ANNALS OF CLINICAL PSYCHIATRY 2021;33(1):e22-e31 doi: 10.127788/acp.0014

REVIEW ARTICLE

Panic disorder: A review of treatment options

Michael Ziffra, MD
Assistant Professor
Department of Psychiatry
Northwestern University Feinberg School of Medicine
Chicago, Ilinois, USA

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 support 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.

CORRESPONDENCE
Michael Ziffra, MD
Department of Psychiatry
Northwestern University Feinberg School of Medicine
446 E Ontario St, Suite 7-100
Chicago, IL 60611 USA

EMAIL
m-ziffra@northwestern.edu

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.

TABLE 1
Medical conditions that can cause symptoms resembling panic attacks

Asthma and other respiratory disorders
Cardiac disorders
Hyperthyroidism
Hyperparathyroidism
Vertigo
Epilepsy
Hypoglycemia
Pheochromocytoma

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

Psychostimulants
Corticosteroids
Thyroid hormone
Beta agonists
Theophylline
Decongestants

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.[40] 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.[41] The mechanism of action of vortioxetine is more complex, having activity on multiple serotonin receptors.[42]

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.[43-49]

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.[50-52] Patients may find bupropion activating or stimulating, which they may experience as a worsening of their anxiety.[40]

Mirtazapine. The evidence base on the use of mirtazapine for PD is not robust, but a few studies have shown some efficacy.[53-59] 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).[60,61]

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.[62-67] 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.[68] 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.[69-72] 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.[73-76] Its antipanic activity is believed to be related to its activity on

gamma-aminobutyric acid (GABA).[70] 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.[72] 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 GABAergic 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.[77-81] 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.[82-84] 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.[85] 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.[85] A 2010 Cochrane Review studied SGAs for use in the treatment of anxiety disorders in general.[86] 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.[86] 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.[87] 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.[88]

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.[89-91] Hydroxyzine has FDA approval for use in GAD, but not for other anxiety disorders. Data on off-label use for PD is minimal.[92] 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.[93-95]

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.[96-100] A 2014 Cochrane Review examining rTMS for the treatment of PD concluded that there is insufficient evidence for making specific conclusions.[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.

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.[101-103] Although many patients report subjective improvement in anxiety symptoms with cannabis, data validating its use for anxiety disorders is limited.[104,105] The evidence is particularly poor regarding potential benefit for PD, and there is considerable data suggesting that cannabis can induce panic symptoms.[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.[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.[111-114]

Herbals and supplements

Patients often turn to herbal medications and other over-the-counter (OTC) supplements to manage anxiety symptoms. **TABLE 3** lists supplements considered to have possible anti-anxiety effects that have been studied for that purpose.[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.[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.[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,[128] and kava is associated with liver failure.[115] For these reasons, OTC supplements cannot be recommended as standard interventions for PD.

TABLE 3
Over-the-counter supplements studied for use in treating anxiety

5-hydroxytryptophan (5-HTP)
Inositol
Kava
Omega-3 fatty acids
Passiflora
St. John's wort
Valerian

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.[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.[133-135] However, because CBT is a minimal-risk intervention, there is little downside to adding CBT to treatment if

TABLE 4
Summary of treatment options for panic disorder

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

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.

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.[20] Cognitive-behavioral therapy also has been shown to be useful in helping patients with PD taper off benzodiazepines.[136-140] 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 have a greater success rate in discontinuing benzodiazepines, compared with those not receiving this intervention.[140] There is also some evidence suggesting that CBT can help manage symptoms when patients with PD are discontinuing use of SSRIs.[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

