

# Evidence-based pharmacotherapy of panic disorder

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## Abstract

This paper reviews the literature on the pharmacotherapy of panic disorder, in order to address the questions (1) what is the first-line pharmacotherapy of choice for panic disorder?, (2) for how long should maintenance pharmacotherapy be continued, and (3) what is the optimal approach to the treatment-refractory patient with panic disorder. A MEDLINE search (1966–2003) was undertaken to collate randomized controlled trials of pharmacotherapy in panic disorder. A review of the evidence indicates that SSRIs are currently the first line agent of choice in panic disorder, and that pharmacotherapy should be continued for at least 1 year. There has been relatively little research on the pharmacotherapy of treatment-refractory panic disorder, and this area requires future attention.

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## Introduction

Panic disorder (PD) with or without agoraphobia is one of the most prevalent of the anxiety disorders. The disorder is also accompanied by significant morbidity and comorbidity. Fortunately, a number of effective treatments for PD are available. This chapter focuses on the pharmacotherapy, assessing the evidence base in order to address questions about (1) the optimal first-line pharmacotherapy of PD, (2) the optimal duration of pharmacotherapy, and (3) the optimal approach to pharmacotherapy in the treatment-refractory patient. In order to ensure that all relevant randomized controlled trials were considered, a MEDLINE search (1966–2003) was undertaken using the key words 'panic' and 'treatment'. In addition, recent meta-analyses of PD, and treatment guidelines on PD were reviewed. We begin by briefly discussing the diagnosis and target symptoms of PD.

## Diagnosis

Panic attacks and agoraphobic avoidance are defined in the DSM-IV-TR (APA, 2000) as follows: A panic

attack is 'a discrete period of intense fear or discomfort, in which four or more of the following symptoms develop abruptly and reach a peak within 10 minutes'. The symptoms listed are: palpitations, sweating, trembling or shaking, sensations of shortness of breath or smothering, feeling of choking, chest pain or discomfort, nausea or abdominal distress, feeling dizzy or faint, derealization or depersonalization, feeling of losing control or going crazy, fear of dying, paresthesias and chills or hot flushes. Agoraphobia is defined as: 'anxiety about being in places or situations from which escape might be difficult (or embarrassing) or in which help may not be available in the event of an unexpected or situationally predisposed panic attack. Agoraphobic fears typically involve characteristic clusters of situations that include being outside the home alone, being in a crowd or standing in a line, being on a bridge, and travelling in a bus, train or automobile'.

Given that panic attacks and agoraphobia occur in different anxiety disorders, a first issue in the assessment of panic symptoms is the accurate differentiation of PD from these other entities. DSM-IV-TR emphasizes that PD is diagnosed when the attacks experienced are unexpected and when at least one of the attacks has been followed by 1 month (or more) of persistent concern about having additional attacks, worry about the implications of the attacks or their consequences, or a significant change in behaviour

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related to the attacks (APA, 2000). Patients suffering from social phobia or PTSD may also suffer from panic attacks, but these attacks are not unexpected. They are related to specific situations: a difficult social situation or a situation that refers to a traumatic event.

When a patient with PD is also extremely afraid of going into public places like shopping centres, trains, cinemas or other situations from which escape would be difficult or in which help would not be available in case of a panic attack, this person is said to have PD with agoraphobia. There is an ongoing debate about the possibility that patients suffer from agoraphobia without panic attacks. In everyday clinical practice it is found very often that severe agoraphobic avoidance without present panic attacks only developed after the occurrence of at least one unexpected panic attack. Phobic behaviour is also common among patients suffering from other anxiety disorders, but in these disorders it is related to the avoidance of specific situations that relate to that anxiety disorder, e.g. getting dirty in patients suffering from OCD, or going to meetings in patients suffering from social phobia.

