Issues in the Assessment of Treatment Response in Panic Disorder With Special Reference to Fluvoxamine

Philip T. Ninan, M.D.

Assessment of treatment response in panic disorder is complicated by the multidimensional aspects of panic disorder and agoraphobia, the short-term benefits from nonspecific aspects of treatment, and placebo response. Response to treatment with psychological and pharmacologic treatments of panic disorder is reviewed in this context. The experience of several Phase III studies of fluvoxamine in the treatment of panic disorder is examined as an illustrative example. When the response to placebo or comparison treatment in a study is high, no conclusion can be drawn about the true efficacy of the active treatment. *(J Clin Psychiatry 1997;58[suppl 5]:24–31)*

There is a need to better understand the nature of symptomatic improvement in panic disorder. A variety of psychotherapeutic[1] and pharmacologic[2] treatments are recommended in panic disorder. It is unclear whether benefits of these treatments are attributable to unique features of each treatment or if nonspecific factors provide the majority of benefits. This article will address these issues with reference to the experience of fluvoxamine, a serotonin selective reuptake inhibitor (SSRI), in panic disorder.

The central component of panic disorder is unexpected attacks of intense anxiety called *panic attacks*.[3,4] From a theoretical perspective, panic attacks can be viewed (1) as a quantitatively greater form of anxiety as seen in generalized anxiety disorder,[5] (2) as a biologically unique phenomenon different from generalized anxiety disorder,[6] or (3) as emanating specifically from fear related to bodily sensations.[7] The latter two are not mutually exclusive. Each approach has treatment implications. Conceptualizing panic attacks as an extension of general anxiety is the basis for providing generic forms of psychotherapeutic treatment such as psychodynamic and relaxation therapy and pharmacologic agents like benzodiazepines for symptomatic control. The hypothesis that there is a unique biological underpinning for panic attacks such as a false suffocation alarm[8] and the ability of challenges (CO_2, caffeine, yohimbine, cholecystokinin) to induce panic attacks implies a biological substrate underlying panic attacks and provides the theoretical basis for pharmacologic treatment with antidepressants. The hypothesis that fear related to bodily sensations underlies the tendency for panic is the basis for providing forms of cognitive behavior therapy.

ASSESSMENT OF PANIC DISORDER

The assessment of panic disorder is complicated by several issues. The diagnosis of panic disorder is based on phenomenology, and, therefore, the measure of the illness is clinically prominent symptomatology and functionality. In illnesses where the pathophysiology is better understood (e.g., diabetes mellitus), clinical symptomatology (e.g., polyphagia, polyuria, and polydypsia) is not necessarily a reflection of the severity of the illness (e.g., blood sugar level). There are several domains of symptoms in panic disorder (e.g., panic attacks, anticipatory anxiety, phobias), and assessment of each is necessary for a comprehensive view of the illness.[9] The value of self-ratings in panic disorder is limited because patients commonly lack a frame of reference of others' experience with the illness. Thus, severity measures will be based on the range of personal experience and expectations. However, as a measure of change, they hold greater validity. Even clinician rated scales share such limitations, as much of the anxiety is not overt and the ratings are based on verbal report.

Though the diagnostic criteria for panic disorder is relatively clear,[10] the presence of comorbidity, both current and lifetime, might be a critical issue in treatment response. Assessment of comorbidity needs to ascertain

From the Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia.

Presented at the closed symposium "Perspectives on Fluvoxamine Therapy," held March 2, 1996, in Orlando, Florida, and sponsored by Solvay Pharmaceuticals in conjunction with the Medical University of South Carolina, Department of Psychiatry and Behavioral Science through an educational grant from Solvay Pharmaceuticals, Inc.

Reprint requests to: Philip T. Ninan, M.D., Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, 1701 Uppergate Drive, Room 126, Atlanta, GA 30322.

whether the panic disorder is primary. This can be based on dominance of symptoms, the temporal sequence of symptom development, cause of impairment, and reason for seeking treatment. Comorbidity with panic disorder is the rule rather than the exception.[11] Similar to other illnesses in medicine, comorbidity could be a measure of severity (e.g., neuropathy in diabetes mellitus). Yet, the majority of treatment studies tend to exclude panic disorder patients who have significant comorbidity, limiting the ability to extrapolate findings to a large spectrum of the clinical population.

If the panic attacks are the main target of treatment, a minimum frequency is required for study entry (e.g., 1–2 per week). It is also important to measure subthreshold or limited symptom panic attacks because they can still result in prominent distress and impairment. The measurement of panic attacks with a daily patient diary needs to assess the symptoms of a panic attack, time, duration, and severity and whether the attacks were unexpected, situation bound, or situation predisposed.[9] Since panic attack frequency is quite variable, the length of baseline assessment should be as long as possible. However, the longer the baseline assessment period, the more likely that the more intensely ill patients will be excluded from studies because of inability to delay treatment.

Anticipatory anxiety is a key component of panic. Anticipatory anxiety can have several meanings including worry or apprehensive preoccupation with having a panic attack (i.e., expectation of a panic attack), fear of the dangerous consequences or aversiveness of a panic attack, and an ongoing tendency to fear related bodily sensations.