1. Diagnostic and statistical manual of mental disorders, 5th ed. American Psychiatric Association; 2013.
2. Lecrubier Y. The impact of comorbidity on the treatment of panic disorder. J Clin Psychiatry. 1998; 59(suppl 8):11-14.
3. Marshall JR. Alcohol and substance abuse in panic disorder. J Clin Psychiatry. 1997;58(suppl 2):46-50.
4. Zvolensky MJ, Bernstein A, Marshall EC, et al. Panic attacks, panic disorder, and agoraphobia: associations with substance use, abuse, and dependence. Curr Psychiatry Rep. 2006;8:279-285.
5. Kessler RC, Chiu WT, Jin R, et al. The epidemiology of panic attacks, panic disorder, and agoraphobia in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2006;63:415-424.
6. Hansson L. Quality of life in depression and anxiety. Int Rev Psychiatry. 2002;13:185-189.
7. Katon WJ. Panic disorder. N Engl J Med. 2006;354: 2360-2367.
8. Simon NM, Fischmann D. The implications of medical and psychiatric comorbidity with panic disorder. J Clin Psychiatry. 2005;66(suppl 4):8-15.
9. Pollack MH, Marzol PC. Panic: course, complications and treatment of panic disorder. J Psychopharmacol. 2000;14(suppl 1):S25-S30. doi: 10.1177/02698811000142S104
10. Katon W. Panic disorder: relationship to high medical utilization, unexplained physical symptoms, and medical costs. J Clin Psychiatry. 1996;57(suppl 10):11-18.
11. Bandelow B, Ruther E. Treatment-resistant panic disorder. CNS Spectr. 2004;9:725-739.
12. Chen M, Tsai S. Treatment-resistant panic disorder: clinical significance, concept and management. Prog Neuropsychopharmacol Biol Psychiatry. 2016;70: 219-226.
13. Slaap BR, den Boer JA. The prediction of nonresponse to pharmacotherapy in panic disorder: a review. Depress Anxiety. 2001;14:112-122.
14. Rosenbaum JF. Treatment-resistant panic disorder. J Clin Psychiatry. 1997;58(suppl 2):61-64.
15. Diemer J, Vennewald N, Domschke K, et al. Therapy-refractory panic: current research areas as possible perspectives in the treatment of anxiety. Eur Arch Psychiatry Clin Neurosci. 2010;260(suppl 2):S127-S131. doi: 10.1007/s00406-010-0143-9
16. Cowley DS, Ha EH, Roy-Byrne PP. Determinants of pharmacologic treatment failure in panic disorder. J Clin Psychiatry. 1997;58:555-561.
17. Berger P, Sachs G, Amering M, et al. Personality disorder and social anxiety predict delayed response in drug and behavioral treatment for panic disorder. J Affect Disord. 2004;80:75-78.
18. Pollack MH, Otto MW, Rosenbaum JF, et al. Longitudinal course of panic disorder: findings from the Massachusetts General Hospital Naturalistic Study. J Clin Psychiatry. 1990;51(suppl A):12-16.
19. Zulfarina MS, Syarifah-Noratiqah S, Nazrun SA, et al. Pharmacological therapy in panic disorder: current guidelines and novel drugs discovery for treatment-resistant patient. Clin Psychopharmacol Neurosci. 2019;17:145-154.
20. Work Group on Panic Disorder. American Psychiatric Association. Practice guideline for the treatment of patients with panic disorder. Am J Psychiatry. 1998; 155(suppl 5):1-34.
21. Canadian Psychiatric Association. Clinical practice guidelines. Management of anxiety disorders. Can J Psychiatry. 2006;51(suppl 2):9S-91S.
22. Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Panic Disorder and Agoraphobia. Australian and New Zealand clinical practice guidelines for the treatment of panic disorder and agoraphobia. Aust N Z J Psychiatry. 2003;37:641-656.
23. Ballenger JC, Davidson JR, Lecrubier Y, et al. Consensus statement on panic disorder from the International Consensus Group on Depression and Anxiety. J Clin Psychiatry. 1998;59(suppl 8):47-54.
24. Pollack MH, Allgulander C, Bandelow B, et al. WCA recommendations for the long-term treatment of panic disorder. CNS Spectr. 2003;8(suppl 1):17-30.
25. Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based pharmacological treatment of anxiety disorder, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharmacol. 2014;28:403-439.
26. Bandelow B, Zohar J, Hollander E, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders - first revision. World J Biol Psychiatry. 2008;9:248-312.
27. National Institute for Health and Clinical Excellence (NICE). Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults: management in primary, secondary, and community care [CG 113]. Last updated July 26, 2019. Accessed November 25, 2020. https://www.nice.org.uk/guidance/cg113
28. Bighelli I, Castellazzi M, Cipriani A, et al. Antidepressants versus placebo for panic disorder in adults. Cochrane Database Syst Rev. 2018;4:CD010676. doi: 10.1002/14651858.CD010676.pub2
29. Bakker A, Van Balkom AJLM, Spinhoven P. SSRIs vs. TCAs in the treatment of panic disorder: a meta-analysis. Acta Psychiatr Scand. 2002;106:163-167.
30. Boyer W. Serotonin uptake inhibitors are superior to imipramine and alprazolam in alleviating panic attacks: a meta-analysis. Int Clin Psychopharmacol. 1995;10:45-49.
31. Bighelli I, Trespidi C, Castellazzi M, et al. Antidepressants and benzodiazepines for panic disorder in adults. Cochrane Database Syst Rev. 2016;9:CD011567.
32. Breilmann J, Girlanda F, Guaiana G, et al. Benzodiazepines versus placebo for panic disorder in adults. Cochrane Database Syst Rev. 2019;3:CD010677.
33. Pollack M, Mangano R, Entsuah R, et al. A randomized controlled trial of venlafaxine ER and paroxetine in the treatment of outpatients with panic disorder. Psychopharmacology. 2007;194:233-242.
34. Ferguson JM, Khan A, Mangano R, et al. Relapse prevention of panic disorder in adult outpatient