A second important diagnostic issue is the differentiation of PD from general medical disorders. Given the high prevalence of PD and its frequent presentation in medical settings, it is important to have a high index of suspicion for this disorder. As many as 3.5% of the general population are estimated to suffer from PD (Eaton et al., 1994; Katerndahl and Realini, 1993), and 1-month prevalence rates are 0.7–2.2% for females and 0.4–0.8% for males (Bijl et al., 1997; Eaton et al., 1991). The prevalence of PD in medical specialities like cardiology and otolaryngology is even much higher: 15% and higher percentages have been reported (Chignon et al., 1993; Stein et al., 1994) and it is, therefore, important to rule out PD in patients presenting with unexplained physical complaints.

For agoraphobia, high prevalence rates are also found with a 1-month prevalence for females of 4.4%, and for males 1.6% (Bourdon et al., 1988). PD usually develops during the third decade of life, with a mean age of onset of 28 yr (Marks, 1987). People with panic attacks may present to primary-care practitioners or to a range of medical specialists. Unnecessary special investigations are frequently ordered.

Conversely, however, a comprehensive medical history and examination may be needed to exclude the presence of physical disorders that can cause the symptoms of a panic attack (Raj and Sheehan, 1987). Well-known causes of panic-like symptoms are hyperfunction of the thyroid, hypoglycaemia and pheochromocytoma. In general, any clinical condition that is associated with physical signs that can occur also

during a panic attack, has the potency to provoke anxiety. The most important mechanism for this is probably the cognitive misinterpretation of these bodily sensations (Clark, 1986). The use of psychoactive substances like caffeine, cannabis or cocaine may also produce panic attacks. Withdrawal from benzodiazepines or alcohol is another cause of panic symptoms. In all these situations, the patient should be diagnosed not with PD, but rather with 'anxiety disorder due to a general medical condition with panic attacks/phobic symptoms' or 'substance-induced anxiety disorder with panic attacks/phobic symptoms'. In some cases, substance abuse may be denied, and drug screening may be required before an accurate diagnosis is made.

Target symptoms in PD include not only panic attacks and agoraphobia, but also comorbid symptoms and associated impairment. PD is frequently associated with mood disorders, other anxiety disorders (e.g. social anxiety disorder), and substance-related disorders. The clinical relevance of diagnosing PD with or without comorbid disorders lies in the fact that patients with comorbidity are more severely and chronically ill, more disabled, utilize services more frequently and are more difficult to treat (Roy-Byrne et al., 2000). Formulated in other words, 'comorbidity' points to a more severe subgroup of PD. PD is characterized by significant distress and functional impairment, and it is important these features are also targeted by treatment interventions.

### Treatment options

Although the pathogenesis of PD remains incompletely understood, a range of effective pharmacological, non-pharmacological, and combination treatments have been developed in the past three decades. Pharmacological treatments mainly comprise treatment with high-potency benzodiazepines and antidepressants. Other medications that have been suggested for the treatment of PD include  $\beta$ -adrenergic blocking agents (e.g. propranolol),  $\alpha_2$ -adrenergic receptor agonists (e.g. clonidine), mood stabilizers (e.g. carbamazepine, lithium), and antipsychotic agents. Propranolol has been found ineffective in controlled trials, while most of these other agents have not been studied systematically.

Behavioural and cognitive therapies have also been found effective for the treatment of PD (Bakker et al., 1999; van Balkom et al., 1997). Questions remain about how best to sequence and combine pharmacotherapy and psychotherapy. In practice, they are frequently combined, with the rationale that this may lead not

only to symptom improvement, but also to a more persistent recovery. Although psychodynamic psychotherapeutic intervention strategies have been developed (Milrod et al., 1997), the efficacy of non-directive therapies has not been documented in controlled studies. Brief psychodynamic psychotherapy has, however, been reported to be helpful in reducing relapse rates following treatment with an antidepressant (Wiborg and Dahl, 1996).

