Review

Neurology® Clinical Practice

A practical approach to detection and treatment of depression in Parkinson disease and dementia

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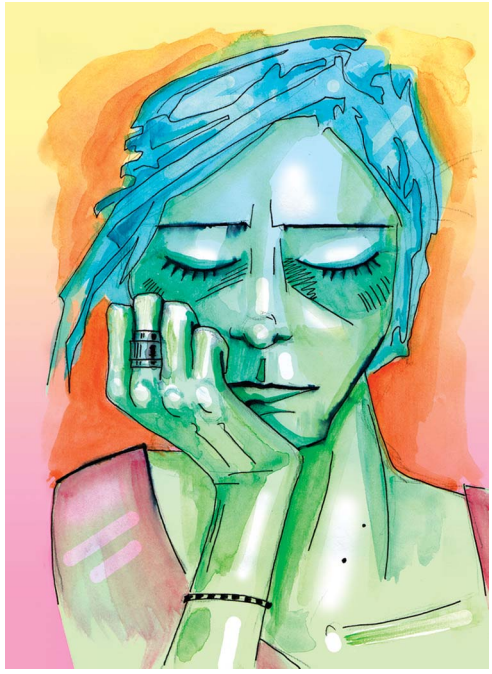
Abstract

Purpose of review: To review the available evidence for the detection and management of depression in Parkinson disease (PD) and dementia. **Recent findings:** Depression is a common comorbidity in those with PD or dementia, and leads to increased morbidity. There are several available and accurate tools for the detection of depression in PD (e.g., Geriatric Depression Scale) and dementia (e.g., Cornell Scale for Depression in Dementia). Treatment of depression depends on patient preference, severity of depression, comorbidities, and available resources. Despite variable evidence, the use of nonpharmacologic strategies to manage depression is suggested. Pharmacologic management is guided by modest evidence in PD and dementia, but also informed by the management of late-life depression (LLD). **Summary:** There is evidence to guide the diagnosis and management of depression in PD or dementia. However, more research is required in this field to better inform clinical decision-making. ***Neurol Clin Pract* 2017;7:128–140**



Depression is common in those experiencing neurodegenerative diseases, such as Parkinson disease (PD) or dementia, and results in poorer patient outcomes.[1,2] Depression is also underdiagnosed and undertreated in these patient populations.[3,4] In PD, depression leads to poor quality of life, cognitive impairment, functional limitations, caregiver burden, less adherence to therapy, and mortality.[5] In addition, depression in PD has been linked to exaggerated motor symptoms and higher disease severity.[6] Thus, comorbid depression represents a target for improving care.[7] Even when diagnosed with depression, just 20% of patients with PD and 18% of patients with dementia receive therapy.[8,9] Assessment is further complicated by evidence suggesting that late-life depression (LLD) may have an overlapping cognitive profile with AD.[10] Depressive symptoms

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in dementia are associated with institutionalization, cognitive decline, mortality, caregiver burden, and greater plaque and tangle burden.[11,12] Similarly, depressive symptoms in mild cognitive impairment (MCI) are associated with greater cognitive impairment and progression to dementia.[13] In addition, depression is commonly associated with other nonmotor or noncognitive symptoms such as anxiety.[14,15] Thus, depression has considerable influence on the risk and course of dementia. While the public health significance of depression alone is profound, as a risk factor and modifying agent in dementia, this is amplified.[2]

Epidemiology

Patients with PD frequently experience symptoms of depression (35%), with 17% of patients experiencing major depression.[16] A recent systematic review and meta-analysis on the prevalence of depression in Alzheimer disease (AD) found significant heterogeneity in estimated rates (5%–48%) based on patient sampling, dementia severity, and diagnostic criteria used.[17] The odds ratio (OR) for depression in patients with dementia compared to those without dementia is 2.64 (95% confidence interval [CI] 2.43–2.86).[18] Depression is even common in MCI, with an omnibus prevalence estimate of 32%,[19] and may herald the progression to dementia.[20]