responders to treatment with venlafaxine extended release. J Clin Psychiatry. 2007;68:58-68.
35. Bradwejn J, Ahokas A, Stein DJ, et al. Venlafaxine extended-release capsules in panic disorder: flexible-dose, double-blind, placebo-controlled study. Br J Psychiatry. 2005;187:352-359.
36. Serretti A, Chiesa A, Calati R, et al. Novel antidepressants and panic disorder: evidence beyond current guidelines. Neuropsychobiology. 2011;63:1-7.
37. Simon NM, Kaufman RE, Hoge EA, et al. Open-label support for duloxetine for the treatment of panic disorder. CNS Neurosci Ther. 2009;15:19-23.
38. Blaya C, Seganfredo AC, Dornelles M, et al. The efficacy of milnacipran in panic disorder: an open trial. Int Clin Psychopharmacol. 2007;22:153-158.
39. Chen M, Liou Y. Milnacipran in panic disorder with agoraphobia and major depressive disorder: a case report. Clin Neuropharmacol. 2011;34:201-202.
40. Stahl SM. Essential Psychopharmacology. 4th ed. Cambridge University Press; 2013.
41. Sahli ZT, Banerjee P, Tarazi FI. The preclinical and clinical effects of vilazodone for the treatment of major depressive disorder. Expert Opin Drug Discov. 2016;11:515-523.
42. Gonda X, Sharma SR, Tarazi FI. Vortioxetine: a novel antidepressant for the treatment of major depressive disorder. Expert Opin Drug Discov. 2019;14:81-89.
43. Stuivenga M, Giltay EJ, Cools O, et al. Evaluation of vilazodone for the treatment of depressive and anxiety disorders. Expert Opin Pharmacother. 2019;20:251-260.
44. Gommoll C, Durgam S, Mathews M, et al. A double-blind, randomized, placebo-controlled, fixed-dose phase III study of vilazodone in patients with generalized anxiety disorder. Depress Anxiety. 2015;32:451-459.
45. Zareifopoulos N, Dylja I. Efficacy and tolerability of vilazodone for the acute treatment of generalized anxiety disorder: a meta-analysis. Asian J Psychiatr. 2017;26:115-122.
46. Sowa-Kucma M, Panczyszyn-Trzewik P, Misztak P, et al. Vortioxetine: a review of the pharmacology and clinical profile of the novel antidepressant. Pharmacol Rep. 2017;69:595-601.
47. Orsolini L, Tomasetti C, Valchera A, et al. New advances in the treatment of generalized anxiety disorder: the multimodal antidepressant vortioxetine. Expert Rev Neurother. 2016;16:483-495.
48. Pae CU, Wang SM, Han C, et al. Vortioxetine, a multimodal antidepressant for generalized anxiety disorder: a systematic review and meta-analysis. J Psychiatr Res. 2015;64:88-98.
49. Shah A, Northcutt J. An open-label, flexible dose adaptive study evaluating the efficacy of vortioxetine in subjects with panic disorder. Ann Gen Psychiatry. 2018;17:19.
50. Serafini G, Pompili M, Fusar-Poli P, et al. Bupropion and panic disorder: case report and review of the literature. J Neuropsychiatry Clin Neurosci. 2011;23:E47-E50.
51. Simon NM, Emmanuel N, Ballenger J, et al. Bupropion sustained release for panic disorder. Psychopharmacol Bull. 2003;37:66-72.
52. Sheehan DV, Davidson J, Manschreck T, et al. Lack of efficacy of a new antidepressant (bupropion) in the treatment of panic disorder with phobias. J Clin Psychopharmacol. 1983;3:28-31.
53. Sarchiapone M, Amore M, De Risio S, et al. Mirtazapine in the treatment of panic disorder: an open-label trial. Int Clin Psychopharmacol. 2003;18:35-38.
54. Carli V, Sarchiapone M, Camardese G, et al. Mirtazapine in the treatment of panic disorder. Arch Gen Psychiatry. 2002;59:661-662.
55. Boshuisen ML, Slaap BR, Vester-Blokland ED, et al. The effect of mirtazapine in panic disorder: an open label pilot study with a single-blind placebo run-in period. Int Clin Psychopharmacol. 2001;16:363-368.
56. Ribeiro L, Busnello JV, Kauer-Sant'Anna M, et al. Mirtazapine versus fluoxetine in the treatment of panic disorder. Braz J Med Biol Res. 2001;34:1303-1307.
