

# GUIDELINE WATCH: PRACTICE GUIDELINE FOR THE TREATMENT OF PATIENTS WITH PANIC DISORDER

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This guideline watch summarizes evidence that has accrued since publication in 1998 of APA's *Practice Guideline for the Treatment of Patients With Panic Disorder* (1). The major topics covered are safety issues, U.S. Food and Drug Administration (FDA) approvals, availability of new medications (including generics), efficacy of pharmacological and psychosocial treatments, efficacy of combined treatments, predictors of treatment response, and treatment of panic disorder in primary care settings.

## ► SAFETY ISSUES

### **Liver failure associated with nefazodone treatment**

The practice guideline cited one open-label trial that used the serotonin modulator nefazodone in the treatment of panic disorder. Nefazodone significantly reduced symptoms of panic disorder in this study (2). Since publication of the guideline, cases of liver failure associated with nefazodone administration have been reported (3–9). The FDA now requires that nefazodone carry a black box warning stating that cases of life-threatening liver failure have occurred in patients treated with the drug. According to the warning, the reported rate of liver failure resulting in death or transplant is approximately 1 case per 250,000–300,000 patient-years of nefazodone treatment. This represents a rate of three to four times the estimated background rate and is likely an underestimate due to incomplete reporting.

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The FDA warning (available at [http://www.fda.gov/medwatch/SAFETY/2002/serzone\\_deardoc.pdf](http://www.fda.gov/medwatch/SAFETY/2002/serzone_deardoc.pdf)) includes the following recommendations:

1. Although there is at present no way to predict who might develop liver failure, nefazodone should not be initiated in patients with acute liver disease or elevated baseline levels of serum transaminases.
2. Patients taking nefazodone should be informed of the risk, signs, and symptoms of liver dysfunction and told to contact their doctors immediately if any signs or symptoms occur (e.g., jaundice, anorexia, gastrointestinal complaints, malaise).
3. Clinicians may consider the value of liver function testing in patients taking nefazodone.
4. Nefazodone should be discontinued if liver toxicity is suspected.
5. Nefazodone is contraindicated in cases in which the drug was previously discontinued because of evidence of liver injury.

Although the practice guideline does not recommend nefazodone as a first-line treatment for panic disorder, there may be instances in which it is considered as a treatment for panic disorder or a co-occurring psychiatric condition in patients without a history of liver disease. In these cases, the increased risk of liver toxicity must be weighed against the possible benefit of pharmacotherapy. Other medications with fewer risks and more efficacy data supporting their use in panic disorder should be considered as alternatives to nefazodone.

### **Suicidality and antidepressant use in children and adolescents**

The practice guideline reports that selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs) are effective for treating panic disorder in adults. Controlled studies of pharmacological treatment of pediatric patients with panic disorder were not available when the 1998 guideline was developed; however, the guideline notes that anecdotal reports and case series suggest that antidepressants are useful in treating pediatric panic disorder (1). In 2004 the FDA issued a warning that “antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies of children and adolescents with major depressive disorder (MDD) and other psychiatric disorders” ([http://www.fda.gov/cder/drug/antidepressants/PI\\_template.pdf](http://www.fda.gov/cder/drug/antidepressants/PI_template.pdf)). It is unknown whether a risk of suicidality extends to longer-term use of antidepressants in children and adolescents.

The FDA warning is based on pooled analyses of 24 placebo-controlled trials of nine antidepressants in pediatric patients with a variety of psychiatric disorders (10). These analyses showed that patients receiving antidepressants displayed a risk of suicidal thinking and behavior that was approximately twice that of patients receiving placebo during the first few months of treatment (4% in the active treatment groups vs. 2% in the placebo groups). It is important to note that no completed suicides occurred in any of the clinical trials.

With respect to suicidality and panic disorder, APA’s practice guideline reports that individuals with panic disorder demonstrate a higher than average rate of suicidal ideation and suicide attempts (although this is less clear for individuals with uncomplicated panic disorder without agoraphobia) and that the presence of co-occurring conditions such as major depression, substance use disorders, and personality disorders increases the risk of suicide attempts (1). The guideline states that clinicians should assess all patients with panic disorder for suicidal ideation and risk, regardless of age or treatment regimen. The FDA warning, which advises increased monitoring for suicidal ideation and behavior in pediatric patients treated with antidepressants, further supports this recommendation.