Phobias have fear (external and interoceptive cues) and avoidance components that should be assessed when the patient is alone. Direct behavioral assessment of phobias as well as self-report and clinician rating are ideally needed to obtain a comprehensive picture of the phobic symptoms.[9]

A global rating of the severity of panic disorder and overall improvement of both panic attacks and phobias is also important. Assessment of functional impairment should cover the domains of social functioning, work, family role, utilization of medical care, and alcohol and other drug abuse.

As occurred for studies with major depression, consistent definitions of response, remission, relapse, recurrence, and recovery are needed for panic disorder.[12] Response is often defined in pharmacologic studies as a 50% reduction in panic attack frequency or a score of much or very much improved on the Clinical Global Impressions (CGI) scale. The definition of remission is more complicated because symptomatic improvement does not necessarily imply a high functioning state. Various methods have been incorporated to assess functionality at the end of a treatment period and also to reliably measure change during treatment. Criteria proposed for assessing such end-state functioning include self-rating of phobic symptoms, a multitask behavioral avoidance test, rater assessment of achievement of goals, panic-free status, and a therapist rating of improvement.[13] Such a composite rating allows the distinction between partial response (including symptomatic improvement in one domain) and remission.

In major depression, relapse is defined as occurring during the period of continuation treatment and recurrence during maintenance treatment. Recovery is defined as remission of symptoms with maintenance of benefits on discontinuation of treatment.

Table 1. Potential Factors That Increase and Decrease Placebo Response

Increasing Factors	Decreasing Factors
Recent cohorts	Older cohorts
Patients responding to advertisements	Referral (clinical) patients
Successful blinding	Partial blinding
	Severity of symptoms
	Comorbidity
	Previous nonresponders

PLACEBO RESPONSE IN PANIC DISORDER

Placebo response rates in panic disorder can be extraordinarily high and often do not differ widely from those of active treatment groups. In a review, Merz[14] reported that after 4 weeks of treatment, the median number of patients taking placebo who were free of panic attacks was 56% of the comparison active treatment, and the median decrease in phobic fear of the placebo patients was 58% of the comparison active treatment.

Several factors might produce placebo effects or otherwise produce improvement in untreated panic disorder patients. Panic attacks fluctuate in frequency and are often dependent on the degree of exposure to triggering situations. Patients tend to enter treatment studies at times of symptomatic exacerbation, which can gradually decrease simply with the passage of time. The nonspecific psychological benefits inherent in any therapeutic relationship bind the experience of anxiety. Further, the expectation of improvement generated by treatment can have the effect of "remoralization."[15] In addition, there are factors that might produce the appearance of placebo effects, although these might also artificially increase the effects of the active treatment. Thus, measurement error (unreliability) might result in statistical regression to the mean.

Factors that can potentially increase or decrease the placebo response rate are listed in Table 1. As more treatments become available clinically, the representativeness of current cohorts entering studies might be different from previous cohorts. Nonresponders to previous treatments entering studies are less likely to respond to active treatment, making differentiation of placebo and active treatment more difficult. Medications with prominent side

effects compromise the blind compared with agents that have fewer side effects. Adverse events can be up to 100% for dry mouth with a tricyclic antidepressant and 89% for sedation with a benzodiazepine.[14] In addition, patients who are responding to treatment reduce their avoidance behavior, which can potentially increase their panic attack frequency.

Patients who joined the study as a result of advertisements and media attention (as compared with clinical patients) might have less severity and be more responsive to nonspecific effects of treatment. Traditional measures of severity include greater scores on rating scales of symptoms, functional disability, or previous nonresponse. However, the presence of comorbidity could also be a mark of greater severity, but such patients are often excluded from trials.

Panic disorder patients who drop out of studies are a problem in the assessment of efficacy. The most frequent reasons for dropping out of panic disorder studies are lack of efficacy and intolerable side effects: the former seen more with placebo and the latter seen more with active medication. Percentage of dropouts was greater in the placebo group in 13 of 14 studies.[14] The one exception had a 37% dropout rate in the active treatment group because of side effects to clomipramine.[16] Lack of efficacy results in a greater dropout rate in the placebo group in almost all clinical studies, and this can be as high as 67% for placebo compared with 14% for the active treatment.[14] Subjects who drop out because of lack of efficacy in the placebo condition artificially raise the response rate among those who remain in the study.

Because of high dropout rates, it is difficult to show a difference between the placebo and active treatments in an analysis of patients successfully completing a study, even with a large sample. Thus, in the alprazolam cross-national (Phase I) study of 526 patients, several of the outcome measures (e.g., number of panic attacks) failed to show significant differences between alprazolam and placebo in the completer analysis ($p < .09$ for total panic attacks), while being significant in the endpoint analysis ($p < .0001$ for total panic attacks).[17] A large dropout rate (> 30%) can also invalidate the assessment of efficacy in an endpoint analysis where the last observation is carried forward.[18] Merz[14] proposes that survival rates should also be an efficacy parameter in placebo-controlled studies of panic disorder.

