Panic disorder: A review of treatment options

BACKGROUND: Panic disorder (PD) is a devastating illness, with numerous patients experiencing significant functional disability and many not achieving full remission with first-line pharmacologic and psychotherapeutic treatments.

METHODS: A search of PubMed, Cochrane Library, and PsychINFO databases was used to identify publications focused on evidence-based treatment of PD.

RESULTS: Selective serotonin reuptake inhibitors (SSRIs) and benzodiazepines are standard first-line pharmacologic treatments for PD. Many other antidepressants can be considered as alternatives to SSRIs, including serotonin-norepinephrine reuptake inhibitors, serotonin multimodal agents, tricyclic antidepressants, monoamine oxidase inhibitors, and mirtazapine. Certain anticonvulsants and antipsychotics may be helpful; however, the evidence base is limited. Buspirone, beta blockers, and hydroxyzine can be considered third-line agents. Currently, there is minimal data supporting the use of electroconvulsive therapy or repetitive transcranial magnetic stimulation (rTMS). There is very little evidence justifying the use of medical cannabis or over-the-counter supplements for PD, and these treatments have risk for adverse effects. Research strongly supports the use of cognitive-behavioral therapy (CBT) for PD.

CONCLUSIONS: Many options exist for the management of PD. Treatments with the strongest evidence include SSRIs, other antidepressants, and CBT. Newer interventions approved for the treatment of depression, such as serotonin multimodal agents, esketamine, and rTMS, merit further investigation for use in PD.
INTRODUCTION

Panic disorder (PD) is a devastating illness, associated with much physical and psychiatric comorbidity and significant functional disability. Patients with PD are at increased risk for other anxiety disorders, depression, suicide, substance abuse, and occupational and social impairment.1–7 Panic disorder is also associated with substantially increased medical comorbidity and increased use of health care resources.8–10

Only a minority of patients with PD achieve full, sustained remission of their symptoms with first-line pharmacologic and psychotherapeutic treatment.11–19 Thus, it is important for clinicians who treat PD to be familiar with all available interventions, as well as the evidence base for these options. This review discusses both first-line treatments for PD as well as other interventions that have been studied as possible alternatives or adjuncts to standard first-line treatments.

METHODS

A literature search was conducted for publications about the treatment of PD, using the PubMed, Cochrane Library, and PsychINFO databases. This included a search for original research, review articles, and treatment guidelines published by the American Psychiatric Association (APA) and similar organizations. Of the identified publications, a review of references was conducted to identify additional articles that were not identified in the original search.

RESULTS

Treatment guidelines
The APA has published guidelines on best practices for management of PD, including recommendations on diagnosis, pharmacologic treatment, and nonpharmacologic interventions.20 Other groups have issued treatment guidelines on PD.21–27 Although there are modest differences among the sets of published guidelines, there is much consensus with respect to recommended evidence-based treatments. Unfortunately, because many of these guidelines have not been recently published or updated, they do not include information on the newest findings about PD treatment.

Diagnosis
Before devising a treatment plan, it is essential to verify that the diagnosis of PD is correct. It is also necessary to determine if the patient has any comorbid diagnoses that are not optimally managed and thus could impede resolution of PD symptoms.

According to DSM-5, PD is characterized by recurrent, unexpected panic attacks. This is accompanied by a 1-month period of at least 1 of the following: persistent concern about having additional attacks or their consequences; or a significant maladaptive change in behavior due to the attacks.1 The mere presence of panic attacks does not indicate a diagnosis of PD. Panic attacks can occur with other psychiatric diagnoses, including other anxiety disorders. It is also important to remember that what a patient defines as a “panic attack” may not meet criteria for a panic attack as defined by DSM-5. Depression, bipolar disorder, and substance use disorders are examples of other psychiatric diagnoses that can be associated with elevated states of anxiety.1

Based on the patient’s precise presentation, a reasonable effort should be made to rule out medical causes of their anxiety symptoms. Multiple medical illnesses are associated with episodes of intense physical symptoms that might resemble panic attacks. TABLE 1 provides examples of medical conditions that can cause symptoms resembling panic attacks. Complicating matters further, many of these conditions are often comorbid with PD, which can make it difficult to determine whether paroxysmal panic-like episodes are due to PD or to a coexisting medical problem.12,14

Substance-induced anxiety disorder must also be ruled out. Use of stimulants such as caffeine, cocaine, and
TABLE 2
Medications that can induce anxiety symptoms

<table>
<thead>
<tr>
<th>Psychostimulants</th>
<th>Corticosteroids</th>
<th>Thyroid hormone</th>
<th>Beta agonists</th>
<th>Theophylline</th>
<th>Decongestants</th>
</tr>
</thead>
</table>

amphetamines can cause symptoms that resemble panic attacks. Withdrawal from CNS depressants such as alcohol, benzodiazepines, and barbiturates can also be associated with states of high anxiety.\(^1\),\(^14\) Medications used to treat other physical conditions also can have anxiety as an adverse effect. Common examples of medications that can induce anxiety are listed in TABLE 2.

