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Treatment in Geriatric Mental Health: Research in Action

Optimal Treatment of Depression and Anxiety in Parkinson's Disease

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ABSTRACT

Depression and anxiety are highly prevalent and have major adverse effects on function and quality of life in Parkinson's disease (PD). Optimal management requires that motor symptoms and psychiatric symptoms be simultaneously addressed. While there is fairly robust evidence for the treatment of motor symptoms, there are no completed randomized controlled trials to guide pharmacological treatment of anxiety in PD and no nonpharmacologic interventions have proven efficacious. Several high-quality trials for depression in PD suggest a number of antidepressants and cognitive behavioral therapy may help, but there is no data on rates of recurrence, comparative efficacy, or augmentation strategies. In order to address the gaps in knowledge, the authors provide a summary of the current evidence for treating depression and anxiety in PD and offer an algorithm that extends beyond the current literature based on clinical experience working in a multidisciplinary specialty center. (Am J Geriatr Psychiatry 2021; 29:530–540)

Highlights

- **What is the primary question addressed by this study?** This article discusses the optimal treatment of anxiety and depression in Parkinson's disease.
- **What is the main finding of this study?** The treatment of anxiety and depression in Parkinson's disease are complicated by overlap with the neurodegenerative process.
- **What is the meaning of the finding?** Collaboration and careful coordination of multidisciplinary care are required to achieve optimal outcomes for anxiety and depression in Parkinson's disease.

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CASE VIGNETTE

Mr. P is a 72-year-old married male with a 7-year history of Parkinson's disease (PD). He had no history of anxiety, major depression, or psychotic illness prior to PD. For the first 6 years he was treated with a combination of the dopamine agonist pramipexole and one tablet of carbidopa-levodopa three times per day. However, he developed an impulse control disorder (hypersexuality) and visual hallucinations last year and pramipexole was tapered off. He is currently treated with carbidopa-levodopa 25/100 mg two tablets 4 times per day. Over the past two months he has stopped attending his current events group and no longer goes to his exercise classes—he often feels too fatigued to participate anyway. He sometimes skips or postpones his appointments with his neurologist, saying, "what's the point they don't have a cure." He denies feeling sad, but feels that he gets less enjoyment out of life and is often frustrated by the things he can no longer do—or that tasks take twice as long—because of PD. During conversations with friends he feels he cannot keep up, feels disengaged, and often responds only after a long pause. He says his appetite is fair, but he is losing weight because he feels full quickly and doesn't "want protein to interfere with the absorption of levodopa." He reports having panic attacks several times per day, characterized by acute onset of anxiety, muscle tension, 'internal' tremor, and feels as if he is panting and cannot take a full breath, prompting two ER visits. After the second ER visit his primary care provider started sertraline 50 mg daily and alprazolam PRN, but the latter caused increased daytime sleepiness and he stopped the former after 2 weeks of therapy without improvement. The episodes continued over the next few months and he was soon taking 2−3 alprazolam per day and found it more difficult to sleep at night due to frequent napping. One day during a particularly bad episode he took two alprazolam and fell over a bedside table when trying to get to the bathroom after napping, breaking his left wrist. While casting his left wrist the orthopedic resident heard him tell his wife that he no longer wanted to live this way, prompting referral to a geriatric psychiatrist.

In the geriatric psychiatrist's office he was noted to be despondent with poor eye contact. His speech was low in volume and he was frequently asked to repeat himself. He was diagnosed with a major depressive disorder and sertraline 50 mg daily was resumed with the instruction that it would be increased by 25 mg every 1−2 weeks as tolerated for an 8-week trial. Alprazolam was stopped and replaced with clonazepam 0.5 mg bedtime. Clonazepam along with a program of sleep hygiene was intended to repair his sleep-wake schedule, reduce the risk of benzodiazepine withdrawal, and provide some relief from anxiety pending response to the primary therapies. Finally, he was asked to keep a journal of his panic attacks noting any triggers or associations with the timing of his PD medications. At his 2-week follow up he was taking sertraline 100 mg daily and clonazepam 0.5 mg bedtime. Although his mood was not significantly better, he was now sleeping through the night. His journal showed that almost all his panic attacks occurred within a half hour of his next dose of levodopa. After consulting with a movement disorder neurologist he was switched from immediate release levodopa to carbidopa and levodopa extended release capsules (Rytary) to provide more continuous dopamine replacement. After several weeks of titration a stable dose of this extended release formulation was established and both his panic attacks and mood improved without further adjustment of sertraline. Upon returning to his geriatric psychiatrist he was tapered off clonazepam without issue.

DISCUSSION

Depression and anxiety are the most prevalent psychiatric symptoms in PD and often have a greater impact on quality of life than the movement symptoms.[1,2] Depression and anxiety have a complex relationship with the disease and while the exact mechanism for this association is unknown, both disturbances occur with increased prevalence across the disease course and when present earlier in life, increase the risk of PD by about 2-fold.[3−5] Depression is now considered a risk factor in the research criteria for prodromal PD.[6] Thus, the potential for depression or anxiety to be an early ("pre-motor") symptom or risk factor of PD complicates our ability to make the etiologic distinction between early life 'idiopathic' depression and anxiety with later development of PD versus mood disorders developing as part of

prodromal PD. Acknowledging this ambiguity, we attempt to provide an approach for management of depression and anxiety in the setting of PD, regardless of this differentiation. Comorbidity between anxiety and depression is higher than that in the general population, yet differential response to treatment and discrete presentation of symptoms suggest they may also be dissociable.[7–9] Historically, efforts to treat psychiatric disorders in PD have been confounded by few or no randomized controlled trials (RCT) upon which to develop evidence-based treatment approaches. This article reviews the pathophysiology and psychopathology of the typical presentation of these disorders in PD using the case vignette as illustration and then summarizes the evidence in the literature for specific treatments. Finally, we provide a clinical algorithm for treating anxiety and depression in PD that extends beyond the current RCT evidence-base using expert opinion and anecdotal experience from movement disorder specialty centers.

