angulation, cavernosal fibrosis, or Peyronie's disease (Pragma Pharmaceuticals 2017; Mead Johnson 2017).

4.4 Onset of Action

Studies conducted regarding the onset of action of trazadone revealed that in patients that respond to the medication, one third of inpatients and one half of outpatients had a significant therapeutic response by the end of the first week of treatment (Mead Johnson 2017; Preskorn and Ross 2004). Three fourths of patients taking the medication noted significant antidepressant effects by the end of the second week with the remaining one fourth of patients requiring 2–4 weeks for a noted therapeutic response (Mead Johnson 2017; Pragma Pharmaceuticals 2017; Georgotas et al. 1982). This time frame of effectiveness is similar to other available antidepressants (Preskorn and Ross 2004).

4.5 Use in Special Populations

Trazodone was categorized as pregnancy category C under the old system of classifying teratogenic risk and has been shown to cause increased fetal loss in rats at six to nine times the maximum dose used in humans (Pragma Pharmaceuticals

2017). No teratogenic effects were noted in rat and rabbit models when trazodone was administered during organogenesis at doses 9–17 times the dose administered in humans (Pragma Pharmaceuticals 2017). There are no adequately controlled studies in pregnant women to draw conclusions about the effect of the medication on a fetus and the medication should be used only if the benefit outweighs the potential risk (Pragma 2017; Mead Johnson 2017). Trazodone has been isolated in the milk of lactating rats suggesting that it may be secreted in human breast milk. Caution should be used when prescribing trazodone to lactating mothers (Pragma Pharmaceuticals 2017). The safety and efficacy of trazodone have not been studied in the pediatric population (Pragma Pharmaceuticals 2017; Mead Johnson 2017).

Trazadone should be used with caution in geriatric populations and should be started at lower doses given the potential for increased plasma concentrations (Pragma Pharmaceuticals 2017; Mead Johnson 2017). Trazadone has not been studied in patients with renal impairment or hepatic impairment and should be used with extreme caution in this patient population given that the medication requires extensive processing in the liver and is excreted primarily in the urine (Pragma Pharmaceuticals 2017; Mead Johnson 2017).

4.6 Drug Interactions

Medication interactions with trazodone have been relatively limited in scope compared to additional antidepressant medications. Clinical trials have shown increased levels of digoxin and phenytoin when co-administered with trazodone (Mead Johnson 2017). Since trazodone is extensively processed in the liver, it has the potential to interfere with medications that utilize the CYP_{3A4} enzymes for processing (Pragma Pharmaceuticals 2017; Preskorn and Ross 2004). Co-administration with strong CYP_{3A4} inhibitors including clarithromycin, itraconazole, and ketoconazole and HIV medications including darunavir, indinavir, ritonavir, and tipranavir is known to increase the plasma concentration of trazadone requiring a dose reduction of the medication (Pragma Pharmaceuticals 2017). Additionally, co-administration with strong CYP_{3A4} inducers including carbamazepine, systemic corticosteroids, phenytoin, phenobarbital, and rifampin will result in reduced doses of trazadone (Pragma Pharmaceuticals 2017).

4.7 Adverse Reactions

The most common adverse reaction noted in patients in clinical trials was drowsiness, which was identified in 24% of outpatients and 41% of inpatients (Pragma Pharmaceuticals 2017; Mead Johnson 2017). The next most common adverse effect was dizziness at 20% and 28% in inpatients and outpatients, respectively (Pragma Pharmaceuticals 2017). Dry mouth and nervousness were additionally noted in patients taking the medication (Mead Johnson 2017). Long-term studies of the medication noted occasional bradycardia in patients that required close

monitoring, and discontinuation of the medication if the patient became symptomatic (Pragma 2017; Mead Johnson 2017).

As with most antidepressants, trazadone has been shown to increase the risk of acute angle-closure glaucoma in patients with anatomically narrow angles and should not be used in patient with known anatomic abnormalities (Pragma Pharmaceuticals 2017). Hyponatremia can occur in patients taking trazadone with reported cases of sodium levels below 100 mmol/L secondary to SIADH. Patients at highest risk for hyponatremia are elderly patients on diuretics and patients that are volume depleted. Treatment consists of stopping the medication and treatment of SIADH with water restriction (Pragma Pharmaceuticals 2017).

4.8 Overdose

The most severe reactions associated with an overdose with trazadone include priapism, respiratory arrest, seizures, and EKG changes including QT prolongation (Mead Johnson 2017). There is no specific antidote for the medication, and treatment consists of supportive care (Pragma Pharmaceuticals 2017; Mead Johnson 2017). Gastric lavage and forced diuresis may be useful in eliminating the drug from the body but have not been extensively studied as a cure for overdose (Mead Johnson 2017). Deaths from overdose with trazodone have been reported in patients that additionally ingested other central nervous system depressants including alcohol, benzodiazepines, and barbiturates (Pragma Pharmaceuticals 2017; Mead Johnson 2017).

5 Vortioxetine

5.1 Indications for Use and Medication History

Vortioxetine is a novel antidepressant that was derived from studies targeting the combination of serotonin transporter inhibition and 5-HT_{1A} receptor modulation for the treatment of major depressive disorder (Sanchez et al. 2015; D'Agostino et al. 2015). This combination of targeted therapy has been proposed to lead to rapid desensitization of the somatodendritic 5-HT_{1A} autoreceptors and enhance antidepressive effects by activating postsynaptic 5-HT_{1A} receptors (Sanchez et al. 2015). Additional research conducted in the development of this medication showed that antagonism of the 5-HT_3 receptor potentiated the extracellular 5-HT effects generated from blocking the serotonin transporter (Sanchez et al. 2015; D'Agostino et al. 2015).

Vortioxetine was FDA approved in 2013 and was found to work as an antagonist, agonist, and partial agonist of multiple serotonin receptors that helps to reduce symptoms of major depressive disorder with increased maintenance of remission (Sanchez et al. 2015; D'Agostino 2015). This medication is an antagonist at 5-HT_3, 5-HT_{1D}, and 5-HT_7 receptors, an agonist at 5-HT_{1A} receptors, and a partial agonist at

5-HT_{1B} receptors (D'Agostino et al. 2015). Vortioxetine is classified by the World Health Organization as a N06AX antidepressant class that is unique compared to all other available antidepressants (Sanchez et al. 2015).

Vortioxetine is indicated for the treatment of major depressive disorder, and the efficacy of the medication for treatment of depression was established in six 6–8-week trials including a study conducted in the aging population and an additional maintenance study in adults (Takeda Pharmaceuticals 2018). All studies showed vortioxetine superiority compared to placebo with treatment of acute depressive episodes and reduced relapse rates (D'Agostino et al. 2015).

5.2 Pharmacology and Metabolism

The exact mechanism of vortioxetine on depressive symptoms is not fully understood but is thought to be due to the enhancement of serotonergic activity in the central nervous system through inhibition of serotonin reuptake (Takeda Pharmaceuticals 2018). Vortioxetine binds with high affinity to the serotonin transporter in addition to the 5-HT_3, 5-HT_{1A}, and 5-HT_7 receptors with moderate affinity binding noted at the 5-HT_{1D} and 5-HT_{1B} receptors (D'Agostino et al. 2015). The binding affinity of this medication is dose responsive in that raising the dose by 5 mg results in a 15% increase in binding affinity up to the maximum dose tolerated (D'Agostino et al. 2015). Blockade of the 5-HT_3 receptor was noted in animal studies to produce increased levels of serotonin, dopamine, norepinephrine, acetylcholine, and histamine in the prefrontal cortex and hippocampus, which are known to be associated with the development of depression (D'Agostino et al. 2015).

Clinical trials on vortioxetine indicated a 75% bioavailability in humans with an average elimination half-life of 57–66 h with oral administration (Sanchez et al. 2015; Takeda Pharmaceuticals 2018). The medication is absorbed in the gastrointestinal tract and extensively metabolized in the liver by oxidation via the cytochrome P450 enzymes including CPY_{2D6}, CYP_{3A4}, CYP_{3A5}, CYP_{2C19}, CYP_{2C9}, CYP_{2A6}, CYP_{2C8}, and CYP_{2B6} along with glucuronic acid conjugation occurring in the liver (D'Agostino et al. 2015; Takeda Pharmaceuticals 2018). The primary enzyme responsible for the metabolism of vortioxetine is CYP_{2D6} with the medication showing no significant induction or inhibition resulting in fewer drug-drug interactions (Sanchez et al. 2015). The resulting metabolites do not penetrate the blood-brain barrier and are thus pharmacologically inactive (D'Agostino et al. 2015; Sanchez et al. 2015; Takeda Pharmaceuticals 2018).

The pharmacokinetics of vortioxetine is linear, time dependent, and dose-proportional when administered in once-daily dosing (Takeda Pharmaceuticals 2018). Peak plasma concentrations occur at 7–11 h after ingestion and are not affected by food (D'Agostino et al. 2015; Takeda Pharmaceuticals 2018). Vortioxetine is 98% protein bound with steady-state concentrations achieved in 2 weeks (D'Agostino et al. 2015; Takeda Pharmaceuticals 2018). The medication is primarily excreted in the urine at 59% with an additional 26% eliminated in the feces (D'Agostino et al. 2015).

5.3 Dosing Recommendations

The recommended starting dose of vortioxetine is 10 mg once daily and can be given with or without food (D'Agostino et al. 2015; Takeda Pharmaceuticals 2018). The dose should be increased as indicated to the maximum dose of 20 mg daily, as higher doses were shown to have improved efficacy in clinical trials (D'Agostino et al. 2015; Takeda Pharmaceuticals 2018). Doses above 20 mg per day have not been evaluated for safety and efficacy. For patients that do not tolerate the higher doses of the medications due to side effects, the dose can be lowered as clinically indicated to the lowest possible dose of 5 mg daily (Takeda Pharmaceuticals 2018; D'Agostino et al. 2015).

Patients should continue to be monitored on the medication with dose reductions as indicated based on efficacy and side effects. Maintenance studies of the medication have shown decreased risk of recurrence of acute depressive episodes compared to placebo (D'Agostino et al. 2015; Takeda Pharmaceuticals 2018). The medication can be discontinued abruptly if needed, but results obtained from clinical trials showed that a reduction in dose from 15 to 20 mg daily to 10 mg daily for 1 week prior to discontinuation resulted in fewer side effects and better tolerability (Takeda Pharmaceuticals 2018; D'Agostino et al. 2015).

The use of vortioxetine is contraindicated in patients with a hypersensitivity to the medication or its components. The development of angioedema has been reported in patients taking this medication (Takeda Pharmaceuticals 2018). Co-administration of MAOIs or use of MAOIs within 21 days of starting vortioxetine is contraindicated due to the risk of serotonin syndrome (D'Agostino et al. 2015; Takeda Pharmaceuticals 2018). Additional serotonergic medications to be avoided with use of vortioxetine include selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, tricyclic antidepressants, buspirone, triptans, linezolid, IV methylene blue, meperidine, fentanyl, pentazocine, lithium, tramadol, St. John's wort, dextromethorphan, and antipsychotic medications (D'Agostino et al 2015; Takeda Pharmaceuticals 2018). Acute angle-closure glaucoma has been reported in patients on vortioxetine prohibiting its use in patient with anatomically narrow angles (Takeda Pharmaceuticals 2018).

Vortioxetine has been shown to cause increased risk of bleeding disorders and hyponatremia (D'Agostino et al. 2015; Takeda Pharmaceuticals 2018). Caution should be used with this medication when the patient is additionally using aspirin, NSAIDs, warfarin, or other anticoagulants as this may result in increased bleeding risk that is most notable in the gastrointestinal tract (Takeda Pharmaceuticals 2018). Hyponatremia has additionally been noted in patients taking vortioxetine due to the development of SIADH with presenting sodium levels at 110 mmL/L (D'Agostino et al. 2015; Takeda Pharmaceuticals 2018). Elderly patients or patients on diuretics are at greatest risk of hyponatremia and should be closely monitored with discontinuation of the medication and water restriction if symptomatic hyponatremia is identified (Takeda Pharmaceuticals 2018).

5.4 Onset of Action

Studies conducted on the onset of action of vortioxetine indicate that patients will often experience improvement in sleep, energy, and appetite within the first 1–2 weeks of treatment with most patients experiencing improvement in depressive symptoms at 2 weeks (Takeda Pharmaceuticals 2018). Full effect of the medication for treatment of major depressive disorder is similar to other antidepressants with 4–6-week duration of therapy prior to significant improvement in symptoms (D'Agostino et al. 2015; Takeda Pharmaceuticals 2018).

5.5 Use in Special Populations

There is very limited human data regarding safety of vortioxetine in pregnancy to determine associated risks to the fetus (Takeda Pharmaceuticals 2018). Animal studies in rats and rabbits showed reduced fetal weight and delayed bone ossification when given the medication during organogenesis at greater than 15 times the dose used in humans (Takeda Pharmaceuticals 2018). No fetal malformations were observed in animal studies (Takeda Pharmaceuticals 2018).

Exposure to serotonergic medications including vortioxetine in late pregnancy may result in an increased risk for neonatal complications requiring prolonged hospitalization, respiratory support, tube feeding, and the development of persistent pulmonary hypertension of the newborn (Takeda Pharmaceuticals 2018). Neonatal complications that have been previously reported in SSRI and SNRI use in pregnancy that are possible with vortioxetine given its similar mechanism of action include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying (Takeda Pharmaceuticals 2018). There is currently no information regarding the presence of vortioxetine in human breast milk or the effects on the breastfed infant. Additionally, there have been no clinical trials conducted with children on this medication (Takeda Pharmaceuticals 2018).

Studies have indicated that no dose adjustments in the medication are required for diverse populations. Clinical trials conducted with the geriatric population indicated that no dose adjustments are indicated based on age (Takeda Pharmaceuticals 2018). No dose adjustments were indicated based on race, gender, ethnicity, renal function, or hepatic impairment (Takeda Pharmaceuticals 2018).

5.6 Drug Interactions

Vortioxetine is primarily metabolized by CYP_{2D6} in the liver and thus has the potential for drug interactions when co-administered with inhibitors or inducers of this enzyme (D'Agostino et al. 2015; Takeda Pharmaceuticals 2018). Co-administration with CYP_{2D6} inhibitors including bupropion, fluoxetine,

paroxetine, and quinidine resulted in increased concentrations of vortioxetine requiring at least a 50% dose reduction in the medication (Takeda Pharmaceuticals 2018). Administration of vortioxetine with cytochrome inducers including rifampin, carbamazepine, and phenytoin resulted in reduced plasma concentrations of the medication requiring increased doses (D'Agostino et al. 2015). It is important to note that the increase in dosage should not exceed three times the original dose (Takeda Pharmaceuticals 2018).

Vortioxetine has been shown to have no significant effect on other central nervous system agents including alcohol, benzodiazepines, or lithium (Takeda Pharmaceuticals 2018). Additionally, no dose adjustments were required with CYP_{1A2} substrates including duloxetine and caffeine, CYP_{2B6} medications including bupropion, and CYP_{3A4} and CYP_{3A5} substrates including budesonide and midazolam (Takeda Pharmaceuticals 2018).

5.7 Adverse Reactions

The most common adverse reaction reported in patients on vortioxetine was nausea that was dose related, mild to moderate in intensity, and more common in females (D'Agostino et al. 2015; Takeda Pharmaceuticals 2018). This side effect commonly occurred within the first week of treatment with 15–20% of the 4,746 patients evaluated in clinical trials experiencing nausea after 1–2 days of treatment. Approximately 10% of patients on the 10–20 mg daily dose reported nausea at the end of the 6–8-week placebo-controlled trials (D'Agostino et al. 2015; Takeda Pharmaceuticals 2018). Sexual dysfunction including reductions in sexual desire, sexual performance, and sexual satisfaction was reported in up to 5% of men and 2% of women compared to placebo (Takeda Pharmaceuticals 2018). In patients with sexual dysfunction at baseline, approximately 34% of women and 29% of men reported increased sexual side effects when on the 20 mg dose of vortioxetine (D'Agostino et al. 2015).

Additional side effects reported in patients on vortioxetine included headaches, dry mouth, and dizziness (D'Agostino et al. 2015; Takeda Pharmaceuticals 2018). Increased incidences of gastrointestinal side effects including nausea, constipation, and vomiting were reported on the 20 mg per day dose compared to the reduced doses of the medication (D'Agostino et al. 2015). Vortioxetine was noted to have no significant effect on weight (Takeda Pharmaceuticals 2018). Serious side effects reported in post-marketing studies at low incidence included hypertensive crisis, increased risk of suicide, and pancreatitis (D'Agostino et al. 2015).

5.8 Overdose

There is limited clinical experience with overdose on vortioxetine with the only reported cases consisting of patients that accidentally consumed 40–75 mg of the medication (D'Agostino et al. 2015). At this dosage, patients reported increased rates

of nausea, dizziness, diarrhea, abdominal discomfort, pruritus, somnolence, and flushing (D'Agostino et al. 2015; Takeda Pharmaceuticals 2018). There are no known antidotes to vortioxetine, and management of an overdose is focused on symptomatic care (D'Agostino et al. 2015; Takeda Pharmaceuticals 2018).

6 Vilazodone

6.1 Indications for Use and Medication History

Vilazodone is an indolalkylamine that is indicated for the treatment of major depressive disorder (Cruz 2012; Sahli et al. 2016; Wang et al. 2016; Trovis 2011). Vilazodone is a selective serotonin reuptake inhibitor and 5-HT_{1A} receptor partial agonist that was approved by the FDA in 2011 and marketed in the United States within that same year (Cruz 2012; Sahli et al. 2016; Wang et al. 2016). This medication works by enhancing serotonergic activity in the central nervous system through selective inhibition of serotonin reuptake with no significant effects noted on norepinephrine or dopamine uptake (Cruz 2012).

Binding of vilazodone has been measured to be 60 times more selective for the 5-HT_{1A} receptor than buspirone, which is the only additional 5-HT_{1A} receptor partial agonist that is approved for clinical use as an antidepressant (Sahli et al. 2016). The partial agonist activity of this medication has been suggested to help reduce the time to effectiveness of SSRIs, which in turn results in more rapid patient response times to the medication (Sahli et al. 2016; Wang et al. 2016). Vilazodone has been shown to reduce the sensitivity of the 5-HT_{1A} receptors through its partial agonist activity that results in overstimulation and downregulation of the autoreceptors in the dorsal raphe nucleus at an increased rate as compared to selective serotonin reuptake inhibitors (Sahli et al. 2016). Testing in animal models showed that the SSRI activity of vilazodone was 30 times more potent than fluoxetine with a significant increase in serotonin levels in the ventral hippocampus and frontal cortex (Sahli et al. 2016; Wang et al. 2016).

The efficacy of vilazodone was established in two 8-week randomized double-blinded placebo-controlled trials in adults with a diagnosis of major depressive disorder (Trovis 2011). Significant improvement in major depressive symptoms were noted in both trials as compared to placebo with similar remission rates as compared to available SSRIs, including citalopram (Hellerstein and Flaxer 2015).

6.2 Pharmacology and Metabolism

The exact mechanism of the antidepressant activity of vilazodone is not completely understood but is thought to be secondary to enhancement of serotonergic activity in the central nervous system through the selective inhibition of serotonin reuptake (Cruz 2012; Sahli et al. 2016; Wang et al. 2016; Trovis 2011). Vilazodone is known to bind with high affinity to the serotonin reuptake sites with no known effects on

norepinephrine or dopamine reuptake resulting in potent selective inhibition of serotonin reuptake (Cruz 2012; Trovis 2011). Vilazodone additionally binds with high affinity to the 5-HT_{1A} receptors as a partial agonist resulting in faster onset of action, greater efficacy, and better tolerability with reduced sexual side effects when compared to other SSRIs (Wang et al. 2016; Hellerstein and Flaxer 2015).

The activity of vilazodone is primarily due to the parent medication with processing of the medication in the liver by the cytochrome P450 enzymes with only 1–2% of the parent medication recovered unchanged in the urine and feces, respectively (Cruz 2012; Sahli et al. 2016; Wang et al. 2016; Trovis 2011). The pharmacokinetics are dose proportional with steady-state levels of the medication obtained within 3 days (Trovis 2011; Sahli et al. 2016). Peak plasma concentrations of vilazodone were observed at 4–5 h after ingestion with a noted half-life of the medication of 20–25 h (Cruz 2012; Trovis 2011; Sahli et al. 2016). Vilazodone has greater bioavailability of 72% when ingested with food compared to only 22% when taken on an empty stomach (Cruz 2012; Trovis 2011). Additionally, this medication is known to be harsh on the GI tract if taken alone often resulting in vomiting that reduced the absorption of the medication by at least 25% (Cruz 2012). Once the medication is absorbed, it is widely distributed throughout the body with 96–99% of vilazodone being protein bound (Cruz 2012; Trovis 2011).

Vilazodone is metabolized in the liver primarily by the CYP_{3A4} enzyme with secondary metabolism noted with the CYP_{2C19}, CYP_{2D6}, and other pathways that utilize carboxylesterases (Cruz 2012; Sahli et al. 2016; Trovis 2011). The presence of mild to moderate renal or hepatic impairment did not affect the clearance of the medication resulting in no indications for dose adjustments in this patient population (Cruz 2012; Trovis 2011).

6.3 Dosing Recommendations

The initial dose of vilazodone recommended by the manufacturer is 10 mg once daily for 7 days, followed by 20 mg once daily for an additional 7 days. This dose can then be increased to the recommended therapeutic dose of 40 mg daily (Trovis 2011; Cruz 2012). The efficacy of the medication has not been extensively studied for long-term use, so the patients on the medication need to be periodically assessed for side effects and clinical efficacy with a titration of the medication down to the lowest effective dose with the fewest side effects (Trovis 2011). A dose taper of the medication that has been shown to reduce discontinuation side effects includes a reduction from 40 mg daily to 20 mg daily for 4 days and a further reduction to 10 mg for 3 days prior to discontinuing the medication (Trovis 2011). Additionally, if the patient is on the 20 mg daily dose, a taper to 10 mg daily for 7 days with resultant discontinuation of the medication has been shown to be effective (Trovis 2011).