Detection and diagnosis

Depression is common in neurodegenerative disease and is a marker for greater disease burden and severity.[2] In addition, depression is intimately linked with cognition, especially in older adults.[21] However, being a heterogeneous disease, there is no clear biomarker or gold standard for diagnosis. Depression is a syndrome diagnosed clinically, including cardinal symptoms of depressed mood and anhedonia, and rating scales are often used to assess and screen for depression. Studies have attempted to determine the best tools for diagnosis of depression in neurodegenerative disease, but have generally found poor correlation between rating scales,[21] low sensitivity,[22] or decreased scale performance with greater cognitive impairment,[23,24] in part due to several misfit items in the cognitively impaired.[25] The best evidence in PD supports the use of the Geriatric Depression Scale (GDS-15), at a cutoff of 5 with pooled sensitivity at 0.91, with nonsignificant heterogeneity.[26] In dementia, the Cornell Scale for Depression in Dementia (CSDD) and Hamilton Depression Rating Scale (HDRS) have higher pooled sensitivities than the GDS,[27] with the CSDD having the highest pooled sensitivity at 0.91 at a cutoff of 6.[27] However, it is unclear if depression in neurodegenerative disease is in fact the same thing as major depression as described in current psychiatric nosology.[2] Thus clinical acumen is also required in differentiating and disentangling depressive symptoms from other neurologic symptoms that can manifest in neurodegenerative disease. Apathy or abulia is common in neurodegenerative disease and is often mistaken for depression, but is generally unresponsive to antidepressant treatment.[28] Meta-analyses have shown a prevalence of apathy in PD of 39.8%, and associated with poorer motor function, greater disability, lower cognitive scores, and a 57.2% comorbidity with depression.[29] Thus, special attention is required for comorbid psychiatric symptomatology, as well as the natural history of symptoms to help confirm the clinical significance and etiology of depressive symptoms when they present in neurodegenerative disease.[13]

Treatment

Both nonpharmacologic and pharmacologic therapies are available for depression in PD and dementia; however, there is a lack of consensus in the evidence for some therapies due to a lack of high-quality evidence.[5,30,31]

Nonpharmacologic therapy

A randomized control trial (RCT) of 80 patients with PD and depression examined cognitive-behavioral therapy (CBT) vs monitoring, and found a decrease in HDRS scores by 7.35 at 10 weeks ($p < 0.0001$) with a number needed to treat of 2.1.[32] The results of a systematic review

found this trial examining CBT, caregiver, and behavior intervention[32] had a higher effect size at 1.57 vs pooled effect for 8 antidepressant trials at 0.69.[30]

A systematic review identified 12 studies looking at CBT or psychodynamic therapy for depression in PD.[33] For the studies (n = 10) that used the HDRS, there was improvement with brief psychotherapy over controls (standard mean difference [SMD] −1.45 [95% CI −2.00 to −0.91]); however, there was high heterogeneity in this estimate (I^2 = 91%, p < 0.00001).[33] There were 2 studies that demonstrated an improvement in cognition on the Montreal Cognitive Assessment (SMD 0.52; 95% CI 0.15–0.88; I^2 = 0%, p = 0.99).[33] Psychodynamic therapy had a larger effect than CBT (SMD −2.02; 95% CI −1.66 to −2.99; I^2 = 93%, p < 0.00001); however, this estimate was potentially skewed due to a small study with large effect.[33]

Other interventions such as group therapy, group psychodrama, education, and multidisciplinary rehabilitation have each demonstrated benefit in single studies.[30,34] Exercise, although effective for other symptoms, has not consistently shown benefit for mood across 4 studies.[35]

Four guidelines review nonpharmacologic management for depression in dementia.[36] These list several interventions such as caregiver involvement, CBT, exercise, stimulation-oriented therapy, reminiscence, and animal therapy.[36] However, there is a concern that this evidence is based on small, low-quality studies.[36]

Psychosocial interventions (CBT, interpersonal therapy, and counseling) were pooled in a systematic review for depression in dementia, and had a positive effect across 6 RCTs compared to usual treatment (SMD −0.22; 95% CI −0.41 to −0.03; I^2 = 21%, p = 0.28]).[31] Despite this, there was no difference noted in cognition or quality of life.[31]