In the treatment of PD, separate options for panic attacks and agoraphobic avoidance behaviour can be distinguished. Pharmacological and cognitive-behavioural therapy (CBT) for panic attacks diminish frequency and severity of panic attacks (Bakker et al., 1999; van Balkom et al., 1997). With pharmacological treatments, accompanying avoidance behaviour also improves, as do comorbid general anxiety symptoms, and, in case of treatment with an antidepressant, there is also reduction in comorbid depressive symptoms (van Balkom et al., 1997). Behavioural treatment strategies without cognitive therapeutic elements, e.g. 'exposure in vivo', may be effective in treating agoraphobic avoidance behaviour, but are not effective for panic attacks (van Balkom et al., 1997). In clinical practice, pharmacological panic management is, therefore, frequently combined with exposure in vivo. In the remainder of this paper, we focus, however, on pharmacotherapy.

### Pharmacotherapy of PD

High-potency benzodiazepines and antidepressants are the best studied pharmacotherapy options for PD. The high-potency benzodiazepines (e.g. alprazolam and clonazepam) have been extensively researched, and appear to be more effective than placebo in the short-term treatment of this disorder (Beauchair et al., 1994; Jonas and Cohon, 1993). Dosage of the high-potency benzodiazepines in PD is higher than the usual dosages used in generalized anxiety disorder (see Table 1). Low-potency benzodiazepines like diazepam may also only have an anti-panic effect at higher doses than normally prescribed for other disorders like generalized anxiety disorder. When effective, panic and phobia symptoms improve soon after the administration of benzodiazepines (Burrows and Norman, 1999).

The majority of studies investigating medication therapy in PD have focused on treatment with antidepressants. Tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and irreversible monoamine oxidase inhibitors (MAOIs) have been proven to be effective in PD (Bakker et al.,

**Table 1.** Start, mean and maximum dosage of drugs effective in panic disorder

	Dosages (mg/d)		
	Start	Mean	Maximum
High-potency benzodiazepines			
Alprazolam	1.5	4–6	–*
Clonazepam	1	2–3	–*
Lorazepam	1	2–4	–*
SSRIs			
Citalopram	10	20–30	60
Fluoxetine	20	20	60
Fluvoxamine	50	100–150	300
Paroxetine	10–20	20–40	60
Sertraline	50	100	200
TCAs			
Clomipramine	25	100–150	250
Imipramine	25	100–150	300
MAOIs			
Phenelzine	10	40–60	–*
Tranylcypromine	10	30–60	–*

SSRIs, Selective serotonin re-uptake inhibitors; TCAs, tricyclic antidepressants; MAOIs, monoamine oxidase inhibitors.

\* Only use mean dosage.

2000; Gorman, 1997). These agents have a slower onset of action than the benzodiazepines, and an initial trial of 6–8 wk is required.

MAOIs such as phenelzine have shown efficacy in the treatment of PD, but are not used on a regular basis since patients need to be on low-tyramine diets to avoid hypertensive crises (Rosenberg, 1999). Within the TCAs, both imipramine and clomipramine have been studied (Cross National Collaborative Panic Study, Second Phase Investigators, 1992; Papp et al., 1997). The currently available SSRIs citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, and sertraline have all been proven more effective than pill-placebo in reducing symptomatology in PD (Ballenger et al., 1998a; Black et al., 1993; Hoehn-Saric et al., 1993; Lecrubier et al., 1997; Michelson et al., 1998; Rapaport et al., 1998; Sharp et al., 1996; Wade et al., 1997). The daily dosages of these antidepressants are similar to those used in the treatment of major depressive disorder (see Table 1).

Indeed, antidepressants that influence the serotonergic system have consistently been shown to have efficacy in the treatment of PD. In contrast, data

on noradrenaline reuptake inhibitors for PD have been less consistent. For example, in a double-blind comparison between the SSRI fluvoxamine and the noradrenaline uptake inhibitor maprotiline, only fluvoxamine demonstrated good anti-panic properties (den Boer and Westenberg, 1988).