Panic disorder is also highly comorbid with other psychiatric diagnoses, including other anxiety disorders, mood disorders, personality disorders, and substance use disorders.\(^1\),\(^5\),\(^12\)-\(^14\) Patients must be assessed for these comorbid illnesses, which then need to be treated in conjunction with the PD.

First-line pharmacologic treatments

**Selective serotonin reuptake inhibitors.** According to most guidelines, antidepressants are recommended as a first-line therapy for the treatment of PD; selective serotonin reuptake inhibitors (SSRIs) are consistently recommended as the treatment of choice. There is a strong evidence base supporting the use of SSRIs as a safe and effective treatment for PD.\(^28\)-\(^30\)

**Benzodiazepines** have been widely studied for use in the treatment of PD and are commonly prescribed for panic symptoms.\(^31\),\(^32\) Most guidelines also cite benzodiazepines as a first-line treatment for PD. Per the APA guidelines, benzodiazepines can be prescribed alone or in conjunction with an antidepressant.\(^20\) Among the various published guidelines, there is no definitive consensus on how long a benzodiazepine should be prescribed, the optimal dosage of specific benzodiazepines, and whether it is more appropriate to prescribe the medication on an as-needed basis or as a standing dose. There is no solid evidence as to whether benzodiazepines are more effective than antidepressants for PD, or whether one specific benzodiazepine is superior to another.\(^31\)

Some clinicians may not be inclined to choose benzodiazepines as a first-line treatment because of the great potential for tolerance, dependence, and withdrawal.\(^32\) Given these facts, clinicians need to decide on a case-by-case basis whether an antidepressant, a benzodiazepine, or a combination of the 2 is most appropriate for a given patient.

According to many published recommendations, after a patient has had 2 unsuccessful trials of SSRIs, alternative strategies should be considered. Clinicians can consider 2 broad strategies when a patient with PD has not achieved remission with an SSRI. One is to augment the SSRI with a second medication. This strategy is typically recommended if the patient has received partial benefit from the original antidepressant and is tolerating it well. The other strategy is to switch to a different medication. This strategy is generally advised if the patient has received only minimal benefit from the original antidepressant, or if it is causing intolerable adverse effects.

**Antidepressants other than SSRIs**

**Serotonin-norepinephrine reuptake inhibitors** (SNRIs) are commonly prescribed for major depressive disorder (MDD) and some anxiety disorders. Serotonin-norepinephrine reuptake inhibitors that are currently FDA-approved for MDD include venlafaxine, desvenlafaxine, duloxetine, and levomilnacipran. Among the SNRIs, venlafaxine has good evidence supporting its use for the treatment of PD, and is the only SNRI FDA-approved for this diagnosis.\(^33\)-\(^35\)

**Duloxetine** is FDA-approved for generalized anxiety disorder (GAD), but desvenlafaxine and levomilnacipran have no FDA approval for any anxiety disorders. Although duloxetine, desvenlafaxine, and levomilnacipran do not have PD as an FDA indication, there is a modest evidence base suggesting these SNRIs may provide benefit for this diagnosis.\(^36\)-\(^39\)

**Tricyclic antidepressants** (TCAs) have an efficacy similar to that of SSRIs for the treatment of PD. Some treatment guidelines consider TCAs to be a reasonable alternative to SSRIs as a first-line treatment, although other guidelines consider them to be a second-line intervention. Although TCAs are effective for the treatment of PD, they have the potential for adverse effects such as sedation, weight gain, anticholinergic adverse effects, and cardiac adverse effects. Also, medication interactions with TCAs are common.\(^40\) Thus, this medication class may not be appropriate for patients with certain
comorbid medical conditions or those who are very sensitive to medication adverse effects.