The FDA black box warning applies to all antidepressants and indicates that the risk of increased suicidal thinking and behavior in pediatric patients must be balanced with the clinical need for pharmacotherapy. It further states that pediatric patients taking antidepressants should be observed closely for clinical worsening, suicidality, or unusual changes in behavior—

particularly in the initial few months of treatment and at times of dose changes. The black box warning advises that caregivers should observe the patient closely and communicate any concerns to the prescribing clinician. Medication guides that describe signs of clinical worsening and suicidality are available for families ([http://www.fda.gov/cder/drug/antidepressants/MG\\_template.pdf](http://www.fda.gov/cder/drug/antidepressants/MG_template.pdf)). Finally, the warning clarifies for which pediatric conditions the antidepressant has received approval (if any).

No antidepressant currently has FDA approval for treatment of pediatric panic disorder. However, these medications are used often enough in clinical practice that it is appropriate to review the following FDA recommendations for psychiatric management of children and adolescents taking antidepressants.

The FDA recommends a specific schedule of face-to-face clinical contacts for the first 12 weeks of treatment for all pediatric patients taking antidepressants. The schedule involves weekly contacts for the initial 4 weeks, biweekly contacts for the next 4 weeks, and a contact at 12 weeks. The warning indicates that prescriptions are to be written for “the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose” ([http://www.fda.gov/cder/drug/antidepressants/PI\\_template.pdf](http://www.fda.gov/cder/drug/antidepressants/PI_template.pdf)). A similar approach is recommended for adult patients with MDD who are starting antidepressants; therefore, these guidelines are also relevant for adult patients with co-occurring panic disorder and depression.

In addition to monitoring patients for signs of general clinical worsening and suicidality, the FDA recommends that patients be assessed for risk of bipolar disorder; this assessment should include inquiring about family history of mood disorders and suicide. According to the FDA, patients at higher risk for bipolar disorder who are prescribed antidepressants should be monitored for signs of transition to hypomanic, manic, or mixed mood states. The FDA further advises that clinicians be alert for signs of increased anxiety or panic, agitation, insomnia, irritability, hostility, aggressiveness, impulsivity, mania, hypomania, akathisia, and other unusual changes in behavior. Although these signs and symptoms are not conclusively linked to suicidal thoughts and behavior, there is concern that they might be precursors to emerging suicidality. Particular concern would be warranted if these symptoms were abrupt in onset, severe, or not previously part of the patient’s presenting complaint. In the event that any of these potential signs of deterioration occur, the FDA recommends that the clinician consider changing the treatment regimen and possibly discontinuing the antidepressant.

It is important to balance the FDA warnings regarding antidepressant use in children against the potential therapeutic benefit of these drugs and the risks of untreated psychiatric illness. Some concern exists that the FDA warnings will deter clinicians from prescribing in cases in which the risk-benefit ratio strongly favors antidepressant treatment. The American Psychiatric Association ([http://www.psych.org/news\\_room/press\\_releases/04-55apaonfdablackboxwarning.pdf](http://www.psych.org/news_room/press_releases/04-55apaonfdablackboxwarning.pdf); [http://www.psych.org/news\\_room/press\\_releases/05-53APAonPsychNewsAnalysis%203\\_.pdf](http://www.psych.org/news_room/press_releases/05-53APAonPsychNewsAnalysis%203_.pdf)) and American Academy of Child and Adolescent Psychiatry ([http://www.aacap.org/press\\_releases/2004/1101.htm](http://www.aacap.org/press_releases/2004/1101.htm)) have commented on this issue.

It is not known whether adults taking antidepressants are at increased risk of suicidality. In adults, published meta-analyses of data from short-term clinical trials have not demonstrated differences in rates of suicide or attempted suicide between individuals treated with antidepressants and those receiving placebo (11, 12). Recent research using population-based computerized health plan records also showed no significant increase in the risk of a serious suicide attempt for patients treated with antidepressants (13). For individuals treated with older antidepressants (e.g., TCAs, trazodone), the risk in the month prior to treatment was comparable to that in the first month of treatment and then declined. For individuals treated with newer antidepressants, the risk was greatest in the month prior to treatment, dropped in the first month of treatment, and continued to decline thereafter. Although numbers of deaths by suicide were small, this risk remained stable over the 6-month period after antidepressant treatment was begun.

The FDA is currently investigating the relationship between suicidality and antidepressant use in adult patients with psychiatric disorders. A public health advisory was released in June 2005 indicating that adults being treated with antidepressant medications, particularly those being treated for depression, should be monitored closely for clinical worsening and suicidality. Monitoring early in treatment and at times of dose changes is emphasized. If clinical worsening or increased suicidality occurs in conjunction with antidepressant treatment, the FDA advises that adult patients be promptly evaluated by the prescribing clinician.