Several individual trials have found benefit with non-psychotherapy interventions such as pet therapy,[37] light therapy,[38] and group music therapy.[39] A recent systematic review looked at music therapy for anxiety and depression in dementia, identifying 10 studies of low quality (n = 10–100 patients per study) with mixed results.[40] Five studies reported a reduction, 3 found no difference, and 1 identified an increase in depression scores.[40] Of the 4 RCTs that examined exercise therapy for depression in dementia, only one demonstrated a decrease in CSDD scores but not on the HDRS.[41]

It is important to note that these studies examining nonpharmacologic interventions are often small and non-randomized, and thus are usually classified as lower quality.[31] In addition, nonpharmacologic interventions often vary considerably even when they are in the same category.[31] For example, music therapy can encompass listening, playing, or singing; this can be done in varied doses by a multitude of practitioners.[40] These fundamental study differences make comparison difficult and make their application at bedside more difficult. One of the main benefits of the psychological interventions is the minimal risk associated with their use.[31] Generally, these therapies are often limited to patients with mild dementia, although some have been adapted for patients with severe dementia and caregivers.[42,43]

Pharmacologic therapy

Pharmacologic therapy is a common component of depression management; however, there is a lack of consensus about the approach. Eight placebo-controlled RCTs examined pharmacologic treatment for depression or anxiety in PD.[30] When pooled across citalopram,[44] sertraline, desipramine,[44] nortriptyline, paroxetine,[45] and venlafaxine,[45] the SMD for antidepressants vs placebo is 0.69 (95% CI −1.51 to 2.93).[30] However, there was significant heterogeneity associated with the estimate, which resolved when the authors performed subgroup analysis.[46] When selective serotonin reuptake inhibitors (SSRIs) were examined separately, the effect size was moderate (SMD 0.44; 95% CI −1.37 to 2.26).[46] Tricyclic antidepressants (TCAs), however, had a large effect (SMD 1.36; CI 95% 0.19–2.52).[46] Thus, the authors concluded that more studies with larger sample sizes and greater methodologic rigor are needed to improve understanding of the effect of pharmacologic therapy.[5,30] In addition, despite their

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improvement in depressive symptoms, there are major concerns with TCAs given the risk of side effects.[46]

An earlier systematic review found the risk ratio (RR) for response to antidepressants compared to placebo to be 1.36 (95% CI 0.98–1.87) across 5 studies for depression in PD.[5] To demonstrate the effect of risk of bias, a sensitivity analysis found an increase in the RR to 1.41 (95% CI 1.01–1.96) when a study of low methodologic rigor was excluded.[5] This further increased to 1.48 (95% CI 1.05–2.10) when only studies with low risk of bias were included.[5] This points to the importance of methodologic rigor and reducing risk of bias in future studies to ensure their resulting estimates are reliable.[5] Important aspects to improve study quality include larger sample sizes, inclusion of patients with different disease severity, placebo-controlled designs, longer follow-up periods, and comparisons of multiple agents.[5]

Although the evidence is mixed, practitioners are prescribing medications for 22% of patients with depression in PD living at home and 50% living in an institution.[47] These patterns of prescribing show in recent data from a Swedish registry study that SSRIs were most commonly prescribed, followed by mirtazapine for those taking antiparkinsonian medications.[47] However, we were unable to identify any trial looking at mirtazapine for depression in PD.

Outside of traditional pharmaceuticals, there have been few studies examining complementary alternative drugs. In a systematic review discussed above, omega-3 supplements had a large effect, with SMD = 0.92 (95% CI 0.15–1.69); however, this was an open-label trial with few patients (n = 18).[30] When pooled across 10 studies, traditional Chinese medicine (TCM) was found to improve scores on the HDRS (weighted mean difference −4.19 [95% CI −5.14 to −3.14]) when combined with pharmacologic therapy vs pharmacologic therapy alone.[48] The majority of included studies were classified as high risk of bias.[48]