**Monoamine oxidase inhibitors (MAOIs)** are effective agents for MDD; however, evidence for their use in the treatment of PD is limited. Similar to TCAs, MAOIs can be problematic in terms of adverse effects and medication interactions. Patients receiving MAOIs must follow a low-tyramine diet, and many medications must be avoided to prevent serotonin syndrome and hypertensive crisis. For these reasons, MAOIs can be considered a second- or third-line treatment.

**Vilazodone and vortioxetine** are 2 newer antidepressants that resemble SSRIs in some respects, but they have additional pharmacologic activity that SSRIs do not. Vilazodone and vortioxetine are sometimes referred to as serotonin multimodal agents, given their multifaceted mechanisms of action. Similar to SSRIs, vilazodone and vortioxetine inhibit reuptake of serotonin. In addition to inhibiting reuptake of serotonin, vilazodone also is a 5-HT1A partial agonist. The mechanism of action of vortioxetine is more complex, having activity on multiple serotonin receptors.

Both vilazodone and vortioxetine have FDA approval for the treatment of MDD; however, neither are approved for PD or any other anxiety disorder. Because these medications are similar to SSRIs, it can be hypothesized that they could provide benefit for PD. Some results have been published on the use of vilazodone and vortioxetine for anxiety disorders. While studies have shown positive findings, the data is overall quite limited.

**Bupropion** is a reuptake inhibitor of norepinephrine and dopamine. Most treatment guidelines do not recommend bupropion for the treatment of PD, even as a second- or third-line therapy. Published data on bupropion for PD has been minimal, and findings have been mixed at best. Patients may find bupropion activating or stimulating, which they may experience as a worsening of their anxiety.

**Mirtazapine.** The evidence base on the use of mirtazapine for PD is not robust, but a few studies have shown some efficacy. Although mirtazapine does not have FDA approval for PD, most treatment guidelines indicate that it can reasonably be considered a second- or third-line treatment. Adverse effects such as sedation and weight gain can limit its acceptability to patients.

**Ketamine and esketamine.** For many years, ketamine has been used off-label for treatment-resistant depression, with some reports of successful results. Esketamine, a derivative of the anesthetic ketamine, was recently approved for treatment of MDD. Compared with traditional antidepressants, ketamine and esketamine have a unique mechanism of action, as they act on the glutamatergic system, specifically as an N-methyl-D-aspartate (NMDA) antagonist. Unlike traditional antidepressants, these agents have a rapid onset of action (within hours) but brief duration of action (approximately a week). Given the antidepressant effects of ketamine and esketamine, investigators have also looked into possible anti-anxiety effects. Unfortunately, the data on their use for anxiety disorders is scant. The available data consists largely of case reports and small open-label studies. The few published studies focus on ketamine specifically, and none focus exclusively on PD. Ideally, future research will clarify whether esketamine can be considered an effective treatment for PD and other anxiety disorders.

**Non-antidepressants**

Beyond antidepressants, many medications have been studied for their potential effectiveness for PD.

**Buspirone**, a partial agonist at the serotonergic 5-HT1A receptor, has FDA approval only for GAD, although its potential use for other anxiety disorders has been explored. While some researchers have investigated buspirone as monotherapy for PD, most have studied it as an add-on to another agent, such as an SSRI. Despite buspirone’s serotonergic activity, there have not been many positive findings validating its effectiveness for PD. A Cochrane Review of buspirone concluded that its efficacy for PD is uncertain due to lack of quality data. Given these facts, at best buspirone could be considered a third-line agent (as an add-on to an antidepressant) when superior options have been unsuccessful.

**Anticonvulsants.** While anticonvulsants are commonly used for management of bipolar disorder, they have also been studied for use in treatment of anxiety. Three anticonvulsants (valproic acid, gabapentin, and pregabalin) have some evidence suggesting potential usefulness for PD. With respect to other anticonvulsants that are commonly used for treatment of bipolar disorder, including lamotrigine, carbamazepine, oxcarbazepine, and topiramate, there is minimal published data validating their use in PD.

**Valproic acid.** There is a modest evidence base supporting the use of valproic acid for PD. Its antipanic activity is believed to be related to its activity on
gamma-aminobutyric acid (GABA). Valproic acid can be an excellent choice for patients with both PD and bipolar disorder because SSRIs and other antidepressants can cause mood destabilization in patients with bipolar disorder. Most treatment guidelines characterize valproic acid as a second- or third-line agent. This is related to both the modest evidence base and various factors that limit its use (including the need for regular blood monitoring and its complex adverse effects profile).