The FDA continues to update its recommendations regarding antidepressants, and their Web site provides several documents that may be of interest to clinicians, including the required warnings for antidepressants ([http://www.fda.gov/cder/drug/antidepressants/PI\\_template.pdf](http://www.fda.gov/cder/drug/antidepressants/PI_template.pdf)), the public health advisory regarding antidepressant use in children and adolescents (<http://www.fda.gov/cder/drug/antidepressants/SSRIPHA200410.htm>), and the public health advisory regarding antidepressant use in adults (<http://www.fda.gov/cder/drug/advisory/SSRI200507.htm>). Additional information may be found at the Web sites of the APA (<http://www.psych.org>) and the American Academy of Child and Adolescent Psychiatry (<http://www.aacap.org>).

## ▶ **FDA APPROVALS AND AVAILABILITY OF GENERICS**

At the time of the practice guideline's publication, paroxetine and alprazolam had obtained FDA approval for treatment of panic disorder. The following medications have obtained approval for treatment of panic disorder since that time: alprazolam XR (extended release), clonazepam, fluoxetine, paroxetine CR (controlled release), sertraline, and venlafaxine ER (extended release). More information about the efficacy of these medications is included in the next section.

The 1998 guideline indicated that use of SSRIs to manage panic disorder might be more expensive than use of other efficacious medications because of the lack of generic preparations. This potential disadvantage of SSRI treatment no longer applies, as generic preparations of citalopram, fluoxetine, fluvoxamine, and paroxetine are now available.

## ▶ **ADDITIONAL RESEARCH ON DRUG EFFICACY**

### **Specific medication classes**

#### **SSRIs**

Clinical trials have continued to support the efficacy and tolerability of SSRIs in the treatment of panic disorder. At the time of the guideline's publication, four SSRIs were available in the United States: fluoxetine, paroxetine, sertraline, and fluvoxamine. Two more SSRIs (citalopram and escitalopram) and a controlled-release preparation of paroxetine are now available.

Since 1998, several additional large-scale randomized, controlled trials (RCTs) have shown fluoxetine (14–16); paroxetine (17, 18), including its controlled-release preparation (19); and sertraline (20–22) to be safe and effective for the treatment of panic disorder. Dose-response investigations suggest that therapeutic dosages are generally about 20 mg/day for fluoxetine (14, 16), 40 mg/day for paroxetine (17), and 50 mg/day for sertraline (20, 21, 23), although it is important to note that some patients may respond to lower doses and others may require significantly higher doses. Since the guideline's publication, fluvoxamine has been the least studied of the older SSRIs; however, its efficacy was supported in one RCT (24) and partially supported in a second, smaller RCT (25), in which it was superior to placebo on several outcome variables but not frequency of full panic attacks.

Citalopram and its *S*-enantiomer, escitalopram, have been approved for treatment of depression since the publication of the practice guideline. Although several RCTs have been con-

ducted to evaluate the efficacy of these medications for panic disorder, neither has been approved for this indication in the United States. Available studies suggest that both citalopram and escitalopram are effective, well tolerated, and safe in the treatment of panic disorder (26–28). Dosages of 20–30 mg/day appear to be most effective for citalopram (26–28), whereas 10 mg/day appears to be an effective dosage for escitalopram (29).

### **Other antidepressants**

TCAs and MAOIs are also effective medications for treatment of panic disorder (1). Because these are older agents, little evidence has accrued since 1998 that would alter or add to the recommendations provided in the practice guideline. Of the “dual” (serotonin and norepinephrine) reuptake inhibitors, venlafaxine ER at dosages of 75–225 mg/day was found to be effective in treating panic disorder (30), and this medication recently obtained FDA approval for this indication. Duloxetine is new to the market, and its efficacy for panic disorder has not been tested.

### **Benzodiazepines**

Benzodiazepines are effective for treatment of panic disorder (1), and the guideline noted that alprazolam had the best evidence base for its antipanic efficacy. Since the guideline’s publication, an extended-release preparation of alprazolam (alprazolam XR) became available and received FDA approval for treatment of panic disorder. The extended-release preparation requires less frequent dosing and may reduce the likelihood of “breakthrough anxiety” that can occur with missed doses of short-acting benzodiazepines (31). Additional studies have shown clonazepam to be a safe and effective treatment for panic disorder (32, 33). Daily dosages of clonazepam in the range of 1–2 mg are effective while minimizing side effects such as somnolence and ataxia (33), and discontinuation of clonazepam is well tolerated if accomplished with a slow taper schedule (32).

