The Side Effect Burden Associated With Drug Treatment of Panic Disorder

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This article reviews the incidences of side effects in placebo-controlled clinical trials of drug therapy in patients with panic disorder. We performed a MEDLINE search for placebo-controlled studies in panic disorder that reported the incidences of side effects, published in English language, peer-reviewed journals between 1992 and 1997. We discuss the side effects experienced by patients receiving tricyclic antidepressants, serotonin selective reuptake inhibitors, and benzodiazepines, the drug classes most commonly prescribed for the treatment of panic disorder. Available evidence suggests that, with respect to tolerability, serotonin selective reuptake inhibitors are the most favorable treatment choice for patients with panic disorder. *(J Clin Psychiatry 1998;59[suppl 8]:39–44)*

Panic disorder tends to be a chronic condition, usually requiring treatment for a minimum of 6 months. Therefore, drug treatments should be well tolerated with few side effects and no behavioral toxicity, to avoid interfering with the patient's daily activities.

As a group, patients suffering from panic disorder have a high rate of medically unexplained physical symptoms and are high utilizers of primary and emergency care services. As they tend to receive a range of prescribed medications, treatment for panic disorder should be free from drug interactions. The potential for interactions with certain foods should also be taken into account, as patients may find long-term dietary restrictions unacceptable. When panic disorder is comorbid with major depression, sufferers are at increased risk of suicide attempts, and so prescribed drugs must be relatively safe if taken in overdose. Ideally, drug treatment should be free of emergent or discontinuation symptoms because many patients who have panic disorder are especially sensitive to physical symptoms, often misinterpreting them as the beginning of a panic attack.

The issue of relative tolerabilities of the different classes of antidepressant drugs has been reviewed extensively. For example, meta-analyses of antidepressant studies in patients with major depression show that serotonin selective reuptake inhibitors (SSRIs) are slightly but significantly better tolerated than tricyclic antidepressants (TCAs), as measured by the total numbers of drop outs from treatment.[1,2] These findings were confirmed by a study of clinical practice in the United Kingdom in which depressed primary care patients receiving SSRIs were less likely to discontinue treatment due to side effects than were patients receiving TCAs.[3] We wished to review the incidence of side effects with antidepressant therapies specifically in patients with panic disorder to assess whether the characteristics of panic disorder patients might result in different treatment recommendations than those for depression. We also reviewed the side effect profiles of the commonly prescribed benzodiazepines. To select papers for this review, we performed a MEDLINE search for placebo-controlled studies in panic disorder, published in English language, peer-reviewed journals between 1992 and 1997 that included search terms such as *panic* and *randomized controlled trial* or *controlled clinical trial* or *double-blind method*. We included only those papers that reported the incidences of side effects.

TRICYCLIC ANTIDEPRESSANTS

The TCAs have been used for the treatment of panic disorder since the 1960s, and were considered first-line treatment for many years. However, the slow onset of action of TCAs and the excitatory symptoms that commonly occur during the first week or two of treatment are major disadvantages of using this class of antidepressant for panic disorder.[4] The side effect profiles of TCAs in panic disorder are reviewed here.

Modigh et al.[5] performed a 12-week, double-blind, placebo-controlled comparison of imipramine (50–250 mg daily) and clomipramine (25–200 mg daily) in the

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Table 1. Incidence (% of patients) of Side Effects Experienced Significantly (p < .05) More Frequently by Patients With Panic Disorder Treated for 12 Weeks With Clomipramine (25–200 mg daily), or Imipramine (50–250 mg daily) Than With Placebo*

	% of Patients			
Side effect	Clomipramine (N = 22)	Imipramine (N = 29)	Placebo (N = 17)	p Value
Dry mouth	100	96	67	.0004
Sweating	77	89	27	.0001
Orthostatism	77	82	33	.002
Obstipation	64	71	27	.01
Headache	14	46	47	.04

*Data from reference 5.

treatment of panic disorder. Table 1 shows the incidences of side effects that occurred significantly more frequently in the active treatment groups than in the group who received placebo. In addition, headache was reported significantly more often by patients receiving imipramine than clomipramine. The relatively high incidence of side effects in the placebo group suggests that these symptoms are indicative of the underlying panic disorder rather than possible drug-related effects.