Major depression occurs in 17% of PD patients, while depressive symptoms are present in 35%.[10] For many suffering from PD, depression may be the most important determinant of quality of life.[11,12] Depression and PD are often interdependent, with the symptoms of one affecting the course of the other. For instance, a meta-analysis of 2064 early untreated PD patients showed that when controlling for baseline depression, the initiation of dopaminergic therapy was delayed for subjects taking tricyclic antidepressants compared to those not taking antidepressants.[13] Longitudinally and in more advanced disease, after controlling for overall level of motor impairment, depressed PD patients have greater disability in physical activities of daily living, such as eating, dressing, hygiene, speech, walking, when compared to those who are not depressed.[14] Encouragingly, at any point in this 6-year longitudinal study, when depression was treated or remitted spontaneously the asymptomatic formerly depressed patients were phase-shifted to the same higher level of functioning as the never depressed PD patients. The relationship between depression and PD also appears to be bidirectional, such that longer duration of PD or poorly treated motor symptoms predicts the failure of depression to remit with treatment.[15] This relationship suggests a mechanistic overlap between motor symptoms and depression in PD. Therefore, in order to optimize overall quality of life and best function depression must be treated to insure the optimal symptomatic management of PD.

In the non-PD elderly population depressed mood may not be the chief complaint, rather social withdrawal, lack of interest or participation in usual activities, and physical complaints such as fatigue, pain, weight loss, or other suspected but unsubstantiated medical symptoms may be the presenting symptom. Depressed PD patients also present this way, and may fail to distinguish between the distress caused by depression and the motor impairment and disability caused by PD. The result can be misattribution of depression as inadequately treated motor symptoms, such that patients may ask for changes to their motor therapies despite objective assessment consistent with optimal motor function. Conversely, inadequately addressed motor symptoms can exacerbate depression and poor control of motor symptoms is associated with failure of depressive symptoms to remit.[15] However, distinguishing between PD and depressive symptoms can be difficult as there is a substantial amount of overlap and the potential for PD symptoms to mimic and confound accurate diagnosis of a depressive episode (Box 1). To avoid overdiagnosis and overtreatment, we recommend focusing on non-overlapping symptoms such as feeling of inappropriate guilt, worthlessness, hopelessness, and suicidal ideation. These "core" depressive symptoms can also be helpful in differentiating depression from apathy, which also presents with decreased interest and social withdrawal.[16] Anhedonia, most properly described as a reduction in the experience of pleasure, may also distinguish depression from apathy, yet interestingly often fails to improve with antidepressant treatment even when other depressive symptoms respond.

Depression in PD can be effectively treated using both pharmacologic and non-pharmacologic interventions. While it is possible that the causal mechanisms and biology of depression in PD are different than those in the general population, the current evidence from RCTs suggests the same therapies, for example, cognitive behavioral therapy, selective serotonin reuptake inhibitors, are often effective and reasonably well-tolerated. However, there are several gaps in the knowledge base for treating depression in PD, such that there is a lack of evidence on comparative efficacy, the use of combined psychotherapy and medication management, noninvasive brain stimulation, and no trials to guide augmentation strategies

Box 1. Parkinson's disease symptoms that could mimic core depressive symptoms in Major Depressive Disorder.

Core depressive symptoms in Major Depressive Disorder	Parkinson's symptoms that may mimic depressive symptoms
Depressed mood	Masked facies, adjustment disorder to diagnosis
Lack of interest of participation in usual activities	PD-related apathy
Weight loss or decrease in or increase in appetite	Wasting of advanced PD, levodopa-induced nausea, dysphagia
Insomnia or hypersomnia	Sleep fragmentation, medication-induced somnolence
Psychomotor agitation or retardation	Levodopa-induced dyskinesia, bradykinesia
Low energy	PD-related fatigue
Diminished ability to think or concentrate	PD-related cognitive impairment with prominent executive deficits
Feelings of inappropriate guilt or worthlessness or hopelessness	Core depressive symptom, no PD mimic
Suicidal ideation or plan	Core depressive symptom, no PD mimic

when monotherapy fails. Despite these limitations, there is a consensus that multidisciplinary care, involving a neurologist and psychiatrist at a minimum, results in the best treatment outcomes.[17–19]

The most frequently used nonpharmacologic interventions currently include psychotherapy, meditation and mindfulness, repetitive transcranial magnetic stimulation (rTMS), and electroconvulsive therapy (ECT). Systematic reviews with meta-analyses and most individual trials have reported evidence of efficacy in RCTs of CBT for depression in PD.[20] Despite this, a 2019 movement disorder society (MDS) review rated cognitive behavioral therapy as only possibly useful in clinical practice and cited evidence suggesting it is likely efficacious but with insufficient evidence for safety.[21] The MDS experts found that most of the CBT trials for PD depression were small, had insufficient adverse outcome reporting, and often had unacceptable bias due to inadequate masking as the placebo condition did not well approximate the CBT intervention. Regardless of how efficacious or safe CBT might be for depression in PD logistical barriers such as lack of insurance parity and poor access to adequately trained CBT therapists often limit its use.[17,22] Currently there is insufficient evidence to recommend other psychotherapies for depression in PD, although a recently published study of a telephone administered CBT offers an alternative that might improve access.[23,24] Several high quality rTMS studies for depression in PD suggest it has acceptable risk and is possibly useful despite insufficient evidence for efficacy and short duration of benefit.[25,26] Case series and reviews suggest that ECT is highly effective for depression and temporarily improves the motor symptoms of PD despite an increased risk of delirium.[27] However, due to a lack of RCT evidence the MDS rates it as investigational in clinical practice due to insufficient evidence of efficacy and safety.[21] Alternative therapies, such as omega 3 fatty acids, mindfulness and meditation, and even psychodrama have been investigated, but have insufficient evidence of efficacy at this time.