IMPLICATIONS FROM THE LITERATURE OF PSYCHOLOGICAL TREATMENTS OF PANIC DISORDER

What can we learn from the literature documenting efficacy of psychological treatments for panic disorder? A number of different psychological treatments including psychodynamic, behavioral, and cognitive strategies have claimed efficacy in panic disorder.

Psychodynamic Therapy

Shear and colleagues[19] developed a psychodynamic model for panic disorder in a detailed study of nine patients. Patients reported symptoms of anxiety dating from childhood, discomfort with aggression, perception of their parents in a negative emotional light, decreased self-esteem, and stresses associated with frustration and re sentiment preceding the onset of panic. They propose a model with neurophysiologic vulnerability predisposing to early fearfulness, disturbed object relations, conflicts between dependence and independence, and catastrophic fears triggering the panic response.

There is a lack of systematic outcome studies of psychodynamic therapy for panic disorder. Yet, because psychodynamic therapy is the most prevalent form of therapy practiced in the United States, it continues to be used in the treatment of panic disorder. Given the potential for high placebo response rates in panic disorder, it is difficult to know whether any symptomatic improvement achieved can be specifically attributed to the therapy provided. On the other hand, patients may derive benefits in domains other than symptomatic control.

Behavioral and Cognitive Therapy

Relaxation techniques aimed to decrease overall physiologic reactivity resulted in 60% of completers (40% endpoint) being panic free.[20] Purely behavior based exposure in a graduated manner aims to reduce phobic anxiety and avoidance, but residual panic attacks often continue. Interoceptive exposure, which addresses fear of bodily sensations, is more successful in reducing panic attack frequency. Bodily sensations are triggered by exercise-induced cardiovascular stimuli, hyperventilation, or with vestibular challenges like the induction of dizziness. These are combined with breathing retraining including breathing into a bag and abdominal breathing.

The cognitive model of panic suggests that normal bodily sensations are catastrophically misappraised and interpreted as frightening and dangerous. This leads to a rapid escalation of anxiety, spiraling arousal, and eventually a panic attack. The so-called spontaneity of panic attacks is questioned, and cognitive factors are seen as playing a critical role. This model describes the development and maintenance of panic attacks and also points to their effective treatment. Treatment includes identifying the catastrophic interpretations, automatic thoughts, and misappraised bodily sensations. Such strategies have been highly effective in eliminating panic attacks. Beck and colleagues[21] reported that 71% of patients were panic free during cognitive therapy compared with 25% who were engaged in supportive psychotherapy. Similarly, Barlow[20] reported that 85% of patients were panic free during panic control treatment, a form of cognitive therapy. Thus, cognitive therapy seems to provide superior symptomatic control compared with other forms of psychological therapies.

However, end-state functioning assessments suggest that remission is not always achieved.

It is interesting in this light that nonprescriptive therapy had considerable efficacy in panic disorder.[22] Nonprescriptive therapy describes panic disorder as a reaction to life stresses, and the therapy focuses on life problems and stresses while the therapist's role is to listen reflectively to help the subject recognize and cope with hidden feelings. Direct advice and prescriptive interventions are not allowed. Seventy-eight percent of the nonprescriptive therapy group were free of panic while engaged in treatment compared with 66% receiving cognitive-behavioral therapy. The lack of a no-treatment comparison group leaves the potential placebo response rate open to question.

The equivalence of the response to both treatments above underlines challenges in interpreting the literature of psychological treatments of panic disorder. How generic are the benefits of treatment? Should a study that does not have a "failed" control group be given any consideration? Patient samples in different studies can show different response rates for control treatments. The reasons for this are unclear. The sampling of patients might be critical as well as subtle investigator-related behaviors. Such issues are relevant to the response seen with placebo treatment.

PHARMACOLOGIC TREATMENT OF PANIC DISORDER

Pharmacologically, benzodiazepines (alprazolam, clonazepam) and antidepressants (tricyclic antidepressants, monoamine oxidase [MAO] inhibitors, serotonin selective reuptake inhibitors) have documented efficacy in panic disorder.[23]

In the two largest panic disorder studies, alprazolam was more effective than placebo and equally effective as imipramine. In the cross-national Phase I trial, alprazolam and placebo were compared in 526 patients with panic disorder. Fifty-one percent of the patients showed marked improvement and 41% achieved moderate improvement compared with 37% marked and 26% moderate improvement shown with placebo.[17] Fifty-nine percent of the patients completing the study trial (55% endpoint) compared with 50% for placebo (32% endpoint) were panic free by the end of the 8-week trial. Alprazolam was also effective in reducing anticipatory anxiety and phobias as well as improving social and occupational functioning. Secondary disability was also reduced significantly compared with placebo. In the Phase II trial of 1168 panic disorder patients, imipramine was slower but equally as effective as alprazolam in the reduction of symptoms and secondary disability.[24]

Imipramine, clomipramine, and other tricyclic antidepressants have documented efficacy in placebo-controlled studies of panic disorder. Phenelzine, an MAO inhibitor, is also more effective than placebo in reducing the symptoms of panic disorder (see reference 23 for review). Serotonin selective reuptake inhibitors, studies with fluvoxamine (reviewed below), a placebo-controlled study of paroxetine,[25] and an open-label trial of fluoxetine[26] have documented efficacy in panic disorder. Paroxetine has recently received approval by the Food and Drug Administration (FDA) for the treatment of panic disorder, although the data from the Phase III studies have not yet been published.