Guidelines recommend considering dopamine agonists and monoamine oxidase inhibitors for depression in PD.[36] A systematic review of 7 studies examined pramipexole (dopamine agonist) for mood, including manufacturer-led RCTs and unpublished data.[49] Pramipexole improved mood (as measured by the Unified Parkinson's Disease Rating Scale [UPDRS]) in 64.7% of patients compared to 43.4% in the placebo group (OR 2.41 [n = 480; 95% CI 1.62–3.58; $p < 0.001$]).[49,50] When looking at those with advanced disease, there was a 2.71 odds of improvement on pramipexole vs placebo (OR 2.71 [95% CI 1.78–4.13; $p < 0.001$]).[49] The concern with this estimate is that no diagnostic criterion was used and UPDRS is not accurate for depression alone nor is it designed to detect changes due to treatment.[49,50] In addition, all trials excluded patients with major depressive disorder (DSM-IV-TR).[49] The largest placebo-controlled RCT (n = 323) was a 12-week study of pramipexole for clinically relevant depressive symptoms (defined as a score ≥5 on GDS-15 and ≥2 on the depression item of the UPDRS) and found a difference in Beck Depression Inventory (BDI) scores of 1.9 ($p < 0.001$) favoring treatment over placebo.[51] What is unclear is whether a change of approximately 2 points represents a clinically meaningful change.[50,51] A recent study looking at rotigotine did not demonstrate improvement in depressive symptoms as measured by the HDRS.[52]

The other nonergot and ergot dopamine agonists have been studied in smaller, mostly non-placebo-controlled studies, demonstrating inconsistent evidence for mood.[50] Along with these concerns, depression is often measured among many neuropsychiatric symptoms in these studies, and is not the primary outcome or measured by gold standard criteria.[50] Conversely,

levodopa has not been shown to be effective.[53] Rasagiline, an MAO-B inhibitor, was studied in a double-blinded placebo-controlled RCT (n = 123), and demonstrated no benefit on the primary outcome (BDI-IA) at 12 weeks.[54] Transcranial magnetic stimulation and electroconvulsive therapy (ECT) have also been demonstrated in a few studies to have an effect in PD with depression.[30,55]

In dementia, 6 trials of pharmacologic therapy (clomipramine, sertraline, fluoxetine, venlafaxine) show a 2.12 odds of response in those with depression on an antidepressant vs those on placebo (OR 2.12 [95% CI 0.95–4.70; $p = 0.07$]) (response rate was defined as either improvement on a global assessment or ≥50% improvement on the HDRS or Montgomery-Åsberg Depression Rating Scale [MÅDRS]).[56] Similarly, there was an OR of 1.97 (95% CI 0.85–4.55; $p = 0.10$) for remission rates (as measured by a score ≤7 on the HDRS, a CSDD score of ≤6, or an "equivalent global rating").[56] The authors concluded that antidepressants had a low adverse event rate, but results were not significant for efficacy.[56] This is in part due to variable methodology and underpowered studies.[56] In fact, these same issues have plagued the study of LLD—older adults require longer trial duration to adequately elicit pharmacotherapeutic effects, there is often greater medical comorbidity, and cognitive impairment results in diagnostic uncertainty.[57]

The Health Technology Assessment Study of the Use of Antidepressants for Depression in Dementia evaluated patients with dementia treated with either sertraline or mirtazapine and found no significant difference in CSDD scores between treatment and placebo at 13 or 39 weeks follow-up (n = 326).[58] There were some typical trial concerns with loss to follow-up, recruitment, and perhaps measurement bias.[58] Safety of these interventions was also assessed with adverse reactions occurring in 46%, 41%, and 26% of the sertraline, mirtazapine, and placebo groups, respectively.[58] The most common reaction with sertraline was gastrointestinal symptoms and drowsiness or sedation with mirtazapine.[58] There was no significant difference between the number of serious adverse reactions between the antidepressant and placebo groups, although more were severe in the antidepressant group.[58] Still, there was no difference in mortality.[58] One key finding was that there were fewer reported neuropsychiatric symptoms, decreased depression scores (not significant), and improved quality of life on one drug (mirtazapine),[58] consistent with emerging data on the role of antidepressants in treating neuropsychiatric symptoms in patients with AD without depression.[59] A small (n = 31) placebo-controlled RCT examining venlafaxine over 6 weeks did not see any significant change in the MÅDRS scores or clinician global impression of change.[60] Overall, there is some evidence regarding the pharmacologic treatment of depression in dementia; however, gaps remain and future studies are needed looking at new agents or approaches.[61]