A number of high quality RCTs for pharmacologic treatment of depression in PD exist. Based strictly on the evidence from RCTs on efficacy and safety venlafaxine and pramipexole have the best evidence, followed by nortriptyline and desipramine which are likely efficacious. The next tier includes medications which had acceptable safety, but insufficient evidence for efficacy and are thought to be possibly useful in clinical practice, including amitriptyline, citalopram, fluoxetine, paroxetine, and sertraline. Finally, there is a category of medications which lacked evidence of efficacy but had reasonable risk and are considered investigational pending additional study, these include the monoamine oxidase inhibitors rasagaline, selegeline, moclobemide and the norepinephrine reuptake inhibitor atomoxetine. Interestingly, the effect size of MAO-I's on mood outcomes was substantial in studies where depression was not the primary outcome.[28] Evidence for other medications is lacking but case-studies and expert opinion suggest there is likely a "class effect" such that other serotonin reuptake inhibitor (SSRIs), serotonin-norepinephrine reuptake inhibitor (SNRIs), and even the atypicals, mirtazapine and buproprion are likely to produce benefit for treating depression. The quality of evidence in the literature is taken into account in the treatment algorithm provided later in this manuscript.

Anxiety disorders occur in 31% of people with PD.[29] The most prevalent type of anxiety disorders are generalized anxiety, panic disorder, and a category formerly called "anxiety disorder not otherwise specified"—now referred to as "unspecified anxiety disorder" in the DSM 5. At least a third of individuals are diagnosed with more than one type of anxiety disorder, and the unspecified type, which is thought to be associated with PD or its dopaminergic therapy, is the most commonly comorbid disorder when two anxiety syndromes are present in the same individual. Often referred to as fluctuation associated anxiety, the episodes are panic-like and most commonly occur during the transition from on-dopamine medication state to the off-state near or at the end of the dopamine medication cycle.[22,30] Although the association between anxiety and a hypodopaminergic state in the striatum is supported by imaging studies it is likely to be more complex involving disruption of the serotonergic modulation of the amygdala creating an imbalance between dopamine and serotonergic systems.[31–34] Clinically, this complexity is evidenced by the observation that optimizing dopamine replacement therapy does not consistently improve anxiety and treating anxiety with serotonergic medications often results in only partial response. Further, treating anxiety in PD is complicated by a higher rate of side effects when using anxiolytics, chiefly the benzodiazepines which are frequently used first line for anxiety in the general population but carry addition risk when used in PD as they increase the risk of falls, delirium, and cognitive impairment.[35] Despite these obstacles, finding safe and effective ways to treat anxiety in PD is important both for reducing the direct morbidity it causes and because comorbid anxiety impedes improvement of depressive symptoms.[36]

Currently, there are no completed RCTs using pharmacotherapy with anxiety as the primary outcome in PD to inform evidence based practice.[22,37] In the multi-center Study of Antidepressants for Depression in PD (SAD-PD) paroxetine and venlafaxine although more effective than placebo for depression, failed to show any benefit for anxiety on secondary outcome measures.[38] Similarly, an RCT comparing citalopram and desipramine to placebo for depression in PD did not show benefit for anxiety.[39] Despite the lack of direct evidence and the discouraging secondary evidence, the current expert clinical recommendations for treating anxiety in PD are to follow the standard of care applied to the general population, which relies on antidepressants augmented with benzodiazepines.

Nonpharmacologic treatments have better evidence, but none sufficient for the Movement Disorder Society to include as evidence based treatment for anxiety in PD as of their 2019 review. Only a few small CBT studies for anxiety in PD exist and they are either underpowered or lack a control group. The Michael J Fox foundation recently funded a trial of CBT for anxiety in PD which should yield useful information about efficacy and the best way to administer this therapy to anxious PD patients. Mindfulness based stress reduction is another promising therapy for treating anxiety in PD, several pilot studies are ongoing and the preliminary results are encouraging. Noninvasive brain stimulation, rTMS and transcranial direct current stimulation (tDCS) in particular, may offer some benefit for anxiety in PD, but no study so far has had anxiety as a primary outcome. One rTMS study found improvement in treatment resistant depression one day after 10 days of stimulations over the dorsal lateral prefrontal cortex (DLPFC) with benefit lasting up to 30 days.[40] A study comparing left vs right tDCS over the DLPFC found no benefit to anxiety, despite finding improvements in depression.[41]

Deep brain stimulation (DBS), an advanced therapy for the treatment of motor symptoms and motor complications of dopaminergic therapy, requires special consideration as it may have implications for anxiety and depression in PD. Although there is strong evidence for efficacy with regard to motor outcomes and improved quality of life[42] post-DBS mood outcomes are likely more complicated, and potentially mediated by both direct effects of stimulation on subcortical regions with connectivity to limbic networks and the reduction of dopaminergic therapy facilitated by successful surgery. While the impact of DBS on mood in individual studies has been mixed, the largest North American trial of PD patients randomized to DBS versus best medical therapy did not show a difference in Beck Depression Inventory II scores, similarly a multicenter international study using propensity score matching for DBS versus usual therapy also found no difference in depression and anxiety ratings.[42,43] It is worth noting that most DBS clinical programs and studies exclude depressed patients at enrollment, which limits the interpretation of these

findings. Although there has been the suggestion that DBS might be associated with suicide or suicidal ideation this was refuted in an analysis of a randomized controlled trial and instead suicidal ideation is more likely the result of depression and possibly post-DBS dopamine reduction.[44,45] Finally, even when DBS is deemed to be successful based on objective clinical outcomes, for example, improvement in UPDRS motor scores, patients may feel disappointed, particularly when expectations are not appropriately managed preoperatively, and demoralization can trigger depressive episodes. Therefore, preoperative screening and expectation management coupled with increased surveillance for mood and anxiety disturbances following surgery and dopamine medication adjustment is strongly recommended.