The advantage of the benzodiazepines includes their ability to provide rapid benefits (usually in the first week) and protection against anticipatory anxiety as well as panic attacks with tolerable side effects. Side effects such as sedation usually resolve with time, although more subtle cognitive and motor effects can continue. However, concern with physiologic dependence and withdrawal phenomena limits the clinical utility of benzodiazepines in the management of panic disorder.

Antidepressants provide comparable efficacy to the benzodiazepines in panic disorder; without the disadvantage of physiologic dependence. However, antidepressants have a slower onset of action. Tricyclic antidepressants, in particular, can induce a hyperstimulatory response in some patients at drug initiation, and anticholinergic and other side effects can be problematic for patients. The use of MAOIs is limited by dietary and drug restrictions. SSRIs, because of their equivalent efficacy and more benign side effect profile, could be the drug of choice in the treatment of panic disorder.

FLUVOXAMINE IN THE TREATMENT OF PANIC DISORDER

Fluvoxamine is the most extensively investigated and reported SSRI in panic disorder, with studies performed on both sides of the Atlantic. In a series of studies conducted in the Department of Biological Psychiatry at the University Hospital of Utrecht in the Netherlands, den Boer and colleagues studied fluvoxamine in panic disorder. The first study[27] compared the efficacy of 150 mg of clomipramine and 100 mg of fluvoxamine for 6 weeks in 38 patients with panic disorder with and without agoraphobia. Both treatments showed a significant reduction in Hamilton Rating Scale for Anxiety (HAM-A) symptoms from baseline ($p < .05$) with no difference between the treatments. Fifteen of 26 patients taking clomipramine and 14 of 24 taking fluvoxamine had a greater than 50% reduction in HAM-A symptoms at the end of 6 weeks and were almost completely free of panic attacks.

To tease out serotonin versus norepinephrine reuptake inhibitors, den Boer and Westenberg[28] subsequently compared fluvoxamine against maprotiline, a specific norepinephrine uptake inhibitor. Forty-four patients with panic disorder (N = 6) and with phobic avoidance (N = 38) were randomly assigned and completed 6 weeks of fluvoxamine

or maprotiline. Dosage for both drugs was increased to 150 mg in a fixed-dose manner. The mean number of panic attacks decreased from 4.1 to 1.6 in the fluvoxamine group compared with no change in the maprotiline group ($p < .05$). There was also a significant decrease in the HAM-A scores with fluvoxamine compared with maprotiline ($p < .05$), although both groups showed a significant decrease in HAM-A scores compared with baseline. There was a 50% reduction in the HAM-A scores in 10 of 20 patients taking fluvoxamine and 5 of 24 taking maprotiline. Adverse effects of fluvoxamine were nausea and headache, while maprotiline caused dry mouth and tremor.

To examine the potential role of the 5-HT_2 receptor in treatment response, Westenberg and den Boer[29,30] compared ritanserin, a specific 5-HT_2 antagonist, and fluvoxamine. Sixty patients with panic disorder, 40 of whom had severe phobic avoidance, were randomly assigned to ritanserin, fluvoxamine, or placebo for 8 weeks. Dose of ritanserin was increased to 20 mg and fluvoxamine to 150 mg in a fixed manner. The frequency of panic attacks was reduced significantly in the fluvoxamine group without any change in the other two groups ($p < .05$). There was a significant reduction in HAM-A scores in the fluvoxamine group compared with placebo and ritanserin ($p < .01$). Phobic avoidance was significantly improved in the fluvoxamine group ($p < .05$) while none occurred in the other two groups.

Westenberg and den Boer[31] concluded from these studies that serotonin reuptake inhibition was effective in the treatment of panic disorder, while maprotiline, a norepinephrine reuptake inhibitor, was not. Further, neither the 5-HT_2 receptor blockade, as provided by ritanserin, nor placebo provided significant benefit in the treatment of panic disorder. These studies are marked by a low dropout rate, benefit in the frequency of panic attacks, general anxiety and avoidance when assessed, and a low placebo response.

The efficacy of fluvoxamine in panic disorder has been explored in several studies conducted in the United States. Hoehn-Saric et al.[32] recruited 50 patients with panic disorder, and 36 patients completed an 8-week double-blind, randomized study of fluvoxamine ($N = 18$, mean dose 206.8 mg) and placebo (mean dose 280 mg). Full symptom panic attacks were significantly reduced in the fluvoxamine group from Week 3 onward ($p < .05$). Anxiety as measured by the Clinical Anxiety Scale (CAS) was significantly reduced by fluvoxamine ($p < .05$), as was disability as measured by the Sheehan Disability Scale ($p < .001$). Side effects were generally mild and transient and included drowsiness, dyspepsia, and headaches.