In a small, placebo-controlled, 6-week comparison of the TCAs clomipramine (100 mg daily) and lofepramine (140 mg daily) in 79 patients with panic disorder, side effects were scored on a 38-item, 3-point scale of severity.[6] Scores were significantly higher in the clomipramine group than the placebo group for nausea, vomiting, constipation, metallic taste, and hand tremor. In the lofepramine group, only nausea was given a significantly higher score than in the placebo group. Of 13 dropouts in the first 3 weeks of the study, 9 of 27 patients were receiving clomipramine, 2 of 26 patients were receiving lofepramine, and 2 of 26 patients were receiving placebo. The high early dropout rate from the clomipramine group (33%) was largely due to failure to tolerate the study medication. Although there was a high incidence of side effects in the first 3 weeks of the study, most side effects resolved as the study progressed.

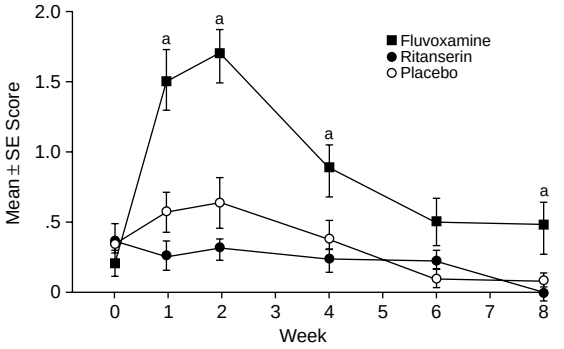
SEROTONIN SELECTIVE REUPTAKE INHIBITORS

The SSRI class of antidepressant has been shown to have superior tolerability to TCAs in patients with depression.[1] Studies with currently available SSRIs have shown them to be effective in the treatment of panic disorder (see den Boer, this supplement), and the available data on their side effect profiles are reviewed below.

Fluvoxamine

Black et al.[7] and de Beurs et al.[8] performed placebo-controlled comparisons of fluvoxamine with psychological treatment in patients with panic disorder. In the study

Figure 1. Mean ± SE Side Effect Score for Nausea (Measured on a 5-Point Scale) in Patients With Panic Disorder Receiving Placebo or Fluvoxamine (150 mg daily)*



*From reference 9, with permission.
[a]p < .05 vs placebo.

by Black et al.[7] involving 75 patients, side effects were assessed during the 8-week treatment period using a 4-point rating scale. The fluvoxamine dosing schedule was flexible, with a maximum daily dose of 300 mg. In the first week of treatment, fluvoxamine-treated patients were significantly more likely to report side effects than were recipients of cognitive therapy (p ≤ .005). From week 4 onward, the fluvoxamine group experienced significantly more side effects compared with patients receiving placebo (p ≤ .01). Interestingly, during the first 4 weeks of the study, patients treated with placebo reported significantly more side effects than patients receiving cognitive therapy. In a 12-week study of 96 panic disorder patients, de Beurs et al.[8] assessed the side effects of fluvoxamine (up to 150 mg daily) and placebo, both in combination with in vivo exposure treatment, using the Fawcett side effect scale. Only 1 side effect, headache, had a significantly greater score in the fluvoxamine plus exposure group than in the placebo plus exposure group (p = .05). The authors point out that all side effects were mild and resolved with continuation of treatment.

In an 8-week, double-blind, placebo-controlled comparison of fluvoxamine (150 mg daily) and the 5-HT_2 antagonist ritanserin in 59 patients with panic disorder, the most notable side effects in the fluvoxamine group were sleepiness, sweating, diarrhea, and nausea (occurring at varying points during the study, all p < .05 compared with ritanserin and placebo).[9] Figure 1 shows the course of the severity of nausea during the study. This was most severe during the first 2 weeks of treatment and gradually improved, although in some patients, nausea remained troublesome throughout the 8-week treatment period. In another small study, by Bakish et al.,[10] 54 patients with panic disorder were given fluvoxamine, imipramine, or placebo. Nausea was not reported in this study. The most common side effect was dry mouth, experienced by about 80% of imipramine-treated patients. Side effects reported

Table 2. Percentage of Patients With Panic Disorder Experiencing Emergent Side Effects During Acute (12 weeks*) and Chronic (36 weeks†) Flexible-Dose Treatment With Paroxetine (20–60 mg daily), Clomipramine (50–150 mg daily), or Placebo

Side Effect	% of Patients		
12 Weeks	Paroxetine (N = 123)	Clomipramine (N = 121)	Placebo (N = 123)
At least 1 side effect	73	89[a]	68
Sweating	22	30	12
Dry mouth	20	50	14
Nausea	20	31	15
Headache	16	17	18
Insomnia	13	10	7
Dizziness	11	18	9
Asthenia	11	14	4
Diarrhea	11	3	4
Constipation	8	17	8
Somnolence	7	11	6
Tremor	5	25	1
Abnormal ejaculation[b]	26	24	2
Impotence[b]	4	15	0
36 Weeks	Paroxetine (N = 68)	Clomipramine (N = 63)	Placebo (N = 45)
At least 1 side effect	62	76	51
Headache	10	11	13
Sweating	10	21	7
Dry mouth	7	14	4
Dizziness	12	11	0
Weight gain	6	14	0
Abnormal ejaculation[b]	12	4	0

*From reference 12, with permission.
†From reference 13, with permission.
[a]p = .002 vs paroxetine.
[b]Gender specific, with percentage calculated for male patients.