Side-effects that occur during the first weeks of treatment with antidepressants can easily be misinterpreted as symptoms of a panic attack, e.g. palpitations, sweating and nausea. In patients unaware of the possibility that such side-effects may occur, an apparent increase in the frequency and intensity of panic attacks may be seen. The best way to prevent such an outcome is to provide patients with sufficient information about the working mechanisms and potential side-effects of antidepressants before treatment with these agents is initiated. Early drop-out, non-compliance and suboptimal treatment outcome can also be enhanced with this strategy. Outcome can be evaluated properly only after 6 wk of treatment.

#### *Antidepressants vs. benzodiazepines*

A number of studies have compared different pharmacological therapies for PD, with the majority of these focusing on the comparison between antidepressants and benzodiazepines. These studies have consistently found similar efficacy. In the largest of these studies, both imipramine and alprazolam were superior to placebo for most outcome measures (Cross National Collaborative Panic Study, Second Phase Investigators, 1992). To date, a total of nine studies comparing imipramine with high-potency benzodiazepines (alprazolam, clonazepam) have been published (van Balkom et al., 1995). Both classes of agent appear effective for panic and phobic symptoms. Differences were observed in the time to response (earlier with benzodiazepines) and drop-out rate (lower with benzodiazepines). Despite these differences, intent-to-treat analyses revealed no significant differences in efficacy at end-point.

#### *TCA vs. SSRI*

Relatively few studies have compared different antidepressants in PD (Bakker et al., 1999; Cassano et al., 1988; den Boer et al., 1987; den Boer and Westenberg, 1988; Lecrubier et al., 1997; Modigh et al., 1992; Nair et al., 1996; Seedat et al., 2003; Tiller et al., 1997; Wade et al., 1997). In most studies, different antidepressants have shown equal efficacy in reducing the total number of panic attacks. In particular, comparison of TCAs and SSRIs has not found differences in efficacy between these classes of medication (Bakker et al., 1999;

Lecrubier et al., 1997; Otto et al., 2001; Wade et al., 1997). Some data suggests that SSRIs have a more rapid onset of action than TCAs (Lecrubier et al., 1997), and that SSRIs are associated with a lower drop-out rate (Bakker et al., 2002).

#### *Combination treatments*

In everyday clinical practice combinations of different medications are frequently used, as well as combinations of pharmacotherapy and CBT. However, the number of controlled studies that include combination treatments is disappointingly low.

The combination of a SSRI with a benzodiazepine is particularly widely used in clinical practice. Early co-administration of (high-potency) benzodiazepines like alprazolam and clonazepam may prevent the initial worsening of anxiety symptoms reported during the first weeks of treatment with a SSRI. The number of well-designed studies that have investigated this strategy is, however, limited. The most recent and important study was carried out by Goddard et al. (2001). They studied double-blind, placebo-controlled co-administration of clonazepam (1.5 mg/d) with open-label sertraline for the first 4 wk of treatment. Fifty patients were randomized, and 34 completed the trial. There was no significant difference in drop-out rate between the sertraline/clonazepam and the sertraline/placebo condition (25% vs. 38%). The intent-to-treat analysis found a higher percentage of responders in the sertraline/clonazepam group at the end of both weeks 1 and 3 of the trial (41% and 63%) in comparison to the sertraline/placebo-treated subjects (4% and 32%). The authors concluded that rapid stabilization of PD can be achieved safely with a sertraline/clonazepam combination, supporting the clinical utility of this type of regimen.

With respect to the combination of medication and psychotherapy, the distinction between benzodiazepines and antidepressants appears relevant. In a large 8-wk study Marks et al. (1993) found no differences in efficacy between alprazolam and exposure, alprazolam and relaxation, placebo and exposure, and placebo and relaxation. However, there were longer-lasting gains with exposure alone than with alprazolam following withdrawal of the medication. In contrast, there is evidence that SSRIs + CBT appear more effective than SSRIs alone.