Data published by Hoehn-Saric et al.[32] were part of a multicenter study involving four academic sites using the same protocol. The combined data (reference 33 and data on file, Solvay Pharmaceuticals) report that 172 patients showed significant efficacy of fluvoxamine compared with placebo at endpoint in the number of full and limited symptom panic attacks ($p < .05$), anxiety ($p < .05$), CGI severity ($p < .029$), phobic avoidance ($p < .05$), and disability ($p < .025$). However, there was no difference in the number of full panic attacks per week or the proportion of patients who were free of panic attacks. Completer analysis had similar conclusions. Nausea, asthenia (weakness), and insomnia were present in more than 10% of patients taking fluvoxamine compared with placebo.

Black et al.[34] randomly assigned 75 patients with panic disorder to receive 8 weeks of fluvoxamine, cognitive therapy, or placebo. The protocol was similar to the one reported by Hoehn-Saric et al.[32] with the addition of a cognitive behavioral cell. Fifty-five patients completed the protocol. The mean dose of fluvoxamine achieved was 230 mg while placebo was 270 mg. The study was not designed to determine the optimal dose of fluvoxamine. The maximum dose allowed was 300 mg. Forty-eight percent were receiving 300 mg; 29% were receiving between 200 and 300 mg; and 24% were receiving less than 200 mg. Fluvoxamine was found to be effective and well tolerated. Panic attack severity score was significantly better while fluvoxamine was compared with placebo ($p < .003$) at endpoint, as was anxiety ($p < .003$) and the CGI ($p < .0004$). Fifty-seven percent of patients taking fluvoxamine at 4 weeks and 90% at 8 weeks showed at least moderate improvement. Eighty-one percent of patients who completed the study at Week 8 were free of panic attacks, compared with 29.4% taking placebo.

In a similar multicenter study of panic disorder, Woods et al.[35] report on 188 patients who entered similar protocol as the above ones. At endpoint, fluvoxamine was significantly better than placebo in the proportion of patients free of panic attacks, reduction in the frequency and severity of panic attacks, CGI, and disability (all $p < .05$). Sixty-four percent of patients taking fluvoxamine and 42% taking placebo were categorized as responders on the CGI ($p < .002$). Side effects that were present over 10% compared with placebo were insomnia, somnolence, and asthenia.

In a complex study of panic disorder with agoraphobia comparing fluvoxamine and psychological treatment, de Beurs et al.[36] studied 96 patients who had panic disorder with moderate or severe agoraphobia. Seventy-six completed, 19 of whom were randomly assigned to fluvoxamine plus exposure, 20 to psychological panic management plus exposure, 18 to exposure alone, and 19 to placebo plus exposure. Treatment was for 12 weeks. Cognitive behavioral therapy was provided for patients in the psychological panic management group. Exposure treatment was provided in the second 6 weeks to all patients and included gradually prolonged self-exposure in vivo. Long-term users of benzodiazepines were included in the study with continuation of their benzodiazepine during the trial.

Table 2. Fluvoxamine in Panic Disorder: Phase III Studies*

Study no.	Design	Drug	Placebo	Study Length	Results: Improvement in Panic Attacks	Anxiety	Avoidance	CGI-I 1 or 2	Adverse Events[a]	Comments
2315/2	DB, MC fixed dose DSM-III-R PD and PDA	FLVX N: 50 = 75 100 = 77 200 = 78 300 = 78 60% female 87% Caucasian	PL N = 77 55% female 84% Caucasian	6 wk (PL lead-in 1 wk)	n.s. median time to panic free status FLVX 100- and 200-mg doses over PL ($p < .05$)	n.s.	n.s.	n.s. PL = 80% FLVX 50 = 70% 100 = 80% 200 = 86% 300 = 77%	nausea FLVX = 42% PL = 20%	majority nonacademic sites
2315/3	DB, MC DSM-III-R PD and PDA	FLVX N = 86 mean dose = 167 63% female 81% Caucasian	N = 88 mean dose = 196 58% female 89% Caucasian	6 wk (PL lead-in 1 wk)	n.s. panic free FLVX 83% PL 78%	n.s.	FLVX > PL $p = .0001$	n.s. FLVX 78% PL 76%	no difference	nonacademic sites
2315/12	DB, MC DSM-III-R PD and PDA	FLVX N = 83 mean dose = 149 65% female 93% Caucasian	N = 89 mean dose = 177 64% female 93% Caucasian	6 wk (PL lead-in 1 wk)	n.s. panic free FLVX 67% PL 68% FLVX > PL $p = .045$ on CYPAS	FLVX > PL $p = .005$	FLVX > PL $p = .031$	n.s. FLVX 73% PL 59%	no difference	nonacademic sites
2315/13	DB, MC DSM-III-R PD and PDA	FLVX N = 75 mean dose = 174 55% female 77% Caucasian	N = 79 mean dose = 222 50% female 68% Caucasian	6 wk (PL lead-in 1 wk)	n.s. panic free FLVX 67% PL 62%	n.s.	n.s.	n.s. FLVX 80% PL 65%	no difference	nonacademic sites

*Data on file with Solvay Pharmaceuticals. Abbreviations: DB = double-blind; MC = multicenter; PD and PDA = panic disorder with and without agoraphobia; n.s. = nonsignificant; FLVX = fluvoxamine; PL = placebo; CGI-I = Clinical Global Impression-Improvement (intent-to-treat); and CYPAS = Cornell-Yale Panic Anxiety Scale measuring panic related factor such as frequency of panic attacks, distress, anticipation, avoidance, and impairment.
[a]Adverse events = noted only if a symptom was greater than 10% in a group.