Table 3. Percentage of Patients Experiencing Treatment-Emergent Side Effects During 12 Weeks of Fixed-Dose Treatment With Citalopram (10–15 mg, 20–30 mg, or 40–60 mg), Clomipramine (60–90 mg) or Placebo*

	Citalopram			Clomipramine	
Side Effect	10–15 mg (N = 97)	20–30 mg (N = 95)	40–60 mg (N = 89)	60–90 mg (N = 98)	Placebo (N = 96)
Headache	33[a]	26	29[a]	16	28
Nausea	27	28	29	30	18
Dry mouth	12[a]	12[a]	17[a]	33[b]	15
Sweating	10	18[b]	16	19[b]	7
Dizziness	9	14	7[a]	18[b]	6
Insomnia	8	11	7	16	7
Abdominal pain	4	5[a]	7[a]	0[b]	5
Tremor	3[a]	7	2	17[b]	5
Constipation	1	3	2	7	2
Anorgasmia	2	9[b]	10[b]	10[b]	0

*From reference 14, with permission.
[a]Significantly different from clomipramine.
[b]Significantly different from placebo.

more often in the fluvoxamine group than in the imipramine group were insomnia and a "funny" taste in the mouth. Overall, the investigators considered fluvoxamine to be better tolerated than imipramine, with fewer side effects reported.

Paroxetine

In a 12-week study by Oehrberg et al.[11] of 120 patients with panic disorder, paroxetine plus cognitive therapy was compared with placebo plus cognitive therapy. Paroxetine doses were increased gradually from 10 to 20 mg daily during the first 2 weeks of the study, and thereafter could be increased up to 60 mg daily depending on efficacy and tolerability. The most commonly reported side effects were nausea (23% in the paroxetine group and 12% in the placebo group) and sweating (23% in the paroxetine group and 5% in the placebo group). Headache was also common, occurring with equal frequency in the paroxetine and placebo groups (22% and 23%, respectively). The authors point out that the side effect profile for paroxetine was as expected for an SSRI, and was not different from that seen in depressed patients treated with paroxetine.

In a 12-week, placebo-controlled comparison of paroxetine (10–60 mg daily) and clomipramine (10–150 mg daily) in 367 patients with panic disorder, paroxetine was better tolerated than clomipramine.[12] Treatment-emergent side effects were reported by 73% of patients in the paroxetine group, compared with 89% in the clomipramine group, and 68% in the placebo group (Table 2). The proportion of patients experiencing side effects during treatment with paroxetine was no different from that during placebo treatment; however, the proportion was significantly greater in the clomipramine group than in the paroxetine group (p = .002). Patients who successfully completed this short-term study could elect to enter a 9-month extension study.[13] By comparing the incidences of side effects in the short- and long-term studies (Table 2), it would appear that certain side effects become less frequent with long-term treatment; for example, the incidence of dry mouth is reduced from 20% in the 12-week study to 7% in the long-term extension in the paroxetine group, and from 50% to 14% in the clomipramine group. Clearly, those patients most troubled by side effects would be least likely to enter the extension study, but the low incidence of side effects in this second, extension study suggests that the emergence of new side effects during long-term treatment is rare. The reduced incidence of side effects during long-term treatment may also be due to the fact that the physical symptoms of the underlying anxiety disorder, which may have been interpreted as drug-associated effects during acute treatment, are in remission.

Citalopram

Wade et al.[14] carried out an 8-week, placebo-controlled comparison of citalopram and clomipramine in 475 patients with panic disorder. Citalopram was given at 3 dose levels: 10–15 mg, 20–30 mg, and 40–60 mg daily. Treatment-emergent adverse events are shown in Table 3. Two side effects, namely sweating and anorgasmia, were significantly more common in the citalopram treatment groups than in the placebo group. Anorgasmia appeared to be the

only dose-related side effect with citalopram. By contrast, 5 side effects were significantly more common in the clomipramine treatment group than in the placebo group: dry mouth, sweating, dizziness, anorgasmia, and tremor. When taken together, these results suggest that citalopram was better tolerated than clomipramine.