In the following section, we offer algorithms for treating anxiety and depression in PD. We use treatments with the best evidence as first tier interventions and then extrapolate beyond this evidence based on our clinical experience in movement disorder specialty settings and the current standard of care for age matched non-PD populations.

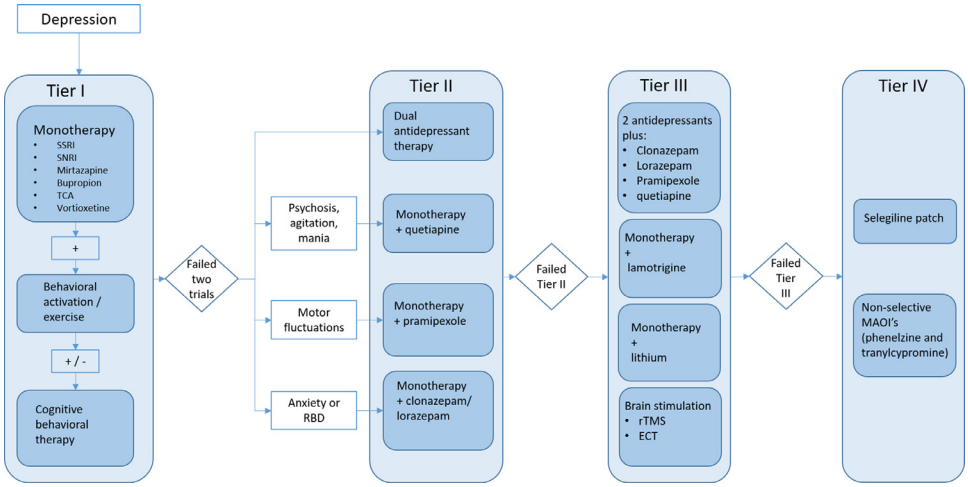
ALGORITHM FOR TREATING DEPRESSION IN PD

Management of any first onset episode of major depression should include a review of medications as some may worsen mood; with the best evidence for this adverse effect coming from, alpha interferon, isotretinoin, certain hormonal treatments, corticosteroids, and VMAT2 inhibitors. Anticholinergics or beta-blockers may be used to treat parkinsonian tremor and could precipitate depressive symptoms. Evaluation for medical comorbidities known to affect mood or approximate depressive symptoms is important as well. Although there is no consensus regarding the specific work up or blood tests, at a minimum we suggest checking a complete blood count, metabolic panel, TSH, B12, and folate. Consider checking a vitamin D level given the increased prevalence of vitamin D deficiency in PD patients and the mixed findings on vitamin D and mood. Always include a cognitive assessment, for example, Montréal cognitive assessment MoCA, as memory impairment, executive dysfunction, and other cognitive impairments may result in underreporting of depressive symptoms and poor compliance with treatment. We strongly recommend forming an alliance with a caregiver as they can assist in making the diagnosis, especially when the patient is poor historian or minimizes symptoms, help with treatment compliance, and provide an extra point of contact which is invaluable in cases when psychosis or suicidal ideation are present.

Once a diagnosis of depression is established assessing the safety of the depressed patient is essential. PD patients are more likely to suffer from suicidal ideation than the general population, but it is unclear whether they attempt or die by suicide more often.[46,47] Regardless, any patient presenting with a depressive episode that includes suicidal ideation should be considered for emergency referral to inpatient care. Although there has been limited research on lethal means in PD suicide, elderly men in general have the highest rate of suicide by firearm and PD is almost 2:1 men to women which suggest screening for firearms is prudent. Currently, aggressively treating depression is thought to be the best intervention to decrease suicide risk.

First line treatment for mild to moderate depression should start with an antidepressant or CBT or both. Currently, there are no comparative efficacy RCTs on which to prioritize one antidepressant over another. However, we recommend starting with one of the best evidence antidepressants from the literature reviewed above and shown in Figure 1. Typically, we start with monotherapy with SNRIs or SSRIs or an atypical like buproprion or mirtazapine. For an extra level of sophistication the savvy physician will consider the idiosyncratic properties of some antidepressants such as the pain relieving properties of SNRIs and tricyclics, the sleep inducing and appetite stimulating properties of mirtazapine, the lack of sexual dysfunction with buproprion, or the potential cognitive benefits of vortioxetine. In addition, be aware that some antidepressants, particularly SSRIs, may cause or worsen tremor, informing patients that this side effect is reversible once the drug is stopped may help improve compliance.[48] Another idiosyncratic consideration of treating depression in PD has to do with the prominence of sleep disturbances and REM sleep behavior disorder (RBD) in PD. Sleep behaviors should be monitored after starting SSRIs and SNRIs as these medications increase the risk of REM sleep without atonia by up to 10-fold in

FIGURE 1. Suggested algorithm for management of depression in Parkinson's disease. SSRI: serotonin reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor; TCA: tricyclic antidepressant; RBD: REM sleep behavior disorder; MAOI: monoamine oxidase inhibitor.



non-PD populations although the impact on risk or frequency of RBD in PD remains uncertain.[49,50]

Once the agent for monotherapy is selected titrate to a minimum effective dose over 2−3 weeks as tolerated by the patient then allow 4−8 weeks for the patient to respond. If the patient fails to respond, increase the dose as tolerated until symptoms improve or the patient reaches the dose ceiling. Within tier I, nortriptyline and desipramine have evidence of efficacy in PD, but they are more lethal in overdose and one must check blood levels, ECG, and watch for orthostatic hypotension, which is often already present from PD itself or dopamine replacement. Therefore, we recommend using tricyclics only after other antidepressants with better safety profiles have been tried. Similarly, because impulse control disorders (ICDs) occur in 14% −17% of people with PD (PwP) on dopamine agonists, we are hesitant to use pramipexole first line for depression before trying other therapies unless there are concurrent motor symptoms that require parallel increases in dopamine replacement therapy.[51] To mitigate the risk of ICDs, the clinician should screen for ICDs especially in younger patients or those with younger age of onset of PD, with a personal or family history of alcoholism, gambling, impulsive or novelty-seeking traits, unmarried, smokers (past or current), and those with mood disorder symptoms who may be at higher risk for ICDs.[51]