Vilazodone is contraindicated for use in patients on MAOIs or in patients that have been taking MAOIs for 14 days prior to initiation of vilazodone due to the risk of serotonin syndrome (Cruz 2012; Trovis 2011). This medication is contraindicated

in combination with tryptophan, SSRIs, SNRIs, triptans, buspirone, tramadol, antipsychotics, or antidopaminergic agents due to the risk of serotonin syndrome (Trovis 2011). This medication has not been studied in patients with seizure disorders and should be prescribed with caution in patients with known seizures.

6.4 Onset of Action

Placebo-controlled clinical trials showed significant improvement in symptoms of major depressive disorder in patients within 1 week of starting vilazodone (Rickels et al. 2009; Pierz and Thase 2014; Hellerstein and Flaxer 2015). Additional studies have shown significant clinical improvement starting in week 2 of therapy and persisting for the duration of therapy when patients were on the 20 mg per day and 40 mg per day dosages (Hellerstein and Flaxer 2015). Data obtained regarding remission of depressive episodes in patients on vilazodone indicated lower rates of remission at weeks 1 and 2 compared to placebo with increased remission noted at 6 weeks of therapy, which is similar to other SSRIs (Hellerstein and Flaxer 2015).

6.5 Use in Special Populations

Vilazodone has not been extensively studied in pregnant women, but studies conducted with pregnant women on SSRIs showed that neonates exposed to serotonergic antidepressants in the late third trimester have developed complications leading to increased hospitalization time due to seizures, hypotonia, hyperreflexia, and temperature instability; requirements for respiratory support due to development of pulmonary hypertension, cyanosis, and apnea; increased incidence of tube feeding with vomiting and hypoglycemia; and neonatal behavioral syndrome consisting of increased tremor, jitteriness, irritability, and constant crying (Trovis 2011; Sahli et al. 2016). The effects of vilazodone on labor and delivery are unknown (Trovis 2011). Animal studies have shown developmental toxicities in rats administered the medication with no teratogenic effects noted in rats or rabbits when the medication was administered during organogenesis at doses 17–48 times the dose administered in humans (Trovis 2011). Fetal weight gain and skeletal ossification were delayed in animals given this high dose of vilazodone (Trovis 2011). Pregnant women should only be treated with this medication if the benefits outweigh the risks to the fetus (Trovis 2011).

There is currently no clinical data regarding vilazodone use in breastfeeding women; however, studies have shown that vilazodone is excreted into the milk of lactating rats and may additionally be present in human breast milk (Trovis 2011; Sahli et al. 2016). The use of vilazodone in pediatric patients has not been studied with no established safety and efficacy data in this population (Trovis 2011). Additionally, this medication has not been extensively studied in the elderly population, so it should be used with caution. Results obtained from a single-dose 20 mg pharmacokinetic study in patients over 65 as compared to patients aged 24–55 years

old showed no requirements for dose adjustments based on age (Trovis 2011). Studies conducted on gender comparisons of the medication indicated no effect of exposure based on gender when adjusted for body weight (Trovis 2011). Studies conducted on patients with mild to moderate renal or hepatic insufficiency showed no requirement for dose adjustment in this population (Trovis 2011; Sahli et al. 2016).

6.6 Drug Interactions

Vilazodone has been noted to increase bleeding risk in patients on NSAIDs, aspirin, and warfarin (Trovis 2011; Cruz 2012; Hellerstein and Flaxer 2015). Epidemiological studies have shown an association between SSRIs and increased upper GI bleeding through the effects of increased serotonin release by platelets on hemostasis (Trovis 2011). The addition of aspirin or NSAIDs can potentiate the risk of bleeding in patients on medications like vilazodone (Trovis 2011; Hellerstein and Flaxer 2015). Increased rates of bleeding have additionally been noted with the combinations of SSRIs and SNRIs with warfarin (Trovis 2011).

Metabolism by CYP_{3A4} is a significant pathway for the elimination of vilazodone in the urine and feces (Trovis 2011). Co-administration of vilazodone with strong inhibitors including ketoconazole can result in an increased plasma concentration of vilazodone of 50% requiring a dose reduction down to 20 mg per day (Trovis 2011; Cruz 2012; Hellerstein and Flaxer 2015). Moderate inhibitors of CYP_{3A4} including erythromycin require dose adjustment to 20 mg daily in patients that have intolerable side effects, with no dose adjustments required in patients on mild inhibitors including cimetidine (Cruz 2012; Trovis 2011). Co-administration with CYP_{3A4} inducers such as carbamazepine requires a twofold increase in vilazodone dose up to 80 mg daily (Hellerstein and Flaxer 2015).

Administration of vilazodone with inhibitors of CYP_{2C19} and CYP_{2D6} is not observed to alter the plasma concentrations of vilazodone as these isoforms play a minor role in the elimination of the medication from circulation (Trovis 2011). Vilazodone was noted to have no clinically significant effects on medications metabolized by CYP_{1A2} and CYP_{2C9} with no effect on the concentrations of caffeine or nifedipine (Trovis 2011). Studies evaluating the interaction between mephenytoin and vilazodone showed an 11% increase in mephenytoin biotransformation suggestive of a minor induction of CYP_{2C19} by vilazodone (Trovis 2011). Additionally, vilazodone has been shown to be a moderate inhibitor of CYP_{2C19} and CYP_{2D6} with inhibitory activity additionally noted with CYP_{2C8} substrates (Trovis 2011).

6.7 Adverse Reactions

The safety of vilazodone was evaluated in 2,177 patients with major depressive disorder with the most commonly reported adverse reactions including GI side effects with diarrhea reported at 28%, nausea reported at 23%, vomiting at 5%,

and insomnia at 6% (Cruz 2012; Trovis 2011; Sahli et al. 2016; Hellerstein and Flaxer 2015; Wang et al. 2016). Additional adverse reactions included dizziness, dry mouth, fatigue, abnormal dreams, decreased libido, arthralgias, and palpitations (Cruz 2012). The majority of adverse effects were reported to be mild to moderate and were self-limited with resolution of symptoms noted in 4–5 days on the medication (Sahli et al. 2016). Discontinuation rates of the medication in patients in clinical trials were shown to be 7.1% in patients on vilazodone compared to 3.2% in patients on placebo (Wang et al. 2016). During the clinical trials, vilazodone was not noted to have a significant impact on weight, vital signs, or EKG changes including QT prolongation (Cruz 2012; Trovis 2011).

6.8 Overdose

There is limited clinical data regarding overdose of vilazodone with only five cases reported in four adults and one child (Trovis 2011). Adverse reactions observed in clinical trials in patients that received doses of 200–280 mg of vilazodone included serotonin syndrome, lethargy, restlessness, hallucinations, and disorientation (Trovis 2011). All reported cases of overdose were treated with supportive care with all patients recovering with treatment. No specific antidote for vilazodone has been identified (Trovis 2011).

7 Conclusions

Understanding the mechanism of action of the different available medications for the treatment of major depressive disorder helps to guide clinicians in selecting the appropriate therapy for patients based on associated comorbidities and risk for side effects. For instance, patients with a significant history of tobacco use and depression may benefit from bupropion due to its combined role in treating nicotine cravings and depression through its effects on norepinephrine and dopamine. Patients with insomnia-predominant symptoms of depression may benefit from mirtazapine use due to blockade of the H_1 receptor, which is known to have a hypnotic effect. Trazadone has also been extensively used for the treatment of insomnia owing to its anxiolytic actions and ability to normalize sleep patterns due to the antagonism of the 5-HT_{2A} receptors, H_1 receptors, and alpha-1 adrenergic receptors. Vortioxetine binds with high affinity to the serotonin transporter in addition to the 5-HT_3, 5-HT_{1A}, and 5-HT_7 receptors resulting in increased levels of serotonin, dopamine, norepinephrine, acetylcholine, and histamine in the prefrontal cortex and hippocampus, resulting in reduced depressive symptoms. Vilazodone binds with high affinity to the 5-HT_{1A} receptors as a partial agonist resulting in faster onset of action, greater efficacy, and better tolerability with reduced sexual side effects when compared to other SSRIs.

These examples help illustrate how understanding the mechanism of action of antidepressant medications in combination with anticipating adverse effects of the

medication through an understanding of receptor binding can help develop individualized targeted therapy for depression in patients. Additional information about the effects of differing doses of the medication can also lead to improved selection of specific medications that are targeted to treat diverse patient populations with major depressive disorder. Analysis of the literature can be daunting in that there are few if any direct comparisons between medications. Methods implored in composing meta-analysis must be reviewed with caution in that numerous studies can be grouped together with increased heterogeneity and substantially different methodology with results that cannot be directly compared. By gaining a deeper understanding of the mechanism of action of the medications and potential side effects, clinicians are better equipped to select individualized targeted therapy for patients with major depressive disorder resulting in improved symptom management and increased remission rates.

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Use of Antidepressants in Patients with Co-occurring Depression and Substance Use Disorders

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Contents

Abstract

This chapter reviews antidepressant treatment considerations and recommendations for patients with co-occurring depression and substance use disorders. Depression and substance use disorders are highly comorbid conditions. Substance use disorders are chronic disorders that result in a cluster of symptoms indicating that an individual continues to use a substance despite significant problems resulting from their use. About 17 million Americans have an alcohol use disorder, and another approximately 7 million individuals have

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other drug use disorders (not including alcohol) in the United States. The rate of any substance use disorder (including alcohol) in individuals with major depressive disorder is 32% based on a national survey. Evidence suggests that the best outcome for individual with co-occurring conditions is treating both conditions simultaneously. Therefore, practitioners should know the following before prescribing antidepressants for patients with co-occurring substance use disorders: (1) treatment recommendations for patients with co-occurring depression and substance use disorders, (2) potential antidepressant interactions with alcohol and drugs of abuse, and (3) do antidepressants have a risk of misuse? Finally, we will summarize antidepressant treatment recommendations for patients with co-occurring depression and substance use disorders.

Keywords

Antidepressants · Co-occurring/comorbidity/dual diagnosis · Depression/major depressive disorder/dysthymia · Nonmedical use · Substance use disorder/addiction · Treatment considerations

1 Overview and Definition of Substance Use Disorders

Substance use disorders are highly prevalent conditions. A recent national epidemiologic survey reports the 12-month and lifetime prevalence of alcohol use disorders to be 13.9% and 29.1%, respectively (Grant et al. 2004). In the same survey, the 12-month and lifetime prevalence of drug use (substances of abuse that are not alcohol) disorders were 3.9% and 9.9%, respectively. Alcohol and drug use disorders are both associated with disability. After adjusting for sociodemographic information and psychiatric comorbidity, respondents with 12-month alcohol or drug use disorders had significantly lower mental health and social functioning than those without substance use disorder (Samet et al 2013).

Substance use disorder is defined as a problematic pattern of substance use leading to clinically significant impairment or distress. A person with a substance use disorder will have an inability to consistently abstain from substance(s); their life activities and time are focused on using substance(s), which leads to impaired functioning in social, occupational, and recreational activities. This person may experience craving and withdrawal symptoms when they attempt to abstain from substance use. See DSM-5 for full diagnostic criteria for substance use disorders (American Psychiatric Association 2013).

2 Prevalence and Prognostic Effects of Co-occurring Major Depression and Substance Use Disorders

2.1 Rates of Co-occurring Major Depression and Substance Use Disorders

Approximately 20% of all persons in the general population with a current substance use disorder (alcohol alone, alcohol plus other drugs, other drugs alone, or other drugs combined) had at least one current independent (i.e., non-substance-induced) mood disorder (Grant et al. 2004). The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) found the 12-month prevalence rate for major depressive disorder (MDD) to be 7.06% when substance-induced depression was excluded, while the 12-month prevalence of MDD and comorbid substance use disorder is 19.2% when substance-induced mood disorders were excluded. The odds of comorbid major depressive disorder and alcohol or other substance use disorders are 1.2 and 1.3, respectively (Grant et al. 2015, 2016). A meta-analysis showed that individuals with drug use disorders (not including alcohol) had a 3.8 times greater risk of having major depression. Along the same lines, individuals with alcohol use disorder have a 3.1 times greater risk of developing MDD. In some cases, MDD becomes a chronic condition, which is defined as continually meeting criteria for a major depressive episode for at least 2 years. Individuals with chronic major depressive disorder are more likely to have a family history of substance use disorders compared with individuals with major depressive disorder that is not chronic in nature (Liu et al. 2010, Rubio et al. 2011). Fifty-four percent of individuals with chronic MDD have a lifetime history of any substance use disorder (41.15% have alcohol use disorder and 19.02% have other drug use disorder) (Blanco et al. 2010).

2.2 Treatment Outcome for Major Depression in Patients with Co-occurring Substance Use Disorders

Depressive symptoms and substance use disorders each have negative effects on the course of one another. In clinical populations, having an alcohol use disorder predicted greater severity of symptoms and poorer outcomes for individuals with mood disorders. For psychiatric inpatients and outpatients with major depressive disorder, having an alcohol use disorder increased the odds of suicidal ideation and attempts by a factor of 2.2 and 6.3, respectively (Sokero et al. 2003). Studies that evaluated the effects of alcohol use disorder on the course of depressive symptoms found that alcohol problems significantly worsen the course of depression (Cook et al. 1991; Mueller et al. 1994). Patients with MDD and substance use disorder (SUD) have greater depressive symptomology and severity of symptoms than patients with MDD alone without SUD. Comorbid patients are more likely to endorse suicidality than patients with MDD who don't have SUD (Davis et al.

2005, 2006). Remission of substance use within the last year reduces the risk of depression in individuals with comorbid MDD and SUD (Agosti and Levin 2006).

3 Differential Diagnosis: Primary Depressive Disorder vs Depression Secondary to Substance Use Disorders

The process of determining the correct diagnoses in individual with co-occurring depressive symptoms and substance use is difficult and has been described in other book chapters (Brower 2009). Depressive symptoms could be those of a primary major depressive disorder or bipolar affective disorder or secondary to substances of abuse. The substance could cause depressive symptoms, as a result of any of the following: chronic use, acute intoxication, withdrawal syndromes, substance-induced depression, or an adjustment disorder with depressed mood (due to multiple psychosocial consequences of substance use and stressors). Differentiating substance-induced depression from major depressive disorder can and is usually difficult, but the distinction is important for treatment recommendations. The usual method for diagnosing a psychiatric disorder is through the clinical interview by taking a detailed history of symptoms including timing, duration, and severity of symptoms. This is no different for patients with comorbid MDD and SUD diagnoses.

A chronology of symptoms is the best way of differentiating between primary MDD verse depression secondary to a substance use disorder. In some cases, the depressive symptoms clearly predate the substance use. In these cases, one would conclude we are dealing with an individual with a primary MDD and comorbid SUD. With that said, the current episode could still be substance-induced depression, which complicates differential diagnosis for the current episode of depression. One would need to question the patient to determine if the current episode is similar to prior episodes of depression in symptomology and severity. If the current episode is similar to previous episodes, this episode is likely a recurrent episode of MDD. If the chronologic history suggests the episode began following a notable change in substance use such as intoxication or withdrawal, or if the nature of the depression is different from prior episodes, this would suggest a substance-induced depression and further exploration of this possibility. The next diagnostic picture to consider is when the depressive symptoms only occur during substance use or substance withdrawal, and during periods of sustained sobriety (4 weeks or longer), there are no any depressive symptoms. This is a simplistic picture consistent of an individual with substance-induced depressive disorder. Whether or not to treat substance-induced depressive symptoms with an antidepressant medication would depend on the severity of symptoms. Medications would be prescribed if the individual is experiencing suicidal or homicidal symptoms or if the depressive symptoms are severe enough to disrupt treatment efforts of SUD.

Other times, the patient history is not clear, and the correct diagnosis is more difficult to determine, because we know MDD is a remitting/relapsing condition. For example, when the patient develops a substance use disorder and symptoms of

depression in the same time frame, the next step is to understand if they have had periods of sustained sobriety (30 days or more) and how these periods relate to symptoms of depression. If during sustained periods of sobriety there were not any depressive symptoms, then the diagnosis of substance-induced depression is possible, but not guaranteed. In this case, the individual may have a primary MDD that happen to have remitted during sobriety, and the person just did not experience a relapse of MDD during remission of SUD.

Finally, if the individual's psychiatric history does not fall into one of the categories described above, an alternative way to differentiate the diagnosis of primary MDD or substance-induced depression would be to monitor depressive symptoms during a period of abstinence. This method is only appropriate, if the depressive symptoms are mild, do not interfere with treatment engagement and adherence, and do not put the patient or others at risk. If the symptoms resolve during sobriety, it may be a substance-induced depressive disorder episode.

4 Treatment Recommendations for Patients with Co-occurring Depression and Substance Use Disorders

When treating individuals with major depressive disorder and substance use disorders (Watkins et al. 2005), the literature supports providing simultaneous treatment for both disorders. Improvement in one disorder will lead to better outcome for the comorbid disorder. If the patient meets criteria for treatment-resistant depression, the prescriber should follow standard practice algorithms for treating MDD (APA 2010). In a meta-analysis of antidepressant medications, there was a modest effect size in reducing depressive symptoms and attaining abstinence/sustained remission of the substance use (Nunes and Levin 2004). Due to the limited number of studies with small sample sizes, there is insufficient data to recommend specific pharmacologic interventions in patients with co-occurring depression and substance use disorders. Mild depressive symptoms in individuals with co-occurring SUD would be addressed by psychotherapy, such as cognitive behavioral therapy and abstinence from substance use disorders. In individuals with moderate to severe depressive symptoms, treatment with medications would be appropriate. Maintenance antidepressant therapy is recommended in individual with primary major depressive disorder. If substance-induced depressive episodes are suspected, clinicians should consider discontinuation of antidepressant medications if abstinence has been maintained and depressive symptoms have resolved for at least 6 months, see Table 1 and Fig. 1 (Brower 2009).

Table 1 Factors that suggest primary MDD verses substance-induced depressive disorder

Primary MDD	Substance-induced disorder
Retrospective history clearly indicates that the onset of depressive symptoms preceded onset of substance use disorder	Retrospective history clearly indicates that substance use disorder preceded onset of depressive symptoms
Retrospective history clearly indicates that depressive symptoms occurred or persisted during periods of abstinence from substances for at least 4 weeks or longer	Retrospective history clearly indicates that depressive symptoms remitted during periods of sobriety last 4 weeks or longer
Family history positive for a first-degree relative with primary MDD	Family history negative for first-degree relative with primary MDD

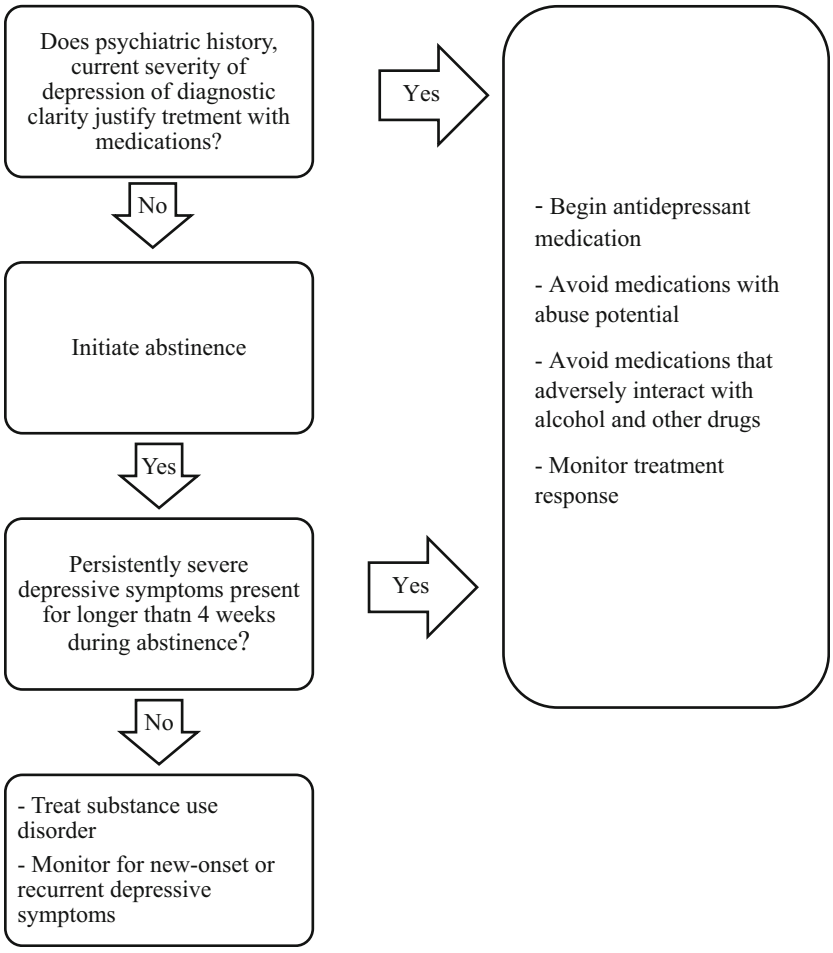

Fig. 1 When to initiate antidepressant medication treatment in a patient with co-occurring disorders

5 Special Considerations in Managing Co-occurring Disorders

5.1 Antidepressant Interactions with Alcohol and Drugs of Abuse

Many drugs of abuse have pharmacokinetic and pharmacodynamics interactions with antidepressants. Table 2 below list drugs of abuse and possible/theoretical pharmacologic interactions (Weathermon and Crabb 1999; Lindsey et al. 2012). Alcohol is metabolized by several enzymes. The primary enzymes are aldehyde dehydrogenase and CYP2E1. In acute infrequent alcohol consumption, aldehyde dehydrogenase metabolizes most of the ethanol consumed. Chronic heavy drinking can increase CYP2E1 activity up to tenfold, with CYP2E1 metabolizing more of the alcohol consumed. The additive effects of alcohol and TCA can lead to excessive sedations and impaired psychomotor performance. Acute use of alcohol may inhibit metabolism of TCA via aldehyde dehydrogenase, while prolonged use of alcohol may stimulate metabolism of TCA via CYP2E1 activity.