Thus, in early work (de Beurs et al., 1995) using a double-blind, placebo-controlled design, fluvoxamine followed by exposure in vivo demonstrated efficacy superior to that of psychological panic management followed by exposure, and exposure in vivo alone.

Similarly, a study by Sharp et al. (1996) included conditions with combinations of placebo with CBT and of fluvoxamine with CBT and the largest and most consistent treatment gains were found in the fluvoxamine with CBT group. Oehrberg and co-workers (1995) investigated paroxetine + standardized cognitive therapy (CT) vs. pill-placebo + CT; paroxetine + CT was significantly more effective than placebo + CT on nearly all efficacy measures.

### Meta-analyses

Since comparisons within one study between different pharmacotherapies are relatively scarce, additional information on the differential efficacy of different agents on panic attacks and agoraphobic avoidance can arguably be derived from comparisons between studies. These comparisons can be performed in a quantitative manner by means of meta-analytical methods.

Several meta-analyses comparing different pharmacological treatments for PD have been published (Bakker et al., 1998; Boyer, 1995; van Balkom et al., 1997; Wilkinson et al., 1991). More recently a number of meta-analyses focusing on the comparison of TCAs and SSRIs have been published (Bakker et al., 2002; Otto et al., 2001). The most relevant results of these studies are summarized here.

The meta-analysis of Wilkinson et al. (1991) included 19 double-blind, placebo-controlled trials of antidepressants ( $n=13$ ) and benzodiazepines ( $n=6$ ) for patients with PD. It showed that active treatment had a 25% greater success rate than placebo over a mean duration of 14 wk. There were no statistically significant differences observed between antidepressants and benzodiazepines.

The meta-analysis of Boyer (1995) reviewed 27 published or presented placebo-controlled, double-blind studies of PD. The serotonin reuptake inhibitors included clomipramine, fluvoxamine, paroxetine, and zimelidine. The comparison treatments were imipramine and alprazolam. All three treatments were significantly superior to placebo in alleviating panic. The serotonin reuptake inhibitors were also significantly superior to both imipramine and alprazolam. The superiority of the serotonin reuptake inhibitors remained, but was less pronounced, when they were compared to the studies which used higher doses of imipramine or alprazolam.

The meta-analysis of van Balkom et al. (1997) evaluated the short-term efficacy of benzodiazepines, antidepressants, psychological panic management, exposure in vivo, and combination treatments in PD

with or without agoraphobia. Included were 52 treatment conditions with medication (28 high-potency benzodiazepines, 24 antidepressants), with 1653 patients at pre-test and 1324 at post-test. Pre/post-effect size Cohen's  $d$  were calculated *within* the treatment conditions. Seven large treatment conditions were used in the main analyses, including high-potency benzodiazepines and antidepressants. Both benzodiazepines and antidepressants were superior to a control condition, consisting of pill-placebo, attention placebo (a non-specific conversation on a regular base with a 'therapist' that does not focus on any specific symptom of the psychiatric disorder) and waiting list for both panic attacks and agoraphobic avoidance. A comparison between high-potency benzodiazepines and antidepressants found no differences in efficacy. In this meta-analysis the combination of antidepressants with exposure in vivo was found to be the most potent short-term treatment of PD with or without agoraphobia, especially with respect to agoraphobic avoidance.

Longer-term follow-up data in the studies included in the meta-analysis of van Balkom et al. (1997) were reported separately (Bakker et al., 1998). Eight studies reported on high-potency benzodiazepines and five on antidepressants. The results were consistent with those of the short-term comparison.