Patients were chosen for agoraphobic avoidance of at least half a year. The primary target of the study was agoraphobic symptoms, and fluvoxamine plus exposure was significantly better than placebo plus exposure. No minimal frequency of panic attacks was required at pre-test. However, there was a reduction in the number of panic attacks in all the groups except the one receiving psychological panic management plus exposure. Fluvoxamine combined with exposure in vivo was no different compared with placebo combined with exposure treatment on panic frequency.

A meta-analysis of 15 studies comparing serotonin reuptake inhibitors and imipramine was reported by Boyer[37] totaling 1054 patients. Both imipramine and serotonin reuptake inhibitors were significantly superior to placebo. Comparison of the effect size across study showed that serotonin reuptake inhibitors were superior to imipramine. There was no significant difference in effect sizes between the groups of serotonin selective reuptake inhibitors and the nonserotonin selective reuptake inhibitor clomipramine.

Similarly, meta-analysis of serotonin reuptake inhibitors compared with imipramine and alprazolam in panic attacks was done in 27 studies totaling 2348 patients.[38] Serotonin reuptake inhibitors were fluvoxamine, clomipramine, paroxetine, and zimelidine. Alprazolam, imipramine, and serotonin reuptake inhibitors were significantly superior to placebo. Comparison of the effect sizes shows that serotonin reuptake inhibitors were superior to both imipramine and alprazolam. There was no significant difference between alprazolam and imipramine.

Efficacy of an SSRI like fluvoxamine has several advantages compared with other pharmacologic agents used in the management of panic disorder. Apart from its efficacy, fluvoxamine has a low side effect profile and no cardiac complications and low risk for lethal overdose. Although there is considerable preliminary evidence suggesting efficacy of fluvoxamine in panic disorder, there are limited data on the dose that is effective and optimal.

PHASE III STUDIES OF FLUVOXAMINE IN PANIC DISORDER

Four Phase III studies in panic disorder, sponsored by the Upjohn Company, were initiated in late 1992 and completed within a year (data on file, Solvay Pharmaceuticals). One of these studies was a fixed-dose study, while the other three were flexible dose studies sharing the same design. A total of 885 patients participated in 48 centers, all of which were nonacademic except for a minority in the fixed-dose trial. Details of the four studies are presented in Table 2.

The fixed-dose study (#2315/2) randomly assigned patients to receive placebo or fluvoxamine at 50-, 100-, 200-, and 300-mg doses. Discontinuation rates were higher for fluvoxamine, and dropouts increased with fluvoxamine doses up to 200 mg (8 for placebo, 17 for 50 mg of fluvoxamine, 22 for 100 mg, 29 for 200 mg, and 26

for 300 mg). Eighty percent of patients taking placebo were categorized as responders on the basis of the CGI scores (≤ 2). The study failed to find a difference between fluvoxamine at any dose and placebo. The only significant difference noted between the treatments was that the median time to panic free status was significantly shorter at doses of 100 and 200 mg of fluvoxamine. The only adverse event that occurred in more than 10% of patients in a group was nausea, which was present in 42% of patients taking fluvoxamine compared with 20% taking placebo.

The three flexible dose studies shared a uniform protocol. They were multicenter, double-blind, flexible dose comparison of fluvoxamine and placebo. Patients were diagnosed as having panic disorder with or without agoraphobia by DSM-III-R criteria. The majority of patients were women and Caucasian. After a single-blind week of placebo (where not all patients were required to have a panic attack), patients were randomly assigned to receive fluvoxamine or placebo for 6 weeks. The dose of fluvoxamine was titrated between 50 and 300 mg, although the mean dose achieved was low to moderate. Response was measured weekly in the number of panic attacks, anxiety, avoidance and globally. In addition, adverse events were also monitored.

The outcome of the three flexible dose studies was generally negative except for statistically significant improvement in avoidance in favor of fluvoxamine in two studies and significant improvement on the Cornell-Yale Panic Anxiety Scale (CYPAS) in one (Table 2). The CYPAS measures panic related factors such as frequency of panic attacks, distress during the attacks, anticipation of attacks, avoidance, and impairment. There was no significant difference in outcome with an endpoint analysis. Generally, there were more patients who discontinued because of lack of efficacy in the placebo condition and more patients who discontinued because of adverse events in the fluvoxamine condition.