Cocaine is metabolized by CYP3A4 and inhibits CYP2D6. Cocaine increases β-receptor stimulation through indirect sympathomimetic actions. The active ingredient in cannabis is delta-9-tetrahydrocannabinol (THC). THC binds to cannabinoid receptors in the brain causing anxiolytic, sedative, analgesic, and psychiatric effects

Table 2 Possible/theoretical pharmacologic drug-medication interaction

Drug	Interaction with	Results
Ethanol	MAOIs	• Alcohol does not interact with MAOI. However, tyramine found in some wines and beer can result in hypertensive crisis and/or headache
	TCA	• Excessive CNS depression and impaired psychomotor performance • Acute alcohol use may inhibit metabolism of tricyclic antidepressants • Prolonged use of alcohol may stimulate hepatic metabolism of TCA • Detoxified alcohol-dependent individual, elimination of imipramine and desipramine were increased
Cannabis	SSRIs	• Mania
	TCAs	• Tachycardia • Delirium
Cocaine	MAOIs	• Hypertensive crisis
Heroin	MAOIs	• Hypotension • CNS depression
MDMA	MAOIs	• Hypertensive crisis • Serotonin syndrome
Methamphetamine	TCA	• Hypertension • CNS stimulation
	MAOIs	• Hypertensive crisis

as well as appetite stimulation. Cannabis is metabolized by CYP3A4 and CYP2C9. Case reports indicate that use of THC and TCAs led to tachycardia and delirium. Fluoxetine co-administered with cannabis led one patient to experience manic symptoms. The exact mechanism of action in these adverse reactions is unknown.

Heroin was originally synthesized from morphine. Heroin is metabolized by hydroxylation and then excreted renally as morphine. The exact mechanism of action of gamma-hydroxybutyrate (GHB) is unclear. GHB is metabolized via Krebs cycle biotransformation. It is converted to carbon dioxide which is eliminated by respiration. There are no any known interactions with antidepressant medications. MDMA (3,4-methylenedioxymethamphetamine) is similar in structure to mescaline and methamphetamine. The mechanism of action of MDMA is believed to be through serotonin (5-HT), dopamine, and norepinephrine reuptake inhibition. MDMA is eliminated 75% unchanged through the kidneys. MAO inhibitors can reduce the breakdown of 5-HT, leading to increased effects of MDMA, which can cause serotonin syndrome and hypertensive crisis.

Finally, methamphetamine increases synaptic levels of dopamine; acutely this results in feeling of well-being, alertness, euphoria, and decreased appetite. Also, methamphetamine causes catecholamine release by adrenal gland, which can lead to hypertension and cardiac arrhythmias. Methamphetamine is metabolized by the liver via aromatic hydroxylation, N-dealkylation, and deamination.

5.2 Do Antidepressants Have Risk of Misuse?

The FDA does not recommend every drug to undergo an evaluation of abuse potential, but because antidepressants have CNS action, potential abuse must be evaluated by animal studies. If the animal studies indicate risk for human abuse, then human studies are conducted (FDA 2013). There have been multiple case reports and case series of patients developing a substance use disorder to antidepressant medications. Most of these individuals also have an alcohol or other substance use disorder. When antidepressants are abused by humans, use is at supra-therapeutic doses (Evans and Sullivan 2014). It is likely that estimates of antidepressant misuse/abuse are underestimated because epidemiological surveys of nonmedical use of prescription medications have focused on scheduled medications (i.e., opioid pain medications) but did not include antidepressant medications. The Drug Abuse Warning Network which collects data from emergency departments estimated in 2011 that there were 1,244,872 emergency department visits involving nonmedical use of prescription or over-the-counter medications, of these 88,965 visits involved antidepressants. The antidepressant medications found in the literature for abuse/misuse were bupropion, monoamine oxidase inhibitors (MAOI), tricyclic antidepressants (TCA), serotonin-norepinephrine reuptake inhibitors (SNRIs), and selective serotonin reuptake inhibitors (SSRIs).

Bupropion's activity in the nucleus accumbens may be implicated in the development of addiction, although this has not been proven and bupropion is not thought to have the same abuse potential as other drugs. This is the same area that is activated

by the reinforcing effects of sympathomimetic drugs such as cocaine and methamphetamine. The case reports summarized described bupropion producing stimulant and cocaine-like euphoric effects in patients who abused bupropion (Evans and Sullivan 2014; Stassinos and Klein-Schwartz 2016).

Like other antidepressants, the monoamine oxidase inhibitors are not considered to have abuse potential; however, there are a few case reports and case series of MAOI abuse. Evans and Sullivan (2014) found phenelzine and tranylcypromine to be the most cited MAOIs in terms of abuse potential in the literature. The reported drug effects for MAOIs are stimulant-like. This could be because the chemical structure is similar to amphetamine. However, the exact mechanism leading to abuse is unknown.

The first cases of TCA misuse were reported in 1978 (Cohen et al. 1978). Amitriptyline is the most commonly abused TCA. Abuse of TCAs was reported to produce the following symptoms: euphoria, being more sociable, and dissociative effects/distorted sense of time (Shenouda and Desan 2013). However, the pharmacologic basis for TCA abuse is unknown. There were two case reports in the literature of venlafaxine abuse by Evans and Sullivan (2014); others were noted by Cikrikcili et al. (2016), bringing the total of published articles to six. In venlafaxine abuse, patients would take excessively high doses (1,950–4,050 mg/daily) to get stimulant-like effects; all patients had a history of substance use disorders. Finally, SSRI antidepressants are the most commonly prescribed antidepressants in the United States. This class of antidepressant had six published articles, involving seven cases all which was the abuse/misuse of fluoxetine (Evans and Sullivan 2014). Abuse of fluoxetine led to stimulant-like effects, such as appetite suppression and euphoria.

6 Summary of Specific Antidepressant Prescribing Recommendations for Patients with Substance Use Disorders

In general, antidepressants reduce depressive symptoms and indirectly improve outcomes of substance use disorders. Untreated depressive symptoms can be a trigger for relapse to substance use. Co-occurring disorders have a complicated course which have negative effects on the course and outcomes of both disorders. Therefore, it is recommended to treat both depression and substance use disorders concurrently to improve treatment outcomes (Watkins et al. 2005). The current evidence is insufficient to make recommendation for or against any specific antidepressant medications. No specific antidepressant appears to be more efficacious for both MDD and SUD. Reviews of the literature indicate antidepressants are effective for MDD and also tend to work in patients with co-occurring disorders (Torrens et al. 2005). This chapter did not review pharmacotherapy for SUD. It is worth noting that pharmacological agents for SUD also tend to work in patients with co-occurring disorders (Tiet & Mausbach 2007).

It is recommended to use treatment guidelines/algorithms, such as APA guidelines for major depressive disorder, when treating MDD in patients with comorbid SUD especially when dealing with treatment-resistant depression (APA 2010). Unfortunately, treatment guidelines are not able to give recommendations to specific medication therapy, due to limited studies evaluating antidepressants in patients with SUD. The best review of the available literature gives the following recommendations for the treatment of individual with co-occurring depression and substance use disorder (Nunes and Levin 2004, 2008; Watkins et al. 2005). Mild depressive symptoms in individuals with co-occurring SUD would be addressed by psychotherapy, such as cognitive behavioral therapy and abstinence from substance use disorders. In individuals with moderate to severe depressive symptoms, treatment with medications would be appropriate. Antidepressant therapy should start with SSRIs, which are the first-line agents in nearly all practice guidelines for treating MDD. SSRIs are good first choice because of safety, tolerability, low sedation, and few concerns about interactions with drugs or alcohol. Noting that fluoxetine and paroxetine may result in opiate withdrawal symptoms in patients using codeine, a few cases of abuse/misuse of fluoxetine have been reported. Next-line agents would be antidepressants with noradrenergic or mixed mechanism of action, such as SNRIs or imipramine or doxepin. Some antidepressants such as bupropion, venlafaxine, and amitriptyline carry a risk of developing a substance use disorder in patients with comorbid substance use disorder. This risk has not been fully quantified, and evidence suggest the risk is limited to case reports. Nonetheless, while these medications are not contraindicated, caution should be used when prescribing bupropion, venlafaxine, and amitriptyline to patients with substance use disorders. Maintenance antidepressant therapy is recommended in individual with primary major depressive disorder. If substance-induced depressive episodes are suspected, consideration should be given to discontinuing antidepressant medications after 6 months of abstinence and after depressive symptoms have resolved for 6 months.

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Treatment of Depression in Women

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Abstract

Women are more likely than men to experience depression throughout the life span. Sex differences in neurochemistry and brain structure, as well as societal factors may contribute to women's increased likelihood of depression. Pharmacological research targeting depression has historically excluded women, leading to a knowledge gap regarding effective antidepressant treatment in women. Antidepressant pharmacokinetics and pharmacodynamics are clearly different in men and women, necessitating a thoughtful approach to their prescription and management. Hormone changes associated with the menstrual cycle, pregnancy, and menopause also contribute to differences in depression and effective antidepressant use in women. Finally, it is important to consider potential interactions between antidepressant drugs and medications specifically used by women (oral contraceptives, tamoxifen, and estrogen).

Keywords

Antidepressant · Depression · Estrogen · Hormones · Menopause · Menstrual cycle · Oral contraceptives · Postpartum · Pregnancy · Premenstrual · Sex differences · Tamoxifen · Women

1 Introduction

1.1 Sex-Related Differences in Clinical Characteristics of Depression

The World Health Organization (WHO) ranks major depression as the leading cause of disability worldwide (Murray et al. 2013; WHO 2017a). In the United States, major depressive disorder (MDD) ranks second among all diseases and injuries as a cause of disability, and persistent depressive disorder (dysthymia) ranks 20th (Murray et al. 2013). The World Health Organization states that depression is the leading cause of days lost to disability for women worldwide (WHO 2017a). Women are 1.5 to 3 times more likely to experience major depression than men, from puberty onward (IOM 2011; Kessler 2003). The cause of this sex difference remains unclear (Stegenga et al. 2012), and there are varying perspectives on the sexual dimorphism of depression (IOM 2011). From a biological perspective, researchers have investigated neurochemical and structural differences when comparing depressed men with depressed women. A societal perspective focuses on the interaction between increased victimization of those with female character traits (IOM 2011). Women may be more comfortable reporting depressive symptoms compared to men, resulting in inflated rates of MDD in women (Poutanen et al. 2009). Others hypothesize that the difference may be ascribed to artifacts involved in the measurement methods used (Romans et al. 2007).

In 2014, Kendler and Gardner examined sex differences in the development MDD using opposite-sex twin pairs (Kendler and Gardner 2014). They found that

low parental warmth, parental loss, neuroticism, lifetime traumas, divorce, social support, and marital satisfaction contribute more strongly to the development of MDD in females (Kendler and Gardner 2014). In males, low self-esteem, drug use disorder, past history of major depression, and distal and dependent proximal stressful life events contribute more strongly to the development of MDD (Kendler and Gardner 2014). During adolescence women are twice as likely as their male counterparts to be prescribed an antidepressant (Fegert et al. 2006). The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial highlighted several findings regarding depression in women (Marcus et al. 2005). The authors found women had a younger age of onset of MDD. Also there were differences between men and women in terms of the symptoms of MDD, in that women had increased anxiety disorders, somatoform disorder, and bulimia (Marcus et al. 2005). Women also experienced longer depressive episodes and increased suicide attempts but were more likely than men to have a total remission of their symptoms (Marcus et al. 2005).

2 Challenge of Adequate Female Representation Within Pharmacological Research

The historical exclusion of women from many clinical trials led to concerns about women's access to safe, appropriate clinical treatment which is still of concern to this day (Table 1) (Weinberger et al. 2010). This exclusion occurred throughout the early history of clinical research but was directly discussed in the 1940s and 1950s when studying diseases prevalent in both sexes, where males, frequently of the Caucasian race, were considered to be the normative study population (Liu and Mager 2016). An additional contributing factor confounding studies is a type of observer bias, which assumes a male's attitude when conducting clinical trials (Pinn 2003). Historically, and to this day, researchers viewed female participation in clinical trials as a potentially confounding factor because of their fluctuating hormone levels related to menstruation and menopause (Wizemann and Pardue 2001; Johnson et al. 2014).

Opinions and actions concerning women's participation in clinical trials in the United States have changed through the years as governmental groups, researchers, and physicians have sought to protect the public's health and also better understand how women respond to medications (Table 1) (Liu and Mager 2016). Much work continues to need to be done in order to address the research gap in order to prevent further health disparities and poor outcomes from medication adverse drug reactions (Johnson et al. 2014; Liu and Mager 2016).

In addition to the issues raised with including women in clinical trials, research on transwomen and nonbinary populations is lacking (Boehmer 2002), including in NIH-funded studies (Coulter et al. 2014). Unfortunately, nearly all of the pharmacological research about depression to date has stratified sex and gender as only male or female and has not included intersex, transgendered, or gender-nonconforming persons (Reisner et al. 2016). This strategy may have misassigned research participants if participants were only given the choice of male or female choices

Table 1 History of including women participants in clinical research

Year	Event (Liu and Mager 2016)
1960	Evidence of fetal malformation from thalidomide use in Europe prevented its approval in the United States and prompted fear of including women of childbearing potential in clinical trials (Regulations, guidance, and reports related to women's health 2017)
1975	National Commission for the Protection of Human Subjects and Biomedical and Behavioral Research promulgates a new rule which includes pregnant women as a vulnerable population (Liu and Mager 2016)
1977	FDA guideline "General consideration for the clinical evaluation of drugs" essentially bans all women of childbearing potential from participating in early phase clinical research, except for life-threatening conditions (Regulations, guidance, and reports related to women's health 2017)
1985	NIH established a Public Health Service Task Force on Women's Health; their recommendations of increased attention to women's health issues led the NIH to develop specific guidelines in 1986 regarding the inclusion of women as subjects in NIH-funded research (IOM 2011)
1988	NIH advisory committee recommends to grant applicants that women be included in studies; if women are not included, clear rationale must be provided (General Accounting Office 1992)
1990	Office of Research on Women's Health established at the NIH (Regulations, guidance, and reports related to women's health 2017)
1993	FDA guideline "Guideline for the study and evaluation of gender differences in the clinical evaluation of drugs" reverses the 1977 guidance (Regulations, guidance, and reports related to women's health 2017). Calling the 1977 guidance "rigid and paternalistic" (US Food and Drug Administration 1993)
1993	Congress mandates adequate inclusion of women in NIH-sponsored clinical trials to determine differences between the sexes (National Institutes of Health 2001)
1994	Office of Women's Health established at the FDA (Henderson 2017)
1994	Institute of Medicine (IOM) report "Women and health research" calls attention to two forms of historical gender bias in the design and implementation of clinical trials (IOM 2010)
1998	FDA regulation stating that New Drug Application (NDA) reports must present safety and efficacy data by sex (US Food and Drug Administration 1998)
2001	IOM report – "Exploring the biological contributions to women's health: does sex matter?" establishes the importance of sex-based biology (Wizemann and Pardue 2001)
2010	IOM report – "Women's health research: progress, pitfalls and promise" highlights areas of advancement and remaining deficiencies in women's health research (IOM 2010)
2014	FDA "Evaluation of Sex-Specific Data in Medical Devise Clinical Studies: Guidance for Industry and FDA Staff" outlines the FDA's expectations regarding sex-specific patient reenrollment, data analysis, and reporting of study information for medical devise applications (Regulations, guidance, and reports related to women's health 2017)

regarding gender (Ansara and Hegarty 2014). Even when transgender people are included in research studies, the data often are not disaggregated (Runnels et al. 2014).

3 Sex and Gender Definition: The Definition of "Woman" in Clinical Research

"Sex" refers to a person's biological status and is typically categorized as male, female, or intersex, with a number of indicators including sex chromosomes, gonads, internal reproductive organs, and external genitalia (American Psychological Association 2015a, b). "Gender" refers to the socially constructed characteristics of women and men – such as norms, roles, and relationships of and between groups of women and men. It varies from society to society and can be changed (WHO 2017b). For some people, sex assignment correlates with gender identity. However, some people have a gender identity that does not correlate with assigned gender; this is often referred to as gender-nonconforming, gender-nonbinary, or sometimes transgender. This is in contrast to individuals whose sex assignment and gender identity align which is referred to as cisgender.

In this chapter, we recognize the difference between assigned sex and chosen gender in an effort to be inclusive of all individuals. However, due to the lack of research, we will focus the remainder of the chapter on those who have been labeled as cis-women and cis-men or women or men whose gender assignment at birth and gender identity align and refer to these individuals as "women" or "men."

4 Sex Differences in the Brain

Sex differences in brain structure are likely a product of the interaction of biological and environmental influences on the brain (McCarthy and Arnold 2011), sex chromosomes (Arnold and Chen 2009), the immune system (Lenz et al. 2013), steroid hormones (Giedd et al. 2012), early life programing such as prenatal nutrition/starving (Heijmans et al. 2008), and postnatal factors such as early child care (Cohen 2017). All likely play a role in sexual differentiation of MDD and perhaps the potential treatments (Ruigrok et al. 2014).

4.1 Size and Volume

There are documented studies of brain size and volume differences between men and women (Ruigrok et al. 2014; Allen et al. 2002; Courchesne et al. 2000; Cosgrove et al. 2007). Volume increases in males are found mostly in bilateral limbic areas and left posterior cingulate gyrus and higher density in left side of the limbic system (Ruigrok et al. 2014). Volume increases in females were most pronounced in areas in the right hemisphere related to language and in addition to several limbic structures such as the right insula cortex and anterior cingulate gyrus (Ruigrok et al. 2014). Young girls have larger hippocampal volumes (Filipek et al. 1994), whereas the amygdala is larger in boys (Caviness et al. 1996). Enzymes for estrogen synthesis and estrogen receptor mRNA have been localized in the hippocampus (McEwen

2001), whereas androgen receptors are more prevalent in the amygdala (Österlund and Hurd 2001).

Imaging studies of depression show crossover between those brain regions that are normally high sexually dimorphic and those that are implicated as abnormal in depression, including the paraventricular nucleus, lateral hypothalamic area, hippocampus, and areas of the amygdala (IOM 2011).

4.2 Sex Differences in Brain Function

A majority of studies have showed that global cerebral blood flow is higher in women than in men (Cosgrove et al. 2007). Direct implication of sex differences in global cerebral blood volume on psychiatric disorders is unclear; however, increased blood flow in the brains of women may lead to better distribution of psychotropic drugs (Cosgrove et al. 2007).

4.3 Sex Differences in Brain Chemistry

There is a wealth of preclinical evidence supporting sex differences in serotonin (Cosgrove et al. 2007; Fink et al. 1998). Whole blood 5HT levels are higher in women compared to men (Ortiz et al. 1988); however men synthesize serotonin significantly faster than women (Cosgrove et al. 2007; Nishizawa et al. 1997). Healthy women have higher 5HT transporter availability in the diencephalon and brainstem compared to men (Cosgrove et al. 2007), and 5HT transporters are selectively decreased in an age-specific manner in depressed women but not in depressed men (Cosgrove et al. 2007; Staley et al. 2006). Women have higher 5HT reuptake transporters in the presynaptic cell and increased 5HT1A receptors in the postsynaptic cell (Cosgrove et al. 2007).

Studies suggest that healthy women may have higher presynaptic dopaminergic tone in the striatum and higher extrastriatal dopamine receptor density and availability compared to men (Cosgrove et al. 2007; Laakso et al. 2002). Higher dopaminergic tone in women may protect against the development of schizophrenia, alcoholism, MDD, and other diseases with disrupted dopamine level disturbances (Cosgrove et al. 2007; Dunlop and Nemeroff 2007). Estrogen may possess neuroprotective qualities in its interaction with the dopamine system (Rao and Kölsch 2003).

Hormonal regulation of the sexual differentiation of the brain starts at the beginning of the second trimester, where the sexual differentiation of the gonads takes place in the first 2 months of pregnancy (IOM 2011; Savic et al. 2010). It is believed that during the intrauterine period, the fetal brain develops in the male direction through the direct action of testosterone on the developing neural tissue and in female direction through the absence of this testosterone surge (Savic et al. 2010). Some risk factors for MDD that have been identified from population-level studies include small for gestational age, low birthweight, obstetric complications (e.g., preeclampsia, oxygen deprivation), second trimester influenza, and second to third

trimester famine (IOM 2011). Estrogen and testosterone have major effects on neuronal growth and development. These effects are region specific in the brain, in areas such as the hypothalamic and amygdala nuclei, the hippocampus, and the medial dorsal thalamus and in areas of the cortex (Savic et al. 2010). Although much of the previous work on the sexual differentiation of the brain has been conducted in animals, magnetic resonance imaging (MRI) of healthy human brains shows that brain regions affected by sex hormones during development are highly sexually dimorphic (i.e., exhibit sex differences in brain volumes relative to the size of the cerebrum) (IOM 2011).