57. Carpenter LL, Leon Z, Yasmin S, et al. Clinical experience with mirtazapine in the treatment of panic disorder. Ann Clin Psychiatry. 1999;11:81-86.
58. Carli V, Faia V, Poterzio F, et al. Mirtazapine in the treatment of panic disorder: an open-label trial. Int Clin Psychopharmacol. 2003;18:35-38.
59. Milan Pavlovic Z. Remission of panic disorder with mirtazapine augmentation of paroxetine: a case report. Prim Care Companion J Clin Psychiatry. 2007;9:396.
60. Lee EE, Della Selva MP, Liu A, et al. Ketamine as a novel treatment for major depressive disorder and bipolar depression: a systematic review and quantitative meta-analysis. Gen Hosp Psychiatry. 2015;37:178-184.
61. Kryst J, Kawalec P, Pilc A. Efficacy and safety of intranasal esketamine for the treatment of major depressive disorder. Expert Opin Pharmacother. 2020;21: 9-20.
62. Glue P, Neehoff SM, Medlicott NJ, et al. Safety and efficacy of maintenance ketamine treatment in patients with treatment-refractory generalised anxiety and social anxiety disorders. J Psychopharmacol. 2018;32:663-667.
63. Taylor JH, Landeros-Weisenberger A, Coughlin C, et al. Ketamine for social anxiety disorder: a randomized, placebo-controlled crossover trial. Neuropsychopharmacology. 2018;43:325-333.
64. Glue P, Medlicott NJ, Harland S, et al. Ketamine's dose-related effects on anxiety symptoms in patients with treatment refractory anxiety disorders. J Psychopharmacol. 2017;31:1302-1305.
65. Ray SM, Kious BM. Sustained resolution of panic disorder, agoraphobia, and generalized anxiety disorder with a single ketamine infusion: a case report. Prim Care Companion CNS Disord. 2016;18. doi: 10.4088/PCC.15l01899
66. Ionescu DF, Luckenbaugh DA, Niciu MJ, et al. Effect of baseline anxious depression on initial and sustained antidepressant response to ketamine. J Clin Psychiatry. 2014;75:e932-e938.
67. Irwin SA, Iglewicz A, Nelesen RA, et al. Daily oral ketamine for the treatment of depression and anxiety in patients receiving hospice care: a 28-day open-label proof-of-concept trial. J Palliat Med. 2013;16:958-965.
68. Imai H, Tajika A, Chen P, et al. Azapirones versus placebo for panic disorder in adults. Cochrane Database Syst Rev. 2014;CD010828.
69. Mula M, Pini S, Cassano GB. The role of anticonvulsants drugs in anxiety disorders: a critical review of the evidence. J Clin Psychopharmacol. 2007; 27:263-272.
70. Van Ameringen M, Mancini C, Pipe B, et al. Antiepileptic drugs in the treatment of anxiety disorders. Drugs. 2004;64:2199-2220.
71. Boutron NN, Ghosh S, Khan A, et al. Anticonvulsant medications for panic disorder: a review and synthesis of the evidence. Int J Psychiatry Clin Pract. 2014;18:2-10.
72. Rakofsky JJ, Dunlop BW. Treating nonspecific anxiety and anxiety disorders in patients with bipolar disorder: a review. J Clin Psychiatry. 2011;72:81-90.
73. Baetz M, Bowen RC. Efficacy of divalproex sodium in patients with panic disorder and mood instability who have not responded to conventional therapy. Can J Psychiatry. 1998;43:73-77.
74. Keck PE Jr, Taylor VE, Tugrul KC, et al. Valproate treatment of panic disorder and lactate-induced panic attacks. Biol Psychiatry. 1993;33:542-546.
75. Woodman CL, Noyes R Jr. Panic disorder: treatment with valproate. J Clin Psychiatry. 1994;55:134-136.
76. Primeau F, Fontaine R, Beauclair L. Valproic acid and panic disorder. Can J Psychiatry. 1990;35:248-250.
77. Joos AA, Zeeck A. Gabapentin in somatoform and panic disorder. J Clin Psychopharmacol. 2013;33:140-142.
78. Pollack MH, Matthews J, Scott EL. Gabapentin as a potential treatment for anxiety disorders. Am J Psychiatry. 1998;155:992-993.
79. Pande AC, Pollack MH, Crockatt J, et al. Placebo-controlled study of gabapentin treatment of panic disorder. J Clin Psychopharmacol. 2000;20:467-471.
80. Lauria-Horner BA, Pohl RB. Pregabalin: a new anxiolytic. Expert Opin Investig Drugs. 2003;12:663-672.