Cholinesterase inhibitors are suggested as an option in the guidelines for dementia to address behavioral and psychological symptoms of dementia, which can include depression.[36] There are few rigorous trials examining solely the effect of the cholinesterase inhibitors on depression in dementia. One non-placebo-controlled 2007 donepezil study (n = 135) found a significant improvement on the GDS-15 in the depressed group from baseline to 16 weeks by approximately 2 points compared to the nondepressed group.[62] Of the studies that report depression, it is often reported as one of many behavioral outcomes or a change on a neuropsychiatric symptom subscale. These studies have, however, noted benefit of cholinesterase inhibitors for behaviors in dementia.[63] Interestingly, a study looking at MCI found that the use of donepezil in those experiencing depression reduced progression to dementia significantly at 1.7 and 2.2 years compared to placebo and vitamin E; however, donepezil is not approved for use in MCI.[64]

There may be specific cases in which ECT is considered an option.[36] Evidence in this area is largely case study and prospective cohort level evidence.[65] One cohort study examined ECT in those with dementia (n = 31) with both unipolar and bipolar depression (mean of 9 sessions)[65] and found there was a significant decrease in MÅDRS scores by 12.28 points.[65]

While there is modest evidence for pharmacologic management of depression in PD, the evidence in dementia is scant.

Along with this, the authors identified an increase in Mini-Mental State Examination (MMSE) score of 1.62 points; conversely, about half of patients developed delirium and 4 had major side effects (atrial fibrillation, ventricular tachycardia, TIA, or prolonged seizure).[65] A major concern for the use of ECT in patients with dementia is the concern for delirium or worsened cognitive outcomes.[65] This was seen in the most recent cohort, where the authors found that cognition prior to ECT predicted post ECT declines in MMSE scores.[65]

Overall approach

When evaluating patients with PD or dementia, screening for depression should incorporate a validated instrument.[36] Positive screens should trigger a full diagnostic clinical interview based on criteria[26,27] and secondary causes of depression should be investigated (table).[36,66,67] Illness severity and suicide risk assessment help establish the acuity of the treatment plan, and inform the need for specialized mental health services or hospitalization.[36,66] This approach is summarized in figure 1.

In most cases, tailored nonpharmacologic treatment strategies should be considered first-line.[36,58] For patients with PD, the evidence supports using brief psychotherapy and CBT.[31,33] For dementia, use of CBT, interpersonal therapy, and counseling may be useful in the earlier stages when the patient still has the ability to participate and retain the therapy.[31] However, as the disease progresses, other techniques such as increasing pleasurable activities, caregiver involvement, light, music, animal, or stimulation-oriented therapy are recommended.[36] Nonpharmacologic strategies can be used on their own or in conjunction with pharmacologic treatment.

While there is modest evidence for pharmacologic management of depression in PD, the evidence in dementia is scant. Nonetheless, patients with neurodegenerative diseases often experience depression and medication trials are common in order to ameliorate patient suffering. The American Psychiatric Association dementia treatment guidelines state the following: "clinical consensus still supports undertaking one or more trials of an antidepressant to treat clinically significant and persistent depressed mood in patients with dementia because of the increased rates of disability, impaired quality of life, and greater mortality associated with depression."[68] Until more data emerge, pharmacologic approaches are conservative, based on clinical experience, and informed by the above evidence as well as guidelines for the treatment of LLD,[57] which incorporate systematic and algorithmic approaches to management.[69] Consistent with guidelines, the adage of "start low and go slow" applies, with longer treatment trials and greater vigilance for adverse drug reactions, as these are more common in the elderly.[57]

An adapted version of the treatment algorithm for LLD[57] is presented in figure 2. In PD, we suggest the use of newer-generation antidepressants, specifically venlafaxine,[45] citalopram,[44] or mirtazapine[47] first-line, due to the favorable side effect profile over TCAs.[46] Although there is evidence for paroxetine,[45] its use is not recommended due to tolerability issues.[57] There are a few trials that demonstrate the benefit of alternative therapies such as omega-3 or TCM, but more study is needed.[46,48] Dopamine agonists, especially pramipexole, may also be part of the treatment plan; however, the evidence is more limited.[50] Despite evidence being limited in dementia, results show safety for the use of sertraline or mirtazapine monotherapy.[58] Alternatively, other antidepressants used in LLD may be considered, such as citalopram/escitalopram, venlafaxine/desvenlafaxine, bupropion, duloxetine, or vortioxetine.[57] Of note, the best evidence for improvement of cognitive symptoms of depression in older