**Gabapentin and pregabalin** are similar. Their mechanisms of action are complex, but their enhancement of GABergic activity is believed to account for their anti-anxiety properties. Although these 2 medications are sometimes prescribed off-label for anxiety, in the United States there is no FDA approval for use in the treatment of any anxiety disorder. The evidence base for gabapentin and pregabalin for PD is limited (and most published data focuses on the former), consisting mostly of case reports and small open-label studies. These medications can be best characterized as third-line options. There is no firm consensus regarding several aspects of their use for PD, including optimal dose, frequency of dosing, whether to take as a standing dose or as-needed, and whether they should be prescribed as monotherapy or in addition to another medication.

**Lithium**, as well as anticonvulsants, are commonly prescribed for the treatment of bipolar disorder. However, the evidence of lithium for PD is meager. Treatment guidelines do not suggest lithium as a reasonable option for PD. The evidence largely consists of case studies in which lithium was used in conjunction with another agent. No published data supports the use of lithium monotherapy for PD. Beyond these facts, the need for regular laboratory monitoring and risk of numerous adverse effects make it a poor choice for PD.

**Antipsychotics**, in particular second-generation antipsychotics (SGAs), are sometimes used off-label for anxiety; however, none of them have an FDA approval for PD. Because the SGAs vary with respect to mechanism of action and adverse effect profiles, it is difficult to make broad statements about this class as a whole in terms of use for PD. Overall, the evidence validating the use of SGAs for PD is not strong. One systematic review identified and analyzed the results of randomized controlled trials (RCTs) of SGAs for PD. Few RCTs were identified, and the overall results were not promising. The authors concluded that there was insufficient evidence to support the use of SGAs for PD. A 2010 Cochrane Review studied SGAs for use in the treatment of anxiety disorders in general. Unfortunately, no studies on PD met the inclusion criteria. Aside from data suggesting that quetiapine may provide benefit for the treatment of GAD, there was no evidence supporting the use of any other SGA for any other anxiety disorders. Given the relative lack of quality data, SGAs can be best considered a third-line intervention when superior options have been exhausted. There is virtually no data suggesting that first-generation antipsychotics (eg, haloperidol, chlorpromazine) are an appropriate option for PD. Beyond the lack of evidence for benefit, there is significant risk for extrapyramidal side effects.

**Beta blockers**. It has been hypothesized that beta blockers could provide benefit for PD, because they would conceivably interrupt many of the physical manifestations of panic attacks that cause distress, such as tachycardia, palpitations, and tremor. Unfortunately, the findings regarding their use for PD have not been promising. Studies have been small in number and low in quality. Treatment guidelines tend to characterize beta blockers as being a third-line intervention. The data on beta blockers for anxiety is generally not very good. Performance anxiety is the only anxiety-related diagnosis for which there is solid evidence of beta blockers’ effectiveness.

**Hydroxyzine** is an antihistaminergic agent used for many purposes (eg, nausea, pruritis). It does have anti-anxiety properties and is sometimes used for treatment of anxiety disorders. There is modest evidence supporting use of hydroxyzine for GAD specifically; however, not all studies have shown clear benefit. Hydroxyzine has FDA approval for use in GAD, but not for other anxiety disorders. Data on off-label use for PD is minimal. At best, it could be considered a third-line agent.

**Neuromodulation**

Interventions involving neuromodulation such as electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS) are often used for treatment-resistant depression. Thus, there has been interest in learning whether these interventions can be effective for patients with anxiety disorders that do not respond to first-line treatments. As of now, the data are minimal.

**Electroconvulsive therapy**. There are no studies substantiating the use of ECT for a primary diagnosis of PD. There are some documented cases of ECT reducing...
panic symptoms when PD was comorbid with another diagnosis (such as MDD) for which ECT was indicated.\textsuperscript{93-95}

\textbf{Repetitive transcranial magnetic stimulation.}

There is some published data about rTMS providing benefit for anxiety disorders. With respect to PD, a number of cases and small randomized trials have been published.\textsuperscript{96-100} A 2014 Cochrane Review examining rTMS for the treatment of PD concluded that there is insufficient evidence for making specific conclusions.\textsuperscript{100} It was advised that more studies be done, with larger sample sizes. Thus, although rTMS shows promise for PD, more data is needed before it can be recommended as a standard intervention.