5 Sex Differences in Pharmacokinetics and Pharmacodynamics

Pharmacokinetic studies for first-generation antidepressants were nearly all conducted in healthy, young men until a mandated change in research culture and legislation in the early 1990s (Bigos et al. 2009). In a study of drug-naive patients with depression before treatment, women had lower maximum velocity (V_{max}) of serotonin uptake in blood platelets (3.4 vs 5.4 pmol/min · 107, respectively; $P = 0.001$) and lower V_{max}/km (uptake efficiency at low extracellular concentrations of serotonin) than did men (4.1 vs 6.1 μL/min · 107; $P = 0.001$) (Fisar et al. 2008). If this finding translates to differential uptake in the brain, it would support the hypothesis that lower serotonin uptake may reflect a sex-linked vulnerability to depression believed to be linked to serotonin (Bigos et al. 2009).

5.1 Pharmacokinetics

Most antidepressants are weak bases and are most effectively absorbed under basic conditions (Bigos et al. 2009). Since women secrete less gastric acid, they have a more basic body chemistry, which could potentially lead to enhanced absorption of antidepressants in the stomach (Grossman et al. 1963).

Women have slower rate of gastric emptying than men, which could also increase the absorption time (Whitley and Lindsey 2009). Colonic transit times are prolonged in women, giving compounds more time to be absorbed (Jung et al. 2003). Despite ideal conditions for antidepressant absorption, the bioavailability of antidepressants is not greater in women (Damoiseaux et al. 2014).

Differences in body composition affect the distribution of drugs; women have a higher percentage of adipose tissue than men, so if a drug is lipophilic, there will be a much larger volume of distribution (V_d) which can result in prolonged half-life and lower plasma concentrations (Greenblatt et al. 1982). Both trazodone and bupropion have a larger V_d in women because of body fat; this is further exaggerated in older adult women (which could also be related to the clearance of the drug from the body in addition to the increased V_d) (Sweet et al. 1995).

Drugs that treat depression are metabolized by, inhibit, and/or induce a wide range of cytochrome P450 enzymes (Ereshefsky et al. 1995). Sex differences in the CYP isoenzyme have been reported for CYP3A4 and CYP1A2; these differences may be confounded when a drug has a high clearance and/or is a co-substrate for both CYP3A4 and P-glycoprotein multidrug resistance 1 pump (MDR1) (Flockhart 2007). Antidepressants that inhibit CYP3A4 (fluoxetine, fluvoxamine, nefazodone, norfluoxetine, selegiline, trazadone) may shift the metabolism of estrogen from CYP3A4 to CYP1A2, which results in decreased production of 16a-hydroxyestrone, which could possibly have an anticarcinogenic effect on estrogen-dependent proliferative diseases such as breast cancer (Thompson et al. 2003).

Estrogen is a substrate for both CYP3A4 and CYP1A2 as well as an inhibitor of CYP1A2; higher levels of endogenous or exogenous estrogens, such as during the luteal phase of menstrual cycle or from estrogen replacement, may impact antidepressant metabolism (Pollock et al. 1999). Giving concomitant administration of CYP1A2-metabolized antidepressants (amitriptyline, clomipramine, fluvoxamine, imipramine, mirtazapine) and estrogen could result in higher plasma levels of both and possibly increase adverse events (Ford et al. 1993).

5.2 Pharmacodynamics

A 2000 study evaluating the response to imipramine and sertraline found that women were more likely to have decreased symptoms of chronic depression with sertraline compared to imipramine (57% vs 46%, respectively; $P = 0.04$) (Kornstein et al. 2000). Postmenopausal women had similar response rates to both sertraline and imipramine in the same study (57–56%) (Kornstein et al. 2000). Women have been reported to respond better to sertraline for the treatment of behavioral disturbances in Alzheimer's disease than men (Lanctot et al. 2002).

Several studies have identified sex differences in the response to fluoxetine. Women had greater increases than did men in tryptophan (83% vs 32%, respectively) and greater decreases in cortisol concentrations (43% and 31%) in response to fluoxetine – this may contribute to a better response in women (Bano et al. 2004). However, another study showed a greater risk of relapse among women after response to fluoxetine for major depression (McGrath et al. 2006). Some research has focused on identifying factors that predict response to antidepressants. A 2009 study found that COMT genotype did not predict response to fluoxetine in female patients (Tsai et al. 2009).

6 Unique Hormone Conditions: Reproductive-Related Depressive Disorders

The longitudinal development of women provides a variety of hormonal conditions which are unique to females: in utero differentiation (see above), menarche, premenstrual, pregnancy, postpartum, and menopause.

6.1 Menstrual and Premenstrual Conditions

A major biological distinction between women and men is the menstrual cycle, which is associated with variations in female sex steroid hormones usually over a 28-day period (Cosgrove et al. 2007).

Cyclic changes in mood, evidenced by premenstrual dysphoric disorder (PMDD) and premenstrual syndromes, suggest that mood can fluctuate with cycling hormone levels (Thompson and Pollock 2001; Yonkers and March 2003). The increased risk for new onset of depression is concurrent with the onset of monthly fluctuations in levels of hormones (Deecher et al. 2008). The increased vulnerability for depressive disorder appears to be intensified by hormonal fluctuations occurring in the late luteal phase (De Ronchi et al. 2005).

During the last several years, the downregulation of neurosteroid biosynthesis has been intensively discussed to be a possible contributor to the development of MDD, anxiety, and PMDD (Schule et al. 2014). In particular, certain 3α-reduced metabolites of progesterone such as 3α,5α-tetrahydroprogesterone (allopregnanolone) and 3α,5β-tetrahydroprogesterone (pregnanolone) are potent positive allosteric modulators of the $GABA_A$ receptor (Reddy 2010; Schule et al. 2014). Allopregnanolone is produced not only by the ovaries and adrenals but also de novo in the brain and because of its lipophilicity can cross the blood-brain barrier where it alters CNS excitability (Paul and Purdy 1992). In patients with MDD and PMDD, neurosteroid concentrations, particularly allopregnanolone, in plasma and cerebrospinal fluid are decreased, and these concentrations normalize after treatment with antidepressants with SSRIs (Broekhoven and Verkes 2003; Porcu et al. 2015). There are certain pharmacokinetic obstacles in using neurosteroids directly for the treatment of depression, given that they have low bioavailability, rapid oxidation to the ketone, addiction potential, and safety and tolerability concerns (Schule et al. 2014; Porcu et al. 2015). Therefore, modulation of neurosteroidogenesis to restore tone has become a novel approach to the treatment of MDD and anxiety, in particular the translocator protein 18 kDa and ligands such as XBD 173 (Schule et al. 2014; Porcu et al. 2015).

6.2 Menopause

The rate of MDD and clinically meaningful elevations in depressive symptoms increases twofold to threefold during menopause transition (Gordon et al. 2015). A recent meta-analysis showed that longer exposure to endogenous estrogens, expressed as older age at menopause and longer reproductive period, is associated with lower risk of depression in later life (Georgakis et al. 2016). After menopausal transition, the incidence of depression in postmenopausal women is similar to that of men (Bebbington et al. 2003).

7 Pregnancy

In a nationally representative survey in the United States that identified pregnant women with major depression, up to 50% received treatment (Ko et al. 2012). Another more recent study showed that only 20% received treatment (Vigod et al. 2016). Untreated disease causes maternal suffering and is associated with poor nutrition, comorbid substance use disorders, poor adherence with prenatal care, postpartum depression, impaired relationships between the mother and her infant and other family members, and an increased risk of suicide (ACOG Committee on Practice Bulletins--Obstetrics 2008; Stewart 2011). Physiologic and pharmacokinetic changes in pregnancy include, but is not limited to, blood volume increase by 40–50%, drop in serum albumin concentration, increased progesterone leading to delayed gastric emptying, and increase in estrogen (Costantine 2014).

Barriers to treatment of antenatal depression include cost, opposition to treatment (e.g., fear of exposing the fetus to antidepressant medication or lack of interest in psychotherapy), unavailability of psychotherapy which could be used as an alternate or adjunct to pharmacotherapy, and stigma (ACOG Committee on Practice Bulletins--Obstetrics 2008; Stewart 2011). In addition, many clinicians are reluctant to use pharmacotherapy because they lack sufficient expertise, even when the patient's depression is too severe to be treated by psychotherapy alone (Osborne et al. 2015). It is recommended that all health professionals discuss mental health with women at each contact during pregnancy (Vigod et al. 2016). A 2009 APA and ACOG joint report found that no randomized trials have evaluated the efficacy or safety of antidepressants, since most studies have excluded pregnant women (Yonkers et al. 2009). For pregnant women with severe unipolar major depression, antidepressant medications are suggested as initial treatment, versus psychotherapy (Yonkers et al. 2009). The association between paroxetine and cardiac defects is more often found in studies that included all malformations rather than clinically significant malformations (Yonkers et al. 2014).

A 2016 study which linked antidepressant use during pregnancy with an increased risk of autism spectrum disorders in children generated media discussion and controversy (Boukhris et al. 2016; Healy 2016; Morales et al. 2018). The 2016 study suggested that using antidepressants, specifically SSRIs, in the second or third trimester, increases the risk of autism spectrum disorder (Boukhris et al. 2016). This study looked at only one developmental outcome, autism, and did not explore the potential harms of untreated depression. A systematic review of several observational studies which examined antidepressant exposure during pregnancy and its association with increased risk of autism and ADHD was completed and highlighted important methodological implications (Morales et al. 2018). Researchers concluded that these observational studies are heterogeneous in their design and suggested that classical comparisons between exposed and unexposed women during pregnancy are at high risk of residual confounding (Morales et al. 2018). In addition, observational studies include retrospective case-control studies, which carry the risk of recall bias. The risks of untreated MDD, to both mother and fetus, often outweigh the risks

associated with antidepressants which have been the reinforced by the statement from the American College of Obstetricians and American Psychiatric Association.

8 Drug Interactions Specific to Women Taking Antidepressants

8.1 Oral Hormonal Contraceptives

Patients and providers may be concerned about the co-administration of hormonal contraceptives with psychotropic medication given the complex pharmacology of these medications. Estrogen is a substrate for both CYP3A4, CYP1A2, and CYP2C9 as well as an inhibitor of CYP1A2 (Berry-Bibee et al. 2016). CYP3A4 is also likely involved with the metabolism of progestins; however the metabolic pathways for progestins found in hormonal contraception are incompletely understood (Berry-Bibee et al. 2016). Combined oral contraceptives (OC) are generally considered moderate inhibitors of CYP1A2 and weak inhibitors of CYP3A4, CYP2C19, and CYP2D6, leading to additional theoretical concerns for drug interactions (Guidance for industry drug interaction studies – study designs, data analysis, implications for dosing, and labeling recommendations 2012).

A 2016 systematic review did not find a statistically significant difference between fluoxetine and OC users versus fluoxetine alone in the treatment response of depression, and there was no statistically significant difference seen in unintended pregnancy (Berry-Bibee et al. 2016). With citalopram, the study found no significant difference in the adjusted odds of remission for OC users compared to non-OC users, and there were no significant differences in side effects between the two groups (Berry-Bibee et al. 2016).The systematic review found limited data on tricyclic antidepressants (TCAs) and bupropion (Berry-Bibee et al. 2016). No data to date exists on drug interactions for non-oral formulations of hormonal contraceptives or long-acting reversible methods of birth control (Berry-Bibee et al. 2016).

8.2 Tamoxifen

A growing and evolving literature has raised concerns about the potential for antidepressant medications, particularly those that are potent CYP2D6, to decrease the clinical efficacy of tamoxifen when used concurrently in women with breast cancer (Breitbart 2011). Tamoxifen (a prodrug) is metabolized by CYP2D6 into its active metabolite endoxifen. In clinical practice providers must avoid potent 2D6 inhibitors (paroxetine, fluoxetine, and sertraline) for the treatment of hot flashes or depression (Breitbart 2011).

8.3 Estrogen in Transwomen with SSRIs

There is no research to date on this topic, despite the increased visibility of transgender women and hormonal treatments.

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Management of Late-Life Depression

J. Craig Nelson

Contents

Abstract

Depression is a common disorder in late life that is associated with poor quality of life, increased disability, and increased all-cause mortality. Rates of completed suicide are the highest in older depressed men compared with any other age group. In this age group, depression is often concurrent with medical illness and it can aggravate the course of medical illness. Cognitive impairment is frequently present and may be the result of the depression itself or may be the consequence of a neurodegenerative disorder such as Alzheimer's disease. Evidence-based psychotherapies, antidepressants, and somatic treatments such as electroconvulsive therapy are employed in the treatment of older depressed adults. Treatment

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may be complicated by the presence of cognitive impairment, other comorbid medical disorders, and medications used to treat these disorders. Certain safety issues such as increased bleeding risk, hyponatremia, decreased bone density and falls may be associated with antidepressant treatment, may be more common in older depressed adults, and their consequences may be more severe in late life. These risks, however, need to be weighed against the hazards of untreated depression. With appropriate care, most older depressed patients can be successfully treated and a positive outcome can have a significant effect on the patient's quality of life.

Keywords
Depression · Geriatric · Late life

Depression is a common disorder in late life. Although the lifetime prevalence of major depression in community samples is lower in older adults than in younger or mixed-age patients (Myers et al. 1984; Kessler et al. 2003), it is still highly prevalent. In reviewing studies of major depression, Blazer found the prevalence of MDD in adults 65 and older to range from 1 to 3% in community-dwelling persons, while the prevalence in clinical and institutional samples was higher, 10–20%. The lower prevalence of MDD in older adults came as a surprise to many; however, Kessler et al. (2003) suggested this may be a cohort effect with the incidence of MDD increasing in younger cohorts. Among older adults, the prevalence of minor depression or clinically significant depressive symptoms is considerably higher than that for MDD (Blazer 2004).

In older patients, depression is associated with increased disability, functional impairment, and all-cause mortality (Bruce et al. 1994a, b; Cuijpers et al. 2013). Rates of completed suicide are the highest in older men compared with any other age group (National Center for Health Statistics 2016). Depression aggravates the course of medical illness. For example, depression occurring shortly after a myocardial infarction or stroke increases mortality (Frasure-Smith et al. 1993; Pratt et al. 1996; Bartoli et al. 2013). Finally, management of illness in older patients often involves managing various chronic diseases. The aim is often improving quality of life. Depression has a greater effect on quality of life than most other medical conditions (Wells et al. 1989), perhaps with the exception of pain. Successful treatment of depression can have a robust effect on the patient's quality of life.

The diagnosis of a major depressive episode or major depressive disorder has changed little since criteria for the disorder were proposed by Woodruff and the Washington University group in Woodruff et al. (1971) and incorporated into DSM III in 1980. Two major distinctions are made in patients with MDE. First, is the depression an episode in the course of bipolar disorder? Second, does the patient have psychotic symptoms? Both of these latter conditions are important because they will likely require different treatment than nonpsychotic, unipolar, MDD. DSM 5 does provide other specifiers for major depression. There may be dimensional

features such as anxiety symptoms (i.e., anxious distress) or categorical conditions such as postpartum depression. Yet these features are thought to modify the presentation and possibly treatment of the syndrome of major depression, rather than be distinct disorders.

Of course the term "major depression" begs the question of "minor depression." Minor depression has not achieved the status of a disorder in DSM 5. In part this reflects lack of agreement about its definition. Most commonly minor depression is defined by two to four symptoms of depression rather than the five or more symptom criteria required by MDD. Most studies of minor depression find it is more common than MDD (Blazer 2004; Nelson 2016). In older patients, the prevalence of clinically important depressive symptoms has been reported to be as high as 16% (Blazer 2004). While it is by definition less severe, it is important because it is common and it is associated with disability (Rapaport and Judd 1998), and a recent study found that among older patients with mild cognitive impairment (MCI), those with persistent subsyndromal symptoms of depression had more rapid progression of their cognitive disorder (Gonzales et al. 2017).

1 Depressive Symptoms in Late Life

Relevant to this chapter is the question of whether depressive symptoms differ in older depressed patients. They may differ in frequency. For example, sleep duration declines with age. In comparison with young patients who may experience hypersomnia during depression, decreased sleep is more common in late-life depression. Increased appetite and overeating may occur in younger patients, while loss of appetite and weight loss are common in late life. Overall the somatic symptoms of depression may be more common in older patients; however, the criteria symptoms remain the same. We examined the frequency of symptoms and symptoms that showed the greatest change during treatment of 728 patients aged 65 or older with major depressive disorder (Nelson et al. 2005). The symptoms most frequent and with the greatest change during treatment in geriatric patients were similar to those found in five studies of mixed-age, non-geriatric samples. Our conclusion was that the symptoms in older patient are more similar to those in younger patients than they are different.

Underdiagnosis or misdiagnosis of depression in older adults does occur, and there appear to be two common reasons. First, the clinician observing an older patient with various medical or situational problems may conclude "wouldn't you be depressed" in this situation. The fact that the depression is understandable does not diminish its importance or mean it does not represent a treatable condition. If the symptoms are present, persist, and affect functioning, those symptoms define depression. The second issue has to do with the somatic symptoms of depression. Older patients are more likely than younger patients to also have comorbid medical illness that could explain some symptoms. This can lead the clinician into pursuing an expensive medical workup, when the problem is really depression. Others have shown that patients who present with somatic symptoms of depression are less likely

to be diagnosed with depression compared with patients who present with mood and psychological symptoms (Kirmayer et al. 1993). This is not just a problem for the clinician, but it may lead the patient to think their somatic symptoms such as fatigue and weight loss are the result of a medical condition. This may explain in part why some patients are reluctant to accept a diagnosis of depression. Of course, both the patient and clinician may hope to find a medical illness in order to avoid the stigma of a psychiatric diagnosis.

If older patients become impaired cognitively, this can affect the presentation of depression. Patients may have less insight about their illness and if memory is impaired, may not remember symptoms present a few days ago. In these situations, the caregiver may be the one to recognize the change. Certain symptoms such as irritability, loss of weight, and lack of interest in favorite activities may be noticed by others. Even then, if patients or the caregivers are asked about the common symptoms of depression, those symptoms are likely to be present.

2 Impaired Cognition

Depression often impairs cognition. This is true in younger patients as well as older patients. In depression, processing speed slows, and patients have trouble concentrating. In the past, the term "pseudodementia" was used to describe depression with cognitive impairment; however, neuropsychological testing demonstrated the impairment is quite real, and Alexopoulos et al. demonstrated an appreciable percentage of such patients go on to develop dementia (Alexopoulos et al. 1993). Thus the cognitive problems in older depressed adults can be associated with depression itself but also be associated with early Alzheimer's disease, vascular disease, or other neurodegenerative disease. As a consequence, older depressed patients may be more severely cognitively impaired than younger patients. Studies in late-life depression find that up to 60% of older depressed patients are impaired in at least one cognitive domain (Butters et al. 2004). Although repeated episodes of depression have been thought to potentially damage the hippocampus and lead to diminished memory, a recent study found that patients with early-onset depression and repeated episodes had less cognitive impairment than those with late-onset depression (Mackin et al. 2014). This does not rule out the possibility that repeated depressive episodes contribute to cognitive decline; however, the data suggest that neurodegenerative disease, which is more common in late-onset patients, plays a more important role in cognitive impairment. In fact, late-onset depression may be a prodrome of the degenerative disease in some patients.

3 Treatment of Late-Life Depression

General Considerations Older patients have a number of features that may influence or complicate treatment. The association of depression with comorbid dementia has been mentioned above. Other medical illnesses are likely to be present. Patients

60–75, sometimes described as the "young-old," often have manageable medical disorders such as hypertension, adult diabetes, and hypothyroidism but without much functional impairment. The "old-old," patients greater than 75 years, are more likely to display functional impairment. Some investigators have suggested that "biological age," which is essentially an index of cumulative medical illness, is more predictive of functional impairment and mortality than chronological age (Brown et al. 2017). These medical disorders are usually accompanied by medications used to treat them. Thus, the clinician evaluating older depressed patients needs to take into account both the other medical conditions and the medications used to treat those disorders when deciding on a course of treatment.

There are other patient attributes associated with aging that need to be taken into account. Impairments in hearing or vision need to be considered during the management of the patient. Impairments such as gait disturbance define vulnerabilities of the patient that need to be considered in relation to the adverse or secondary effects of a particular medication. Agents that are associated with gait disturbance are more likely to exacerbate pre-existing gait disturbance. Poor nutrition and weight loss are more common in older patients, and case reports suggest such patients may lose even more weight on fluoxetine, an SSRI that tends to be associated with weight loss acutely (Brymer and Winograd 1992). In this case, a medication associated with weight gain can be an advantage.

Finally, when considering the course of treatment, the patient's preference plays an important role. This is important for some obvious reasons, e.g., the patient is more likely to be adherent to a treatment they endorse. However, with some exceptions, mild to moderate depression appears to respond to either medication or psychotherapy so if both treatments are available in their community, it is reasonable for the patient to choose.

Pharmacologic Considerations A variety of pharmacologic changes may occur in older patients. Absorption may be slower. Volume of distribution may change as the percentage of lean body mass declines. Yet, these changes are usually minor in comparison to the differences among individuals with respect to drug clearance. Most medications used to treat depression are cleared by the cytochrome P450 system in the liver, and dosing of these medications will need to be adjusted for changes in the P450 system. For example, the 3A4 pathway, the largest metabolizing pathway, slows with age (von Moltke et al. 1993). Alternatively, population-based data for drugs such as desipramine and nortriptyline indicate the 2D6 pathway appears to be less effected by age (Cutler et al. 1981; Georgotas et al. 1986; Katz et al. 1989; Nelson et al. 1985, 1995). Elimination of drugs by the kidney is usually less of a factor for most drugs used in depression, with the exception of drugs primarily cleared by the kidney such as lithium. Renal clearance does decline with age and will affect such drugs. A greater proportion of milnacipran and levomilnacipran than other antidepressants are cleared by the kidney and may be affected. The hydroxy metabolites of the tricyclics are affected by renal clearance (Nelson et al. 1988; Young et al. 1985).

