Antidepressants in Panic Disorder

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Antidepressants have been used to treat patients with panic disorder almost since these drugs were first introduced. Tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), serotonin selective reuptake inhibitors (SSRIs), and other antidepressants have all been studied, with varying results, in patients with panic disorder. The MAOIs are believed by some clinicians to be the most potent antipanic agents, but their considerable side effects limit their use. The tricyclic antidepressants imipramine and clomipramine are well established in treating panic disorder, although today many clinicians choose an SSRI as their first-line agent. Data supporting this clinical preference for SSRIs are just now becoming available. *(J Clin Psychiatry 1997;58[suppl 2]:20–24)*

Although panic disorder did not become an official diagnostic entity until publication of the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* (*DSM-III*) in 1980, symptom clusters consistent with panic attacks were described well before the advent of modern psychopharmacology.[1] Thus, it is not surprising that antidepressants have been used to treat panic disorder–like syndromes since their introduction. Over the past 30 years or so, some antidepressants have become well-established antipanic drugs, some are evolving as promising agents, and some have fallen by the wayside. The last decade has seen no shortage of reviews of the pharmacotherapy of panic disorder.[2–13] This overview provides a further update on the use of antidepressants in patients with panic disorder.

ANTIDEPRESSANTS IN PANIC DISORDER

Tricyclic Antidepressants

Between 1958 and 1961, Klein and Fink[14] treated 215 inpatients with imipramine to determine patterns of behavioral response. Fourteen of the patients had "episodic anxiety" characterized by "the sudden onset of inexplicable panic attacks, accompanied by rapid breathing, palpitations, weakness, and a feeling of impending death." Although sedatives and phenothiazines were ineffective, imipramine stopped the panic attacks. At discharge, 79% of the patients were improved, and 21% were much improved or had recovered. In 1964, Klein[15] confirmed these initial observations in a small (N = 13), double-blind, placebo-controlled study.

At least 13 double-blind, placebo-controlled studies have been conducted of imipramine in the treatment of phobic anxiety, agoraphobia plus panic attacks, phobia plus panic attacks, and panic disorder. According to Matuzas and Jack,[4] in 10 of these 13 studies imipramine was more effective than placebo, and in the other three the failure to separate from placebo may have been related to how the results were analyzed, short study duration, or small sample size. However, when Boyer[16] reviewed 12 double-blind, placebo-controlled studies of imipramine in patients with DSM-III panic disorder, he concluded that imipramine was superior to placebo in only six of these studies. The disagreements between authors appear to depend on which outcome measures they considered most important.

Overall, clinicians generally agree that imipramine is the best-studied tricyclic antidepressant and that its antipanic effectiveness is well established. Clomipramine, however, is not far behind, as evidenced by promising open studies[17,18] and positive double-blind trials.[19–26] For example, Johnston et al. found clomipramine more effective than placebo in a 28-week study of 94 women with agoraphobia; results were reported for both the 8-week[24] and 28-week[25] data.

In 8-week (N = 60)[23] and 12-week (N = 68)[26] studies, clomipramine was more effective than placebo and had advantages over imipramine in terms of overall effectiveness, onset of action, and effectiveness at lower dose. These observations require confirmation, especially in view of a placebo-controlled comparison of clomipramine and lofepramine (a tricyclic whose major metabolite is desipramine) that found no significant drug-placebo difference in panic attack frequency, a higher clomipramine dropout rate in the first 3 weeks (33% versus 8% for lofepramine), and a slow onset of effect (4 weeks) for both drugs on those measures that did separate from placebo

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(all three treatment groups also received behavior therapy).[21] At the end of 6 months, there were no significant differences in efficacy between the two drugs. The authors concluded that "overall, the only factors separating the two trial drugs were the greater acceptability, lower dropout rate and lower side effect scores for lofepramine and, for clomipramine, a slightly faster onset of action and marginal superiority in symptom reduction in patients able to tolerate side effects of this drug for at least 4 weeks."[21]

In a 6-week, double-blind study of patients with anxiety disorder (some of whom had panic disorder),[22] clomipramine and fluvoxamine were equally effective in improving anxiety symptoms, while clomipramine bested fluvoxamine in reducing symptoms of depression. The higher daily dose of clomipramine (150 mg versus 100 mg for fluvoxamine) may have accounted for this difference.

Desipramine is considerably less well studied as a panic disorder treatment. Although open trials[27,28] support its effectiveness, a 12-week placebo-controlled study[29] found no difference with regard to the primary outcome variable, panic attack frequency. By Week 12, 85% of the patients treated with desipramine and 76% of those receiving placebo had no panic attacks. In view of the surprisingly high placebo response, one wonders whether the 67% panic-free response to nortriptyline in an open study should be viewed as encouraging or discouraging.[30]

In summary, there are two well-established tricyclic antipanic drugs—imipramine and clomipramine—and others that show promise (desipramine, lofepramine, and nortriptyline). To conclude that all tricyclic antidepressants are effective or that the more potent serotonin uptake inhibiting tricyclics are preferred would be premature.