\textbf{Cannabis}

The use of cannabis for medical purposes has increased in recent years, which has raised questions as to whether it can provide benefit in the treatment of anxiety. In the United States, some states have approved cannabis for medical use for patients with posttraumatic stress disorder, but none have approved its use for PD or other anxiety-related disorders.\textsuperscript{101-103} Although many patients report subjective improvement in anxiety symptoms with cannabis, data validating its use for anxiety disorders is limited.\textsuperscript{104,105} The evidence is particularly poor regarding potential benefit for PD, and there is considerable data suggesting that cannabis can induce panic symptoms.\textsuperscript{106-110} Many factors complicate clinicians’ ability to make recommendations on the use of cannabis for anxiety disorders. Any given variety of cannabis can contain numerous cannabinoids with multiple psychoactive and physical effects. Cannabinoids have complex effects on both excitatory neurotransmitters such as glutamate and inhibitory neurotransmitters such as GABA.\textsuperscript{103} Thus, how a given patient would respond to cannabis is virtually impossible to predict. In addition, most of the published research on cannabis is about its use for recreational purposes rather than medical purposes, which limits the applicability of that research. Beyond the lack of data supporting the use of cannabis for PD, many documented adverse effects, including physical, psychiatric, and cognitive effects, create strong arguments against its use.\textsuperscript{111-114}

\textbf{Herbals and supplements}

Patients often turn to herbal medications and other over-the-counter (OTC) supplements to manage anxiety symptoms. \textbf{TABLE 3} lists supplements considered to have possible anti-anxiety effects that have been studied for that purpose.\textsuperscript{115-126} While some of these supplements have modest evidence validating their use for other problems (for example, St. John’s wort for depression or valerian for insomnia), almost none of them have data supporting their use specifically for PD. Two double-blind studies have provided positive evidence for use of inositol, a sugar alcohol believed to mediate intracellular second messenger systems, for PD. However, beyond these 2 studies, additional positive evidence is lacking, and some studies of inositol for PD have had negative findings.\textsuperscript{123-126} Other issues must be considered when evaluating OTC supplements. Manufacturers of supplements are not well regulated, and the safety and efficacy of a given product cannot be guaranteed.\textsuperscript{127} Also, patients may be unaware that some of these agents can have significant adverse effects. For example, St. John’s wort may cause significant drug interactions due to activation of cytochrome P450 enzymes,\textsuperscript{128} and kava is associated with liver failure.\textsuperscript{115} For these reasons, OTC supplements cannot be recommended as standard interventions for PD.

\textbf{Cognitive-behavioral therapy}

Psychotherapy is an extremely important component of the treatment of PD. Specifically, cognitive-behavioral therapy (CBT) has a robust evidence base supporting its use for PD.\textsuperscript{129-132} Most published treatment guidelines cite CBT as a first-line intervention for PD. It may be of particular appeal to patients who are reluctant to take medication or who have had difficulty tolerating medication. Patients can receive CBT as an alternative to medication or in combination with medication. Data is mixed as to how much additional benefit combined treatment provides over medication or CBT monotherapy.\textsuperscript{133-135} However, because CBT is a minimal-risk intervention, there is little downside to adding CBT to treatment if
a patient is not achieving remission with medication. The APA guidelines recommend combined CBT and medication for patients with moderate-to-severe PD symptoms, or those not remitting with medication. Cognitive-behavioral therapy also has been shown to be useful in helping patients with PD taper off benzodiazepines. Because weaning off benzodiazepines causes withdrawal that resembles PD symptoms, patients may experience this as a worsening of their PD. This can impede the sustained discontinuation of these medications. Panic Control Treatment for BZ Discontinuation (PCT-BD) uses specific interventions (eg, psychoeducation, interoceptive exposure, and cognitive restructuring with respect to beliefs about panic and withdrawal symptoms) to facilitate the process of weaning off benzodiazepines. Patients treated with PCT-BD were found to experience fewer panic attacks and depressive symptoms, and a greater sense of control over panic compared to patients treated with standard care.