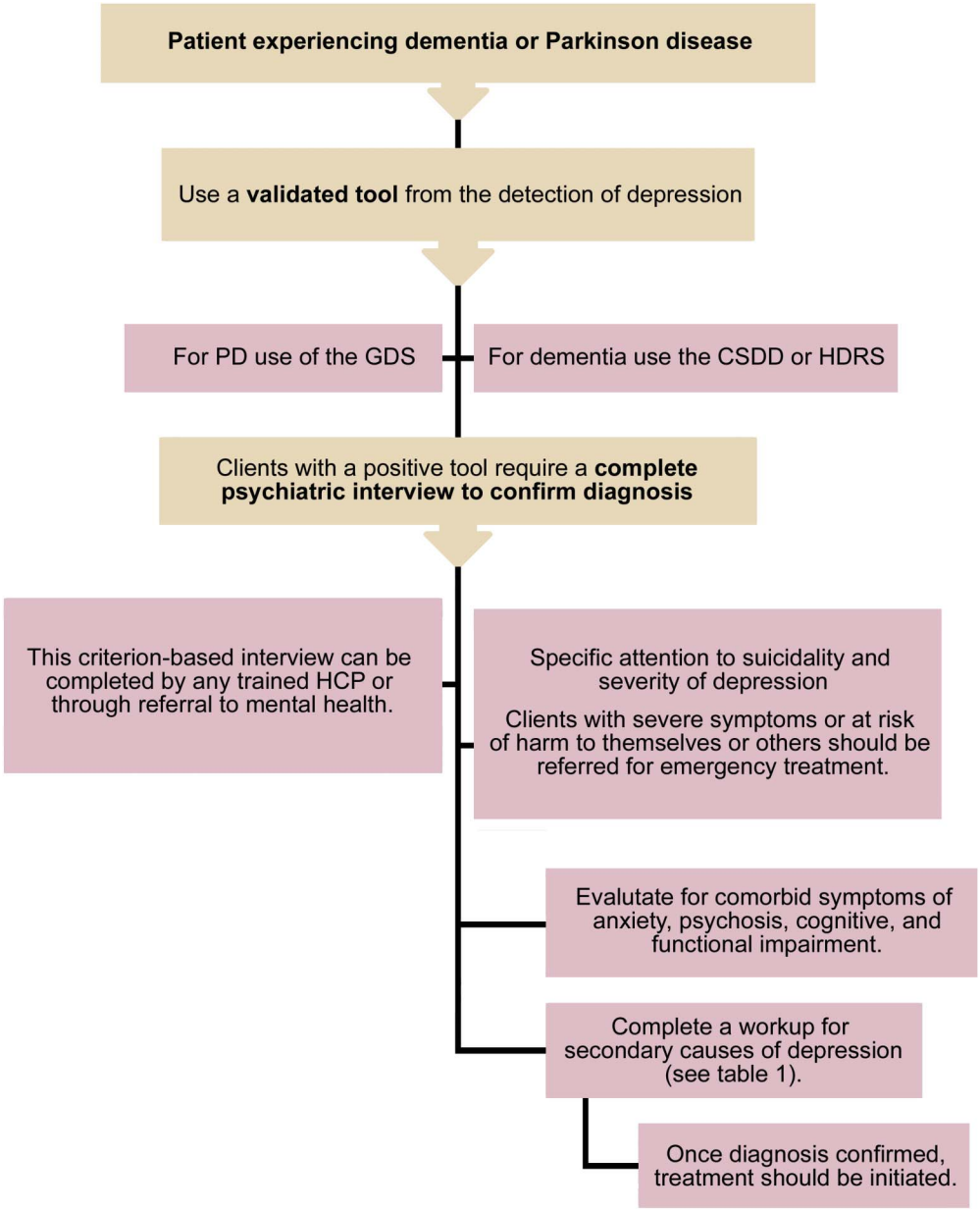
Table Possible secondary causes of depression[66,67]

