The Long-Term Treatment of Panic Disorder

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Panic disorder is a chronic and recurring condition, and there is therefore a need for long-term therapy. This paper reviews data from long-term studies of drug treatment for panic disorder to address issues of whether medication benefits persist, whether improvement can continue over several months or years, the tolerability of long-term treatment, patient selection for long-term treatment, and when and how to stop medication. The main conclusion is that long-term drug treatment of panic disorder is necessary, effective, and safe. Serotonin selective reuptake inhibitors offer benefits of ease of dosing, good tolerability, and no safety or dependence problems; TCAs are often poorly tolerated, and benzodiazepines are associated with dependence problems. Withdrawal from all types of medication should be considered, slow, planned, and individualized; some patients require an indefinite duration of treatment.
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Panic disorder is becoming increasingly recognized among clinicians as a chronic and recurring condition.[1] There is, therefore, a need for drug therapies that are suitable for prolonged use. A plethora of studies has established the antipanic efficacy of benzodiazepines, tricyclic antidepressants (TCAs), and serotonin selective reuptake inhibitors (SSRIs) over the short term. Fewer studies have considered the use of antipanic agents over the long term, but available data do suggest that efficacy is maintained with continued treatment and relapse prevented.

The aim of this paper is to review data from studies of the long-term treatment of panic disorder to address a number of questions: do gains persist, can improvement occur over several months, is long-term treatment well tolerated, who should receive long-term treatment, and when and how should medication be stopped.

CONTINUED TREATMENT OVER THE LONG TERM

It is common clinical practice to maintain patients with panic disorder on treatment over the long term. Two studies with a naturalistic follow-up showed that 47% to 70% of patients were still receiving a TCA or benzodiazepine 2.5 years after their initial entry into a clinical study.[2,3]

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Naturalistic Long-Term Outcomes

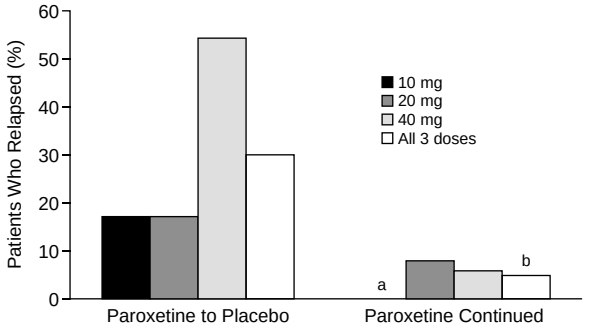
Naturalistic long-term outcomes, after initiating TCA therapy, were examined by Noyes et al.[2,4] in a study involving 107 patients with panic disorder or agoraphobia with panic attacks. At a follow-up of 2.5 years, most patients (79%) perceived that they had experienced at least a moderate improvement in symptoms (measured on a 5-point rating scale: no improvement, slight, moderate, marked, very marked), although only 14% were completely free of symptoms. Of 50 patients who were still on treatment, all were receiving a TCA; 16 had discontinued treatment for at least 1 month but then subsequently resumed treatment, most commonly because of relapse (N = 13). Side effects led to treatment discontinuation in 37 patients (35%) and were considered to be dose-limiting in 16 of 40 patients who experienced no response or only a slight improvement during TCA therapy.

Katschnig et al.[5] followed up for 4 years 367 patients who had taken part in international multicenter placebo-controlled trials of alprazolam and imipramine. In general, the status of this group of patients improved during the 4 years following the end of the drug trial, in terms of panic attack frequency, phobic avoidance, and disability. With regard to continued treatment, most patients (77%) received no psychotropic medication during the follow-up period; 16% and 7% reported continuous use of benzodiazepines (with or without antidepressants) and antidepressants only, respectively. The use of medication during the follow-up period was not significantly related to outcome, although there tended to be a worse outcome with continuous benzodiazepine use than with no medication or continuous use of antidepressants. An important predictor of outcome was the level of phobic avoidance at baseline, which was significantly related to a worse outcome regarding panic attacks and phobic avoidance, whereas the

frequency of panic attacks at baseline was not related to outcome.

The importance of measuring multiple clinical dimensions of panic, rather than just panic attack frequency, was further highlighted in a review[6] of 16 follow-up studies in patients with panic disorder: remission rates were 30% to 80% for panic attacks but 33% to 61% for functional impairment and 18% to 64% for phobic avoidance. Less is known about how to treat phobic avoidance and disability than panic attacks.

