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Editorial

Can (or Should) We Treat Depression and Anxiety in Parkinson's Disease Algorithmically?

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Does the presence of comorbid Parkinson's disease (PD) change the management of depression or anxiety? If so, are the differences and the evidence base sufficient enough to support the creation of an algorithmic framework? In this issue of *AJGP*, Pontone and Mills have authored a well-written and extensively referenced Research in Action article[1] that concludes that the answer is 'yes' to each of these questions. Accordingly, they embark on an effort to operationalize care approaches for these common psychiatric symptoms. While some might disagree with their conclusions or the validity of their exercise, what is not up for debate is the profound importance of addressing depression and anxiety in Parkinson's disease—they often cause greater distress and disability[2] than the classically described motor symptoms, and they can present significant clinical challenges that interplay with neurological management, thereby demanding a level of collaborative and interdisciplinary care that can be difficult to achieve.

Despite the formidable challenge that depression and anxiety in the setting of PD can pose to the clinician, psychiatric non-motor symptoms were historically thought to be distinct from the disease process. James Parkinson himself wrote that "the senses and intellects [are] uninjured" in his first accounts of the illness.[3] We now understand that these non-motor symptoms can be as much a part of PD[4] as are the characteristic tremor, festination, and posture first described by the disease's namesake. This is of the utmost importance when considering the management of depression and anxiety in the patient with PD because they first must be differentiated from other similar, but distinct, symptoms or syndromes. For example, apathy is a common syndrome in PD and is difficult to distinguish from depression. Additionally, anergia, slowed movements, sleep

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disturbance, and weight loss are all common both to PD and major depression, and as such, may be (mis)attributed to either. Similarly, exacerbation of anxiety (and sometimes mood) can be caused by periods of insufficient (or supratherapeutic) dopaminergic therapy,[5] with a very different treatment approach required in these cases. Fortunately, Pontone and Mills present several markers to assist in navigating these diagnostic dilemmas, which is a necessary precondition for the proper use of their treatment algorithms.

Before we consider the proposed algorithms themselves, however, it is worth commenting upon the appropriateness of their creation. There is no universally accepted answer as to when it is appropriate to create a treatment algorithm in medicine. Prior literature suggests that any algorithm should rise to the level of 'suitable justification' in its branch points and recommendations.[6] Unfortunately, 'suitable justification' itself lacks a widely agreed-upon definition, and so assessing the unique context of each algorithm is as important as the algorithm itself. That said, within PD, there is a relative lack of studies addressing the management of depression and, in particular, anxiety. Thus, the presented algorithms are based on limited evidence and expert opinion, raising the question of whether they live up to the standard of 'justification' required to support their creation in the first place. While we agree with the authors that the benefits of these algorithms outweigh their downsides, this limited foundation can lead to at least two types of biases.

First, strictly adhering to only the highest levels of evidence in these circumstances can bias toward the few treatments that happen to have been studied. This, in turn, may result in a rigidity that fails to account for patient-specific nuances, such as varying clinical considerations at different stages in the progression of this neurodegenerative illness. For example, the depression algorithm presents tricyclic antidepressant medications (TCAs) as a first-tier option, which may be appropriate given the evidence of their efficacy presented in the article. TCAs have risks, of course, which may be amplified in the setting of a patient with PD who is experiencing cognitive decline or orthostasis. Likewise, the inclusion of benzodiazepine medications in the second tier for the management of anxiety may be unwise for a fall-prone patient. Fortunately, the authors clearly articulate these considerations in their prose, but the nuance may be missed if one reviews only the algorithms themselves.

Just as a limited evidence base can bias towards the few treatments that have been studied with positive results, it also can lead to a second form of bias away from other promising but less studied options. Put another way, the absence of evidence is not evidence of absence.[7] The end result may be that treatments withheld to the second or third tiers in the algorithm might more appropriately be considered earlier. For example, the clinician could consider rTMS treatment for depression sooner than the authors' proposed tier III. As is widely true in PD research, the evidence regarding rTMS antidepressant efficacy in this population is limited; however, the authors include certain antidepressant medications (i.e., bupropion, mirtazapine) in their first tier not because of strong evidence of their efficacy but instead based on the expectation that there is a "class effect." A similar logic could be applied to rTMS, and when one considers the highly favorable risk-benefit profile of rTMS and the frequency with which Parkinsonian patients are unable to tolerate common antidepressant medication side effects (e.g., patients with PD-related cognitive impairment, autonomic dysfunction, or REM sleep behavior disorder), it is worth questioning whether rTMS belongs in the same tier as ECT.

