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REVIEW

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Evidence-based pharmacotherapy of panic disorder: an update

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Abstract

The evidence-based pharmacotherapy of panic disorder continues to evolve. This paper reviews data on first-line pharmacotherapy, evidence for maintenance treatment, and management options for treatment-refractory patients. A Medline search of research on pharmacotherapy was undertaken, and a previous systematic review on the evidence-based pharmacotherapy of panic disorder was updated. Selective serotonin reuptake inhibitors remain a first-line pharmacotherapy of panic disorder, with the serotonin noradrenaline reuptake inhibitor venlafaxine also an acceptable early option. Temporary co-administration of benzodiazepines can be considered. Maintenance treatment reduces relapse rates, but further research to determine optimal duration is needed. For patients not responding to first-line agents several pharmacotherapy options are available, but there is a notable paucity of data on the optimal choice.

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Introduction

Panic disorder is a common mental disorder that is associated with significant morbidity. Fortunately, effective treatments for panic disorder are available, and include both medication and cognitive behavioural therapy (CBT). Ongoing research on the pharmacotherapy of panic disorder makes it timely to update an evidence-based approach to the pharmacotherapy of panic disorder (Bakker *et al.* 2005). Here we briefly emphasize the importance of adequate care before reviewing the available pharmacological evidence on treating panic disorder, focusing in particular on (1) the optimal first-line pharmacotherapy of panic disorder, (2) the optimal duration of maintenance therapy, and (3) the optimal approach to pharmacotherapy in the treatment-refractory patient. To reveal relevant research conducted in the past 5 yr (i.e. since the previous review article in this journal; Bakker *et al.* 2005), a Medline search (2003–2010) using the terms 'panic' and 'treatment' was undertaken.

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Importance of adequate care

Panic disorder is a common mental disorder, with a 12-month prevalence rate of 1.8% (Goodwin *et al.* 2005). Only a minority of those affected receive adequate care.

The main reason is that not all patients seek help. It may take years before individuals with panic disorder seek help, and only about one third of those affected seek help within the year of onset (Wang *et al.* 2005*a*). The gap between those affected and those seeking help for panic disorder is about 50% (Kohn *et al.* 2004; Wang *et al.* 2005*b*).

When seeking help, individuals with panic disorder frequently turn to medical specialists or to emergency units (Hirschfeld, 1996; Katerndahl & Realini, 1995; Leon *et al.* 1995; Rees *et al.* 1998; Salvador-Carulla *et al.* 1995), probably due to the predominance of physical symptoms. Misdiagnosis by the general practitioner (Rees *et al.* 1998) or by the cardiologist at the emergency unit is common (Harvison *et al.* 2004; Kuijpers *et al.* 2000). Thus, even those who seek help often go unrecognized.

Once the correct diagnosis has been made, delivery of care is often not in concordance with the advice provided in practice guidelines (Bruce *et al.* 2003). It is regrettable that only a minority of individuals with panic disorder receive evidence-based treatment, given the unfavourable long-term course of panic disorder and the impact of panic on daily life. We briefly discuss these aspects below.

Course

The course of panic disorder in the general population may be chronic or recurrent (Batelaan *et al.* 2010*a*, *b*; Eaton *et al.* 1998; Kessler *et al.* 2006; Wittchen *et al.* 2008). In addition, comorbid disorders tend to develop during the course of panic disorder (de Graaf *et al.* 2003; Johnson *et al.* 1990; Kessler *et al.* 1998; Wittchen *et al.* 2003). Finally, it should be noted that even when panic symptoms remit, other psychiatric pathology may be present (Wittchen *et al.* 2008).

Impact

Panic disorder has a negative impact on well-being and on health perception (Katerndahl & Realini, 1997; Klerman *et al.* 1991), and is associated with impaired functioning (Kessler *et al.* 2006; Wittchen *et al.* 1998) and absence from work (Alonso *et al.* 2004; Kouzis & Eaton, 1994, 1997). In addition, panic disorder may be associated with suicidal ideation and/or attempts (Cougle *et al.* 2009; Goodwin & Roy-Byrne, 2006; Lepine *et al.* 1993; Weissman *et al.* 1989), even if the impact of comorbid disorders on this association is a matter of debate (Hornig & McNally, 1995) and although the evidence that panic disorder causes suicidality remains unclear (Sareen *et al.* 2005*a*). Panic disorder is also associated with medical morbidity, including cardiovascular disease (Chen *et al.* 2009; Gomez-Caminero *et al.* 2005; Sareen *et al.* 2005*b*; Smoller *et al.* 2007). Some studies report increased mortality rates in individuals with panic disorder as a result of suicide (Coryell *et al.* 1982) or cardiovascular disease (Coryell *et al.* 1982; Grasbeck *et al.* 1996; Smoller *et al.* 2007). Finally, panic disorder causes considerable economic costs to society, compared to healthy persons and to other psychiatric disorders (Andlin-Sobocki & Wittchen, 2005; Batelaan *et al.* 2007; Salvador-Carulla *et al.* 1995).