81. Montgomery S, Emir B, Haswell H, et al. Long-term treatment of anxiety disorders with pregabalin: a 1 year open-label study of safety and tolerability. Curr Med Res Opin. 2013;29:1223-1230.
82. Camara EG. Lithium potentiation of antidepressant treatment in panic disorder. J Clin Psychopharmacol. 1990;10:225-227.
83. Feder R. Lithium augmentation of clomipramine. J Clin Psychiatry. 1988;49:458.
84. Cournoyer J. Rapid response of a disorder to the addition of lithium carbonate: panic resistant to tricyclic antidepressants. Article in French. Can J Psychiatry. 1986; 31:335-338.
85. Perna G, Alessandra A, Raffaele B, et al. Is there room for second-generation antipsychotics in the pharmacotherapy of panic disorder? A systematic review based on PRISMA guidelines. Int J Mol Sci. 2016;17:551.
86. Depping AM, Komossa K, Kissling W, et al. Second-generation antipsychotics for anxiety disorders. Cochrane Database Syst Rev. 2010;CD008120.
87. Steenen SA, van Wijk AJ, van der Heijden GJMG, et al. Propranolol for the treatment of anxiety disorders: systematic review and meta-analysis. J Psychopharmacol. 2016;30:128-39.
88. Davidson JRT. Pharmacotherapy of social anxiety disorder: what does the evidence tell us? J Clin Psychiatry. 2006;67:20-26.
89. Guaiana G, Barbui C, Cipriani A. Hydroxyzine for generalised anxiety disorder. Cochrane Database Syst Rev. 2010;CD006815.
90. Llorca PM, Spadone C, Sol O, et al. Efficacy and safety of hydroxyzine in the treatment of generalized anxiety disorder: a 3-month double-blind study. J Clin Psychiatry. 2002;63:1020-1027.
91. Ferreri M, Hantouche EG. Recent clinical trials of hydroxyzine in generalized anxiety disorder. Acta Psychiatr Scand Suppl. 1998;393:102-108.
92. Iskandar JW, Griffeth B, Rubio-Cespedes C. Successful treatment with hydroxyzine of acute exacerbation of panic disorder in a healthy man: a case report. Prim Care Companion CNS Disord. 2011;13: PCC.10l01126. doi: 10.4088/PCC.10l01126
93. Rapinesi C, Serata D, Del Casale A, et al. Electroconvulsive therapy in a physically restrained man with comorbid major depression, severe agoraphobia with panic disorder, and histrionic personality disorder. J ECT. 2012;28:72-73.
94. Chang TG, Wang CH, Chiu NY, et al. Application of electroconvulsive therapy in treatment of retinitis pigmentosa comorbid with major depressive disorder and panic disorder. J ECT. 2011;27:e57-e58.
95. Figiel GS, Zorumski CF, Doraiswamy PM, et al. Simultaneous major depression and panic disorder: treatment with electroconvulsive therapy. J Clin Psychiatry. 1992;53:12-15.
96. Prasko J, Záleský R, Bares M, et al. The effect of repetitive transcranial magnetic stimulation (rTMS) add on serotonin reuptake inhibitors in patients with panic disorder: a randomized, double blind sham controlled study. Neuro Endocrinol Lett. 2007;28:33-38.
97. Mantovani A, Aly M, Dagan Y, et al. Randomized sham controlled trial of repetitive transcranial magnetic stimulation to the dorsolateral prefrontal cortex for the treatment of panic disorder with comorbid major depression. J Affect Disord. 2013;144:153-159.
98. Machado S, Santos V, Paes F, et al. Repetitive transcranial magnetic stimulation (rTMS) to treat refractory panic disorder patient: a case report. CNS Neurol Disord Drug Targets. 2014;13:1075-1078.
99. Dresler T, Ehlis AC, Plichta MM, et al. Panic disorder and a possible treatment approach by means of high-frequency rTMS: a case report. World J Biol Psychiatry. 2009;10(pt 3):991-997.
100. Li H, Wang J, Xiao Z. Repetitive transcranial magnetic stimulation (rTMS) for panic disorder in adults. Cochrane Database Syst Rev. 2014;2014:CD009083.
101. Steenkamp MM, Blessing EM, Galatzer-Levy IR, et al. Marijuana and other cannabinoids as a treatment for