BENZODIAZEPINES

Certain benzodiazepines are well established in the short-term management of anxiety disorders, their main advantage being a rapid therapeutic onset. However, their long-term use for often chronic conditions such as panic disorder is hindered by their potential to cause dependence.[15,16] There is evidence that some patients with panic disorder have particular difficulty discontinuing benzodiazepine treatment compared with patients suffering from generalized anxiety disorder, as they may misinterpret their physical withdrawal symptoms as representing a re-emergence of panic symptoms.[17]

Alprazolam

Lydiard et al.[18] investigated the effect of 2 fixed doses of the high-potency benzodiazepine alprazolam (2 mg and 6 mg daily) in a placebo-controlled study involving 94 patients with panic disorder. Side effects that appeared to be more common in the active treatment groups than in the placebo group were sedation, ataxia, slurred speech, nasal congestion, diarrhea, and decreased libido. A greater number of patients in the 6-mg group than in the 2-mg group experienced ataxia (61% vs. 40%) and slurred speech (61% vs. 33%); although a statistical analysis was not performed on the side effect data, it can not be concluded that these side effects were dose dependent. More patients in the placebo group than in the alprazolam groups reported palpitations and excessive sweating, which are typical symptoms of panic disorder.

Alprazolam is available in 2 formulations: tablets, usually given as a 4-times-daily dosing regimen, and also as an extended-release formulation, that can be given once daily. Two studies have investigated the extended-release formulation in panic disorder patients.[19,20] In the Pecknold et al. study,[19] 209 patients with panic disorder were treated with a flexible-dose regimen of standard alprazolam, extended-release alprazolam, or placebo. Table 4 shows the incidence of side effects during the 6-week treatment period. Two side effects, drowsiness and incoordination, occurred in a significantly higher proportion of patients in the active treatment groups than in the placebo group ($p < .001$). There was no significant difference in the incidence of side effects between the 2 formulations of alprazolam. Similar results were reported by Schweizer et al.[20] in a placebo-controlled study of extended-release alprazolam in 194 patients with panic disorder or agoraphobia and panic attacks. Drowsiness and incoordination were the only side effects to occur significantly more often in the alprazolam group than in the placebo group ($p < .001$). Although a high proportion of patients suffered from drowsiness during the study (88%), tolerance appeared to develop to this effect, as only 18% continued to complain of drowsiness by the sixth week of treatment. Side effects that were reported with equal frequency in the alprazolam and placebo groups were headache and nervousness.

Table 4. Percentage of Patients With Panic Disorder Experiencing Side Effects During 6 Weeks of Flexible-Dose Treatment With Standard Alprazolam Tablets, Extended-Release Alprazolam, and Placebo*

Side Effect	Standard Alprazolam (N = 70)	Extended-Release Alprazolam (N = 70)	Placebo (N = 69)
Drowsiness	86	79	49[a]
Weakness	43	39	30
Cognitive disorder	43	41	28
Incoordination	39	41	16[a]
Dry mouth	31	30	23
Sleep disorder	25	32	31
Gastrointestinal distress	25	28	34
Malaise	20	30	30
Palpitations	12	17	30

*From reference 19, with permission.
[a]$p < .001$ vs active treatment.

A similar side effect profile was observed in the Cross-National Collaborative Panic Study. Phase 1 of this study was a placebo-controlled trial of alprazolam in 525 patients with panic disorder,[21] while phase 2 compared alprazolam with imipramine and placebo in over 1000 patients with panic disorder.[22] A greater proportion of patients receiving alprazolam experienced sedation, fatigue, memory problems, slurred speech, amnesia, and ataxia than those receiving imipramine or placebo. Sedation was the most common side effect, but tended to subside over the course of the studies. Patients receiving imipramine reported dry mouth, constipation, difficulty in urinating, excessive sweating, tremor, and sleep disturbances. Consistent with the symptoms of panic disorder, patients in the placebo group experienced insomnia, excitement, headache, tachycardia, hyperventilation, chest pain, sleep disturbances, irritability, dizziness, and tremor.