Monoamine Oxidase Inhibitors

Almost from their introduction, the monoamine oxidase inhibitors (MAOIs) have been used successfully to treat various anxiety syndromes, including atypical depression, anxiety hysteria, phobic anxiety, and anxiety neurosis.[31] In one report,[32] a patient with symptoms of anxiety responded fully to isocarboxazid and chlordiazepoxide but relapsed when the MAOI was stopped:

> On the day he was seen, while in the street, he was brought to a halt by a sense of constriction in the chest and a feeling of panic. His heart was racing and thumping; he was shivering with cold and sweating profusely, and was unable to stand without support. He feared he was about to die.[32(p7)]

The nonspecific, irreversible MAOIs (especially phenelzine) are widely considered the most potent of all antipanic drugs. While this may well be true, all of the placebo-controlled trials of these drugs (one with iproniazid and five with phenelzine) were published before 1982.[3] In general, sample sizes tended to be small, diagnoses mixed, and doses fairly low. Whether the results of these studies could (or should) be generalized to DSM-III, DSM-III-R, or DSM-IV panic disorder is unclear. For example, the iproniazid study[33] enrolled patients with severe agoraphobia. There was no mention of panic attacks, and the anxiety assessed by the study was "the degree of anxiety experienced when travelling alone." Iproniazid was significantly more effective than placebo in reducing anxiety but not in reducing avoidance behavior.

In the most definitive study of an MAOI, Sheehan et al.[34] treated 57 "endogenous anxiety" patients with either phenelzine (45 mg/day), imipramine (150 mg/day), or placebo over 12 weeks. By Week 6, both drugs separated from placebo. At the end of the study, phenelzine was better than imipramine on most outcome measures, although statistical significance was reached on only two scales (the Work and Social Disability Scale and the Symptom Severity and Phobic Avoidance Scale). Specifics about side effects were not provided, but the authors noted that phenelzine was better tolerated than imipramine. The fairly low doses of both drugs may have compromised their overall effectiveness.

In a 6-month open study of 40 patients with DSM-III diagnoses of either panic disorder or agoraphobia with panic attacks treated with phenelzine (mean daily dose = about 55 mg), Buigues and Vallejo[35] found that 97.1% of the 35 patients who completed the study responded with "a total suppression of panic and subpanic symptom attacks, as well as with a substantial reduction in the sustained or generalized anxiety measures."

As effective as the irreversible, nonspecific MAOIs might be, their side effect profiles and propensity for serious adverse food and drug interactions limit their appeal. Therefore, clinicians are focusing on the safer and better tolerated reversible inhibitors of monoamine oxidase A (RIMAs). The RIMA brofaromine has shown antipanic efficacy in open and controlled studies. Garcia-Borreguero et al.[36] noted improvement in all 14 inpatients with panic disorder treated openly with brofaromine 150 mg/day. In a 12-week, placebo-controlled study of 30 patients with panic disorder, van Vliet et al.[37] reported that "a clinically relevant improvement was found in more than 70% of the patients treated with brofaromine, whereas no significant improvement was observed on placebo." Although patients in both the brofaromine and placebo groups showed a similar decrease in the number of panic attacks, brofaromine was more effective in decreasing avoidance behavior, the intensity of the panic attacks, and the distress caused by panic.

In an 8-week, double-blind comparison of 88 patients with panic disorder with or without agoraphobia, brofaromine and clomipramine were found to be equally effective.[38] Dropout rates were quite high, with only 37% of patients treated with brofaromine and 51% of those treated with clomipramine completing the trial. Another double-blind study reported only in abstract form[39] found

that brofaromine and fluvoxamine were equally effective in treating panic disorder. While showing considerable promise as a treatment for panic disorder, brofaromine descended into oblivion when the manufacturer terminated development of the drug in 1993.[40]

Moclobemide, a RIMA widely available worldwide (but not in the United States) as an antidepressant, has been studied for its antipanic effect, but thus far, no reports have been published. Like brofaromine, moclobemide is no longer being developed in this country.

In summary, the MAOIs (particularly phenelzine) have established efficacy as antipanic drugs, although the research to support this statement is not overwhelming. Unless the RIMAs become available in the United States, MAOIs are likely to remain backups to the safer and better tolerated alternatives.