Figure 1. Percentage of Patients With Panic Disorder Who Relapsed After Responding to 3 Months of Paroxetine Treatment (10, 20, or 40 mg) and Who Were Randomly Assigned to Receive Either the Same Dose of Paroxetine or Placebo for a Further 3 Months*



*Data from reference 9.
[a]No relapse on 10 mg of paroxetine.
[b]p = .002, all 3 doses paroxetine to placebo.

Table 1. Long-Term Follow-Up of Patients With Panic Disorder After 6 Months of Treatment With Imipramine, Cognitive Therapy, or Applied Relaxation*

Status	Imipramine	Cognitive Therapy	Applied Relaxation
Patients who were free from panic attacks and functional disability,			
At 6 months	55	65	35
At 15 months	45	70	32
Patients who relapsed, % within 6–15 months	40	5	26

*Data from reference 11.

Do Medication Benefits Persist?

Persistent benefits with continued treatment of panic disorder were demonstrated in naturalistic follow-up studies by Burrows et al.[7] and Marchesi et al.[8] In 69 patients with panic disorder who showed initial improvements in panic attacks and phobia ratings after 2 months of treatment with alprazolam, efficacy was maintained with continued treatment for at least 8 months.[7] Similarly, improvements in panic attacks and agoraphobia were maintained over a 12-month period on continued treatment of 49 panic patients with a combination of imipramine and lorazepam: at the end of the study, 75% of patients were free of panic attacks and 69% were free of phobic avoidance.[8]

Recent controlled data on maintained efficacy with continued treatment have been obtained with the SSRI paroxetine.[9] Eighty patients with panic disorder who responded to 3 months of maintenance treatment with fixed doses of paroxetine (10, 20, or 40 mg/day) were randomly assigned to either continue paroxetine or switch to placebo for a further 3 months. Only 5% of those who continued to take paroxetine experienced a relapse (defined as a return to the number of panic attacks experienced at baseline or more than a 2-point rise on the Clinical Global Impressions severity scale), compared with 30% of those who switched from paroxetine to placebo; the switch from 40 mg of paroxetine to placebo led to the greatest relapse rate of 55% (Figure 1).

Early, but important, relapse prevention data were provided by Zitrin et al.[10] in 1978. A total of 39 patients with panic disorder who showed a moderate or marked improvement in phobic avoidance and associated anxiety during 6 months of treatment with imipramine (plus behavioral therapy or supportive psychotherapy) were discontinued from all forms of therapy and followed for a further 12 months. Recurrence of phobic symptoms was experienced by 26% of patients over the 12-month period; around one-half of the relapses occurred within a few months and the rest later, and thus patients were at risk over the entire 12-month period.

In a more recent study by Clark et al.,[11] 64 patients with panic disorder received imipramine, cognitive therapy, or applied relaxation for 6 months, and panic attacks and functional disability were monitored at 3, 6, and 15 months. Benefits persisted over time: the proportion of patients who were free from panic attacks and functional disability at 15 months was almost identical to that seen at 6 months (Table 1). However, among patients who were panic-free at 6 months, 40% of those who discontinued imipramine therapy relapsed and required further treatment by 15 months; corresponding relapse rates after discontinuation of successful cognitive and applied relaxation therapy were 5% and 26%, respectively.

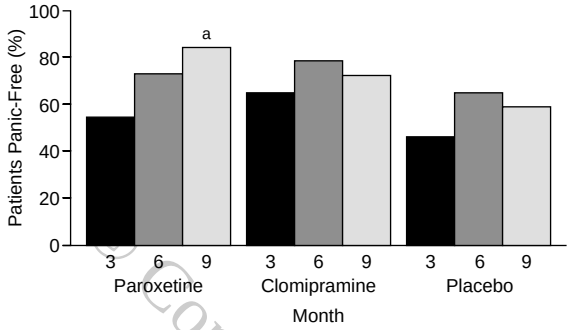
Taken together, data demonstrate variable rates of relapse: the Judge and Steiner study[9] shows a 30% relapse rate after paroxetine discontinuation, whereas imipramine literature[10–14] suggests a figure of 26% to 40%.

Can Improvement Continue Over Several Months, or Even Years?