Clonazepam

Treatment with the high-potency benzodiazepine clonazepam has been investigated in a small placebo-controlled study of 29 patients with panic disorder by Beauclair et al.[23] The maximum daily dose of clonazepam permitted was 5 mg. Again, the most common side effects were drowsiness, reported by 9 clonazepam-treated patients compared with no patients in the placebo group ($p < .001$), and impaired memory (3 clonazepam-treated patients and no placebo-treated patients, $p < .07$). Sexual problems were reported by 3 patients in the clonazepam group, namely anorgasmia, erectile dysfunction, and de-

Table 5. Percentage of Patients With Panic Disorder Experiencing Treatment-Emergent Side Effects During 8 Weeks of Flexible-Dose Treatment With Alprazolam, Diazepam, or Placebo*

Side Effect	Diazepam (N = 81)	Alprazolam (N = 77)	Placebo (N = 77)
CNS			
Drowsiness	84	77	42[a]
Fatigue	57	44	42
Impaired thinking	44	38	22[a]
Memory problems	40	34	31
Neuromuscular			
Incoordination	56	40	17[a]
Slurred speech	32	23	5[a]
Genitourinary			
Urinary difficulty	17	16	10
Menstrual irregularity	18	12	6
Libido decrease	19	13	5[a]
Libido increase	19	8	4[a]
Sexual dysfunction	7	3	1
Gastrointestinal			
Appetite decrease	22	20	20
Appetite increase	32	30	14[a]
Weight gain	24	17	14
Weight loss	12	14	8

[a] $p < .05$ vs active treatment.
*From reference 24, with permission.

creased libido, compared with none in the placebo group ($p = .07$).

Diazepam

The low-potency benzodiazepine diazepam was compared with alprazolam by Noyes et al.[24] in an 8-week, placebo-controlled study involving 241 patients with panic disorder and/or agoraphobia. Dosing was flexible, with maximum daily doses of 100 mg for diazepam and 10 mg for alprazolam. Table 5 lists the treatment-emergent side effects reported by patients during the study. There were no significant differences in the side effects experienced by diazepam- or alprazolam-treated patients. As in the alprazolam studies described previously, the most frequent side effects were those involving the central nervous system, such as drowsiness, impaired thinking, incoordination, and slurred speech. Overall, sedation was most severe during the first week of the study and gradually diminished thereafter, although sedation remained more severe in the active treatment groups than in the placebo group throughout the study. Interestingly, benzodiazepine treatment resulted in increased occurrence of decreased libido, as well as reports of increased libido, compared with placebo.

DISCUSSION

When selecting drug treatment for the patient with panic disorder, it is particularly important to consider the side effect profile of the chosen agent. Patients with panic disorder appear to be especially sensitive to physical side effects, often misinterpreting them as anxiety symptoms, and thus starting the vicious circle of escalating anxiety that leads to a further panic attack. For this reason, we considered it of interest to review the side effects associated with pharmacotherapy, specifically in patients with panic disorder. Compared with the great number of studies investigating drug therapy in depressed patients, there are relatively few treatment studies in patients with panic disorder. From the studies reviewed here, it would appear that the side effect profiles of antidepressants are similar in patients with panic disorder compared with those seen in depressed patients. The comparative studies appear to show that SSRIs are generally better tolerated than TCAs in panic disorder patients,[10,12,14] with evidence that some side effects may be dose related.[14]

We chose to review only placebo-controlled studies. The importance of this choice can be seen in the high incidence of certain side effects seen in the placebo treatment groups in the selected studies. For example, the incidences of headache and insomnia seen with paroxetine or citalopram treatment were similar to those in the placebo treatment groups.[12,14] Thus, it is important to distinguish true treatment-emergent side effects from the symptoms of the underlying anxiety disorder. This, of course, is difficult to do in clinical practice.

All classes of drug are associated with side effects. However, the side effect profiles of certain drug classes may be preferable when considering the long-term management of panic disorder. For example, the anticholinergic side effects caused by TCA treatment may not be severe in some patients, but many find them troublesome, and this may affect their compliance with long-term treatment. Benzodiazepines cause sedative side effects that have an impact on the patient's daily social or occupational activities, for example driving, or operating machinery. These particular side effects are a major disadvantage when the aim of treatment is for the patient to resume his or her normal functioning. SSRIs, TCAs, and benzodiazepines are all associated with sexual side effects, such as loss of sexual interest, delayed ejaculation, inability to ejaculate, and delayed or absent orgasm. Sexual dysfunction may be an unrecognized cause of noncompliance, because although patients may find these side effects unacceptable, they are likely to be underreported unless patients are specifically asked about them.[25,26] Most antidepressant-related side effects resolve or improve with long-term treatment, and patients should be reassured that any symptoms they experience will usually be short-lived.

In summary, the side effect profiles associated with pharmacotherapy for panic disorder are not appreciably different from those seen in depressed patients. The evidence suggests that as a group, the SSRIs have the most favorable side effect profile for patients with panic disorder.

Drug names: alprazolam (Xanax), clomipramine (Anafranil), clonazepam (Klonopin), diazepam (Valium and others), fluvoxamine (Luvox), imipramine (Tofranil and others), paroxetine (Paxil).

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