### **Relative efficacy and tolerability of medications**

The literature that has accumulated over the past 8 years generally suggests that the large number of SSRIs, TCAs, and benzodiazepines used to treat panic disorder are equivalent in their efficacy (34–38). Early studies of SSRIs with small samples may have overestimated their efficacy in treating panic disorder; the majority of recent research suggests that SSRIs are effective but not superior in efficacy to older antidepressants in treating panic disorder. Two meta-analyses that compared SSRIs with other antidepressants showed that all classes of medications had similar effects on panic, agoraphobia, depression, and general anxiety (34, 37).

Although one meta-analysis found no difference in dropout rates for SSRIs and other antidepressants (37), the majority of studies suggest that SSRIs are better tolerated than TCAs (34, 37, 39–41). Many patients taking TCAs endure side effects such as increased heart rate, dry mouth, constipation, sweating, and weight gain, even with long-term use (42, 43).

### **Maintenance treatment**

A common theme emerging from the last decade of research is the importance of maintenance pharmacotherapy. Studies of fluoxetine (15), paroxetine (44, 45), sertraline (46), imipramine (47), and clomipramine (48) all have demonstrated a benefit of continuing medication 6–12 months after acute treatment. Maintenance pharmacotherapy should be considered for most patients as a means of preventing recurrence of panic disorder symptoms and promoting continued symptom relief and better functioning.

## **Psychosocial treatment**

Cognitive behavior therapy (CBT) has continued to demonstrate short- and long-term efficacy in clinical trials (49–54) and meta-analyses (55). The effects of CBT have been shown to be at least as robust as those of first-line pharmacotherapies (49, 50, 52, 56), and patients receiving CBT may have less risk for relapse following treatment withdrawal (49). The efficacy of CBT has been established in both individual and group modalities (56), and across clinical research (49), community mental health (57), and primary care settings (52, 53, 58).

CBT is a relatively underutilized treatment given its substantial evidence base for treatment of panic disorder (59). A considerable amount of recent research on CBT has focused on enhancing the efficiency and accessibility of this intervention. For example, one RCT showed that a five-session CBT protocol was comparable in efficacy to a standard-length protocol (51). Studies also have been conducted that evaluate the impact of self-administered CBT treatments for panic disorder. One RCT failed to find differences between fully self-administered CBT-oriented bibliotherapy, self-monitoring, and wait-list control groups on measures of panic disorder severity (60). Moreover, many patients dropped out of the study, suggesting that they had difficulty completing a course of CBT without any support of a professional. Results are more encouraging when self-directed CBT is combined with minimal therapist contact (61). Minimal therapist contact typically includes brief phone calls, meetings, or email to provide encouragement, clarify treatment concepts, and troubleshoot problems. Several clinical trials have shown that CBT-oriented bibliotherapy plus minimal therapist contact (61) and Internet-delivered CBT plus minimal therapist contact (62) are superior to control approaches. In some cases, primarily self-administered versions of CBT even may produce results that approximate those of therapist-administered CBT (63–65). More research is needed to determine for which patients primarily self-administered treatment is sufficient.

Other psychotherapies either have not been tested in a controlled manner or have failed to demonstrate efficacy comparable to that of CBT and pharmacotherapy. An RCT of eye movement desensitization and reprocessing (EMDR) found that EMDR was comparable to an attention-placebo control condition in reducing symptoms of panic disorder (66). In addition, an emotion-focused psychotherapy that featured exploration, empathic listening, and supportive strategies was inferior to CBT and imipramine and comparable to placebo in its effects on panic disorder (67). Psychodynamic psychotherapy remains a widely used treatment for panic disorder (59), although more research is needed to determine its utility in controlled trials. Panic-focused psychodynamic psychotherapy has been described (68) and tested in one pilot uncontrolled trial (69), with 16 of 21 patients achieving criteria for remission.

## **Combination treatments**

Prescribing a combination of a benzodiazepine and an antidepressant is a common acute treatment of panic disorder. Recent studies suggest that administering a benzodiazepine in conjunction with an antidepressant confers a short-term benefit of quicker stabilization of panic disorder symptoms. This has been demonstrated with a clonazepam/sertraline combination (70) and a clonazepam/paroxetine combination (18). It appears that benzodiazepines facilitate early improvement of panic disorder symptoms; however, the advantage of the combination wears off quickly (i.e., individuals receiving SSRIs alone “catch up” to those receiving the benzodiazepine/SSRI combination after the first few weeks of treatment). The benefit of quicker stabilization of panic disorder symptoms should be weighed against the possibility of an increased side-effect burden when benzodiazepines are added to antidepressant therapy.