Causes	Actions
Neurologic disorders	Evaluate history and examine
Parkinson disease	
Dementia	
Stroke	
Prescription medications	Medication review, evaluate chronic pain
β-Blockers	
Calcium channel blockers	
Steroids	
Narcotics	
Benzodiazepines	
Chemotherapy	
Interferon-α	
Immunosuppression	
Endocrine	
Hypothyroidism	Thyroid-stimulating hormone
Hypercalcemia	Calcium + albumin
Diabetes	Evaluate risk, Hgb A1C
Osteoporosis	Evaluate falls and fracture risk
Alcohol or substance use	Evaluate risk and use toxicology screen
Hematologic or rheumatologic	
Anemia	Complete blood count
Chronic inflammation	Evaluate symptoms
Chronic renal failure	Electrolytes, creatinine
Cardiorespiratory	Evaluate symptoms
COPD, OSA, sleep disorders	
CHF	
B_{12} deficiency	B_{12} level
Gastrointestinal	Evaluate symptoms
Inflammatory bowel disease	
Hepatobiliary disease	
Chronic infections	Evaluate risk, evaluate symptoms
HIV, hepatitis, syphilis	
Chronic lung infections	
Malignancy	Evaluate risk and symptoms, consider age-appropriate screening

Abbreviations: CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; OSA = obstructive sleep apnea.

adults is with duloxetine and vortioxetine,[57] whereas citalopram demonstrated a decline in MMSE scores and QTc prolongation in a dementia agitation trial.[59] Alternatively, a cholinesterase inhibitor could be considered, which may also improve behaviors.[62,63] While there is very good evidence for the utility of atypical antipsychotics (alone or as augmenting agents) in

Figure 1 An approach to the initial screening, diagnosis, and workup of depression in Parkinson disease (PD) or dementia



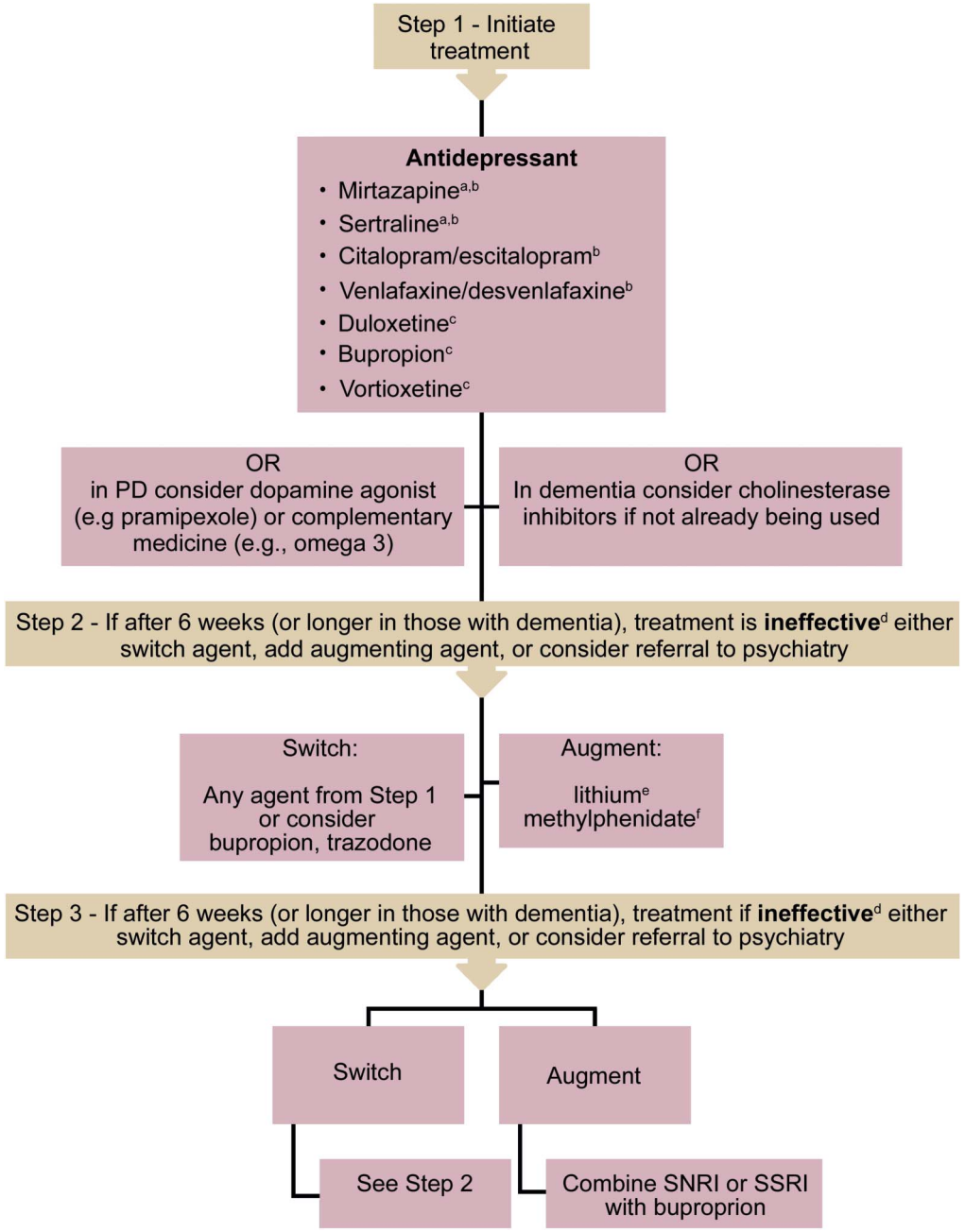
CSDD = Cornell Scale for Depression in Dementia; GDS = Geriatric Depression Scale; HCP = health care provider; HDRS = Hamilton Depression Rating Scale.