Indeed, the individual patient's disease stage and pathophysiology must be considered for optimal management of psychiatric symptoms in PD. The substantia nigra famously degenerates in PD, but so too does the ventral tegmental area.[8] With this in mind, perhaps it is no surprise that the direct dopamine receptor agonist pramipexole has some of the best data for antidepressant efficacy in PD. Nonetheless, Pontone and Mills reasonably assign it to the second tier given the risk of adverse effects such as inducing impulse control behaviors (ICBs). Interestingly, the trial which demonstrated pramipexole's efficacy published in 2010 did not report a single case of treatment emergent ICBs[9]; psychiatrists should not necessarily shy away from using this medication, especially in coordination with the patient's neurologist. The doses of pramipexole for depression should start lower and go slower than doses used for treating motor symptoms, as the degree of dopaminergic deficiency in the limbic system is unlikely to be the same as that of the motor system—careful calibration is

imperative. The potential effects of this medication on the motor system also must be considered, however, highlighting the complexity that can be involved in clinical management.

This leads us to the next, and perhaps most important, factor in the successful treatment of depression and anxiety in PD. There is simply no replacement for strong collaboration between psychiatry and neurology. As noted above, depression and anxiety can both be affected by the dopaminergic on/off state. Motor symptoms can increase distress or worsen anxiety and depression. Likewise, depression and anxiety can worsen motor symptoms. The relationship is bidirectional, as should be the relationship between psychiatrists and neurologists in the care of these patients. The shared-care relationship is evident even within the presented anxiety and depression algorithms. This is most notable in that three of four 'special cases' for anxiety management identified in the algorithm, all of which occur quite commonly, require the psychiatrist to work directly with the neurologist to address anxiety. Truly, any dopaminergic medication change can be thought of as a psychiatrically relevant medication change, and in the setting of these overlapping symptom clusters, best outcomes usually result from combining the optimization of dopaminergic medications with further targeting of depression and anxiety using treatments in the algorithms. Every effort should be made to coordinate psychiatrist-managed and neurologist-managed medication changes in keeping with the adage of 'one change at a time.' For patients with a deep brain stimulation (DBS) device, the same principles apply both for adjustments to stimulation settings and the decrease in dopaminergic medications that usually follow DBS activation (especially in the case of subthalamic nucleus stimulation), both of which can have an impact on motor and non-motor symptoms. This is an increasingly important consideration as DBS becomes more frequently utilized in the treatment of PD at earlier stages in the disease course.

Notwithstanding the caveats noted above, the authors of this article deserve praise for addressing the challenge of creating a widely usable treatment algorithm for commonly encountered problems that are too often lacking easy clinical solutions. In a perfect world, every patient with PD would be connected to a team of neurologists and psychiatrists with appropriate specialization working in close communication. But, short of that perfect world, articles such as this by Pontone and Mills provide an important resource for clinicians struggling with a complex patient population and surely will serve to improve the care that these patients receive. With recent evidence suggesting that the risk of suicide is increased in the PD population,[10] such help is as timely as ever.

References

1. Pontone GM, Mills KA: Optimal treatment of depression and anxiety in Parkinson's disease. Am J Geriatr Psychiatry 2021; 29:530–540
2. Duncan GW, Khoo TK, Yarnall AJ, et al: Health-related quality of life in early Parkinson's disease: the impact of nonmotor symptoms. Mov Disord 2014; 29:195–202;doi:10.1002/mds.25664
3. Parkinson J: An Essay on the Shaking Palsy. London: Whittingham & Rowland..., for Sherwood, Neely & Jones, 1817
4. Weintraub D, Mamikonyan E: The neuropsychiatry of Parkinson disease: a perfect storm. Am J Geriatr Psychiatry 2019; 27 (9):998–1018;doi:10.1016/j.jagp.2019.03.002
5. Witjas T, Kaphan E, Azulay JP, et al: Nonmotor fluctuations in Parkinson's disease: frequent and disabling. Neurology 2002; 59 (3):408–413;doi:10.1212/wnl.59.3.408
6. Feinstein AR: An analysis of diagnostic reasoning. The construction of clinical algorithms. Yale J Biol Med 1974; 47(1):5–32
7. Altman DG, Bland JM: Absence of evidence is not evidence of absence. BMJ 1995; 311(7003):485;doi:10.1136/bmj.311.7003.485
8. Alberico SL, Cassell MD, Narayanan NS: The vulnerable ventral tegmental area in Parkinson's disease. Basal Ganglia 2015; 5(2-3):51–55;doi:10.1016/j.baga.2015.06.001
9. Barone P, Poewe W, Albrecht S, et al: Pramipexole for the treatment of depressive symptoms in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled trial. Lancet Neurol 2010; 9(6):573–580;doi:10.1016/S1474-4422(10)70106-X
10. Chen Y, Yu S, Hu Y, et al: Risk of suicide among patients with Parkinson disease. JAMA Psychiatry 2021; 78(3):293–301; doi:10.1001/jamapsychiatry.2020.4001