At any point, regardless of which antidepressants are used, exercise is probably universally helpful and can improve mood and potentially slow disease progression.[52] Similarly, CBT can be added to augment response and although other forms of psychotherapy may also be useful there is currently no evidence for using them in PD. Clinical discretion is required between tier I and II when a partial response is achieved without remission verses a nonresponse. In the case of nonresponse or equivocal response switching to another agent is likely the dominant strategy. However, a partial response will force the clinician to weigh the risk of polypharmacy using the generally more rapid strategy of augmenting with an additional agent against the delay of switching to an antidepressant from another class. For patients failing to achieve a significant response or remission after two successive single antidepressant trials we recommend moving to an augmentation strategy. No direct evidence exists for combining CBT, antidepressants, or other psychiatric medications for treatment-resistant depression in PD, however, generalizing evidence from non-PD populations, we suggest the approach in Figure 1. Special circumstances such as the presence of psychosis, agitation, motor fluctuations, anxiety, or RBD may be best addressed by the use of augmenting agents that serve a dual purpose. Patients who fail the initial augmentation attempt

may try an additional augmentation strategy in tier II or move to tier III. Strategies in Tier III generally represent a higher risk of potential side effects due to idiosyncratic properties of the medications for example, lithium kidney and thyroid issues, worsens tremor; lamotrigine increased risk of cognitive slowing and falls, or greater polypharmacy, for example, two antidepressants plus an augmenting agent, or the additional risk of delirium and anesthesia exposure with ECT. Interventions can also be considered Tier III when there is insufficient evidence of efficacy despite reasonable safety, for example, TMS. Failing tier III, patients may move to tier IV which is based on evidence in non-PD populations that "atypical depression" sometimes responds to monoamine oxidase inhibitors but we advise caution given the greater risk of Parkinson's-related dysautonomia when using nonselective monoamine oxidase inhibitors.

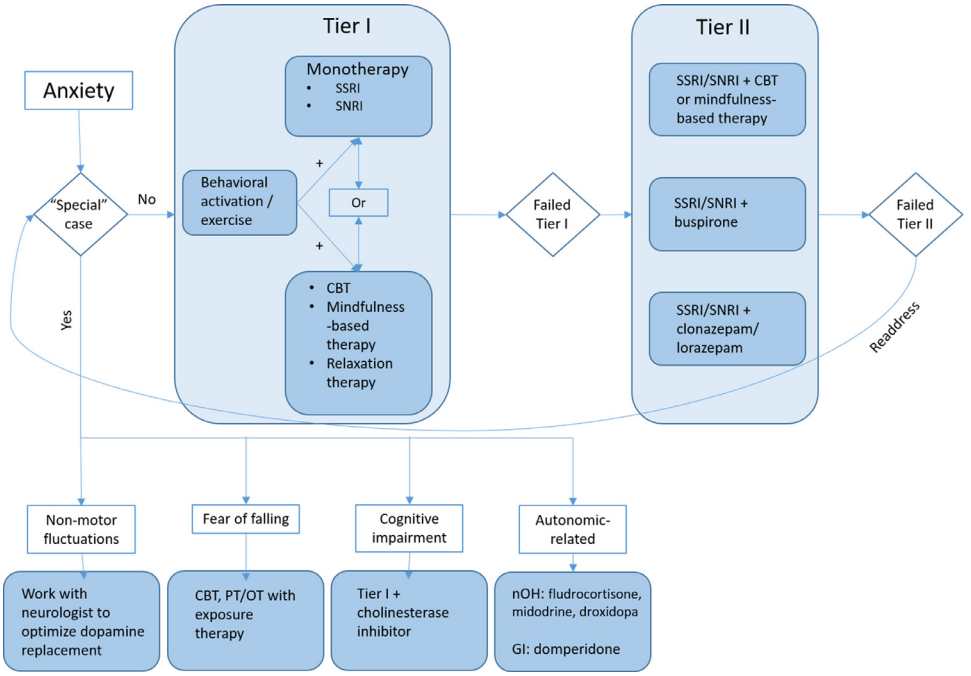
We have found that deciding when to introduce nonpharmacologic interventions has as much to do with access as indication. We generally recommend CBT to any patient who does not experience an expedient and complete remission of depressive symptoms, though the caveats regarding access to CBT can be a barrier, as mentioned above. Similarly, rTMS and ECT are often relegated to specialty treatment centers and are pursued with trepidation by practitioners unfamiliar with PD. In cases of severe depression with and without psychosis ECT may be the treatment of choice despite limited evidence in PD populations. The existing literature on ECT in PD suggests it can be highly efficacious with antidepressant response achieved much faster than with medications combined with a transient improvement in motor symptoms, albeit with an increased risk of delirium.[27] Despite several high quality RCTs rTMS has insufficient evidence of efficacy which combined with its exceedingly transient benefit lead us to relegate its use to cases of patient or clinician preference.