A more recent meta-analysis exclusively focused on the short-term efficacy of SSRIs vs. TCAs (Bakker et al., 2002). Included were 43 studies, published prior to or during 1999 (34 randomized, nine open), including 53 treatment conditions, 2367 patients at pre-test and 1804 at post-test. Outcome was measured by the proportion of patients becoming panic-free, and with pre/post-Cohen's  $d$  effect sizes, calculated for four clinical variables: panic, agoraphobia, depression, and general anxiety. The results are summarized in Table 2, and indicated no differences between SSRIs and TCAs on any of the effect sizes, with both groups of antidepressants equally effective in reducing panic symptoms, agoraphobic avoidance, depressive symptoms and general anxiety. Also the percentage of patients free of panic attacks at post-test did not differ across treatments. As mentioned earlier, the number of drop-outs was significantly lower in the group of patients treated with SSRIs (18%) vs. TCAs (31%). The main conclusion was that SSRIs and TCAs have equal efficacy in the treatment of PD, but SSRIs are better tolerated.

It can be concluded from these data that treatment with antidepressants may result in complete remission of both panic attacks and agoraphobic avoidance. Addition of exposure in vivo may help to overcome

**Table 2.** Characteristics of treatment conditions and effect-sizes at post-test

	TCA's	N*	SSRIs	N*
Treatment conditions	30		23	
Male/female ratio	0.50	n = 25	0.51	n = 22
Age ( $\pm$ s.d.)	34.4 ( $\pm$ 4.1)	n = 26	35.5 ( $\pm$ 5.4)	n = 22
Illness duration (yr) ( $\pm$ s.d.)	8.4 ( $\pm$ 2.8)	n = 22	9.6 ( $\pm$ 1.0)	n = 13
Weeks of treatment ( $\pm$ s.d.)	9.7 ( $\pm$ 4.7)	n = 30	9.6 ( $\pm$ 2.7)	n = 22
Number of patients				
Pre-test	1059	n = 30	1308	n = 23
Drop-out (%)	327 (31%†)	n = 30	236 (18%†)	
Completer	732		1072	
Patients free of panic attacks at post-test (%)	304/510 (60%)	n = 16	539/985 (55%)	n = 18
Panic				
<i>d</i> ( $\pm$ s.d.)	1.46 ( $\pm$ 0.84)	n = 20	1.26 ( $\pm$ 0.41)	n = 9
Agoraphobia				
<i>d</i> ( $\pm$ s.d.)	1.15 ( $\pm$ 0.50)	n = 15	1.10 ( $\pm$ 0.49)	n = 11
Depression				
<i>d</i> ( $\pm$ s.d.)	1.25 ( $\pm$ 0.69)	n = 13	1.41 ( $\pm$ 0.99)	n = 13
Anxiety				
<i>d</i> ( $\pm$ s.d.)	1.27 ( $\pm$ 0.58)	n = 16	1.55 ( $\pm$ 0.84)	n = 16

*d*, Cohen's *d* effect size; s.d., standard deviation.

\* Number of treatment conditions providing data with respect to this item.

†  $\chi^2 = 32.8$ , d.f. = 1,  $p < 0.001$

agoraphobic avoidance that does not respond to monotherapy with medications (van Balkom et al., 1997).

### First-line pharmacotherapy for PD

There are two categories of medications with sufficient evidence to support their use as a first-line treatment for PD: high-potency benzodiazepines and antidepressants. There are several reasons for choosing antidepressants rather than benzodiazepines. Perhaps the most important is the adverse effect profile of the benzodiazepines, including problems with withdrawal. Furthermore, in contrast to antidepressants, benzodiazepines are not effective in reducing the depressive symptomatology that often accompanies PD (van Balkom et al., 1997). Finally, the risk of relapse or recurrence of PD after discontinuation of the benzodiazepines is relatively high. It is not surprising, therefore, that antidepressants have become the first-line pharmacotherapy of choice in the treatment of PD.