Patients who were responders (i.e., no panic attacks) in the above studies were continued on fluvoxamine for an additional 6 weeks, following which patients were again randomly assigned to continue fluvoxamine or receive placebo for an additional 5 weeks. Discontinuation of fluvoxamine resulted in a significant increase in the number of panic attacks, anxiety, and avoidance (but no difference on the CGI) compared with continuation of fluvoxamine.

The above studies indicate that fluvoxamine was generally not significantly better than placebo in the treatment of panic disorder with or without agoraphobia. However, this is in conflict with the earlier studies that uniformly show efficacy of fluvoxamine compared with placebo. How can one explain this discrepancy? The most obvious explanation is the high placebo rate in each of the studies. If response is categorized as scoring 1 or 2 (very much or much improved) on the CGI, the placebo response was 59% to 80% in the different studies. Such a high rate of response to placebo makes it extremely difficult to show superior efficacy in a comparison treatment.

Potential sources of a placebo response in the Phase III trials include the nonspecific psychological support provided in the studies, unknown reliability of the assessment measures, lack of significant differences in side effects, and the nature of patients entering these studies. The patients entering these studies were rated as moderately ill and could have responded to nonspecific factors. Further, the studies were performed predominantly at nonacademic sites with patients recruited largely through advertisements rather than treatment-seeking clinical populations. The general lack of significant differences in the experience of side effects between fluvoxamine and placebo maintained the blind effectively.

Design issues were also worthy to note. In the fixed-dose study, there was a tendency for a dose response relationship at least until 200 mg. The doses used in the flexible dose studies might have been inadequate to show the optimal response. There was only a week of single-blind placebo lead-in, with no requirement of a panic attack during the baseline assessment, excluding improvement in the number of panic attacks as a criteria for improvement in several of the patients. The length of active treatment in the studies was limited to 6 weeks. Termination of the study on the same day as the final assessments contaminated termination and follow-up issues with the final assessment. Thus, on several occasions, benefits that were evident at the week prior to termination were not present at termination. This might be particularly relevant in panic disorder, where exit events have potent psychological significance and are uniquely difficult for patients to handle.

DISCONTINUATION OF FLUVOXAMINE

In a report of 14 patients, Black et al.[39] reported on the effects of abrupt discontinuation of fluvoxamine in patients who had been continuously taking fluvoxamine and responded for between 7 and 8 months. Twelve of the 14 patients developed symptoms. The most frequent were dizziness, headaches, irritability, and nausea. Other symptoms that occurred in more than 20% of individuals included fatigue, poor concentration, chest pain, tremor, and other gastrointestinal symptoms. Symptoms peaked on the fifth day after discontinuation. These symptoms were different from recurrence of panic disorder, which occurred in two patients.

CONCLUSION

When the response to placebo or an active comparison treatment is high in a study, no conclusion can be drawn about the true efficacy of the treatment under study if it too has a good response. The response to nonspecific aspects of treatment is interesting in light of the high medical

(including psychiatric) morbidity and functional disability associated with panic disorder.

It is important to publish negative studies because of "file-drawer effects" where negative studies are selectively unpublished. This is particularly relevant when meta-analyses are performed. Given the number of Phase III studies performed by the pharmaceutical industry, and still unpublished, it is clear that the experience with fluvoxamine is not unique.

Drug names: alprazolam (Xanax), clomipramine (Anafranil), clonazepam (Klonopin), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), maprotiline (Ludiomil), paroxetine (Paxil), phenelzine (Nardil), yohimbine (Yocon and others).