3.1 Choice of Treatments for Late-Life Depression

Psychotherapy is effective for late-life depression as are various somatic treatments. Among the somatic treatments, antidepressants are by far the most commonly employed. Neuromodulation treatments have also been employed in older depressed adults and have been reviewed elsewhere (McDonald 2016). Electroconvulsive therapy (ECT) is in relatively common use, and in some centers, older depressed patients are disproportionately represented. ECT is one of the few treatments that has been reported to be more effective in older vs. younger patients (O'Connor et al. 2001). ECT is one of the treatments of choice for major depression with psychotic features, and this disorder tends to be more common in older patients. Apart from anesthesia issues, the most common shortcoming of ECT in older patients is confusion. Brief-pulse square-wave current has reduced this adverse effect. The recent Pride study reported a 61% remission rate in older patients with depression using right unilateral ultrabrief pulse ECT and reported that it was associated with minimal adverse cognitive effects (Kellner et al. 2016). Transcranial magnetic stimulation also appears to be of value in older depressed adults. Because the integrity of cortical circuits in older patients might be impaired, older depressed adults may require a larger cumulative dose than younger patients. One sham-controlled trial in older depressed patients with vascular depression demonstrated dose-dependent efficacy over sham treatment although actual remission rates were lower than that reported for ECT (Jorge et al. 2008). The efficacy of vagal nerve stimulation in older depressed adults has not been reported. Both ECT and TMS are considerably more expensive than medications and require a greater time commitment from the patient. ECT usually requires 6–12 treatments given 3 times a week. TMS is usually given daily for 6 weeks. As a consequence, these treatments are usually reserved for treatment-resistant patients. While the efficacy of ECT appears to be reduced in treatment-resistant patients (Prudic et al. 1996), its efficacy is still better established than TMS in such patients.

3.2 The Evidence Base for Psychotherapy in Late-Life Major Depression

Huang et al. (2015) reviewed the evidence for psychotherapy in late-life depression. The authors found 27 controlled studies of psychotherapy with 37 comparisons in older depressed patients. These trials included 2,408 patients whose mean age was 71 years. Several types of psychotherapy were included, and several types of controls were employed. The first observation of this study was that the type of control group had a substantial effect on the magnitude of the effect of psychotherapy. For example, trials using a waitlist control showed a big effect of treatment (therapy vs. control, effect size = 0.94), and there was little improvement within the waitlist condition. Alternatively, trials using supportive therapy or treatment as usual as the control had a smaller between-group effect size, ES = 0.39 and ES = 0.28, respectively. Three trials included placebo plus clinical management. The magnitude

of change within the placebo and clinical management control was relatively similar compared to the change within the supportive therapy controls, in part because clinical management involves many of the same elements as supportive therapy, e.g., education, attention, and reassurance.

The other important finding of this study is that problem-solving therapy, a type of cognitive therapy, is the best established psychotherapy in older depressed adults in terms of level of evidence. Other reviews have concluded that cognitive behavioral therapy is well supported and appears more effective than interpersonal therapy (Mackin and Areán 2005).

3.3 Antidepressant Treatment

Antidepressants remain the most commonly administered somatic treatment. In primary care and areas where psychotherapy is unavailable, antidepressants are the primary treatment. Nonpsychotic unipolar major depression is the best-studied indication for the second-generation antidepressants, such as SSRIs and SNRIs. Psychotic depression and bipolar depression have usually been excluded from trials because these conditions require different treatments.

The efficacy of second-generation antidepressants in late-life depression has been previously systematically reviewed, and meta-analyses have been performed (Mittmann et al. 1997; Wilson et al. 2001; Nelson et al. 2009; Kok et al. 2012). Two of these reviews were published in 1997 and 2001 before most of the trials of second-generation antidepressants were performed; thus, the recent reviews are more relevant for the drugs in current use. For this chapter, the systematic review and meta-analysis of second-generation antidepressants by Nelson et al. (2009) were updated. Trials selected were randomized placebo-controlled trials that included community-dwelling adults, 60 years or older, with major depressive disorder. All studies excluded patients with bipolar disorder, psychotic features, or dementia. Studies limited to a single medical disease such as poststroke depression were not included because the findings may be unique to that specific medical illness. In addition to ten trials previously reported (Nelson et al. 2009), two recent trials were found – a trial of duloxetine (Robinson et al. 2014) and a 3-arm trial comparing vortioxetine, duloxetine, and placebo (Katona et al. 2012). The search revealed no reports of placebo-controlled trials of mirtazapine, vilazodone, desvenlafaxine, or levomilnacipran in MDD patients 60 years or older.

The meta-analysis of the 12 trials with 16 comparisons is shown in Fig. 1. The overall odds ratio was 1.43 (95% CI 1.28, 1.60; $z = 6.40$, $p < 0.00001$). There was considerable heterogeneity, $I^2 = 70\%$, suggesting factors other than the antidepressants also contributed to the variability in outcomes. The test for differences between drug groups (SSRIs vs. SNRIs vs. bupropion) was not significant. Bupropion and venlafaxine failed to separate from placebo, but there was only one trial of these drugs. The simple pooled response rates were 45.8% for the active antidepressants and 35.3% for placebo, and the difference results in a number needed to treat (NNT) of 10.

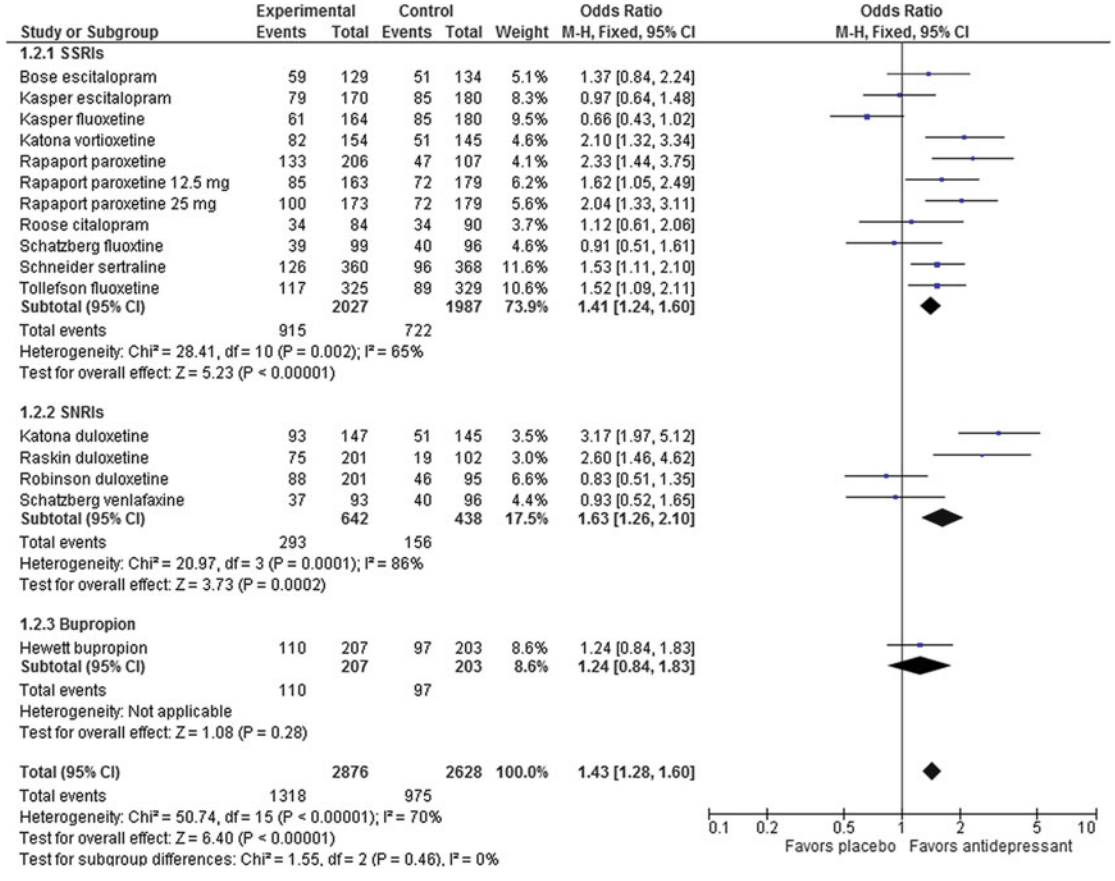

Fig. 1 Meta-analysis of second-generation antidepressants in late-life major depression (age ≥60 years). The forest plot and analysis is adapted from an analysis published previously (Nelson et al. 2008) with the addition of two trials completed since that publication

The efficacy of antidepressants in older patients is less than that reported in non-geriatric trials. Two large meta-analyses (Walsh et al. 2002, $N = 75$ trials; Papakostas and Fava 2009, $N = 182$ trials) of placebo-controlled trials in non-geriatric samples both found a NNT of 6. The differences in older and younger patients are similar to results reported by Tedeschini et al. (2011) who reviewed trials in young and old patients and found that in six placebo-controlled trials of antidepressants in patients over 65 years of age, antidepressants were not more effective than placebo.

In the controlled trials of second-generation antidepressants, adverse event discontinuation rates were higher with medication than placebo, but these rates were not unusually high relative to non-geriatric studies. The withdrawal rates for any reason were 23.3% (683/2,930) for drug vs. 20.8% (423/2,035) for placebo, and the discontinuation rates for adverse events were 11.5% (338/2,930) for drug and 6.7% (136/2,035) for placebo. Although the discontinuation rates for adverse events were higher in the drug vs. the placebo groups, the nature of the side effects and their seriousness were not dissimilar from mixed-age samples. Yet it should be noted most of the patients in the late-life depression trials were the "young-old." Only one trial limited recruitment to patients 75 years or older (Roose et al. 2004).

Predictors and Moderators of Response Given the lower response rate and smaller drug-placebo differences in late-life depression, it is reasonable to investigate what explains the difference. Nelson et al. (2009) examined if anxious depression, defined using the anxious-somatization factor on the Hamilton Depression Rating Scale (HDRS), influenced response as reported by STAR*D (Fava et al. 2008). Eight of the first ten RCTs of second-generation antidepressants in late-life MDD were able to provide unpublished data, which demonstrated no significant drug-placebo difference in the anxious and less anxious patients. In a second meta-analysis, individual patient data was obtained from all ten of the first group of late-life MDD trials (Nelson et al. 2013). Several potential moderators were examined. The primary limiting factor was whether the information had been collected. Age, sex, and depression severity were available for all the trials. Age of onset and course (single episode vs. recurrent) were available for seven trials. All the trials used the Mini-Mental State Exam to assess cognition, but several of the trials only recorded if the score was above the threshold for inclusion; thus, actual MMSE scores were not available for several studies. Seven trials including 2,283 subjects could be included in the analysis. The first interesting finding was that age did not have a significant moderating effect on the drug-placebo difference when other variables were taken into account. The variable with the largest and a significant moderating effect on the drug-placebo difference was the lifetime duration of major depression (current age – age of onset of MDD). As the lifetime duration grew longer, the placebo response rate declined, and the drug-placebo difference grew larger. In patients with a lifetime duration of 2 years or less, the drug response and placebo response rates were relatively similar (51.5% vs. 47.7%). In patients with a 10-year history of MDD and at least moderate depression (HAMD $\geq$21), the NNT was 4.

The preceding studies of moderators of response were exploratory analyses. Other studies, however, support the findings. Two trials of antidepressants in patients with MDD and heart disease (mean age 57 and 58) (the Sertraline Antidepressant Heart Attack Trial [SADHART] [Glassman et al. 2006] and the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy [CREATE] Trial [Lespérance et al. 2007]) found minimal differences between drug and placebo in patients having their first depressive episode. The drug-placebo difference became larger and significant in patients with recurrent depression. Montgomery et al. (2015) examined seven potential moderators of drug-placebo differences in a pooled analysis of five placebo-controlled levomilnacipran trials. They found the lifetime duration of depression was one of only two moderators of response. In patients with a lifetime MDD history less than 2 years, the difference in response rates between drug and placebo did not differ. As lifetime duration of depression became longer, the placebo response rate declined, and the drug-placebo difference became larger. Although this study was not in late-life patients, the findings are very similar to the prior study in older adults and replicate those findings. A very recent study (Zilcha-Mano et al. 2018) used machine learning to examine potential moderators of response in the "old-old" study mentioned above. They also found duration of MDD was one of the moderators and level of education achieved was the other. In this analysis, education was a stronger moderator than deficient response inhibition based on the Stroop Color Word Test reported previously as a moderator in this same sample (Sneed et al. 2007). Disentangling the relationships of education with various aspects of cognition and how they relate to treatment response will require further study.

Other *predictors* that are quite relevant in older patients are pain and medical illness. Bair et al. (2004) found the response rate to SSRIs for depression was lower in 573 patients in primary care if pain was severe. Although the study was not limited to an elderly sample, it seems relevant to older patients given the prevalence of pain in that group. Iosifescu et al. (2003) found response and remission rates declined in patients with greater medical burden. Alternatively, another study of 728 older depressed patients found sertraline was more effective than placebo in those with ($N = 442$) and without ($N = 286$) comorbid medical illness (Sheikh et al. 2004). The differences in the two studies are that the Iosifescu study examined predictors of fluoxetine response based on severity of medical burden, while the Sheikh study examined moderators of the drug-placebo difference based on the presence or absence of medical illness. Together, they suggest that antidepressants are more effective than placebo in patients with medical illness, but the absolute response rate may decline as medical burden becomes more severe.

Other Types or Subtypes of Late-Life Depression Controlled trial data are limited for treatment of late-life minor depression and dysthymia (or mild persistent depression). Williams et al. (2000) compared the efficacy of paroxetine and problem-solving therapy with placebo in subjects 60 years or older who had minor depression or dysthymia and were treated in primary care. Paroxetine was more effective than placebo but PST was not. Paroxetine was effective in both minor

depression and dysthymia. The PROSPECT study examined the effectiveness of an intervention involving physician education and care management in a primary care setting (Bruce et al. 2004). The intervention was administered with usual care antidepressants or psychotherapy. Subjects aged 60 years or older with major depression or "clinically significant" minor depression were included. The intervention had a greater effect than usual care on suicidal ideation and depressive symptoms in the overall group and in those with major depressive disorder; however, these effects were not significant in the minor depression group. Symptom change was smaller in those with minor depression, but they were less severe at the start. Percent change in the minor depression group, 39%, was similar to that in the MDD group, 40%, but percent change was greater on placebo in the minor depression group than in MDD. Devanand et al. (2005) conducted a RCT in 90 subjects aged 60 and older with dysthymia. The efficacy of fluoxetine appeared limited, rates of response were fairly low on both fluoxetine and placebo, but the sample size was not powered to detect small differences. In short, the evidence base for antidepressants in minor depression and dysthymia is suggestive of efficacy, but the evidence base is small.

Similarly, the evidence for pharmacologic treatment of psychotic depression is limited, but a single high-quality study is illuminating (Meyers et al. 2009). The 12-week study compared olanzapine plus sertraline vs. olanzapine plus placebo in 117 younger and 142 older (>60 years) patients with psychotic major depression. Combination treatment was more effective than olanzapine monotherapy, and the efficacy and tolerability of the combination were similar in both age groups.

Perhaps the least well studied type of depression in older depressed adults is depression in the frail elderly. To some extent, the residential setting has served as a proxy for the frail or very old elderly. One single-site double-blind RCT found nortriptyline was more effective than placebo although the number of patients responding was similar to the number discontinuing because of adverse effects (Katz et al. 1990). This was a small study of 30 patients whose average age was 84. Although the number of RCTs in residential or nursing home settings is very small, there is a larger database examining depressed patients with specific medical disorders, such as stroke, heart disease, Parkinson's disease, and other disorders. Since the interaction of depression with the medical disorder may differ among the disorders, this focus seems appropriate.

3.4 Relapse Prevention

Kok et al. (2012) performed a systematic review and meta-analysis of placebo-controlled trials to prevent relapse or recurrence. They found eight trials with nine comparisons meeting their criteria. Four of the trials employed a tricyclic (TCA) and one phenelzine. These five trials were published between 1989 and 2000. Four trials, published between 2002 and 2007, examined the SSRIs. Overall, the meta-analysis showed a significant advantage for prevention of relapse with an odds ratio of 0.23 (95% CI 0.18, 0.40). Risk of relapse with the antidepressant was 25.1% in the drug

group and 52.4% in the placebo group. This difference results in a robust NNT of 4. NNTs in the TCA and SSRI subgroups were not significantly different. Because clinicians are likely to use second-generation antidepressants, the NNT for the SSRIs, which was 5 (exact 4.2) is reported here. One of the four SSRI trials, which failed to show an effect, included patients with MMSE scores as low as 12, which is in the dementia range (Wilson et al. 2001). One of the trials included patients who were treated and then maintained on adjunctive therapy (Reynolds et al. 2006). However, if that trial is removed from the analysis, the odds ratio is minimally affected. The NNT for the geriatric trials is quite similar to that found by Geddes et al. (2003) in non-geriatric relapse prevention trials (NNT = 5 [exact NNT = 4.3]).

3.5 Late-Life Treatment-Resistant Depression

Prospective controlled trials of treatment-resistant depression in older adults are rare. Steffens et al. (2011) reported a retrospective analysis of three pooled trials of aripiprazole. Among the 409 patients 50 years and older, aripiprazole was more effective than placebo. Recently, Lenze et al. (2015) completed the first prospective controlled acute phase study in late-life depression. They compared response in 181 patients who failed an 8-week initial trial of venlafaxine and were then randomized to adjunctive aripiprazole or placebo. A significantly higher rate of remission was observed with aripiprazole than with placebo, 44% vs. 29%. A subsequent analysis of the data found that the advantage of aripiprazole was maintained in patients who were unimpaired on the Trail Making Test (a test of executive dysfunction) (Kaneriya et al. 2016), while those who were impaired on the TMT showed no difference between aripiprazole and placebo. Level of anxiety predicted lower remission rates but did not moderate the drug-placebo difference. In this trial, medical comorbidity and the color word interference task did not predict or moderate response. A more comprehensive discussion of adjunctive strategies in late-life depression has been reported previously (Nelson 2013); however, to date the aripiprazole study described above is the only prospective controlled acute phase study of an adjunctive agent in late-life depression.

3.6 Depression with Impaired Cognition

Impaired cognition may predict treatment response and may require different treatments. In the 1990s, there was considerable interest in using magnetic resonance imaging as a new tool to explore depression. A discovery that generated considerable interest was the finding of hyperintensities in older depressed adults. The hyperintensities appeared related to vascular disease and led to the vascular depression hypothesis described by Alexopoulos et al. (1997). This syndrome was associated with executive dysfunction on neuropsychological testing. Although the imaging data did not prove useful for predicting response to treatment, executive dysfunction appeared to be predictive. Pimontel et al. (2016) recently reviewed the

studies of neuropsychological predictors of antidepressant response. The majority of studies compared response to antidepressants – mainly SSRIs and SNRIs – in subjects with and without executive dysfunction (ED). The most common tests of ED employed were the Initiation-Perseveration subscale of the Dementia Rating Scale (Mattis 2004) and the Stroop Color Word Test (Golden and Freshwater 2002). Most of the studies found subjects with ED responded less well than subjects without ED. Only one study was placebo-controlled. This was the "old-old" study, an 8-week trial of citalopram vs. placebo in outpatients 75 years and older (Roose et al. 2004). This study failed to find an advantage for citalopram in the full sample, but in those without ED, citalopram was more effective than placebo (Sneed et al. 2007). In the patients with ED, those on citalopram actually did worse than placebo patients. Although the number of patients with ED was small, the study indicated that ED was both a predictor and moderator of response. As noted above, however, another analysis of this data found education an even stronger moderator than executive dysfunction based on deficient response inhibition (Zilcha-Mano et al. 2018).

The study of ED and the larger issue of cognition in late-life depression continue to receive attention. Up to 60% of older depressed patients display impaired cognition in at least one domain (Butters et al. 2004). Many of these individuals would receive a diagnosis of mild cognitive impairment. Devanand et al. (2005) conducted an open-label, 12-week study of sertraline in older depressed patients with MCI. In the intent-to-treat sample, 44% responded. Three studies have employed cognitive enhancing agents as adjuncts to improve depressive symptoms or cognition. The first two studies failed to find galantamine superior to placebo when added to antidepressants (Holzhemier et al. 2008; Elgamal and MacQueen 2008). The third study of 23 subjects with MDD and MCI found that verbal memory improved as depression improved during an initial open-label 8-week SSRI trial (Pelton et al. 2008). During the randomized 12-week trial, patients who were randomized to receive donepezil had further improvement in memory compared with those on placebo (Pelton et al. 2014).

Reynolds and colleagues explored the potential benefits of adjunctive donepezil during maintenance treatment of depression in older adults with MDD (2011). After acute treatment with antidepressants for 12–16 weeks, responders continued on the antidepressant and were randomized to receive additional donepezil or placebo over the next 2 years. Of the 130 randomized patients with MDD, 57 had MCI. Among the MCI patients, donepezil appeared to reduce progression to dementia at 1 year, but the effect was not sustained at 2 years. The authors also found that donepezil significantly increased relapse of depression. The observation that donepezil, a cholinergic agent, causes depression relapse is consistent with earlier observations that anticholinergic effects of tricyclic antidepressants may contribute to antidepressant effects (Janowsky et al. 1974) and the more recent demonstration of rapid antidepressant effects with scopolamine, an anticholinergic agent (Furey and Drevets 2006). This observation is of considerable importance because donepezil and the other acetylcholinesterase inhibitors are likely to be given as cognitive

enhancers to patients with a history of depression. Clinicians will need to carefully consider the risk/benefit questions in such patients.