We recommend continuing antidepressant therapy for at least 1 year based on literature in non-PD populations and anecdotal clinical experience. At one year, if not in remission consider continuing treatment or augmenting to improve response. For first depressive episodes in remission after one year consider tapering and stopping antidepressant therapy. For patients with recurrent episodes, but currently in remission, consider extending treatment for an additional year or even chronically as antidepressant therapy may reduce the risk of relapse.[53]

ALGORITHM FOR TREATING ANXIETY IN PD

Up to a third of PwP have what is considered to be unspecified anxiety disorders by DSM 5 criteria. Unspecified anxiety disorders cause clinically significant distress or impairment in function but do not meet full criteria for any of the disorders in the anxiety disorder class, with the most common being anxiety associated with fluctuations in dopamine medication.[22] Due to the high prevalence of unspecified anxiety we recommend using anxiety rating scales to diagnose anxiety in PD. Combining the Parkinson Anxiety Scale with a symptom journal describing any triggers for anxiety including when anxiety occurs in the context of the timing of PD medications will usually capture most clinically relevant anxiety disturbances. Similar to depression, assessment of anxiety in PD can be confounded by overlap with PD symptoms. For instance, autonomic dysfunction occurs in up to 70% of PwP and can cause palpitations, lightheadedness, stomach cramping, sweating, hot flashes, and other paroxysmal symptoms that are often experienced as panic or panic-like attacks.[22,54] Anxiety related to cognitive impairment, particularly PD-associated executive dysfunction is also common and is typically triggered by situations when patients feel overwhelmed due to task demands or feel pressure to perform a task in front of others. Similarly, fear of falling, often considered a type of specific phobia, is even more frequent in PwP than the general elderly and may drastically limit independent daily functioning. Finally, psychosis characterized by paranoia sometimes causes anxiety and requires careful evaluation to distinguish from other anxiety disorders as it requires different management. Given the high prevalence of atypical anxiety syndromes in PD and their potential association with both motor and nonmotor symptoms of the disease, working with the neurologist to achieve optimal control of PD is an essential first step to alleviating anxiety. Comorbidity with cardiovascular disease, chronic pain, diabetes, gastrointestinal problems, hyperthyroidism, and lung disease can also be associated with anxiety and should be addressed.[55]

FIGURE 2. Suggested algorithm for management of anxiety in Parkinson's disease. SSRI: serotonin reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor; CBT: cognitive-behavioral therapy; PT: physical therapy; OT: occupational therapy; nOH: neurogenic orthostatic hypotension; GI: gastrointestinal symptoms.



Once comorbidity has been addressed, the motor and nonmotor symptoms of PD are optimally treated and associations with on-off state, fear of falling, or autonomic symptoms are clarified the next phase of treatment for PD anxiety can begin. Due to the lack of evidence for efficacy in both pharmacologic and non-pharmacologic treatments for anxiety in PD we strongly recommend an approach that prioritizes safety and tolerability in the first tier of treatment (Fig. 2). On-off anxiety should be treated primarily by optimizing motor treatments with the neurologist and should include things like shorter dosing intervals, switch to carbidopa and levodopa extended release capsules (Rytary), add rasagiline, consider augmentation with a dopamine agonist, or some new dopamine formulations (injected or intranasal or transdermal) which address malabsorption issues as possible causes. In special cases with mixed tremor (rest and postural or kinetic) propranolol may help both with tremor and anxiety if it does not worsen or cause orthostatic hypotension. Similarly, in cases when distressing paresthesia is present in addition to anxiety, gabapentin may be considered although direct evidence for efficacy against anxiety in PD is lacking. Anxious patients, in general, require frequent follow up as they worry about side effects and will sometimes abandon medications due to fear and anticipation of side effects if not reassured.

While an article of this kind cannot hope to address the gap in knowledge on comparative efficacy between interventions, it can guide readers on the best strategies for implementation and risk mitigation in PD—essentially focusing more on effectiveness. For instance, the knowledge that the benefit of antidepressant medications, used for depression or anxiety, can be confounded when motor symptoms are not optimally treated is a common and impactful issue in PD. Although the algorithm may not be radically different than existing treatment approaches it highlights that interventions used for motor symptoms, for example, dopamine agonists, may be especially potent for mood in the PD population and that augmentation strategies such as antipsychotics and lithium may not be well tolerated given their outsized risk of adverse events in PD. These issues result in a significant reordering of the standard depression

treatment algorithm in a PD population compared to non-PD populations.

AUTHOR CONTRIBUTIONS

Both authors contributed to the conception and design of the study, drafted the work, approved the final version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