Available pharmacological evidence

Pharmacological agents with sufficient evidence to support their use in the treatment of panic disorder include antidepressants [the selective serotonin reuptake inhibitors (SSRIs), the serotonin noradrenaline reuptake inhibitor (SNRI) venlafaxine, several tricyclic antidepressants (TCAs) and the irreversible MAO inhibitor (MAOI) phenelzine], and benzodiazepines. First, we review antidepressants and benzodiazepines with regard to efficacy in acute and long-term treatment, the side-effects and risks involved, drop-out rates, onset of action and efficacy in comorbid conditions. This comparison will be used to determine which agents should be considered first-line treatments. Next we review data on optimal duration of maintenance therapy and optimal approach to pharmacotherapy of treatment-refractory patients.

Antidepressants

Efficacy in acute phase treatment

Antidepressants acting on the serotonergic system are effective in treating panic disorder. These include the SSRIs (citalopram, fluvoxamine, fluoxetine, paroxetine, sertraline) (Bakker *et al.* 2002; Hoehn-Saric *et al.* 1993; Lecrubier *et al.* 1997; Michelson *et al.* 1998; Pollack *et al.* 1998; Stahl *et al.* 2003; Wade *et al.* 1997), the TCAs imipramine and clomipramine (CNCPS, 1992; Papp *et al.* 1997), the SNRI venlafaxine (Bradwejn *et al.* 2005; Liebowitz *et al.* 2009; Pollack *et al.* 2007*a*, *b*), and the irreversible MAOI phenelzine (Sheehan *et al.* 1980; Tyrer *et al.* 1973).

During the past few years the SSRIs paroxetine controlled-release formulation (paroxetine CR) and escitalopram, and the SNRI venlafaxine extended-release (venlafaxine XR) have been thoroughly investigated in panic disorder. Three double-blind placebo-controlled trials investigating paroxetine CR were pooled, allowing analysis of a total study population of 889 panic disorder patients. Paroxetine CR (25–75 mg/d) was superior to placebo on the primary outcome measure, percentage of patients who were free of panic attacks in the 2 wk prior to endpoint (Sheehan *et al.* 2005). In a 10-wk randomized controlled, double-blind trial (total $n = 366$, $n = 128$ with escitalopram), escitalopram (5–10 mg/d) was more effective than placebo (Stahl *et al.* 2003). Finally, the SNRI venlafaxine XR (75–225 mg/d) has been found significantly more effective than placebo in several randomized controlled, double-blind trials (Bradwejn *et al.* 2005; Liebowitz *et al.* 2009; Pollack *et al.* 2007*a*, *b*; for an overview see Kjernisted & McIntosh, 2007). The daily dosages of these antidepressants when used for panic disorder are similar to those used for major depressive disorder (see Table 1).

Table 1. Dosage of drugs effective in panic disorder (mg/day)

Drug name	Start	Mean	Maximum
Antidepressants			
SSRIs			
Citalopram	10	20–30	60
Escitalopram	5	10	20
Fluoxetine	20	20	60
Fluvoxamine	50	100–150	300
Paroxetine	10	20–40	60
Sertraline	50	100	200
SNRIs			
Venlafaxine	37.5	75–150	225
TCAs			
Clomipramine	25	100–150	250
Impiramine	25	100–150	300
Benzodiazepines			
Alprazolam	1.5	4–6	–[a]
Clonazepam	1	2–3	–[a]
Diazepam	5–10	40–50	–[a]
Lorazepam	1	2–4	–[a]
MAOIs			
Phenelzine	10	40–60	–[a]

[a] Only use mean dosage.

Efficacy in long-term treatment

The SSRIs (i.e. citalopram, fluvoxamine, paroxetine) (Holland *et al.* 1994; Lecrubier & Judge, 1997; Lepola *et al.* 1998) and the TCAs (Curtis *et al.* 1993; Lecrubier & Judge, 1997; Mavissakalian & Perel, 1992) all remain effective in the treatment of panic disorder over the long-term (follow-up periods up to 2 yr). Recently, a 6-month placebo-controlled discontinuation study found that time to relapse was significantly longer in the venlafaxine XR group than the placebo group (Ferguson *et al.* 2007). No studies investigating the long-term efficacy of phenelzine have been conducted.