3.7 Efficacy of Antidepressants for Depression in Patients with Dementia

A related question is whether antidepressants are effective in dementia. We conducted a systematic review and meta-analysis of the studies of antidepressants in dementia (Nelson and Devanand 2011). Seven controlled trials were found. Patients had the diagnosis of probable Alzheimer's dementia although in one study, patients with vascular dementia were also included. The diagnosis of depression was quite variable and included both MDD and minor depression or dysthymia. Among the seven trials, antidepressants were not significantly more effective than placebo. Shortly after this meta-analysis was published, a larger study ($N = 326$) comparing sertraline, mirtazapine, and placebo in depressed patients with dementia was reported (Banerjee et al. 2011). Neither of the active drugs was more effective than placebo. It is unclear if dementia itself interferes with response or if there are other factors at play. In the Banerjee study and the largest prior study (Rosenberg et al. 2010), most of the patients were having their first depressive episode (personal communication with Drs. Banerjee and Rosenberg 2011). It is possible that in these patients with a short lifetime history of depression, placebo response was relatively robust as previously observed (Nelson et al. 2013) and that antidepressants might still have a role in depressed patients with a longer history of depression.

3.8 Differences Among the Antidepressants

The meta-analyses of antidepressants in older depressed adults do not indicate differences in efficacy among the antidepressants with the possible exception that single studies of venlafaxine and bupropion failed to show these drugs superior to placebo. However, given the much larger database for these agents demonstrating efficacy in mixed-age patients, these findings would appear to be of doubtful significance. As the APA guideline for selection of antidepressants concluded, selection of an antidepressant is likely to be based on factors other than efficacy (Fig. 2) (Practice guideline for MDD 2000).

Factors influencing drug selection are similar to those in younger patients although certain factors may become more prominent in older adults. For example, pain is a common comorbid condition in older adults. Evidence supporting the efficacy of duloxetine for pain has led to its approval by the FDA in painful diabetic neuropathy, fibromyalgia, and chronic pain. Controlled trials support the efficacy of venlafaxine in pain syndromes; however, these data are more limited. Although amitriptyline has never been approved for use in pain syndromes, it was widely used for this purpose for decades. Because of its wide use and its high lethality in overdose, it is associated with more deaths than all other antidepressants combined

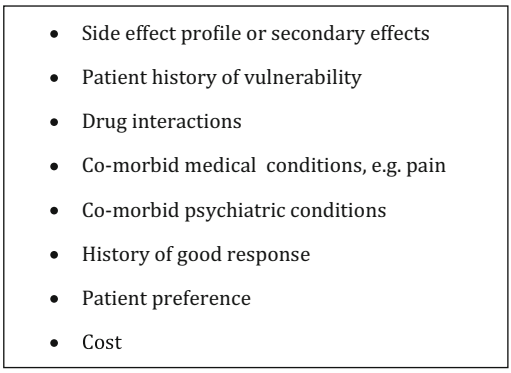

Fig. 2 Factors influencing drug selection in older depressed adults

(Nelson and Spyker 2017). Although some data suggest amitriptyline is more effective than selective serotonin uptake inhibitors in depressed inpatients (Anderson and Tomenson 1994), this advantage is not established in outpatient samples. For pain syndromes, a network meta-analysis found duloxetine and venlafaxine comparable in efficacy to the tricyclics for pain (Griebeler et al. 2014). The use of amitriptyline should be considered carefully given the availability of safer medications.

Another potential difference among the antidepressants is their effects on cognition. The tricyclic antidepressants have potent anticholinergic effects. These effects are considered a disadvantage in the treatment of older depressed adults with impaired cognition. As a group, the second-generation antidepressants had minimal or no anticholinergic effects. There is limited data suggesting some antidepressants may have more favorable effects on cognition. In a study of 453 older depressed adults, both vortioxetine and duloxetine improved memory and learning more than placebo, but vortioxetine had a greater effect on the digit symbol substitution test (Katona et al. 2012). Path analysis suggested this effect was independent of improvement in depression. Relatively similar findings for vortioxetine were found in a trial of younger patients (Mahableshwarkar et al. 2015). In two 12-week comparison trials, sertraline was found to have greater effects on processing speed (measured by the digit symbol test) and verbal recall than fluoxetine (Newhouse et al. 2000) or nortriptyline (Bondareff et al. 2000). Each of the studies in older depressed adults excluded patients with a MMSE score of <24. This threshold would not necessarily exclude patients with mild cognitive impairment; yet, none of the studies examined if the beneficial effects on processing speed differed in patients with and without MCI. To summarize the findings in this important area, both vortioxetine and sertraline may be especially useful for improving processing speed in older depressed adults; however, studies of effects on cognition are limited, and it is not clear if this apparent beneficial effect will be obtained in depressed patients whose cognition is in the impaired range or in patients whose impairment is the result of neurodegenerative or vascular disease.

Similar to younger patients, the secondary effects of antidepressants can be an advantage in some older patients. In older patients, sleep disturbance most often

takes the form of insomnia. Mirtazapine, which is a potent antihistamine and is relatively more sedating, can be useful for such patients. Older patients are also more likely to have lost weight during their depression. In patients over 75 years, acute treatment with fluoxetine has been associated with significant weight loss (Brymer and Winograd 1992), while mirtazapine may help patients gain weight. Bupropion, one of the least sedating antidepressants, can be useful in older patients already receiving other sedating agents.

Because older patients are more likely to be receiving other medications for medical illness, consideration of drug interactions becomes a more important issue in older patients. Several of the antidepressants are inhibitors of various cytochrome P450 enzyme pathways. Fluoxetine, paroxetine, bupropion, and duloxetine are inhibitors of the 2D6 pathway. Some agents, e.g., sertraline and escitalopram, have less pronounced drug interactive effects, but their effects on the 2D6 pathway can become more important at high dose. Venlafaxine and mirtazapine have few drug interactive effects. Nefazodone inhibits the 3A4 pathway. Fluoxetine and fluvoxamine inhibit the 2C9 and 2C19 pathways. For further discussion of drug interactions, see Fiaturi and Greenblatt (2018) in this text.

3.9 Safety Issues in Older Adults

Hyponatremia There are a variety of safety issues that become especially important in older adults either because they occur with great frequency or their occurrence can have more profound consequences. Hyponatremia is one of these safety concerns that is more common in older adults. Although findings have been variable, most observational studies implicate the serotonin reuptake inhibitors as particular offenders (De Picker et al. 2014). A study from Ontario found a fivefold increase in the rate of hospitalization for hyponatremia with SSRIs; however, the absolute rate was only 1.3% (Gandhi et al. 2017). Recently Leth-Møller et al. (2016) examined the timing of the onset of hyponatremia using the Danish National Registry. The frequency of hyponatremia was highest in the first 14 days following initiation of treatment suggesting that a blood sample taken at that time might be especially useful for detecting this problem. These authors found that if antidepressants were compared at the time of the first sodium collection, duloxetine, venlafaxine, and mirtazapine had lower rates of hyponatremia than the SSRI compounds.

Bleeding The effect of SSRIs and SNRIs on bleeding has received considerable attention. Antidepressants have effects on platelets that affect blood clotting. When platelets are produced, they do not contain serotonin. During their 14-day life span, platelets take up serotonin through serotonin transporters that cover their surface. SSRIs and SNRIs block the uptake of serotonin into the platelet, and this has been presumed to be the mechanism by which these antidepressants cause bleeding. Although exact mechanisms are not been firmly established, medications that block uptake of serotonin are associated with bleeding (de Abajo 2011). Upper GI bleeding appears to be most common. A relatively recent systematic review and

meta-analysis found 22 controlled cohort or case-controlled studies of upper GI bleeding (Jiang et al. 2015). Bleeding was more common in patients on SSRIs (OR = 1.55; CI 1.35, 1.78) than those not on those drugs. Risk of bleeding was further increased in those also on NSAIDs (OR = 3.72) or on SSRIs + antiplatelet agents (OR = 2.48). In cases on three drugs, SSRIs + NSAIDs + antiplatelet agents, the OR was 9.13. Alternatively acid-suppressing drugs (proton pump inhibitors) reduced the risk of bleeding in cases on SSRIs (OR = 0.81; CI 0.43, 1.53).

A systematic review and meta-analysis of eight studies of postpartum bleeding found an increased risk associated with both the SSRIs and SNRIs, with a higher rate for the SNRIs (Jiang et al. 2016). Two systematic reviews and meta-analyses of the risk of stroke and intracranial bleeding found SSRIs were associated with an increased risk of hemorrhagic stroke (Hackam and Mrkobrada 2012; Shin et al. 2014). The second of these also found an increased risk of ischemic stroke among SSRI users. These risks did not appear to differ for SSRIs and SNRIs (Lee et al. 2016). Yet, while the differences in risks were significantly higher in cases on SSRIs, the actual rates of ischemic stroke (~3.4/10,000) or intracerebral hemorrhage (~3/100,000) were very low (Shin et al. 2014).

Ironically, SSRIs have been used in non-depressed poststroke patients for their presumed neurotrophic effects. Mead et al. (2013) found 52 randomized controlled trials of SSRIs used in poststroke patients. About 2/3 of the trials were in poststroke depression, but 1/3 were not. Most subjects were between 60 and 70 years of age. SSRIs did improve disability; however, only 2 trials of 347 patients reported bleeding as an outcome. The risk ratio for bleeding was elevated, RR = 1.63 (95% CI 0.2, 13.05), but not significant. Although prospective randomized controlled trials would be expected to produce higher quality data than observational studies, the two studies of 347 cases were far too small to detect expected differences in bleeding rates. This is the reason of course that observational studies with very large databases are employed.

Finally, when weighing the risk of intracerebral hemorrhage in stroke patients, the clinician will need to consider the following findings. Depression risk is elevated poststroke; about 30% of poststroke patients develop depression (Robinson and Jorge 2016). Depressed patients poststroke are three times more likely to die than non-depressed patients over a 10-year period following a stroke (Morris et al. 1993). Escitalopram and problem-solving therapy reduce the risk of depression poststroke relative to placebo (Robinson et al. 2008). Escitalopram enhances cognition poststroke at 1 year compared with placebo or problem-solving therapy, and these effects are independent of its effects on depression (Jorge et al. 2010). Twelve weeks of treatment of poststroke depression with nortriptyline or fluoxetine during the first year was associated with twice the survival rate at 9 years (Jorge et al. 2003). In short, there appear to be significant benefits of antidepressant treatment to prevent or treat poststroke depression, while the risk of further bleeding is relatively rare.

Bone Density, Demineralization, Fractures, and Falls Another safety issue is the possible effect of SSRIs and SNRIs on bone density and vulnerability to fracture. The ultimate risk of fractures is the consequence of the interaction of the effects of

antidepressants on bone density and the effects of antidepressant medications on falls. Stubbs et al. (2016) performed a meta-analysis of 13 comparisons from 10 studies of bone density at the hip and 7 studies of the spine in depressed and non-depressed cases over 60 years of age. There was a significant decrease in bone density in the depressed cases, but the effect size was small. In addition, poor nutrition, which can be more common in depressed patients, may have an additive effect reducing bone density (Kindilien et al. 2018). Depression is also a risk factor for falls. Kvelde et al. (2013) found 14 studies of this question, and the meta-analysis produced an odds ratio of 1.46 indicating a significant increase in falls in depressed subjects. A subsequent prospective study of 488 subjects aged 70 years or more found depressive symptoms, antidepressant use, high physiologic fall risk, and poorer executive functioning each were associated with falls (Kvelde et al. 2015). A multivariate analysis found depressive symptoms and antidepressants each independently contributed to falls. Alternatively, an ongoing study of 1,057 women found SSRIs were associated with worse physical functioning (e.g., reduced grip strength, walking speed, etc.) but not reduced bone density at the femoral neck, hip, and spine (Larsson et al. 2018). This study did not control for depression, and the reduced physical function found in SSRI users may be secondary to depression. Yet these results differ from a meta-analysis of 11 studies that found SSRIs were associated with reduction in bone mineral density (Zhou et al. 2018). To summarize, it does appear that both depression and antidepressants increase the risk of falls and fractures even if the question of effects on bone mineral density is not resolved.

These findings lead to the question of whether the risk of falls varies among the antidepressants. A recent meta-analysis of 248 studies addressed this question (Seppala et al. 2018). The analysis included SSRIs, tricyclic antidepressants, antipsychotics, and benzodiazepines. The odds ratio for the SSRIs, OR = 2.02 (95% CI 1.85, 2.20), was greater than that for the tricyclics, OR = 1.41 (CI 1.07, 1.86); antipsychotics, OR = 1.54 (CI 1.28, 1.85); or benzodiazepines, OR = 1.42 (CI 1.22, 1.65). The authors allowed that they could not account for prescribing bias; in other words, SSRIs may have been prescribed in patients at greater risk for falls based on the assumption that SSRIs are safer. Considering that prescribing bias may have shifted over time, two studies from 20 years ago were examined. A case-controlled study of 8,239 cases in Ontario examined risk of hip fracture (Liu et al. 1998). Odds ratios, adjusted for comorbidities such as depression and dementia, were relatively similar for SSRIs and TCAs, 2.4 and 2.2, respectively. Thapa et al. (1998) reported an inception cohort study of new users of TCAs, SSRIs, or trazodone in a nursing home setting. The authors adjusted rate ratios for comorbidities and concurrent medications. In this study, the adjusted rates were higher for TCAs than SSRIs, 2.0 vs. 1.8, but the difference between rates was small. As the authors noted, rates of falls and related injuries would not be "materially reduced" by the use of SSRIs. These data collected in studies performed over a 20-year period suggest that falls occur with both the SSRIs and TCAs, and it cannot be concluded that SSRIs are safer. A mechanism to explain these effects of SSRIs has not been established. Laghrissi-Thode et al. (1995a) reported that sertraline increased body sway during the first week of treatment, while nortriptyline did not, although the

effect was gone after 2 weeks. Subsequent studies by the same group and others failed to find similar effects with paroxetine and other SSRIs (Laghrissi-Thode et al. 1995b; Li et al. 1996). For now, clinicians will be faced with difficult decisions regarding the use of SSRIs in the elderly with data showing an increased risk of falls but without a mechanism to explain it and with meager data on the efficacy of SSRIs or SNRIs in the frail elderly. Given the association of antidepressants and falls, use of psychotherapies such as CBT or problem-solving therapy may be a desirable alternative in mild to moderate depression if the patient is able to actively participate. In more severe depression or in patients who are not able to actively participate, antidepressants are likely to be needed.

4 Conclusions

Depression is common in late life, and it has a number of serious adverse consequences. The randomized controlled trials of antidepressants in late life suggest the advantage of antidepressants compared to placebo given with clinical management is small, but moderators of the drug-placebo difference are emerging. Age itself does not appear to moderate outcome. A long history of depression is associated with reduced response to placebo and more robust drug-placebo differences. Patients with a short history of depression or in their first episode of depression are still relatively responsive to placebo and supportive management. Impaired cognition, principally in the form of executive dysfunction, appears to have an adverse effect on response to antidepressants. A number of safety issues are associated with the serotonergic antidepressants, and these hazards occur more frequently in older depressed adults than in younger patients. Yet these potential hazards needed to be weighed against the severe effects of depression on the patient's sense of well-being and on the course of their various medical illnesses. The treatment of poststroke depression is one of the best examples of evidence showing that treatments can reduce symptoms of depression, reduce the chance of depression occurring, and can have beneficial effects on the course of illness including improved cognition and reduced disability. It is one of the best examples showing that the benefits of treatment are worth the risks.

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The Use of Antidepressants in Bipolar Depression

John L. Beyer

Contents

Abstract

Depression remains a significant debilitating and frequent phase of illness for patients with bipolar disorder. There are few FDA-approved medications for its treatment, only one of which includes a traditional antidepressant (olanzapine-fluoxetine combination), despite studies that demonstrate traditional antidepressants are one of the most commonly prescribed class of medications for bipolar patients in a depressive episode. While traditional antidepressants remain the primary option for treatment of unipolar depression, their use in bipolar depression has been controversial due to a limited efficacy evidence and the concern for potential harm. This chapter reviews the current data concerning the use of traditional antidepressants in bipolar disorder, and the current expert treatment guideline recommendations for their use.

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1 Introduction

The lifetime prevalence of bipolar disorders (BD) in the United States is approximately 4% (1% bipolar I disorder, 1% bipolar II disorder, and 2% subthreshold bipolar disorder) (Merikangas et al. 2007). While having a depressive episode at some point during the illness is not required for the diagnosis of bipolar I (BPI) disorder, over 90% will experience at least one depressive episode; most will experience multiple recurrent depressive episodes. In fact, BPI patients undergoing naturalistic treatment have been noted to have three times more depressive episodes than mania (Kupka et al. 2007), making depressive symptoms and depressive episodes the most common mood problem that BPI patients experience.

For bipolar II (BPII) patients, the struggle with depression is even greater. First, diagnostic criteria for BPII require that a patient have experienced at least one depressive episode in addition to a hypomanic episode. Second, naturalistic studies demonstrate that depressive episodes are 17 times more frequent than hypomania. This makes depressive symptoms and depressive episodes the most common mood state for BPII patients.

These depressive episodes in bipolar disorders are not benign. They are responsible for significant personal and occupational disruptions; they are complicated by multiple psychiatric and medical comorbidities; they are associated with cognitive dysfunction; and they are identified as a cause of shortened life expectancy (Post 2016).

Despite the high prevalence of bipolar depression and its severe consequences, there is a relative deficit in clinical treatment research compared with bipolar mania. Whereas in 2017, 12 medications were approved by the Food and Drug Administration (FDA) for bipolar mania, only 3 medications were approved for bipolar depression (lurasidone, olanzapine/fluoxetine combination, and quetiapine/quetiapine XR). None of the common "mood stabilizers" (carbamazepine, lamotrigine, lithium, valproate) have been approved by the FDA for the treatment of bipolar depression; nor have any of the antidepressants (with the exception of fluoxetine when used in combination with olanzapine).

The limited options of approved treatments have led to much discussion on what the optimal treatment algorithms should be in bipolar depression. In the late 1990s, conventional treatment of bipolar depression typically included antidepressant augmentation of mood stabilizers. But in the past two decades, there have been increasing concerns that use of antidepressants in BD may be both ineffective and potentially harmful to patients by causing switching from depression to mania (or inducing rapid cycling) (Fountoulakis 2010; Licht et al. 2008; Salvi et al. 2008).

Despite these concerns, traditional antidepressants continue to be the most commonly prescribed class of medication for bipolar depression, a finding documented

in several recent studies of practice patterns in both the United States (Baldessarini et al. 2007; Broeks et al. 2017; Hooshmand et al. 2018) and Europe (Greil et al. 2012; Karanti et al. 2016; Kessing et al. 2016). Recommendations for the use of traditional antidepressants in bipolar disorder are based on a clinical research literature that is often limited and inconsistent and which may run counterintuitive to many clinician's training and clinical experience (Pacchiarotti et al. 2013). Further, the level of recurrence and relapse of depression in patients with BD despite "adequate" treatment can be extremely challenging to both the patient and clinician. Thus, treatment choices are complicated by limited evidence-based data in the presence of a high-intensity, frequently relapsing disease. So not only is bipolar depression the most difficult-to-treat phase of bipolar disorder, there is also a rolling debate in psychiatry over the optimal treatment, particularly as to the role of traditional antidepressants in bipolar depression (Greil et al. 2012).

This raises the question of why are traditional antidepressants still so frequently used and what is their actual role in the treatment of bipolar depression.

This chapter will focus on the current literature for the efficacy and safety of antidepressant use in bipolar depression. What is the role of traditional antidepressants in bipolar disorder? Are they efficacious? Are they safe? It should be noted that this chapter will not review the current full recommendations for the treatment of bipolar depressions, but rather focus only on traditional antidepressant use in bipolar depression.

2 The Challenge of Differentiating Depression Diagnosis in MDD and BD

In previous editions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), "bipolar" disorders and "unipolar" major depressive disorders were both listed under the general category of "mood disorders"; but in the DSM-5 (APA 2013), they have been separated into two distinct sections. This separation highlights the increasing scientific view that these two mood disorders are distinct entities, each with differing presumed causes, treatment responses, and courses of illness. However, the DSM-5 (as with previous versions) has continued to use identical symptom criteria for diagnosing depressive episodes in the context of either BD or unipolar MDD. The only difference is in the supporting criteria – primarily whether or not the patient has experienced an episode of mania/hypomania in the past. This use of similar diagnostic criteria highlights many clinicians' experiential view that these two disorders are essentially the same (Vöhringer and Perlis 2016). This separation of the mood disorder categories, but continued use of similar diagnostic criteria, presents clinicians with a unique clinical challenge: how to correctly identify and treat a depressive episode appropriately. And because most patients with BD present with the onset of depression, one-half to two-thirds are initially misdiagnosed (Lish et al. 1994; Hirschfeld et al. 2003).

As of yet, we do not have any clear biomarkers that can be used to discriminate depressive episodes in MDD and BD. This means that the most reliable strategy for clearer diagnostic certainty is in the observation of the longitudinal course of the

illness. By definition, if you follow the course of illness for a depressed patient long enough, all BD patients will at some point exhibit a hypomanic or manic episode. Obviously, in the midst of a depressive episode, this criterion is less helpful.