Two studies illustrate that improvement can continue with prolonged administration of antipanic therapy.[5,15]

The efficacy of paroxetine, clomipramine, or placebo was assessed over a 9-month period in a controlled study involving 176 patients with panic disorder.[12] During treatment with paroxetine, 55% of patients were free from panic attacks by 3 months, and the proportion continued to increase to 84% over the next 6 months (Figure 2). With

Figure 2. Percentage of Patients Who Are Panic-Free After 12, 24, and 36 Weeks of Treatment With Paroxetine, Clomipramine, and Placebo for Panic Disorder*



*Data from reference 15.
[a]p = .004, paroxetine versus placebo at 9 months.

Table 2. Percentage of Patients With No Panic Attacks, No/Mild Phobic Avoidance, and No/Mild Functional Disabilities After Treatment With Imipramine, Alprazolam, or Placebo*

	Pretreatment	1 Year	4 Years
Panic-free	0	24	39
No/mild phobic avoidance	15	39	60
Functional disability			
No/mild work disability	12	48	82
No/mild family disability	19	53	77
No/mild social disability	7	41	70

*Data from reference 5.

clomipramine and placebo, however, the proportion of patients with no panic attacks increased only until month 6, and decreased thereafter.

Greater improvements in panic symptoms, phobic avoidance, and various aspects of functional disability (work, family, and social) were observed after continued treatment with imipramine, alprazolam, or placebo for 4 years than for 1 year in a naturalistic follow-up study of 367 patients with panic disorder (Table 2).[5] For example, the proportion of patients with no or only mild work disability increased from 12% pretreatment to 48% at 1 year and to 82% at 4 years.

These studies show that patients with improvements in symptoms and functional disability can continue to improve on prolonged treatment over months or even years. With aggressive pharmacotherapy, sustained response rates are seen over a 6- to 9-month period.

TOLERABILITY OF LONG-TERM TREATMENT

In the 9-month comparative study[15] of paroxetine, clomipramine, and placebo, there was no difference in the proportion of patients reporting at least one adverse event during treatment (62%, 76%, and 51%, respectively). However, a higher incidence of withdrawals due to adverse events occurred with clomipramine (19%) than with either paroxetine or placebo (both 7%). The equivalent low relapse rate between paroxetine and placebo is evidence that paroxetine is well tolerated. The high incidence of withdrawals due to adverse events seen with clomipramine substantiates previous evidence that TCAs are not well tolerated. For example, the Noyes et al. study[4] reported earlier in this paper noted a 35% incidence of discontinuations due to side effects of TCAs.

Few studies have addressed the issue of long-term dosing schedules. In a follow-up study[12] of patients with pure panic disorder and agoraphobia (i.e., with no comorbid depression) who had shown a good and stable response to imipramine over an initial 6-month treatment period, slowly reducing the dose to half the baseline level (mean of 168 mg to 83 mg) for a further 12 months led to a low relapse rate of 7%. These data support further research into whether a reduced maintenance dose is sufficient after successful short-term treatment or whether better management is achieved with the original dose. Although a pertinent question for all classes of antipanic agent, it is of major importance for TCAs due to their problematic side effects, but is somewhat less of an issue for SSRIs.

PATIENT SELECTION FOR LONG-TERM TREATMENT

Prolonged treatment is appropriate for most patients, but particularly when there are high levels of persisting symptoms, comorbidity exists, previous relapses have occurred with serious consequences, or multiple external stressors are present. Unfortunately, there is a reluctance by some physicians and patients to consider long-term medication: education is needed to encourage the acceptance and appropriate long-term use of effective and well-tolerated drug treatment.

Prognostic factors can provide useful predictive information on treatment outcomes. Using data from a 12-month follow-up of 48 patients who discontinued treatment with imipramine, alprazolam, or placebo after completing an 8-month maintenance period, Rickels et al.[16] identified 2 major predictors of a panic-free outcome: a low baseline score on the Hamilton Rating Scale for Anxiety and completion of the 8 months of treatment. Predictors of a medication-free status at follow-up were a low baseline phobia score, no prior use of antipanic medication, and completion of the 8 months of treatment.

Predictors of outcome after benzodiazepine treatment have been examined in 2 studies.[17,18] Pollack et al.[17] showed that the presence of dysthymia and severe panic and agoraphobia symptoms at the start of therapy was associated with poor outcome after short-term treatment with alprazolam or clonazepam. Over the long term, poor outcome was associated with a long duration or chronicity of the illness and the presence of agoraphobia or social

phobia. Abelson and Curtis[18] demonstrated that disinhibition at the hypothalamic-pituitary-adrenal axis before alprazolam treatment is a predictor of poor outcome at 2 years.