Serotonin Selective Reuptake Inhibitors

Based on a meta-analysis of randomized, prospective, double-blind, placebo-controlled studies of imipramine, alprazolam, and serotonin selective reuptake inhibitors (SSRIs) for the treatment of DSM-III or DSM-III-R panic disorder, Boyer[16] concluded that all three were superior to placebo, but that SSRIs were superior to imipramine and alprazolam. The SSRIs included in the analysis were fluvoxamine (N = 5), clomipramine (N = 3), paroxetine (N = 1), and zimelidine (N = 1). One wonders if the conclusions would have been the same if only SSRIs had been compared with the tricyclic antidepressants.

In terms of published reports, fluvoxamine is the best studied SSRI for treating panic disorder. In double-blind studies, it was more effective than placebo,[41–46] as effective as clomipramine (in a mixed anxiety disorder population)[47] and imipramine,[41] and more effective than maprotiline[48] and ritanserin (a 5-HT_2 receptor antagonist).[49]

Black et al.[44] compared fluvoxamine, cognitive behavior therapy, and placebo as treatments for panic disorder. At Week 4, at least moderate improvement was noted in 57% of patients treated with fluvoxamine, 40% of those receiving cognitive therapy, and 22% of those taking placebo. At Week 8 (completer analysis), freedom from panic attacks was noted in 81% of the patients in the fluvoxamine group, 53% of those in the cognitive therapy group, and 29% of those in the placebo group (the difference between the fluvoxamine and placebo groups was the only comparison to reach statistical significance).

Fluoxetine has shown promise as an antipanic agent, both openly[50] and in a small (N = 21) double-blind comparison with desipramine,[51] although Altshuler[52] described two depressed patients who actually developed panic attacks when treated with fluoxetine. Patients with panic disorder may be unusually sensitive to the activating side effects of fluoxetine so that quite low starting doses may be necessary.[53] Results of a large, controlled, multicenter efficacy study are pending.

Paroxetine* has gained attention as an antipanic agent based on the results of three double-blind, placebo-controlled studies.[54–56] In a meeting abstract, Dunbar[54] reported that paroxetine and clomipramine were equally effective, that both were more effective than placebo, and that paroxetine was better tolerated than clomipramine. Oehrberg et al.[56] compared paroxetine with placebo (with both groups receiving cognitive behavior therapy) over 12 weeks and found that paroxetine was more effective on two of the three primary outcome measures. However, onset of action was slow; the drug did not achieve statistical significance over placebo until Week 6 on one measure (50% or greater reduction in panic attacks) and until Week 12 on another (reduction in panic attacks to one or none over a 3-week period). Of particular interest was the finding of Steiner et al.[55] (presented as a meeting abstract) in a 10-week, fixed-dose (10, 20, or 40 mg/day), placebo-controlled study of 278 patients that statistically significant differences in primary outcome measures were reached only for the 40-mg dose (and then only on three of four measures).

A preliminary analysis of 191 patients in a 12-week, multicenter, placebo-controlled, fixed-dose (50, 100, or 200 mg/day) study of sertraline (N = 320) has been published in abstract form.[57] The number of panic attacks was significantly reduced in the 100-mg, 200-mg, and pooled sertraline groups compared with the placebo group. As with fluoxetine, there has been a report of panic attacks precipitated by sertraline.[58]

In summary, the SSRIs are rapidly emerging newcomers in the panic disorder field. Their clinical acceptance has actually preceded the well-designed research studies that support their efficacy. As with other antidepressants, their onset of action is slow and the effective dose range is similar to that required for depression. As yet, there have been no direct comparative studies of the various SSRIs in treating panic disorder.

Other Antidepressants

Geracioti[59] reported that "panic attacks were completely eliminated" in the first four patients he treated with low doses of venlafaxine. The same cannot be said for bupropion, which was ineffective in an open study of 13 patients with panic disorder.[60] Results with trazodone have been equivocal, with one study finding it to be less effective and less well tolerated than imipramine or alprazolam[61] and another suggesting some promise[62] (neither were double blind). Inositol, a glucose isomer, in a dosage of 12 g/day was found to be more effective than placebo in reducing the frequency and severity of panic attacks and the severity of agoraphobia in a 4-week, double-blind,

* In May 1996, paroxetine was approved by the Food and Drug Administration for the treatment of panic disorder with or without agoraphobia.

crossover study.[63] (Inositol earned inclusion as an antidepressant based on its favorable performance in a prior placebo-controlled study of depression.)