Side-effects and risks involved

Side-effects of antidepressants differ partly across various classes of antidepressants (APA, 2009). The most common side-effects of the SSRIs include headaches, irritability, gastrointestinal complaints, insomnia, sexual dysfunction, weight gain, increased anxiety, drowsiness and tremor. The most common side-effects of venlafaxine as reported in panic disorder patients are nausea, dry mouth, constipation, anorexia, insomnia, sweating, somnolence, tremor and sexual dysfunction. Monitoring of blood pressure is advised given the increase in blood pressure that is sometimes observed. In TCAs the most commonly reported side-effects in panic disorder patients are anticholinergic effects, increased sweating, sleep disturbance, orthostatic hypotension and dizziness, fatigue and weakness, cognitive disturbance, weight gain, and sexual dysfunction. Specific concern is needed when treating elderly patients with TCAs as orthostatic hypotension may result in falls. In addition, arrhythmias may occur in patients with pre-existing cardiac conduction abnormalities, and in case of an overdose. The irreversible MAOI phenelzine has an unfavourable side-effect profile, including hypotension, weight gain, sexual dysfunction, paresthesia, myoclonic jerks, dry mouth, oedema and sleeping problems. Probably more important, to avoid life-threatening hypertensive crisis, adherence to a strict low tyramine diet is required (Rosenberg, 1999).

To prevent side-effects, it is advised to start treatment with antidepressants at a low dosage. Of special importance is the finding that panic symptoms often increase in the first weeks of treatment with SSRIs, venlafaxine or TCAs. This may be partly due to misinterpreting physical side-effects as symptoms of a panic attack. Psycho-education should aim to prevent such misinterpretations, and slow dose titration is recommended. To lower anxiety symptoms and to achieve a more rapid stabilization of panic symptoms, temporary addition of benzodiazepines during the initial phase of antidepressant treatment can also be considered (Goddard *et al.* 2001; Pollack *et al.* 2003).

Drop-out rates

During SSRI treatment of panic disorder 18% of patients drop-out prematurely (Bakker *et al.* 2002). The recently investigated agents paroxetine CR, escitalopram, and venlafaxine are all well tolerated in panic disorder patients, and hence, reported drop-out rates were relatively low: 11% of patients treated with paroxetine CR (Sheehan *et al.* 2005), 6.3% of patients treated with escitalopram (Stahl *et al.* 2003) and 1–12% of patients treated with venlafaxine (Kjernisted & McIntosh, 2007). With TCAs, about 30% of patients drop-out of treatment (Bakker *et al.* 2002). Due to the unfavourable side-effect profile of MAOIs, drop-out rates are high.

Onset of action

For all antidepressants, onset of action in panic disorder is relatively slow. As a result, an assessment of outcome should be made only after several weeks of treatment.

Efficacy in comorbid conditions

Antidepressants are effective for a range of anxiety disorders and depressive disorder, which are commonly comorbid with panic disorder (Bandelow *et al.* 2008).

Benzodiazepines

Efficacy in acute phase treatment

The benzodiazepines alprazolam, clonazepam, diazepam and lorazepam are superior to placebo in the acute phase treatment of panic disorder (CNCPS, 1992; Van Balkom *et al.* 1995, 1997). The mean dosages of benzodiazepines used in acute treatment are provided in Table 1.

Efficacy in long-term treatment

Controlled studies up to 32 wk with alprazolam (Ballenger, 1991; Burrows *et al.* 1993), and an open study with clonazepam lasting over 1 yr (Pollack *et al.* 1986) showed that these benzodiazepines are efficacious in maintenance treatment. Sometimes the daily dosage could be reduced while remaining efficacious.

Side-effects and risks involved

Side-effects of benzodiazepines include sedation, fatigue, ataxia, slurred speech, memory impairment, and weakness (APA, 2009). Usually, treatment is started at a low dose to diminish side-effects. Caution is advised in prescribing benzodiazepines for elderly patients because of a higher risk of falls, and for patients driving vehicles because of a higher risk of motor vehicle accidents. When prescribed for long-term use, dependence may occur. Hypothetically, this may have two adverse consequences: dose escalation and problems withdrawing the medication. While dose escalation does not appear a common consequence of long-term benzodiazepine use, problems when discontinuing benzodiazepines are frequently reported, especially during the last half of the taper period (APA, 2009).

Drop-out rates

In panic disorder trials, drop-out rates due to side-effects are about 15% for benzodiazepines (LSMRG, 2009).

Onset of action

Benzodiazepines have a fast onset of action, i.e. they produce effects as soon as an effective dose is administered (Burrows & Norman, 1999).