There are several other markers that may be helpful. Firstly, BD tends to manifest its symptoms earlier in patients' lives compared with MDD. A retrospective assessment of a large mood disorder cohort has found that roughly one-third of BD patients experience symptom onset prior to age 13 and another third experience symptoms between ages 13 and 18 (Perlis et al. 2004a, b). This finding, age of first episode, is among the most reliable features associated with BD risk and has been supported by numerous studies (Benazzi 2009; Pini et al. 2005; Perlis et al. 2006). Secondly, BD patients tend to receive more psychotropic medications over time due to multiple severe symptom episodes and more frequent recurrences (Swann et al. 2005; Angst et al. 2003). Thirdly, gender differences may be present between MDD and BD. Women are twice as likely as men to experience MDD while equally likely to experience BPI (Kessler et al. 2003).

However, none of these markers are clear-cut points that can be used to confirm the diagnosis. The number of people who struggle with MDD (lifetime prevalence 16.6%) far exceeds those with BPI (lifetime prevalence 1–3%). Thus age of onset and severity of illness observations are rather diluted by the larger sample populations. The most that can be said when seeing an individual patient is that the younger the onset of mood episodes or the more severe the symptoms, the greater should be the concern for BD. And as to the gender difference, it is complicated by the fact that in BPII patients, depressive episodes are not only significantly more common than hypomanic episodes, but the diagnosis is more prevalent in women than men (Hendrick et al. 2000).

There is a developing literature suggesting that bipolar and unipolar depressive episodes may be differentiated based on nosology. Although DSM-5 diagnostic criteria for major depressive episodes in the context of MDD and BPD are identical, there are selected clinical features that may be observed more often in MDD or BPD. Studies by Mitchell and colleagues found higher rates of atypical symptoms (such as hypersomnia, hyperphagia, and leaden paralysis) as well as psychomotor retardation, greater difficulty with cognition, more early morning awakening, more pronounced worsening of morning mood, and more frequent psychotic symptoms in bipolar depression relative to unipolar depression (Mitchell et al. 2008, 2011). Other researchers have suggested that irritability or "anger attacks" may be a marker of a mixed episode bipolar depression (Perlis et al. 2004a, b; Goodwin and Jamison 2007). Studies also suggest subtle differences between symptom profiles across disorders. For instance, atypical neurovegetative symptoms (hypersomnia and hyperphagia) may be more prevalent in BDII depressive episodes (Benazzi 2003). Another study showed that BDII patients, compared with MDD patients, had more prevalent suicidality and higher levels of psychomotor restlessness and agitation (Hantouche and Akiskal 2005). However, these symptoms may be subtle, and Vöhringer and Perlis (2016) note that clinicians who seek a single rating scale or group of clinical features that reliably distinguish BPD from MDD during the depressive phase of illness are likely to be disappointed.

Thus, only longitudinal follow-up truly allows for reliable diagnosis when individuals present in a depressive episode. For both clinicians and patients, a willingness to recognize that any initial diagnosis is provisional, subject to later reexamination, could help to diminish the rates and consequences of misdiagnosis of these two disorders.

Yet it remains important that MDD and BD be differentiated because there is predictive validity in making the correct diagnosis. The diagnosis conveys important information about the prospective course of the illness and the probable treatment selection/response. In general, MDD responds robustly to traditional antidepressants, whereas BD episodes do not.

3 Effectiveness of Traditional Antidepressants in Bipolar Depression

3.1 Efficacy of Antidepressants as Monotherapy

Most treatment guidelines and consensus statements of the past decade have routinely recommended that antidepressant monotherapy should be avoided in BPI (Pacchiarotti et al. 2013) (Table 1). The reasoning reflects concerns about the possibility of inducing a switch in the mood episode and that antidepressant monotherapy could worsen the course of the mood disorder with more frequent episodes and decreased periods of wellness (see Sect. 4 on Adverse Effects below) (Goldberg and Truman 2003). However, this position does not address whether antidepressant monotherapy is effective. There have been a few studies published that have evaluated efficacy of antidepressant monotherapy in bipolar depression.

Bipolar I Depression Amsterdam and Shults (2005) randomized 34 bipolar depressed patients to either fluoxetine (10–30 mg), olanzapine (5–20 mg), and olanzapine/fluoxetine (5–15 mg/10–40 mg) combination or placebo over an 8-week trial. A significant reduction in depressive symptoms was noted with all active treatments but no difference between treatments. Further, in their study acute treatment trial, there was no evidence of increased treatment-emergent manic symptoms. Unfortunately, this study was very small, representing less than ten patients per treatment arm.

The EMBOLDEN II study (McElroy et al. 2010), evaluating the efficacy of quetiapine in BD, randomized a total of 740 depressed bipolar patients (478 bipolar I, 262 bipolar II) to either monotherapy paroxetine (20 mg), quetiapine (300 or 600 mg), or placebo. After 8 weeks, quetiapine monotherapy was found to be effective in treating depressive symptoms, but there was no significant change in MADRS total score for paroxetine monotherapy compared with placebo. As for the potential switch to mania with monotherapy antidepressant use, there was no difference between paroxetine and placebo (10.7 and 8.9%), though it should be noted that the switch rate was much lower with quetiapine compared with paroxetine and placebo. The author's conclusion was

Table 1 Randomized, placebo-controlled clinical trials of traditional antidepressants used for the acute treatment of bipolar depression

	N	Bipolar type	Treatment arms	Duration (weeks)	Outcome measure	Results
Mendlewicz and Youdim (1980)	58 (34 with BP)	BP (Feighner criteria)	Deprenil + 5-HTP + benzerazide, or 5-HTP + benzerazide, or placebo	5	HDRS	DPL + 5-HTP was more effective than PBO
Himmelhoch et al. (1982)	59 (29 with BP)	DSM-III BPI (10) and BPII (19)	Tranylcypromine or placebo	10	CGI score	TCP more effective than PBO
Cohn et al. (1989)	89	DSM-III BD	Fluoxetine, or imipramine, or placebo Note: Lithium used concomitantly by 25% of sample	6	HADRS	FLX was more effective than IMI, which was more effective than PBO
Nemeroff et al. (2001)	117	DSM-III-R BDI	Imipramine + lithium, or paroxetine + lithium, or placebo + lithium Note: Some patients may also have received carbamazepine or valproate in addition to lithium	10	≤7 HDRS; ≤2 CGI	PXT and IMI augmentation were more effective than PBO at low LI levels; no difference at high LI levels
Tohen et al. (2003)	833	DSM-IV BDI	Olanzapine monotherapy, or olanzapine/fluoxetine combination, or placebo	8	MADRS	OLZ is more effective than PBO; OLZ/FLX is more effective than either OLZ or PBO
Shelton and Stahl (2004)	30	DSM-IV BDI (21) and BDII (9)	MS + paroxetine + placebo, or MS + risperidone + placebo, or MS + paroxetine + risperidone Note: MS could be valproate, lithium, carbamazepine, or topiramate	12	HDRS-17	No significant differences among treatment groups
Amsterdam and Shults (2005)	34	DSM-IV BDI (32) and BDII (2)	Olanzapine monotherapy, or fluoxetine monotherapy, or olanzapine/fluoxetine combination, or placebo	8	HDRS	No significant differences among active treatment groups. All were superior to PBO
Sachs et al. (2007)	366	DSM-IV BDI (240) and BDII (114)	MS + paroxetine, or MS + bupropion, or MS + placebo Note: MS could be lithium, valproate, carbamazepine, or atypical antipsychotic	26	Clinical monitoring form	No significant difference. Nonsignificant trend favored MS + PBO

Yatham et al. (2016)	344	DSM-IV BPI	MS + agomelatine, or MS + placebo Note: MS could be lithium or valproate	8 and 52	MADRS	No significant difference
Ghaemi (2015)	119	DSM-IV BPI (75) and BDII (44)	MS + citalopram, or MS + placebo Note: MS could be lithium, valproate, carbamazepine, antipsychotic, lamotrigine, or a combination of above meds	6	MADRS	No significant difference

FLX fluoxetine, *IMI* imipramine, *LI* lithium, *MS* mood stabilizer, *OLZ* olanzapine, *PBO* placebo, *TCP* tranylcypromine

that although paroxetine monotherapy was not an efficacious treatment, it was not a high-risk acute treatment option (Amit and Weizman 2012).

Bipolar II Depression Traditionally, the potential risk of a hypomanic switch in BPII patients has been estimated to be lower than in BPI patients, but treatment guidelines have not endorsed antidepressant monotherapy due to the same concerns of treatment-emergent hypomania. There are a few published studies that have evaluated the efficacy of traditional antidepressants in BPII.

Amsterdam and Shults (2005) conducted an open-label study examining the response rate of fluoxetine monotherapy (10–80 mg) in 148 BPII depressed patients over 14 weeks. The response rate was 59.5% and the remission rate was 58.1%. Unfortunately 6 patients (4.1%) had treatment-emergent hypomanias (defined as a YMRS score $\geq$8), while 29 patients (19.6%) were noted to have a subsyndromal hypomania (defined as an episode lasting up to 3 days with 4 or more symptoms, or as an episode lasting $\geq$4 days with $\leq$3 symptoms). Despite this, the authors concluded that fluoxetine monotherapy was an effective and relatively safe short-term treatment for BPII depression.

Parker et al. (2006) randomized ten BPII depressed patients to escitalopram monotherapy in a double-blind, placebo-controlled crossover study lasting 9 months. The authors noted that the escitalopram treatment led to a significant reduction in depression severity, percentage of days depressed, and percentage of days impaired when compared with placebo. Further, they noted no indication that the SSRI led to a worsening of illness course.

Amsterdam and Shults (2008) randomized 83 BPII depressed patients to a 12-week open-label trial of either venlafaxine monotherapy or lithium monotherapy. Thirty-four venlafaxine-treated patients (79.1%) completed the trial, but only 15 of the lithium-treated patients (37.5%) did so ($P < 0.0005$). Venlafaxine monotherapy had both a greater reduction in HAM-D 28 scores (−6.57 points, 95% CI, −11.97 to −1.18; $p = 0.017$) and a larger proportion of treatment responders (58.1 vs 20.0%; $P < 0.0005$) and treatment remitters (44.2 vs 7.5%; $P < 0.0005$). The authors then switched 17 of the lithium nonresponders to venlafaxine. Results showed venlafaxine produced significantly greater reductions in HAM-D ($P < 0.0005$), CGI/S ($P < 0.0005$), and CGI/C ($P < 0.0005$) scores vs. prior lithium. There was no difference in mean YMRS scores between treatment conditions. In a follow-up study of venlafaxine versus lithium monotherapy in 129 BPII depressed subjects, Lorenzo-Luaces and Amsterdam (2018) reported venlafaxine was superior to lithium in reducing symptoms of depression during acute treatment; however, there were no significant differences between treatments in quality-of-life ratings.

Agosti and Stewart (2007) conducted a post hoc analysis of a double-blind study, which compared the relative efficacy of placebo, imipramine (average dose 250 mg/day), and phenelzine (average dose of 60 mg/day) in depressed outpatients. BPII depressed response rates were 57% for imipramine and 52% for phenelzine, compared with 23% in the placebo arm. No patient developed manic symptoms that required medication discontinuation or mood stabilizer augmentation.

Altshuler et al. (2017) conducted a 16-week, double-blind, multisite comparison study, in which 142 BPII depressed subjects were randomized to receive lithium monotherapy ($N = 49$), sertraline monotherapy ($N = 45$), or combination treatment with lithium and sertraline ($N = 48$). The treatment response rate for the overall sample was 62.7% ($N = 89$), without significant differences between groups.

3.2 Efficacy of Antidepressants as Adjuncts to Mood Stabilizers

Until 2002, all BP expert consensus guidelines recommended using antidepressants as first-line treatment for acute BP depression (Table 1). However, the American Psychiatric Association (APA) guidelines published in 2002 (APA 2002) recommended that lithium or lamotrigine should be first-line treatments and relegated antidepressants to second-line options. The authors expressed concern about the limited data demonstrating antidepressant efficacy and concerns that they may be associated with worsening of illness (Ghaemi et al. 2003).

In 2004, Gijsman et al. (2004) published a meta-analysis of 12 clinical trials in bipolar depression (1,088 patients) using antidepressants (SSRIs, TCAs, MAOIs) primarily as adjuncts to mood stabilizers. The main findings were that antidepressants were more effective than placebo as adjunctive therapy in trials up to 10 weeks, and that they did not induce more switching to mania (the rate for antidepressants was 3.8%; rate for placebo was 4.7%).

In a sub-analysis, the authors reviewed the five identified published trials that were placebo-controlled randomized comparisons with various antidepressants for the treatment of acute bipolar depressive episodes. It should be noted that most (about 75%) but not all of the subjects in the trials were also on a mood stabilizer or atypical antipsychotic. The five trials included the following:

1. Tohen et al. (2003) conducted a large registration study ($n = 456$) comparing olanzapine/fluoxetine combination ($n = 86$ at 6/25 mg, 6/50 mg, or 12/50 mg doses) or olanzapine monotherapy ($n = 370$ at 5–20 mg doses) with placebo ($n = 377$). Results showed that the olanzapine/fluoxetine combination was significantly better than olanzapine monotherapy, which was significantly better than placebo for treatment response. Remission criteria were met by 24.5% (87/355) of the placebo group, 32.8% (115/351) of the olanzapine group, and 48.8% (40/82) of the olanzapine-fluoxetine group. Treatment-emergent manic symptoms did not differ among the three groups (about 6% over the 8-week trial).
2. Cohn et al. (1989) evaluated fluoxetine ($n = 30$), imipramine ($n = 30$), or placebo ($n = 29$) in bipolar depression. They reported that 86% of the fluoxetine-treated patients responded (50% improved in HAM-D scores) compared with 57% of the imipramine-treated and 38% of the placebo-treated patients. Of note, only 22 of the 89 subjects were on concomitant lithium.
3. Himmelhoch et al. (1982) evaluated the use of tranylcypromine in anergic depressed patients. In their sample of 59 depressed patients, 10 were BPI and

19 were BPII. They noted that improvement on tranylcypromine after week 1 was greater than that on placebo after week 6.

4. Mendlewicz and Youdim (1980) studied the use of the MAOI L-deprenyl (in combination with L-5-HTP and benzerazide) versus placebo in 58 depressed patients (34 with BPD). They found a significant improvement for the combination therapy compared with placebo.
5. In the fifth trial, Nemeroff et al. (2001) compared the efficacy and safety of imipramine ($n = 39$) or paroxetine ($n = 35$) with placebo ($n = 43$) in the treatment of 117 BP depressed patients on stable doses of lithium. Results showed that there were no significant differences in the Hamilton depression scale or CGI severity of illness scale among the three groups. They did note that among patients with low serum lithium levels (<0.8 meq/l), paroxetine and imipramine were superior to placebo. They concluded that antidepressants may not be useful adjunctive therapy for BP depressed patients with high serum lithium levels, but may be beneficial for patients who cannot tolerate high serum lithium levels or have symptoms that are refractory to the antidepressant effects of lithium.

Gijsman et al. (2004) used these studies to evaluate antidepressant efficacy by clinical response (<50% improvement in HAM-D or MADRS or moderate-to-marked improvement in the CGI scale) and remission (defined as a HDRS ≤7 and a MADRS ≤12). The first four trials included data on clinical response. They calculated that of the 662 total patients (213 assigned to experimental group and 449 assigned to placebo group), there was a significant advantage in achieving response for the group treated with antidepressants compared with placebo (NNT = 4.2; 95% CI = 3.2–6.4). Only two of the studies (Tohen et al. 2003; Nemeroff et al. 2001) included data on remission. They calculated that of the 573 total patients (160 assigned to the experimental group and 413 assigned to the placebo group), there was a significant advantage for the group treated with antidepressants compared with placebo (NNT = 8.4; 95% CI = 4.8–33). Given the limited risk, the authors suggested that SSRIs may be an effective treatment for acute bipolar depression.

This study received a lot of discussion in the literature. Critics noted concerns that the studies included in the analysis were of short duration (4–10 weeks duration) and included a mixture of bipolar patients (including bipolar II depression or mixed episodes), thus potentially underestimating the risk of antidepressant-induced manias or further mood destabilization (Amit and Weizman 2012).

In 2011, Sidor and MacQueen published an updated meta-analysis of antidepressant use as augmentation treatment for acute bipolar depressions. They identified six additional studies that assessed antidepressant use in the acute treatment of bipolar depression that had been published since Gijsman's 2004 analysis. They combined this information with earlier studies for a total of 15 studies that contained 2,373 subjects. Their meta-analysis found that antidepressants were not statistically superior to placebo or mood stabilizers for acute bipolar depression. They also noted that

for studies that had more sensitive criteria to define a mood "switch," antidepressant use had higher rates than placebo or mood stabilizers.

Sidor and MacQueen also conducted a sub-analysis of six studies identified that were double-blind, placebo-controlled comparisons. These included three of the studies identified by Gijsman et al. (2004) (Tohen et al. (2003) study of olanzapine/fluoxetine, Cohn et al. (1989) study of fluoxetine and imipramine, and Nemeroff et al. (2001) study of imipramine and paroxetine), but they excluded two others (Himmelhoch et al. (1982) study of tranylcypromine and Mendlewicz and Youdim (1980) study of L-deprenyl) due to concerns that the studies did not distinguish between unipolar and bipolar patients in the outcome measures. Sidor and MacQueen also included three more recent placebo-controlled trials.

1. Shelton and Stahl (2004) conducted a trial of 30 BPI/BPII depressed patients who were receiving a stable dose of a mood stabilizer. They randomly assigned the patients to 12 weeks of double-blind treatment in one of three arms: risperidone (plus placebo), paroxetine (plus placebo), or risperidone plus paroxetine. All three groups experienced significant reductions in depression ratings from baseline to endpoint; but there were no significant differences between groups. The switch rate into mania or hypomania was very low, with only one patient in the paroxetine plus placebo condition experiencing mild hypomania.
2. In the study by Amsterdam and Shults (2005) (previously discussed in the antidepressant monotherapy section), 32 BPI and 2 BPII MDE patients were randomized to receive double-blind therapy with fluoxetine monotherapy 10–30 mg daily, olanzapine monotherapy 5–20 mg daily, combined therapy with fluoxetine 10–40 mg plus olanzapine 5–15 mg daily, or placebo for up to 8 weeks. There were significant reductions over time in mean HAM-D 28 and MADRS ratings for all treatment groups ($p < 0.006$). However, there were no differences among treatment conditions ($p =$ ns). There was no significant increase in YMRS scores over time in any treatment group. In contrast, there was a significant reduction in the mean YMRS score in the fluoxetine-treated patients over time ($p = 0.008$).
3. Sachs et al. (2007) published results from a clinical trial within the larger National Institute of Mental Health (NIMH) effectiveness study, the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). As part of the trial, the investigators conducted a multicenter, double-blind, randomized, placebo-controlled study of either bupropion or paroxetine as adjuncts to treatment with a mood stabilizer (primarily lithium, valproate, or carbamazepine). 366 BPI and BPII subjects with depression were treated for up to 26 weeks. The primary outcome was the percentage of subjects in each treatment group who achieved durable recovery (8 consecutive weeks of euthymia). The authors did not find a significant difference between the groups that received adjunctive antidepressant treatment and the group that received only mood stabilizer plus placebo. 23.5% (42/179) of the subjects who received adjunctive antidepressant therapy to a mood stabilizer achieved durable recovery, while 27.3% (51/187) of subjects treated with mood stabilizer monotherapy achieved durable recovery. Further, the

rates of treatment-emergent mania were similar between the two groups. Overall, the authors concluded that use of adjunctive bupropion or paroxetine to mood stabilizers in bipolar depression was associated with neither increased efficacy nor increased risk of treatment-emergent affective switch.

Of the six double-blind, placebo-controlled clinical trials, four (Tohen et al. 2003; Shelton and Stahl 2004; Amsterdam and Shults 2005; Cohn et al. 1989) supported efficacy for antidepressants in bipolar depression, while two (Nemeroff et al. 2001; Sachs et al. 2007) did not. Sidor and MacQueen (2011) then conducted a meta-analysis of the five placebo-controlled trials that measured clinical response (all studies except Nemeroff et al. 2001). The pooled treatment effect for the 342 subjects treated with antidepressants compared to the 565 subjects treated with placebo revealed a small, but nonsignificant, benefit of antidepressant over placebo (relative risk = 1.18; 95% CI, 0.99–1.40; $p = 0.06$).

Sidor and MacQueen also conducted a meta-analysis the four studies (1,346 subjects) that assessed clinical remission (Tohen, Sachs, Shelton, Nemeroff). Results showed that subjects assigned to antidepressant treatment did not have a significantly better remission rate than those receiving placebo (RR = 1.20; 95% CI, 0.98–1.47; $p = 0.09$).

In 2013, Vázquez et al. (2013) also conducted a meta-analysis of placebo-controlled trials in acute bipolar depression that focused on or included an antidepressant treatment arm. They identified seven trials (with ten different comparison arms) meeting their inclusion criteria. These included five of the studies noted above (Cohn et al. 1989; Nemeroff et al. 2001; Tohen et al. 2003; Shelton and Stahl 2004; Sachs et al. 2007) but also included two studies that had an antidepressant monotherapy treatment arm (Agosti and Stewart 2007; McElroy et al. 2010) (see description of studies above). Their analysis found superiority of antidepressants over placebo (relative risk = 1.43, 95% CI = 1.11–1.84; $z = 2.76$, $p = 0.006$).

Finally, in 2016, McGirr and colleagues conducted the most recent meta-analysis of placebo-controlled trials in acute bipolar depression focused on second-generation antidepressants. They identified six trials (1,383 patients) for review. These included Nemeroff et al. (2001), Tohen et al. (2003), Shelton and Stahl (2004), and Sachs et al. (2007) as previously reviewed. In addition, they also included two studies completed in 2015.