posttraumatic stress disorder: A literature review. Depress Anxiety. 2017;34:207-216.
102. Mead A. The legal status of cannabis (marijuana) and cannabidiol (CBD) under U.S. law. Epilepsy Behav. 2017;70:288-291.
103. Baron EP. Comprehensive review of medicinal marijuana, cannabinoids, and therapeutic implications in medicine and headache: what a long strange trip it's been… Headache. 2015;55:885-916.
104. Crippa JA, Zuardi AW, Martín-Santos R, et al. Cannabis and anxiety: a critical review of the evidence. Hum Psychopharmacol. 2009;24:515-253.
105. Turna J, Patterson B, Van Ameringen M. Is cannabis treatment for anxiety, mood, and related disorders ready for prime time? Depress Anxiety. 2017;34: 1006-1017.
106. Petrowski K, Conrad R. Comparison of cortisol stress response in patients with panic disorder, cannabis-induced panic disorder, and healthy controls. Psychopathology. 2019;52:26-32.
107. Coscas S, Benyamina A, Reynaud M, et al. Complications psychiatriques de la consommation de cannabis [Psychiatric complications of cannabis use]. Rev Prat. 2013;63:1426-1428. French.
108. Deas D, Gerding L, Hazy J. Marijuana and panic disorder. J Am Acad Child Adolesc Psychiatry. 2000;39:1467.
109. Zvolensky MJ, Bernstein A, Sachs-Ericsson N, et al. Lifetime associations between cannabis, use, abuse, and dependence and panic attacks in a representative sample. J Psychiatr Res. 2006;40:477-486.
110. Grotenhermen F. Die wirkungen von cannabis und THC [The effects of cannabis and THC]. Forsch Komplementarmed. 1999;6(suppl 3):7-11. German.
111. Hill KP. Medical marijuana for treatment of chronic pain and other medical and psychiatric problems: a clinical review. JAMA. 2015;313:2474-2483.
112. Walsh Z, Gonzalez R, Crosby K, et al. Medical cannabis and mental health: a guided systematic review. Clin Psychol Rev. 2017;51:15-29.
113. Nugent SM, Morasco BJ, O'Neil ME, et al. The effects of cannabis among adults with chronic pain and an overview of general harms. Ann Intern Med. 2017;167:319-331.
114. Radhakrishnan R, Wilkinson ST, D'Souza DC. Gone to pot – a review of the association between cannabis and psychosis. Front Psychiatry. 2014;5:54.
115. Kinrys G, Coleman E, Rothstein E. Natural remedies for anxiety disorders: potential use and clinical applications. Depress Anxiety. 2009;26:259-265.
116. Ravindran AV, da Silva TL. Complementary and alternative therapies as add-on to pharmacotherapy for mood and anxiety disorders: a systematic review. J Affect Disord. 2013;150:707-719.
117. Saeed SA, Bloch RM, Antonacci DJ. Herbal and dietary supplements for treatment of anxiety disorders. Am Fam Physician. 2007;76:549-556.
118. Jorm AF, Christensen H, Griffiths KM, et al. Effectiveness of complementary and self-help treatments for anxiety disorders. Med J Aust. 2004;181(S7):S29-S46.
119. Miyasaka LS, Atallah AN, Soares BG. Passiflora for anxiety disorder. Cochrane Database Syst Rev. 2007;1: CD004518.
120. Sarris J, Kavanagh DJ. Kava and St. John's wort: current evidence for use in mood and anxiety disorders. J Altern Complement Med. 2009;15:827-836.
121. Miyasaka LS, Atallah AN, Soares BG. Valerian for anxiety disorders. Cochrane Database Syst Rev. 2006;4: CD004515.
122. Pittler MH, Ernst E. Kava extract for treating anxiety. Cochrane Database Syst Rev. 2003;1:CD003383.