The relative efficacy of different groups of antidepressants in the treatment of PD and related symptoms is, however, still a matter of debate (Bakker et al., 2002; Otto et al., 2001). To date, no differences in efficacy have been demonstrated between the two groups

of antidepressants that are used most frequently, SSRIs and TCAs (Bakker et al., 2002; Otto et al., 2001). However, there are indications that the drop-out rate differs significantly in favour of the SSRIs (Bakker et al., 2002). Drop-outs may occur for different reasons, varying from ineffectiveness to serious side-effects. The lower drop-out rate of SSRIs is most likely due to a more tolerable side-effect profile. Side-effects of TCAs may also prevent therapeutic doses of these drugs being given. Taken together, this has led to a preference for SSRIs over TCAs in both clinical practice and in consensus guidelines (Ballenger et al., 1998b; Bandelow et al., 2002).

There is no data that show clear advantages of one of the SSRIs over the others. All six that are currently available (citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, and sertraline) have been found to be effective in the treatment of PD in double blind, placebo-controlled trials.

During the first weeks of treatment with a SSRI it may be helpful to add a low dose of a high-potency benzodiazepine (alprazolam, clonazepam) as an additional medication (Goddard et al., 2001). This may result in more rapid stabilization and higher response rates during the first weeks of treatment. The risk of an initial worsening of anxiety symptoms is probably

reduced by this regimen as well. The main problem that may result from prescribing a benzodiazepine as a co-medication is that patients refuse to stop taking this agent. This may lead to dependency and other problems related to long-term use of benzodiazepines. In our clinical practice we mention the possibility of taking a benzodiazepine during the first 2 or 3 wk of treatment with an antidepressant. We tell the patients that they can decide themselves whether they want this co-medication, but that the duration of the prescription is strictly limited to 3 wk.

It has been suggested that the treatment of PD requires a lower starting dose of the antidepressant compared with depression to prevent an initial worsening of symptoms and reduce the rate of drop-out due to adverse effects. In patients who have previously been unable to tolerate a standard dose of antidepressant medication, this would certainly seem a rational approach. However, explaining to the patient that such a regimen may be associated with a delayed response, may lead to the patient to choose to start a therapeutic dose sooner. In such cases, patients should be made aware of the possibility of early transient side-effects, and the possibility of lowering the dose to help cope with these.

#### How long should maintenance pharmacotherapy be continued?

As PD runs a chronic course, long-term treatment outcome may be more important than short-term efficacy. CBT appears to have long-term benefits, and generally, the short-term results are maintained. Naturalistic follow-up studies of psychotherapy have been published as long as 9 yr after short-term treatment (Emmelkamp et al., 1992).

The long-term effect of psychopharmacological treatments for PD has received less attention. A major clinical problem is the fact that treatment gains may disappear after tapering off the medication. This is perhaps especially true for the high-potency benzodiazepines. Relapse rates up to 80% have been reported following complete withdrawal from alprazolam (Noyes et al., 1991).

There is relatively little data that addresses the optimal duration of pharmacotherapy for PD. Mavissakalian and Perel (1992) reported that when responders to a 6-month trial of imipramine were treated at half-dose for another 6 months, they maintained their improvement. This group of patients showed significantly lower relapse rates than a group of patients treated with imipramine for 6 months only. These data suggest that successful pharmacotherapy

**Table 3.** Treatment options for refractory patients

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Step 1*	SSRI (for at least 4 wk in a therapeutic dosage)
Step 2*	Another SSRI
Step 3*	Tricyclic antidepressant (clomipramine or imipramine)
Step 4	High potency benzodiazepine (in a high dosage)
Step 5*	Monoamine oxidase inhibitor

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\* Early co-administration of clonazepam or alprazolam may be considered.

should be continued for at least 1 yr. There are also papers that have reported positively on long-term treatment with the SSRIs fluoxetine and paroxetine (Lydiard et al., 1998; Michelson et al., 1999). Important consensus guidelines have reached the conclusion that medication should be taken for at least 1 yr (Ballenger et al., 1998b; Bandelow et al., 2002).

Nevertheless, a more recent paper by the same authors (Mavissakalian and Perel, 2002) concluded that neither the duration of treatment with imipramine nor the method of discontinuation were predictors of relapse. In this study, the rate of relapse after only 6 months of treatment was identical to the rate of relapse after 12–30 months of treatment. The main limitation of these findings is the limited sample size: only 51 patients were included in the analyses.