Two naturalistic follow-up studies[2,13] have reported major depression in 20% of panic disorder patients and suggested that patients who have either a history of depression or do not respond well to treatment are primarily susceptible to depression.

WHEN AND HOW TO STOP MEDICATION

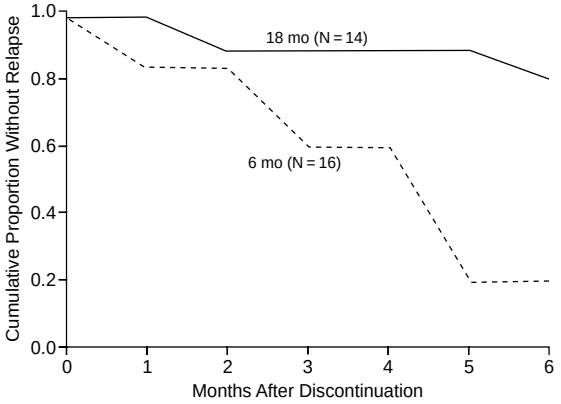
Discontinuation of medication can be considered when sustained remission is achieved and when patients have acquired anxiety management skills, feel ready, and have a stable life situation. Clearly, treatment should be stopped immediately if side effects become intolerable or potentially toxic, or if a loss of effect is apparent.

For benzodiazepines, TCAs, SSRIs, and in particular, monoamine oxidase inhibitors, medication should be withdrawn slowly (or tapered) in a planned manner, irrespective of the reason for discontinuation. Patient education about their therapy, as well as support, should be offered at onset of and throughout treatment and at withdrawal. For some patients, behavioral psychotherapy can be helpful in achieving a successful taper, particularly after benzodiazepine treatment.

In the Rickels et al. study[16] of prognostic factors of taper difficulty and withdrawal symptoms after discontinuation from imipramine, alprazolam, or placebo, a moderate or marked withdrawal syndrome was experienced by 63% of alprazolam-treated patients, but by none of those tapering imipramine or placebo. The severity of panic attacks at baseline, and not the daily alprazolam dose, appeared to predict taper difficulty. These data highlight the significant risk of dependence problems with benzodiazepines, especially alprazolam. There is no evidence that SSRIs and TCAs are associated with dependence problems.

There is limited evidence on whether reinstitution of medication is beneficial in patients who relapse after withdrawal from treatment. In a study[14] of imipramine treatment in patients with panic disorder and agoraphobia, discontinuation followed either acute treatment (6 months, N = 16) or acute plus maintenance treatment (18 months, N = 14). Lower relapse rates (defined as requiring treatment after return of panic and/or agoraphobia symptoms) were observed in the maintenance treatment group: at 6 months after discontinuation, only 20% of the maintenance group had relapsed, compared with 80% of the acute treatment group (Figure 3). These findings demonstrate that imipramine maintenance treatment protects against relapse, and an extrapolation is that reinstitution of medication may be appropriate in patients who relapse after discontinuation from short-term treatment.

Figure 3. Cumulative Proportions of Patients Without Relapse After Discontinuation From Imipramine After 6 and 18 Months of Treatment*



*From reference 14, with permission.

FUTURE CONSIDERATIONS

A number of unanswered questions pertinent to the long-term treatment of panic disorder remain, including whether the effective dose can be lowered for maintenance therapy, the optimal long-term therapy to treat anxiety sensitivity and phobic avoidance symptoms, and for how long remission following long-term treatment is sustained.

CONCLUSIONS

Available data indicate that long-term treatment of panic disorder is necessary, effective, and well tolerated. Full benefits may take some months to occur, and some patients require an indefinite duration of treatment. SSRIs offer sustained benefit and ease of dosing without problems associated with tolerability, safety, or discontinuation. Intolerable side effects are common with TCAs, and benzodiazepines are associated with dependence problems. With all medications, withdrawal should be slow, planned, and individualized, and possible complementary benefits from psychosocial treatment should be considered.

Drug names: alprazolam (Xanax), clomipramine (Anafranil), clonazepam (Klonopin), imipramine (Tofranil and others), lorazepam (Ativan and others), paroxetine (Paxil).

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