DISCLOSURE

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References

1. Balestrino R, Martinez-Martin P: Neuropsychiatric symptoms, behavioural disorders, and quality of life in Parkinson's disease. J Neurol Sci 2017; 373:173–178;doi:10.1016/j.jns.2016.12.060
2. Kuhlman GD, Flanigan JL, Sperling SA, et al: Predictors of health-related quality of life in Parkinson's disease. Parkinsonism Relat Disord 2019; 65:86–90;doi:10.1016/j.parkreldis.2019.05.009
3. Lin CH, Lin JW, Liu YC, et al: Risk of Parkinson's disease following anxiety disorders: a nationwide population-based cohort study. Eur J Neurol 2015; 22:1280–1287;doi:10.1111/ene.12740
4. Shiba M, Bower JH, Maraganore DM, et al: Anxiety disorders and depressive disorders preceding Parkinson's disease: a case-control study. Mov Disord 2000; 15:669–677, https://doi.org/10.1002/1531-8257(200007)15:4<669::aid-mds1011>3.0.co;2-5
5. Wang S, Mao S, Xiang D, et al: Association between depression and the subsequent risk of Parkinson's disease: a meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry 2018; 86:186–192; doi:10.1016/j.pnpbp.2018.05.025
6. Heinzel S, Berg D, Gasser T, et al: Update of the MDS research criteria for prodromal Parkinson's disease. Mov Disord 2019; 34:1464–1470;doi:10.1002/mds.27802
7. Broen M, Leentjens A, Hinkle JT, et al: Clinical markers of anxiety subtypes in Parkinson disease. J Geriatr Psychiatry Neurol 2018; 31:55–62;doi:10.1177/0891988718757369
8. Sagna A, Gallo JJ, Pontone GM: Systematic review of factors associated with depression and anxiety disorders among older adults with Parkinson's disease. Parkinsonism Relat Disord 2014; 20:708–715;doi:10.1016/j.parkreldis.2014.03.020
9. Wee N, Kandiah N, Acharyya S, et al: Depression and anxiety are comorbid but dissociable in mild Parkinson's disease: a prospective longitudinal study of patterns and predictors. Parkinsonism Relat Disord 2016; 23:50–56;doi:10.1016/j.parkreldis.2015.12.001
10. Reijnders JS, Ehrt U, Weber WE, et al: A systematic review of prevalence studies of depression in Parkinson's disease. Mov Disord 2008; 2:183–313;doi:10.1002/mds.21803
11. Carod-Artal FJ, Ziomkowski S, Mourão Mesquita H, et al: Anxiety and depression: main determinants of health-related quality of life in Brazilian patients with Parkinson's disease. Parkinsonism Relat Disord 2008; 14:102–108;doi:10.1016/j.parkreldis.2007.06.011
12. Müller B, Assmus J, Herlofson K, et al: Importance of motor vs. non-motor symptoms for health-related quality of life in early Parkinson's disease. Parkinsonism Relat Disord 2013; 19:1027–1032;doi:10.1016/j.parkreldis.2013.07.010
13. Paumier KL, Siderowf AD, Auinger P, et al: Tricyclic antidepressants delay the need for dopaminergic therapy in early Parkinson's disease. Mov Disord 2012; 27:880–887;doi:10.1002/mds.24978
14. Pontone GM, Bakker CC, Chen S, et al: The longitudinal impact of depression on disability in Parkinson disease. Int J Geriatr Psychiatry 2016; 31:458–465;doi:10.1002/gps.4350
15. Ravina B, Elm J, Camicioli R, et al: The course of depressive symptoms in early Parkinson's disease. Mov Disord 2009; 24:1306–1311;doi:10.1002/mds.22572
16. Pagonabarraga J, Kulisevsky J, Strafella AP, et al: Apathy in Parkinson's disease: clinical features, neural substrates, diagnosis, and treatment. Lancet Neurol. 2015; 14:518–531;doi:10.1016/S1474-4422(15)00019-8
17. Pontone GM, Dissanayaka N, Dobkin RD, et al: Integration and extension of specialty mental healthcare services to community practice in Parkinson disease. Am J Geriatr Psychiatry 2019; 27:712–719;doi:10.1016/j.jagp.2019.03.005
18. Taylor J, Anderson WS, Brandt J, et al: Neuropsychiatric complications of Parkinson disease treatments: importance of multidisciplinary care. Am J Geriatr Psychiatry 2016; 24:1171–1180; doi:10.1016/j.jagp.2016.08.017
19. Wade DT, Gage H, Owen C, et al: Multidisciplinary rehabilitation for people with Parkinson's disease: a randomised controlled study. J Neurol Neurosurg Psychiatry 2003; 74:158–162; doi:10.1136/jnnp.74.2.158
20. Zhang Q, Yang X, Song H, et al: Cognitive behavioral therapy for depression and anxiety of Parkinson's disease: A systematic review and meta-analysis. Complement Ther Clin Pract 2020; 39:101111;doi:10.1016/j.ctcp.2020.101111
21. Seppi K, Ray Chaudhuri K, Coelho M, et al: Update on treatments for nonmotor symptoms of Parkinson's disease-an evidence-based medicine review. Mov Disord 2019; 34:180–198; doi:10.1002/mds.27602
22. Pontone GM, Dissanayka N, Apostolova L, et al: Report from a multidisciplinary meeting on anxiety as a non-motor manifestation of Parkinson's disease. NPJ Parkinsons Dis 2019; 5:30; doi:10.1038/s41531-019-0102-8
23. Dobkin RD, Mann SL, Gara MA, et al: Telephone-based cognitive behavioral therapy for depression in Parkinson disease: a randomized controlled trial. Neurology 2020; 94:e1764–e1773; doi:10.1212/WNL.0000000000009292
24. Pontone GM, Mills KA: A call for better depression treatment in people with Parkinson disease. Neurology 2020; 94:691–692; doi:10.1212/WNL.0000000000009285
25. Brunoni AR, Chaimani A, Moffa AH, et al: Repetitive transcranial magnetic stimulation for the acute treatment of major depressive episodes: a systematic review with network meta-analysis. JAMA Psychiatry 2017; 74:143–152;doi:10.1001/jamapsychiatry.2016.3644