REFERENCES

1. Wilson GT. Behavior therapy. In: Karasu TB, chair. American Psychiatric Association Task Force on Treatment of Psychiatric Disorders. Washington, DC: American Psychiatric Press; 1989;3:2025–2036
2. Salzman C. Treatment with antianxiety agents. In: Karasu TB, chair. American Psychiatric Association Task Force on Treatment of Psychiatric Disorders. Washington, DC: American Psychiatric Press; 1989;3:2036–2052
3. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Press; 1994
4. Klein DF. Delineation of two drug-responsive anxiety syndromes. Psychopharmacology (Berl) 1964;5:397–408
5. Hollister LE. Panic disorder: old wine in new bottles? Integrative Psychiatry 1992;8(2):75–90
6. Liebowitz MR, Fyer AJ, Gorman J, et al. Recent developments in the understanding and pharmacotherapy of panic attacks. Psychopharmacol Bull 1986;22:792–796
7. Barlow DH. Behavioral conception and treatment of panic. Psychopharmacol Bull 1986;22:802–806
8. Klein DF. False suffocation alarms, spontaneous panics, and related conditions: an integrative hypothesis. Arch Gen Psychiatry 1993;50:306–317
9. Shear MK, Maser JD. Standardized assessment for panic disorder research. Arch Gen Psychiatry 1994;51:346–354
10. Liebowitz MR. Functional classification of anxiety-panic. International Clinical Psychopharmacology 1993;8(suppl 1):47–52
11. Cassano GB, Perugi G, Musetti L. Comorbidity in panic disorder. Psychiatric Annals 1990;20:517–521
12. Frank E, Prien RF, Jarrett RB, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder: remission, recovery, relapse and recurrence. Arch Gen Psychiatry 1991;48:851–855
13. de Beurs E, Dyck RV, van Balkom AJLM, et al. Assessing the clinical significance of outcome in agoraphobia research: a comparison of two approaches. Behavior Therapy 1994;25:147–158
14. Merz WA. Placebo response in panic disorder: a review. Eur Psychiatry 1994;9:123–127
15. Howard KI, Kopta SM, Krause MS, et al. The dose-effect relationship in psychotherapy. Am Psychol 1986:159–164
16. Fahy TJ, O'Rourke D, Brophy J, et al. The Galway study of panic disorder, I: clomipramine and lofepramine in DSM III-R panic disorder: a placebo controlled trial. J Affect Disord 1992;25:63–70
17. Ballenger JC, Burrows GD, Dupont R, et al. Alprazolam in panic disorder and agoraphobia: results from a multicenter trial, I: efficacy in short term treatment. Arch Gen Psychiatry 1988;45:414–422
18. Leber P. Policy for the review of efficacy of NDAs by FDA. Division of neuropharmacological drug product. 1986;Doc33697p
19. Shear MK, Cooper AM, Klerman GL, et al. A psychodynamic model of panic disorder. Am J Psychiatry 1993;150:859–866
20. Barlow DH. Long-term outcome for patients with panic disorder treated with cognitive behavioral therapy. J Clin Psychiatry 1990;51(12, suppl A): 17–23
21. Beck AT, Sokol L, Clark DA, et al. A crossover study of focused cognitive therapy for panic disorder. Am J Psychiatry 1992;149:778–783
22. Shear MK, Pilkonis PA, Cloitre M, et al. Cognitive behavioral treatment compared with nonprescriptive treatment for panic disorder. Arch Gen Psychiatry 1994;51:395–401
23. Ballenger JC. Panic disorder: efficacy of current treatments. Psychopharmacol Bull 1993;29:477–486
24. Cross National Collaborative Panic Study, Second Phase Investigators. Drug treatment of panic disorder: comparative efficacy of alprazolam, imipramine and placebo. Br J Psychiatry 1992;160:191–202
25. Oehrberg S, Christeansen PE, Behnke K, et al. Paroxetine in the treatment of panic disorder: a randomized double-blind, placebo-controlled study. Br J Psychiatry 1995;167:374–379
26. Schneier FR, Liebowitz MR, Davies SO, et al. Fluoxetine in panic disorder. J Clin Psychopharmacol 1990;10:119–121
27. den Boer JA, Westenberg HGM, Kamerbeek WDJ, et al. Effect of serotonin uptake inhibitors in anxiety disorders: a double-blind comparison of clomipramine and fluvoxamine. Int Clin Psychopharmacol 1987;2:21–32
28. den Boer JA, Westenberg HGM. Effect of a serotonin and noradrenaline uptake inhibitor in panic disorder: a double-blind comparative study with fluvoxamine and maprotiline. Int Clin Psychopharmacol 1988;3:59–74
29. Westenberg HGM, den Boer JA. Serotonin influencing drugs in the treatment of panic disorder. Psychopathology 1989;22(suppl 1):68–77
30. den Boer JA, Westenberg HGM. Serotonin function in panic disorder: a double blind placebo controlled study with fluvoxamine and ritanserin. Psychopharmacology (Berl) 1990;102:85–94
31. Westenberg HGM, den Boer JA. New findings in the treatment of panic disorder. Pharmacopsychiatry 1993;26(suppl):30–33
32. Hoehn-Saric R, McCleod DR, Hipsley PA. Effect of fluvoxamine on panic disorder. J Clin Psychopharmacol 1993;13:321–326
33. Hoehn-Saric R, Fawcett J, Munjack DJ, et al. A multicenter, double-blind, placebo-controlled study of fluvoxamine in the treatment of panic disorder. Neuropsychopharmacology 1994;10(suppl 3):102S
34. Black DW, Wesner R, Bowers W, et al. A comparison of fluvoxamine, cognitive therapy, and placebo in the treatment of panic disorder. Arch Gen Psychiatry 1993;50:44–50
35. Woods S, Black D, Brown S, et al. Fluvoxamine in the treatment of panic disorder in outpatients: a double-blind, placebo-controlled study. Neuropsychopharmacology 1994;10(suppl 3):103S
36. de Beurs E, van Balkom JLM, Lange A, et al. Treatment of panic disorder with agoraphobia: comparison of fluvoxamine, placebo and psychological panic management combined with exposure and of exposure in vivo alone. Am J Psychiatry 1995;152:683–691
37. Boyer W. Serotonin uptake inhibitors are superior to imipramine in alleviating panic attacks: a meta-analysis. In: Mendlewicz DG, Brunello RG, eds. Current Therapeutic Approaches to Panic and Other Anxiety Disorders. Basel, Switzerland: Karger, Int Acad Biomed Drug Res; 1994;8: 55–60
38. 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
39. Black DW, Wesner R, Gabel J. The abrupt discontinuation of fluvoxamine in patients with panic disorder. J Clin Psychiatry 1993;54:146–149