treatment of geriatric depression, these agents are not recommended due to the risk of all-cause mortality in dementia, worsened symptoms, and lack of evidence in PD.[36,57] Again, overall conservative approaches should be used considering the best available safety and efficacy evidence, with vigilance for emerging data and newer trials.

DISCUSSION

Given the burden of depression, it is important that there are clear evidence-based strategies for management. Along with this, health care practitioners need to consider the available evidence and their local resources to plan appropriate interventions for these patients. It is clear from the

Figure 2 Treatment algorithm



This algorithm is a suggested approach looking at the available evidence in dementia and Parkinson disease (PD) and the evidence available for prescribing in late-life depression in the 2016 CANMAT guidelines.[57] All of the above drugs have side effects, drug-drug interactions, and drug-disease interactions. When choosing an agent, it is important to be informed of these, and how they apply to the patient. All these concerns need to be discussed with the patient to allow the patient to make an informed decision and express his or her preference. Consider drug initiation at the lowest possible dose, with slow titration. [a]Due to limited evidence in dementia, one must consider agents that do not have robust evidence; however, the results demonstrate safety for the use of sertraline or mirtazapine.[58] [b]In PD, tricyclic antidepressants demonstrated more benefit to mood, but at the risk of worsening motor symptoms.[46] As such, the current recommendation is to consider selective serotonin reuptake inhibitors (SSRIs) or mirtazapine first line.[36,44,45,47] [c]No explicit evidence in dementia or PD, but there is evidence in late-life depression. [d]Prior to changing medication, evaluate for medication adherence, tolerability, and side effects. [e]Augmenting agents should be used with caution; consider expert consultation. Lithium has been shown to have adverse effects and is not recommended in PD.[66] [f]Augmenting agents should be used with caution; consider expert consultation. Methylphenidate is associated with adverse effects, such as agitation in dementia.[70] SNRI = serotonin and norepinephrine reuptake inhibitor.

evidence that there is a gap in our understanding of the treatment of depression in PD and dementia, and higher quality studies are needed. Until that evidence is presented, a conservative adaptation of approaches to manage LLD is recommended.

Take-home points

- *Detection of depression in neurodegenerative disease is facilitated by using both valid rating scales and clinical acumen.*
- *Refer to psychiatry for assessment in atypical or treatment-resistant cases.*
- *Management of depression requires clinicians to consider several factors including patient preferences, illness severity (including suicidality), and comorbidities (both medical and psychiatric).*
- *First-line therapy should include nonpharmacologic treatment (e.g., CBT) if possible.*
- *While additional PD and dementia-specific evidence on pharmacologic therapy of depression is needed, clinicians should inform their choice by the available evidence in LLD.*

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