123. Benjamin J, Levine J, Fux M, et al. Double-blind, placebo-controlled, crossover trial of inositol treatment for panic disorder. Am J Psychiatry. 1995;152: 1084-1086.
124. Palatnik A, Frolov K, Fux M, et al. Double-blind, controlled, crossover trial of inositol versus fluvoxamine for the treatment of panic disorder. J Clin Psychopharmacol. 2001;21:335-339.
125. Benjamin J, Nemetz H, Fux M, et al. Acute inositol does not attenuate m-CPP-induced anxiety, mydriasis and endocrine effects in panic disorder. J Psychiatr Res. 1997;31:489-495.
126. Mukai T, Kishi T, Matsuda Y, et al. A meta-analysis of inositol for depression and anxiety disorders. Hum Psychopharmacol. 2014;29:55-63.
127. Abdel-Tawab M. Do we need plant food supplements? A critical examination of quality, safety, efficacy, and necessity for a new regulatory framework. Planta Med. 2018;84:372-393.
128. Soleymani S, Bahramsoltani R, Rahimi R, et al. Clinical risks of St John's wort (Hypericum perforatum) co-administration. Expert Opin Drug Metab Toxicol. 2017; 13:1047-1062.
129. Otto MW, Deveney C. Cognitive-behavioral therapy and the treatment of panic disorder: efficacy and strategies. J Clin Psychiatry. 2005;66(suppl 4):28-32.
130. Landon TM, Barlow DH. Cognitive-behavioral treatment for panic disorder: current status. J Psychiatr Pract. 2004;10:211-226.
131. Rayburn NR, Otto MW. Cognitive-behavioral therapy for panic disorder: a review of treatment elements, strategies, and outcomes. CNS Spectr. 2003;8:356-362.
132. Pompoli A, Furukawa TA, Imai H, et al. Psychological therapies for panic disorder with or without agoraphobia in adults: a network meta-analysis. Cochrane Database Syst Rev. 2016;4:CD011004.
133. Furukawa TA, Watanabe N, Churchill R. Combined psychotherapy plus antidepressants for panic disorder with or without agoraphobia. Cochrane Database Syst Rev. 2007;1:CD004364.
134. Imai H, Tajika A, Chen P, et al. Psychological therapies versus pharmacological interventions for with or without agoraphobia in adults. Cochrane Database Syst Rev. 2016;10:CD011170.
135. Watanabe N, Churchill R, Furukawa TA. Combined psychotherapy plus benzodiazepines for panic disorder. Cochrane Database Syst Rev. 2009;1:CD005335.
136. Spiegel DA, Bruce TJ, Gregg SF, et al. Does cognitive behavior therapy assist slow-taper alprazolam discontinuation in panic disorder? Am J Psychiatry. 1994;151:876-881.
137. Otto MW, Pollack MH, Meltzer-Brody S, et al. Cognitive-behavioral therapy for benzodiazepine discontinuation in panic disorder patients. Psychopharmacol Bull. 1992;28:123-130.
138. Otto MW, Pollack MH, Sachs GS, et al. Discontinuation of benzodiazepine treatment: efficacy of cognitive-behavioral therapy for patients with panic disorder. Am J Psychiatry. 1993;150:1485-1490.
139. Otto MW, Hong JJ, Safren SA. Benzodiazepine discontinuation difficulties in panic disorder: conceptual model and outcome for cognitive-behavior therapy. Curr Pharm Des. 2002;8:75-80.
140. Otto MW, McHugh RK, Simon NM, et al. Efficacy of CBT for benzodiazepine discontinuation in patients with panic disorder: further evaluation. Behav Res Ther. 2010;48:720-727.
141. Whittal ML, Otto MW, Hong JJ. Cognitive-behavior therapy for discontinuation of SSRI treatment of panic disorder: a case series. Behav Res Ther. 2001;39:939-945.