### TABLE 4

**Summary of treatment options for panic disorder**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>Strong evidence base. Considered a first-line treatment. There is a risk for tolerance and dependence.</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Good evidence base. Is the only SNRI that has FDA approval for PD.</td>
</tr>
<tr>
<td>Other SNRIs</td>
<td>A few studies have suggested potential benefit for PD. No SNRI other than venlafaxine has FDA approval for PD.</td>
</tr>
<tr>
<td>TCAs</td>
<td>Strong evidence base. Often considered second-line due to risk for adverse effects and drug interactions.</td>
</tr>
<tr>
<td>MAOIs</td>
<td>Modest evidence base. Use may be limited by risk for adverse effects and drug interactions.</td>
</tr>
<tr>
<td>Serotonin multimodal agents</td>
<td>Hypothesized to have efficacy similar to that of SSRIs. A few studies have shown benefit for anxiety disorders, mostly GAD.</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Most treatment guidelines do not recommend. Data is very limited, and results are mixed at best. May worsen anxiety in some.</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>A few studies have shown benefit, although it does not have FDA approval for PD. Sedation and weight gain can be problematic.</td>
</tr>
<tr>
<td>Ketamine and esketamine</td>
<td>Evidence base is very limited. A few case reports and open-label studies have shown anxiolytic effects of ketamine.</td>
</tr>
<tr>
<td>Buspirone</td>
<td>Although effective for GAD, evidence for PD is very limited. Most research has studied it as an add-on to an antidepressant.</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Modest evidence base. A good option for patients with comorbid bipolar disorder.</td>
</tr>
<tr>
<td>Gabapentin and pregabalin</td>
<td>Data limited to case reports and open-label studies. More data exists for gabapentin than for pregabalin. Can be considered reasonable third-line options.</td>
</tr>
<tr>
<td>Lithium</td>
<td>Not recommended, given poor evidence and challenging adverse-effect profile.</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Limited evidence base supporting use of second-generation antipsychotics; can be considered a third-line option. First-generation antipsychotics are not recommended.</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>Although effective for GAD, very limited evidence for PD. Can be considered a third-line option.</td>
</tr>
<tr>
<td>ECT</td>
<td>May treat comorbid PD when ECT is used for another indication. Otherwise, no evidence supporting use of ECT for PD.</td>
</tr>
<tr>
<td>rTMS</td>
<td>Data is limited, but a few small studies have shown promise.</td>
</tr>
<tr>
<td>Cannabis</td>
<td>Not recommended. Can worsen anxiety; risk for other psychiatric and medical adverse effects.</td>
</tr>
<tr>
<td>OTC supplements</td>
<td>Not recommended. Poorly regulated; risk for adverse effects.</td>
</tr>
</tbody>
</table>

CBT: cognitive-behavioral therapy; ECT: electroconvulsive therapy; GAD: generalized anxiety disorder; MAOIs: monoamine oxidase inhibitors; OTC: over-the-counter; PD: panic disorder; rTMS: repetitive transcranial magnetic stimulation; SNRIs: serotonin-norepinephrine reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors; TCAs: tricyclic antidepressants.
to have a greater success rate in discontinuing benzodiazepines, compared with those not receiving this intervention.\(^\text{140}\) There is also some evidence suggesting that CBT can help manage symptoms when patients with PD are discontinuing use of SSRIs.\(^\text{141}\)

**CONCLUSIONS**

A variety of options are available for management of PD, each with a distinct set of advantages and disadvantages. Table 4 summarizes basic information about all of the treatment options discussed in this review. Selective serotonin reuptake inhibitors, benzodiazepines, and CBT are first-line treatments for PD; all have strong evidence supporting their use. Often these treatments are used in combination, which treatment guidelines generally recommend for patients with severe or treatment-resistant PD. Published treatment recommendations and newer studies have provided guidance on alternative options for patients who do not respond to first-line treatments. Beyond SSRIs, other pharmacologic options to consider include alternative classes of antidepressants, as well as non-antidepressants. Among the non-antidepressants, options include buspirone, valproic acid, gabapentin, pregabalin, SGAs, beta blockers, and hydroxyzine. These interventions are quite varied with respect to mechanism of action, evidence base, and adverse-effect profiles. Presently, lithium, ECT, cannabis, and OTC supplements cannot be recommended as appropriate interventions for PD. Certain treatments approved in recent years for MDD, such as serotonin multimodal agents, esketamine, and rTMS, have shown some promise for the treatment of PD. However, the evidence base for these interventions is still limited, and they cannot yet be recommended as standard treatments for PD. Ideally, future research will clarify whether any of these can considered viable options for PD.

**DISCLOSURE:** The author reports no financial relationships with any companies whose products are mentioned in this article, or with manufacturers of competing products.

### REFERENCES

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