Studies that have combined medication and psychosocial treatment have failed to show a clear and lasting advantage for the combination treatment (49, 50). One small study found some benefit of combining an SSRI with very brief CBT for panic (71). The interactions between medication and CBT are complex, as demonstrated by a large RCT that compared acute and

maintenance treatment using CBT, imipramine, CBT plus imipramine, CBT plus placebo, and placebo alone (49). All active treatment groups in this study were superior to pill placebo, and there were no significant differences between CBT alone and imipramine alone in the acute or maintenance phase of the study. CBT plus imipramine was equivalent to CBT plus placebo at posttreatment and superior to CBT plus placebo at 6-month follow-up. However, CBT plus imipramine also was associated with the highest rate of relapse after treatment withdrawal. The researchers concluded that addition of CBT did not help reduce relapse following imipramine discontinuation, and addition of imipramine actually appeared to reduce the durability of CBT's effects. At best, combination treatment produced a superior response in the 6 months of maintenance treatment, but this was at the expense of greater relapse following withdrawal of CBT. It is important to note that these results are specific to the CBT/imipramine combination, and more investigation of combining alternative medications and psychosocial treatments for panic disorder is needed.

### **Predictors of treatment response**

Factors that affect response to pharmacological and psychosocial treatments for panic disorder remain poorly understood. Virtually all investigations of characteristics that contribute to treatment response have been undertaken post hoc and with relatively small samples. Some studies suggest that comorbidity affects response to standard treatments. Presence of co-occurring social phobia in patients with panic disorder has been associated with decreased response to paroxetine treatment and a paroxetine/CBT combination (72). In addition, fears of social catastrophes that could result from panic attacks predicted poorer response to both imipramine and CBT (73). Studies examining the impact of co-occurring axis II diagnoses on treatment response have shown mixed results; most (72, 74) but not all (75) suggest that co-occurring personality disorders are associated with poorer response to treatment.

The issue of treating individuals who fail to respond to their first prescribed medication or psychosocial treatment also has been left largely unexplored. One small study showed that adding paroxetine to CBT in patients who failed a trial of CBT led to significant improvements in anxiety and agoraphobic behavior (76). However, considerably more research is needed to address the issue of treatment-resistant panic disorder and the role of sequenced treatments.

### **Treatment of panic disorder in primary care**

One advance in clinical research over the last decade has been the focus on “effectiveness” research that is conducted in real-world clinical settings as opposed to clinical research centers. Studies in primary care settings have shown that collaborative care improves outcomes for patients with panic disorder. One study demonstrated that a collaborative care intervention that included enhanced patient education, two visits with a psychiatrist, and telephone follow-ups improved outcomes for patients with panic disorder (77). Relative to treatment as usual, individuals receiving collaborative care were more likely to receive adequate medication treatment, adhere to medication recommendations, and improve significantly on measures of anxiety, depression, and disability. The collaborative care intervention also was associated with significantly more anxiety-free days and good cost-effectiveness (78).

Use of CBT in primary care settings also improves outcomes for patients with panic disorder (58). Patients who were randomly assigned to an intervention that provided up to six sessions of CBT and algorithm-based pharmacotherapy achieved higher rates of remission, response, and functioning compared with patients who received treatment as usual. These advantages were observed through the final assessment point in the study, which was 12 months postbaseline. The superior outcome of the intervention group was attributed to CBT, since most patients in the treatment-as-usual group received medication consistent with the study algorithm.

## ▶ CONCLUSION

The clinical research that has been conducted since publication of the APA's *Practice Guideline for the Treatment of Patients With Panic Disorder* (1) does not contradict any of the guideline's basic recommendations. Clinicians treating patients with panic disorder should be aware of the safety issues associated with antidepressants, the availability of a broader range of new efficacious medications, and the likely benefit of maintenance pharmacotherapy. Cognitive behavior therapy remains the psychosocial treatment with the largest research base and most demonstrated efficacy for treatment of panic disorder. A clear benefit of adding medication to CBT has yet to be established, and there is a paucity of data examining the addition of CBT to medication. Other psychotherapies either have proved inferior to medication and CBT or have not been evaluated in controlled trials. Finally, more research is needed on assessing the long-term impact of medications and psychosocial treatments, combining medication and psychosocial treatments, identifying factors that predict treatment response, and ameliorating treatment-resistant panic disorder.

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