1. Yatham et al. (2016) examined the efficacy of agomelatine (an antidepressant approved in Europe but not in the United States that has melatonin receptor agonist and 5HT2c receptor antagonist properties) versus placebo as adjuncts to lithium or valproate in bipolar depression. 344 subjects were enrolled for the 8-week trial. No significant differences in the improvement of depressive symptoms were observed between the two groups. Adverse events (including mood switching) were reported to be low and similar in both groups.
2. Ghaemi (2015) conducted a study of 119 BPI and BPII depressed subjects on a traditional mood stabilizer or atypical antipsychotic (or both). Subjects were

randomized to adjunctive citalopram or placebo for 6 weeks. No significant improvement was reported for the citalopram over placebo.

In their meta-analysis of these six studies, McGirr and colleagues found that second-generation antidepressants were associated with a small but significant improvement in clinician-rated depressive symptom scores, but there were no differences in clinical response and remission rates. They further found that there was no increased risk of treatment-emergent mania or hypomania during the acute treatment period. Based on the data, they calculated that adjunctive antidepressants in BP depression have a number needed to treat (NNT) of 15 and number needed to harm (NNH) of 19.

In a commentary on the study, Vieta and Garriga (2016) noted that though the analysis effect size was small, it was significantly affected by the agomelatine trial (Yatham et al. 2016) that had a large placebo response (53%) and increased risk of mood switching. If that trial were excluded from the analysis, it was estimated that the effect size would be larger and the switch rates even further reduced. Overall, they interpreted the data as suggesting that adjunctive antidepressant treatment efficacy is limited (though significant) and the tolerability is good (but risk remains significant).

Two naturalistic studies have evaluated possible predictors of who would respond to antidepressant treatment. Pacchiarotti et al. (2011a, b, c) found that a previous response to antidepressants was a good prognostic indicator of response to current antidepressant treatment. Post et al. (2012) found that a history of frequent antidepressant use in the past and a more severe course of illness were poor prognostic indicators of current antidepressant response.

3.3 Long-Term Use of Antidepressants in Bipolar Disorder

As noted previously, use of traditional antidepressants in bipolar disorder is common (Table 2). This would occur either for the acute treatment of BP depression (as noted above), or as prophylactic/maintenance treatment, or both. While there is no evidence that antidepressants may prevent manic episode relapse, there may be a prophylactic effect on depressive episodes.

Altshuler et al. (2003) followed 84 subjects who had achieved remission from their BP depression with the addition of an antidepressant to an ongoing mood stabilizer over a 1-year period. They found that patients who discontinued antidepressant treatment experienced a shorter latency to depressive relapse ($\chi^2 = 9.63$, $p = 0.002$) and were more likely to relapse (70% compared with 36%). In a later analysis, Altshuler et al. (2009) noted that the patients who had a good response to acute treatment with a mood stabilizer augmented by an antidepressant would probably maintain that response with the same continued treatment over a year's period of time. Patients who achieved only a partial acute antidepressant response were less likely to further improve when the same treatment was sustained.

Table 2 Randomized, placebo-controlled clinical trials of traditional antidepressants used for the long-term treatment of bipolar depression

	N	Bipolar type	Treatment arms	Duration (months)	Outcome measure	Result
Prien et al. (1973)	122 (44 with BP)	MDD and BPI	Imipramine monotherapy, or lithium monotherapy, or placebo	24	New manic or depressive episodes that required hospitalization or other medication intervention	In BP subjects, LI was significantly better at preventing recurrence than IMI or PBO
Quitkin et al. (1981)	75	BPI	Lithium + imipramine, or lithium + placebo	24	New manic or depressive episode	No significant difference between groups
Kane et al. (1982)	22	BPII	Lithium monotherapy, or imipramine monotherapy, or lithium + imipramine, or placebo	19	New manic or depressive episode	LI more effective in preventing relapse of either depression or hypomania in BPII compared to IMI or PBO
Prien et al. (1984)	114	BP	Lithium monotherapy, or imipramine monotherapy, or lithium + imipramine, or placebo	24	New manic or depressive episode, or poor response	LI and the LI/IMI treatments were superior to IMI in preventing manic recurrences and were as effective as IMI in preventing depressive episodes. LI/IMI combination provided no advantage over LI monotherapy
Johnstone et al. (1990)	40 (13 BP)	DSM-III-R BP and MDD	Lithium monotherapy, or lithium + amitriptyline	36	New manic or depressive episode	No significant difference between groups
Amsterdam and Shults (2010a, b)	81	DSM-IV BPII and NOS	Fluoxetine monotherapy, or lithium monotherapy, or placebo	8	New manic or depressive episode	Risk of relapse was significantly lower with FLX compared with LI. No difference in relapse time between LI and PBO
Ghaemi et al. (2010)	70	DSM-IV BPI	MS + continued antidepressant, or	36	Clinical monitoring form	AD continuation trended (but not clinically significant)

		(49) and BPII (21)	MS + discontinued antidepressant			toward less severe depressive symptoms and mildly delayed depressive episode relapse without increased manic symptoms. No benefits in prevalence or severity of new depressive or manic episodes, or overall time in remission, occurred

AD antidepressant, *FLX* fluoxetine, *IMI* imipramine, *LI* lithium, *MS* mood stabilizer, *OLZ* olanzapine, *PBO* placebo

Leverich et al. (2006) followed depressed bipolar patients who had responded to treatment with venlafaxine, bupropion, or sertraline added to standard mood stabilizers for up to 1 year. They found that only 15–25% had no further episodes, though there was no placebo arm for comparison.

Amsterdam and Shults (2010b) examined the safety and efficacy of long-term fluoxetine monotherapy, lithium monotherapy, and placebo therapy in preventing relapse and recurrence of BPII depressive episodes. They randomized 81 patients who had responded to an open-label fluoxetine monotherapy treatment study to receive 50 weeks of monotherapy with fluoxetine, lithium, or placebo. The risk of relapse and the length of time to relapse were significantly better for patients receiving fluoxetine compared with lithium and placebo. There were no differences in hypomanic symptoms among treatment groups.

In contrast, Ghaemi et al. (2010) conducted an antidepressant discontinuation randomization study as part of the STEP-BD program. They found that there was no significant symptomatic benefit, robust depressive episode prevention, or enhanced remission rates for patients who continued on long-term antidepressant treatment, but they did note that patients receiving antidepressants with mood stabilizers tended toward less severe depressive symptoms and mildly delayed depressive episode relapse without an increase in manic symptoms. It should be noted that a rapid cycling course predicted three times more depressive episodes with antidepressant continuation.

There have been a few meta-analyses on the efficacy of long-term antidepressant use in bipolar disorder. Ghaemi et al. (2008) conducted a meta-analysis of seven long-term trials (350 BP patients) that included antidepressants. They found that long-term antidepressant treatment was associated with a statistically significant and moderate reduction in the recurrence of depression compared to control (RR 0.73, 95% CI 0.55–0.97, $p = 0.03$, NNT = 11.1) but with a significant increased risk of mania (RR 1.72, 95% CI 1.23–2.41, $p = 0.002$, NNH = 7). There was no significant difference in new depression for antidepressants with or without mood stabilizers versus mood stabilizers, antidepressant with mood stabilizers versus mood stabilizers alone, and antidepressant versus mood stabilizers (three comparisons, $n = 118$). The authors concluded that compared with giving a mood stabilizer alone, adding an antidepressant yielded neither major protection from depression (RR = 0.84; 95% CI 0.56–1.27; NNT = 16) nor substantial increase in risk of mania (RR = 1.37; 95% CI 0.81–2.33; NNH = 16).

More recently, Liu et al. (2017) reviewed 11 trials with 692 bipolar disorder patients. Their analysis found that antidepressants were superior to placebo in reducing new depressive episodes without increasing the risk of new manic/hypomanic episodes either used as monotherapy or in combination with a mood stabilizer. Further, subgroup analyses suggested that these findings were more powerful for BPII than BPD I. However, the authors also noted that compared with mood stabilizer monotherapy, antidepressant monotherapy significantly increased the risk of affective switch with no improvement in prophylaxis of new depressive episodes. Overall, the authors concluded that long-term antidepressant treatment may reduce

new depressive episodes with no significantly increased risk of treatment-emergent mania/hypomania, particularly in BPII.

In contrast to these findings, Vöhringer et al. (2015) treated 21 BPI and 49 BPII depressed subjects with antidepressants plus mood stabilizers to sustained euthymia for 2 months. They conducted an open randomization to either continue or discontinue the antidepressants, following the patients for up to 3 years. They found that both BPI and BPII depressed patients showed improvement in depressive frequency when antidepressants were continued, but this finding was much stronger in BPI rather than BPII patients.

4 Adverse Events Associated with Traditional Antidepressants in Bipolar Disorder

4.1 Antidepressants and Mood Switching

The potential for antidepressants to induce a mood switch from depression to mania/hypomania has been well recognized since the introduction of tricyclics in the 1950s (Ball and Kiloh 1959; Leyberg and Denmark 1959). However, several questions remain as to their potential harm. These include: What is the exact risk for antidepressant switch? Are all antidepressants equal in their potential to induce mood switching, or do some have greater/less risk? Does the presence of a mood stabilizer decrease the risk of mood switching? Are certain types of bipolar disorder more likely to be associated with mood switching risk? Do antidepressants have the potential to cause increased frequency in mood cycling or worsening of the bipolar course?

The risk for antidepressant-induced switching is unclear. There are several reasons for this. First, because of the nature of BD, assessing causality of mood change to an antidepressant versus other causes (including the unpredictable spontaneous nature of the disease) is complicated (Licht et al. 2008). Second, randomized trials that report the mood switching have used multiple different criteria to define a mood switch (e.g., scale assessed change, investigator assessment, hospital admission) making comparisons difficult to interpret (Fornaro et al. 2018). Further, the term "switching" probably does not fully capture the full range of concerns that include symptom aggravation (from the development of subsyndromal symptoms to full-episode mania switch) or the potential longer-term alterations of episode frequency or amplitude (Berk et al. 2010). Because of this, the recent International Society of Bipolar Disorders' (ISBD) consensus guidelines have recommended using the term "treatment-emergent affective switch" instead of antidepressant-induced switch (Tohen et al. 2009), to emphasize association without implying causality.

Studies reporting switch rates of antidepressant use in bipolar depression have been mixed. Some have found associations (Altshuler et al. 1995; Boerlin et al. 1998; Peet 1994; Prien et al. 1973; Truman et al. 2007; Valentí et al. 2012), while others have not (Angst 1985; Lewis and Winokur 1982; Visser and Van Der Mast

2005). Tondo et al. (2010) conducted a meta-analysis review of 35 studies that included data on mood switching, type of antidepressant used, and the presence of mood stabilizers. They found that overall risk of spontaneous switching in BP depressed patients to hypomania or mania was high (13.8%), but the risk of switching in patients taking antidepressants was only slightly higher (15.3%). Sidor and MacQueen (2011) found pooled switch rates of 8% with either antidepressant or placebo treatment in research clinical trials for bipolar depression, indicating no difference between spontaneous and antidepressant-associated risks. Fornaro et al. (2018) found the cumulative incidence of treatment-emergent mania among an identified 1,316 BP depressed subjects over 20 randomized controlled trials (RCTs) was 11.8%. In the STEP-BD trial, Sachs et al. (2007) reported that in the 6-month double-blind placebo-controlled trial, rates of mood elevations were indistinguishable (10.1% compared with 10.7%) between subjects receiving a mood stabilizer plus an antidepressant (bupropion or paroxetine, $N = 179$) and those receiving a mood stabilizer plus placebo ($N = 197$).

However, these studies should be cautiously interpreted because observation studies consistently find higher levels of manic switching compared with randomized clinical trials. For example, whereas Fornaro et al. (2018) found in their meta-analysis of placebo-controlled clinical trials that only 11.8% had treatment-emergent mania, they noted that the cumulative incidence of treatment-emergent mania among 1929 patients with BD over 12 prospective open studies was 14.4%, while the cumulative incidence of treatment-emergent mania among 4,767 patients with BD over 15 retrospective studies was 30.9%. Allain et al. (2017) have suggested that these disparate findings suggest either randomized clinical trials underestimate mood switching or observational studies overestimate mood switching.

Several meta-analyses reviewed previously have evaluated specific antidepressant-associated switch risk. Peet (1994) reported that the rate of treatment-emergent switch occurred substantially more often with tri- and tetracyclics (11.2%) than with SSRIs (3.7%) or placebo (4.2%). Gijsman et al. (2004) noted in their meta-analysis that with the exception of tri- and tetracyclics and venlafaxine, switching was uncommon. Tondo et al. (2010) noted that though the risk of mood switching was not significantly different in patients on antidepressant from those not taking antidepressants, tri- and tetracyclics carried a higher risk for new mania/hypomania than SSRIs or MAO inhibitors. Finally, Sidor and MacQueen (2011) found that SSRIs and bupropion were not associated with more switching than placebo during short-term treatment, but noted that studies employing sensitive criteria to define switching reported higher switch rates for tri- and tetracyclics and venlafaxine than for SSRIs and bupropion. These studies suggest that tricyclic, tetracyclic, and SNRI antidepressants may have a higher risk of inducing mood switches than most SSRIs (see also Vázquez et al. 2013; Tondo et al. 2010; Post et al. 2006; Vieta et al. 2002).

There is limited evidence about the protective effects mood stabilizers may have in preventing mania/hypomania during treatment with antidepressants. In their comprehensive review, Tondo et al. (2010) found a lack of evidence that treatment with mood stabilizers protects against mood elevation in bipolar patients, with or

without antidepressant co-treatment, but they also cautioned that there is a lack of appropriate controls or randomization with which to make an adequate assessment. In contrast, a more recent study by Viktorin et al. (2014) used the Swedish national registries to identify 3,240 patients with bipolar disorder who started treatment with an antidepressant (2005–2009). Amazingly, they discovered that 35% of the identified bipolar patients were being treated with antidepressant monotherapy. Their analysis determined that the increased risk of treatment-emergent mania was confined to patients on antidepressant monotherapy (2.83, 95% CI = 1.12, 7.19). Patients treated with antidepressants who also were taking a mood stabilizer did not appear to have that risk (0.79, 95% CI = 0.54, 1.15). The limited risk of switching in the mood stabilizer augmented group appeared to further decrease after the first 3 months of treatment.

Clinical experience has noted that the risk of switch may also vary according to bipolar type. Early research suggested that patients with BPII are at lower risk of switching than those with BPI (Himmelhoch et al. 1982; Amsterdam et al. 1998; Parker et al. 2006; Amsterdam and Shults 2010a, b). This finding was supported in a post hoc analysis from the Stanley Foundation Bipolar Network study (Altshuler et al. 2006) and a systematic meta-analysis review of 13 prospective studies (Bond et al. 2008) in BPI and BPII depression.

Factors that may be associated with a higher risk of switching include previous antidepressant-induced mood switching, rapid cycling, younger age of onset, comorbid anxiety or substance use disorders, subsyndromal manic symptoms, and number of previous manic episodes (Gorwood et al. 2016; Scott et al. 2017; see Vázquez et al. 2013 for a more complete discussion). Pacchiarotti et al. (2011a, b, c) found that depressed bipolar patients first exposed to antidepressant monotherapy had higher switch rates and more suicide attempts than those treated with antidepressant/mood stabilizer combinations.

4.2 Antidepressants and Cycle Acceleration

Similarly, there has been concern expressed that antidepressants can accelerate episode frequency or induce rapid cycling in bipolar patients (Licht et al. 2008). This was reported in several case series (Kukopulos et al. 1980; Yildiz and Sachs 2003; Wehr and Goodwin 1979; Azorin et al. 2008). In a prospective longitudinal study, Bauer et al. (2005) compared the frequency and pattern of mood changes between BD patients treated with antidepressants or not. They found that those treated with antidepressants were depressed on twice as many days as those not so treated (29.0% compared with 14.8%). As part of the STEP-BD study, Ghaemi et al. (2010) randomized BP patients recovering from an acute depressive episode to continuing or not continuing antidepressant treatment. They found that a previous rapid cycling course predicted over three times more depressive recurrences with continued antidepressant treatment per year.

4.3 Antidepressants and Suicidal Behaviors

In 2007, the black box warning for antidepressants included recommendations that all persons initiating antidepressant therapy should be monitored closely for the possible development of suicidal ideation and behaviors. At this time, evidence that antidepressants may alter the risk of suicidal behavior in bipolar patients remains uncertain. Two retrospective studies (Yerevanian et al. 2007; Pacchiarotti et al. 2011a, b, c) found more suicidal behaviors in patients receiving antidepressants than in those receiving mood stabilizers with or without antidepressants. However, Leon et al. (2014) reported on a 27-year longitudinal study of antidepressant use in 206 subjects with BPI, 139 with BPII, and 361 with UP. In mixed-effect survival analyses, those with BPI had a significant reduction in risk of suicidal behavior by 54% (HR = 0.46; 95% CI, 0.31–0.69; $t = -3.74$; $P < 0.001$) during periods of antidepressant exposure compared to propensity-matched unexposed intervals. Similarly, the risk was reduced by 35% (HR = 0.65; 95% CI, 0.43–0.99; $t = -2.01$; $P = 0.045$) in BPII. Interestingly, there was no evidence of an increased or decreased risk with antidepressant exposure in unipolar disorder. Similarly, two prospective studies (Bauer et al. 2006; Tondo et al. 2008) of antidepressant use in BD depressed patients did not find evidence of altered risk for suicidal ideation or behaviors.

It should be noted that this association may be more likely to be seen in BD patients with mixed episodes. Three studies (Valentí et al. 2011; Pacchiarotti et al. 2011a, b, c; Baldessarini et al. 2012) have found an association of lifetime mixed episodes and higher rates of antidepressant use with increased risk of suicide behaviors.

5 Conclusions

Traditional antidepressant use in BD continues to be a source of controversy in psychiatry. Overall efficacy data has suggested that there may be a role for traditional antidepressant use in BD depressions but that the effect is not the robust response seen in studies of unipolar depression treatment. Further, the mediocre efficacy data must be weighed against the potential that traditional antidepressants may have for doing harm. Unfortunately, these decisions are being based upon a relative paucity of data compared with need. Given the amount of disability and suffering caused by depressive episodes in bipolar disorder, and the limited amount of placebo-controlled trials in acute bipolar depression (and the even more rare number of trials in longer-term treatment), is it any wonder that practicing psychiatrists are unsure of how to make use of antidepressants? Further, it is believed that the continued high use of traditional antidepressants may be due in part to the limited options, efficacy, and tolerability of other treatments (Fountoulakis 2010), or the need to treat comorbidities (such as anxiety disorders), or perhaps even pressure from patients themselves asking for relief from the symptoms of depression (Vieta 2014).

Even experts in the field struggle to find consensus. Parker et al. (2017) compared 11 expert consensus guidelines generated between 2002 and 2015. They noted that

while there was some consistency on key recommendations, there was also substantial inconsistencies, limiting the generation of any "meta-consensus" model for managing bipolar depression.

In 2013, the International Society of Bipolar Disorders (ISBD) convened a task force of identified experts to review the data and make recommendations on antidepressant use in BD (Pacchiarotti et al. 2013). Their published review noted the striking incongruity between the wide use of antidepressants in clinical practice and the weak evidence base for their efficacy and safety; yet that same limited database also limited the consensus of recommendations. The task force reached a consensus on only 12 statements about the use of antidepressants in bipolar disorder. These are listed in Table 3. Even then, some of the statements were felt to be open to debate. For example, Tundo et al. (2015) conducted a 12-week, open-label clinical trial of 255 mood disorder patients with depression (154 UP, 49 BPI, 52 BPII) treating them using the ISBD guidelines for 12 weeks. They found response and remission rates did not differ significantly among the three groups.

Table 3 Recommendations from the ISBD task force on antidepressant use in bipolar disorder

Acute depression treatment
1. Adjunctive antidepressants may be used for an acute bipolar I or II depressive episode when there is a history of previous positive response to antidepressants
2. Adjunctive antidepressants should be avoided for an acute bipolar I or II depressive episode with two or more concomitant core manic symptoms in the presence of psychomotor agitation or rapid cycling
Maintenance treatment
3. Maintenance treatment with adjunctive antidepressants may be considered if a patient relapses into a depressive episode after stopping antidepressant therapy
Monotherapy
4. Antidepressant monotherapy should be avoided in bipolar I disorder
5. Antidepressant monotherapy should be avoided in bipolar I and II depression with two or more concomitant core manic symptoms
Mood switching
6. Bipolar patients starting antidepressants should be closely monitored for signs of hypomania or mania and increased psychomotor agitation, in which case antidepressants should be discontinued
7. The use of antidepressants should be discouraged if there is a history of past mania, hypomania, or mixed episodes emerging during antidepressant treatment
8. Antidepressant use should be avoided in bipolar patients with a high mood instability (i.e., a high number of episodes) or with a history of rapid cycling
Mixed states
9. Antidepressants should be avoided during manic and depressive episodes with mixed features
10. Antidepressants should be avoided in bipolar patients with predominantly mixed states
11. Previously prescribed antidepressants should be discontinued in patients currently experiencing mixed states
Drug class
12. Adjunctive treatment with norepinephrine-serotonin reuptake inhibitors or tri- and tetracyclics should be considered only after other antidepressants have been tried and should be closely monitored because of an increased risk of mood switch or destabilization

Interestingly, the dropout rate was significantly higher for patients with UP (18.2%) than for patients with BPI (2%) and BPII (7.7%) disorder. When antidepressant safety was reviewed, one patient with BPI depression had a suicide attempt, and antidepressant-emerging mood switch was observed in 2.9% of patients of bipolar patients. The authors concluded that the ISBD guidelines were effective, though they recommended partially modifying ISBD Recommendations 1 and 4, to include potential responders and to improve safety. Obviously, recommendations for antidepressant use in bipolar disorder will continue to require further revisions and clarification in the future as more research allows.

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