Relapse prevention for patients who want to discontinue their medication can potentially be enhanced by the addition of psychotherapy. An interesting study by Wiborg and Dahl (1996) reported that patients treated with clomipramine plus brief psychodynamic psychotherapy had significantly lower relapse rates 18 months after treatment than patients treated with clomipramine alone. Research on long-term treatment and discontinuation of therapies requires more attention, for pharmacotherapy as well as psychotherapy. The conflicting results of the limited data that are available with respect to the optimal duration of pharmacotherapy underlines this need.

#### What is the optimal approach to the treatment-refractory patient?

Despite advances in the pharmacotherapy of PD, not all patients respond to the first trial of medication. Unfortunately, there is very little persuasive data with respect to this topic. We suggest that when an SSRI fails, irrespective of the reason, a second SSRI is a

reasonable next step to take next. Co-medication with a benzodiazepine, preferably a high-potency benzodiazepine like alprazolam or clonazepam, can also be considered on a case by case basis, depending on the clinician's judgement.

If a second SSRI is not effective, then a third choice of medication may be a TCA, e.g. clomipramine or imipramine. Such an agent can also be combined with a benzodiazepine. Subsequent options for pharmacological treatment of refractory patients include a high dose of high-potency benzodiazepines (up to 6 mg alprazolam or the equivalent), and treatment with an irreversible MAOI, e.g. phenelzine.

The addition of CBT to non- or partial medication responders should also be considered. Table 3 summarizes the strategies in case of non-response to first-line pharmacotherapy.

### Conclusion

When untreated, PD may run a chronic course, with a waxing and waning of symptoms. The high prevalence and significant disability associated with PD, as well as the frequent co-occurrence of PD with mood disorders and substance abuse disorders underline the importance of having effective treatments available. Fortunately, recent decades have witnessed the development of a number of effective treatments, including psychopharmacological interventions.

With regard to the short-term treatment of PD, several standard pharmacological and psychological interventions show equal efficacy in reducing panic, agoraphobia and related complaints. Nevertheless, SSRIs are increasingly viewed as a pharmacotherapy of choice, partly because benzodiazepines have relatively little effect on the depressive symptoms that often complicate PD. Short-term co-medication with high-potency benzodiazepines may be a useful strategy in some cases.

For both pharmacotherapy and psychotherapy it is still unclear how long treatment should be continued, in what dose medication should optimally be continued after remission of symptoms has been achieved, and what the optimal approach to refractory patients is. After withdrawal of short-term benzodiazepine and antidepressant treatment there are relatively high percentages of relapse. Data for valid comparisons of the differences in relapse between different medication classes is not yet available.

With regard to the combination of different treatment strategies, there is some evidence that the combination of an antidepressant and exposure in vivo produces the largest treatment gains in PD.

Agoraphobic behaviour in particular may respond well to this combined strategy. It is, however, unclear how long and at what dosage the medication should be continued, and what the optimal duration and frequency of the exposure treatment is.

Another important issue that remains to be fully resolved is the costs that accompany different treatment strategies. Drop-out due to adverse side-effects of medication, lack of efficacy, lack of compliance and relapse after cessation of medication are important factors that increase the total cost of treatment with pharmacological agents. Psychotherapeutic interventions also have associated costs. Further work on the cost-efficacy of the treatment of PD is required.

In the interim, we suggest that when patients suffer from panic attacks with no or only limited avoidance then treatment of first choice is an SSRI, but that when patients suffer from agoraphobic avoidance due to their panic attacks, exposure should be added. Our advice is to give the antidepressant first, and start formal exposure after the first positive effects of the medication have occurred. The antidepressant should be continued at least 9 months after maximal efficacy has been attained. Psychotherapy should continue throughout this whole period, and can be stopped after patients have been free of medication for at least some months.

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### Statement of Interest

None.

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