26. Chen J, He P, Zhang Y, et al: Non-pharmacological treatment for Parkinson disease patients with depression: a meta-analysis of repetitive transcranial magnetic stimulation and cognitive-behavioral treatment [published online ahead of print, 2020 Apr 7]. Int J Neurosci 2020: 1–14;doi:10.1080/00207454.2020.1744591
27. Borisovskaya A, Bryson WC, Buchholz J, et al: Electroconvulsive therapy for depression in Parkinson's disease: systematic review of evidence and recommendations. Neurodegener Dis Manag 2016; 6:161–176;doi:10.2217/nmt-2016-0002
28. Mills KA, Greene MC, Dezube R, et al: Efficacy and tolerability of antidepressants in Parkinson's disease: a systematic review and network meta-analysis. Int J Geriatr Psychiatry 2018; 33:642–651;doi:10.1002/gps.4834
29. Broen MP, Narayen NE, Kuijf ML, et al: Prevalence of anxiety in Parkinson's disease: a systematic review and meta-analysis. Mov Disord 2016; 31:1125–1133;doi:10.1002/mds.26643
30. Pontone GM, Williams JR, Anderson KE, et al: Anxiety and self-perceived health status in Parkinson's disease. Parkinsonism Relat Disord 2011; 17:249–254;doi:10.1016/j.parkreldis.2011.01.005
31. Du CX, Guo Y, Zhang QJ, et al: Involvement of prelimbic 5-HT_7 receptors in the regulation of anxiety-like behaviors in hemiparkinsonian rats. Neurol Res 2018; 40:847–855;doi:10.1080/01616412.2018.1493962
32. Picillo M, Santangelo G, Erro R, et al: Association between dopaminergic dysfunction and anxiety in de novo Parkinson's disease. Parkinsonism Relat Disord 2017; 37:106–110;doi:10.1016/j.parkreldis.2017.02.010
33. Sun YN, Wang T, Wang Y, et al: Activation of 5-HT_1A receptors in the medial subdivision of the central nucleus of the amygdala produces anxiolytic effects in a rat model of Parkinson's disease. Neuropharmacology 2015; 95:181–191; doi:10.1016/j.neuropharm.2015.03.007
34. Sun YN, Yao L, Li LB, et al: Activation and blockade of basolateral amygdala 5-HT_6receptor produce anxiolytic-like behaviors in an experimental model of Parkinson's disease. Neuropharmacology 2018; 137:275–285;doi:10.1016/j.neuropharm.2018.05.016
35. By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel: American Geriatrics Society 2019 Updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2019; 67:674–694;doi:10.1111/jgs.15767
36. Moonen AJ, Wijers A, Leentjens AF, et al: Severity of depression and anxiety are predictors of response to antidepressant treatment in Parkinson's disease. Parkinsonism Relat Disord 2014; 20:644–646;doi:10.1016/j.parkreldis.2014.02.025
37. Pontone GM, Williams JR, Anderson KE, et al: Pharmacologic treatment of anxiety disorders in Parkinson disease. Am J Geriatr Psychiatry 2013; 21:520–528;doi:10.1016/j.jagp.2012.10.023
38. Richard IH, McDermott MP, Kurlan R, et al: A randomized, double-blind, placebo-controlled trial of antidepressants in Parkinson disease. Neurology 2012; 78:1229–1236;doi:10.1212/WNL.0b013e3182516244
39. Menza M, Dobkin RD, Marin H, et al: A controlled trial of antidepressants in patients with Parkinson disease and depression. Neurology 2009; 72:886–892;doi:10.1212/01.wnl.0000336340.89821.b3
40. Pal E, Nagy F, Aschermann Z, Balazs E, et al: The impact of left prefrontal repetitive transcranial magnetic stimulation on depression in Parkinson's disease: a randomized, double-blind, placebo-controlled study. Mov Disord 2010; 25:2311–2317; doi:10.1002/mds.23270
41. Doruk D, Gray Z, Bravo GL, et al: Effects of tDCS on executive function in Parkinson's disease. Neurosci Lett 2014; 582:27–31; doi:10.1016/j.neulet.2014.08.043
42. Weaver FM, Follett K, Stern M, et al: Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. JAMA 2009; 301:63–73;doi:10.1001/jama.2008.929
43. Jost ST, Ray Chaudhuri K, Ashkan K, et al: Subthalamic stimulation improves quality of sleep in Parkinson disease: a 36-month controlled study. J Parkinsons Dis 2020; doi:10.3233/JPD-202278, Advance online publication. https://doi.org/10.3233/JPD-202278
44. Voon V, Krack P, Lang AE, et al: A multicentre study on suicide outcomes following subthalamic stimulation for Parkinson's disease. Brain 2008; 131(Pt 10):2720–2728;doi:10.1093/brain/awn214
45. Weintraub D, Duda JE, Carlson K, et al: Suicide ideation and behaviours after STN and GPi DBS surgery for Parkinson's disease: results from a randomised, controlled trial. J Neurol Neurosurg Psychiatry 2013; 84:1113–1118;doi:10.1136/jnnp-2012-304396
46. Hinkle JT, Perepezko K, Mari Z, et al: Perceived treatment status of fluctuations in Parkinson disease impacts suicidality. Am J Geriatr Psychiatry 2018; 26:700–710;doi:10.1016/j.jagp.2018.01.005
47. Shepard MD, Perepezko K, Broen M, et al: Suicide in Parkinson's disease. J Neurol Neurosurg Psychiatry 2019; 90:822–829; doi:10.1136/jnnp-2018-319815
48. Morgan JC, Kurek JA, Davis JL, et al: Insights into pathophysiology from medication-induced tremor. Tremor Other Hyperkinet Mov (New York, N.Y.) 2017; 7:442;doi:10.7916/D8FJ2V9Q
49. Lee K, Baron K, Soca R, et al: The prevalence and characteristics of REM Sleep without Atonia (RSWA) in patients taking antidepressants. J. Clin Sleep Med 2016; 12:351–355;doi:10.5664/jcsm.5582
50. Kotagal V, Albin RL, Müller ML, et al: Symptoms of rapid eye movement sleep behavior disorder are associated with cholinergic denervation in Parkinson disease. Ann Neurol 2012; 71:560–568;doi:10.1002/ana.22691
51. Weintraub D: Impulse control disorders in Parkinson's disease: a 20-year odyssey. Mov Disord 2019; 34:447–452;doi:10.1002/mds.27668
52. Reynolds GO, Otto MW, Ellis TD, et al: The therapeutic potential of exercise to improve mood, cognition, and sleep in Parkinson's disease. Mov Disord 2016; 31:23–38;doi:10.1002/mds.26484
53. Borges S, Chen YF, Laughren TP, et al: Review of maintenance trials for major depressive disorder: a 25-year perspective from the US Food and Drug Administration. J Clin Psychiatry 2014; 75:205–214;doi:10.4088/JCP.13r08722
54. Berrios GE, Campbell C, Politynska BE: Autonomic failure, depression and anxiety in Parkinson's disease. Br J Psychiatry 1995; 166:789–792;doi:10.1192/bjp.166.6.789
55. Bower ES, Wetherell JL, Mon T, et al: Treating anxiety disorders in older adults: current treatments and future directions. Harv Rev Psychiatry 2015; 23:329–342;doi:10.1097/HRP.0000000000000064