CONCLUSION

Many antidepressants also are effective antipanic drugs. In fact, more antidepressants have had favorable clinical trial results for panic disorder than have not. Although most controlled trials have been short term, clinical experience supports longer-term effectiveness. Of interest is the finding that relapse after drug discontinuation is considerably less common among patients treated with imipramine for 18 months compared with those treated for only 6 months.[64]

For the most part, comparisons of the various antidepressants suggest similar efficacy, although many of these drugs have not been directly compared. No antidepressant has been shown conclusively to have a rapid benzodiazepine-like onset of action. Whether there are clear differences among antidepressants in terms of onset of action remains to be determined. The few dose-finding studies that have been conducted suggest that conventional antidepressant dosages are required for effective antipanic treatment. Because a substantial number of patients with panic disorder are quite sensitive to the unpleasant activating effects of antidepressants, initial dosing should be conservative.

While the SSRIs have become the antipanic drugs of choice of many clinicians, research support for this preference is just starting to emerge. The high placebo response in many panic disorder studies suggests a cautious approach to accepting clinical lore before the results of large, well-designed, double-blind, placebo-controlled studies are available. A final issue of broader impact to the panic disorder field is the recognition that to comprehensively assess the effectiveness of treatment, outcome measures must evaluate more than just the decrease in the number of panic attacks.

Drug names: alprazolam (Xanax), bupropion (Wellbutrin), chlordiazepoxide (Librium and others), clomipramine (Anafranil), desipramine (Norpramin and others), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), isocarboxazid (Marplan), maprotiline (Ludiomil), nortriptyline (Pamelor and others), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor).

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Discussion

Drug Therapy

Dr. Rosenbaum: How should treatment be initiated in a patient with panic disorder? How can physicians overcome the paradoxical effects, such as anxiety and jitteriness, of the tricyclic antidepressants used to treat these patients?

Dr. Jefferson: You must start with very low doses—as low as possible—and titrate the dose upward over several weeks. Patients also must be forewarned about possible side effects and assured that side effects do not mean they will not respond to treatment. However, these caveats may decrease the use of tricyclic antidepressants. One reason why better results have been seen with serotonin selective reuptake inhibitors (SSRIs) is that they are fairly easy to use, although anxiety and jitteriness can also occur with these drugs.

Dr. Pollack: Many clinicians who prescribe SSRIs also start patients on a benzodiazepine to address early difficulties associated with initiation of treatment.

Dr. Barlow: Are these patients continued on the combination therapy indefinitely?

Dr. Charney: It may be possible to discontinue the benzodiazepine after obtaining the early benefit and continue the antidepressant alone, although our results suggest otherwise. We studied the combined use of a benzodiazepine and an antidepressant in patients with panic disorder. Patients in this study were randomly assigned to treatment with imipramine plus placebo or imipramine plus alprazolam. After 4 weeks of treatment, the placebo and alprazolam were tapered off over 2 weeks. Patients treated with alprazolam improved more quickly than did those who received placebo. However, symptoms recurred when alprazolam was discontinued, and the drug had to be reinstated for most patients in this group. Alprazolam discontinuation may have prevented imipramine from working. In the placebo group, the continued effects of imipramine were not inhibited.

A longer trial of alprazolam may have prevented these difficulties. However, with a longer duration of alprazolam treatment, concerns arise over dependence and withdrawal symptoms. Overall, our study suggested that combining alprazolam with imipramine was not a good approach.

Dr. Ballenger: Although your results suggest otherwise, combining a benzodiazepine with an antidepressant is common clinical practice in treating patients with panic disorder. Yet we know that when the benzodiazepine is tapered a month or two later, patients become worse. Is this a result of withdrawal symptoms or do the two drugs have overlapping but not identical spectra of action? In fact, that is what I believe.

Dr. Marshall: Aren't there data suggesting that primary care physicians as a group tend to underdose tricyclic antidepressants for patients with panic disorder, which may account for the poor response of these patients to treatment?

Dr. Jefferson: Data are available for depressed patients, but not for those with panic disorder. It appears that primary care physicians, like most other practitioners, are now prescribing SSRIs more frequently than tricyclic antidepressants. However, reports do not usually break down prescribing practices by disorder or provide information on the actual diagnosis or the drug dose used.

Dr. Rosenbaum: What duration of treatment do you recommend?

Dr. Jefferson: Data from Mavissakalian and colleagues indicate that the longer a patient is treated (18 months versus 6 months), the lower the relapse rate after the medication is discontinued. Yet few data are available to pinpoint the optimal duration of therapy. Studies are needed to determine whether 18 months of treatment is better than 12 months, or whether 12 months is better than 6 months, and so on. It is clear that panic disorder tends to be a chronic condition and that stopping treatment is associated with a high likelihood of relapse.

Dr. Barlow: Are there any data on the treatment of adolescents with panic disorder?

Dr. Jefferson: Although many adolescents are included in various studies, I have not seen separate analyses for this group of patients.