Efficacy in comorbid conditions

Benzodiazepines are generally thought ineffective for comorbid depressive disorders (Bandelow *et al.* 2008).

Optimal first-line pharmacotherapy

With regard to efficacy in acute treatment, comparable efficacy has been revealed when directly comparing antidepressants (imipramine) and benzodiazepines (alprazolam, clonazepam) (Van Balkom *et al.* 1995), SSRIs and TCAs (Bakker *et al.* 1999, 2002; Lecrubier *et al.* 1997; Otto *et al.* 2001; Wade *et al.* 1997), and when comparing various SSRIs (Dannon *et al.* 2007). In one study, a high dosage of venlafaxine (225 mg) proved to be superior to 40 mg paroxetine on the primary outcome measure (percentage of patients free from full-symptom panic attacks) and on one of the secondary outcome measures (improvement on the Panic Disorder Severity Scale) (Pollack *et al.* 2007*a*). In panic disorder, only one trial administered either escitalopram, citalopram or placebo. However, in this trial no direct comparisons between escitalopram and citalopram were made (Stahl *et al.* 2003). As described above, both antidepressants (SSRIs, SNRI venlafaxine, TCAs) and benzodiazepines remain effective over the long term.

Given the comparable efficacy of the pharmacological classes described above in acute-phase treatment and the efficacy in long-term treatment, other considerations determine which agent should be considered the first-line pharmacotherapy of panic disorder. These include side-effects and risks involved, drop-out rates, the time of onset of action, and efficacy in comorbid symptomatology.

Considering these aspects, SSRIs and venlafaxine should both be considered first-line agents. Given the slow onset of action and the potential for increased anxiety during the initial phase of treatment with antidepressants, temporary co-administration of a benzodiazepine should be considered. SSRIs and venlafaxine are effective in acute and long-term treatment, have an acceptable side-effect profile, acceptable drop-out rate, and are effective in comorbid depression. Direct comparisons between SSRIs and venlafaxine with regard to onset of action, side-effect profile or drop-out rates have not been made in panic disorder. Similarly, direct comparisons of the tolerability profile and onset of action of recently investigated agents (paroxetine CR, escitalopram) and other SSRIs are lacking.

TCAs may have a slower onset than SSRIs (Lecrubier *et al.* 1997). In addition, TCAs have a less

tolerable side-effect profile than SSRIs given that they have more anticholinergic effects, and are generally less safe than SSRIs. Finally, reported drop-out rates are higher for TCAs compared to SSRIs (Bakker *et al.* 2002).

Benzodiazepines have a faster onset of action and lower drop-out rates compared to TCAs (Van Balkom *et al.* 1995). The tolerability of benzodiazepines is usually good, but patients may suffer from drowsiness and cognitive side-effects. Another disadvantage is that these drugs may lead to benzodiazepine dependence. Moreover, benzodiazepines are generally thought ineffective with regard to comorbid psychopathology such as depressive disorders, whereas antidepressants are not (Bandelow *et al.* 2008). This is of importance, because depressive disorders often complicate panic disorder (Ravelli *et al.* 1998). In summary, benzodiazepines as monotherapy should not be regarded as a first-line treatment in view of their side-effect profile (which includes dependence) and in view of their lack of efficacy in treating comorbid conditions.

The irreversible MAOI phenelzine should be prescribed only in case of severe and treatment-refractory panic disorder given the side-effect profile and risks involved, and the high drop-out rates.

Optimal duration of pharmacotherapy

Considering the long-lasting, often relapsing course of panic disorder, optimizing the long-term outcome and thus reducing the vulnerability to relapse should be a main goal of treatment (Andrews, 2003; Batelaan *et al.* 2010*a*; Fava & Mangelli, 1999). Discontinuation of pharmacotherapy frequently results in relapse (Ferguson *et al.* 2007; Lecrubier & Judge, 1997; Lotufo-Neto *et al.* 2001; Marks *et al.* 1993; Mavissakalian & Perel, 1999; Noyes *et al.* 1989, 1991; Rapaport *et al.* 2001; Spiegel *et al.* 1994). For example, 37% of patients experienced a relapse within 10 wk of discontinuing clomipramine, and another 43% of patients within about $1\frac{1}{2}$ yr (Lotufo-Neto *et al.* 2001), over one third relapsed within the first year of imipramine discontinuation (Mavissakalian & Perel, 1999), and half of those who discontinued venlafaxine relapsed within 6 months (Ferguson *et al.* 2007).

The consistent finding that maintenance pharmacotherapy may prevent relapse when compared to medication discontinuation (Donovan *et al.* 2010) can be considered an argument to continue pharmacotherapy for a longer period. Another argument for continuing pharmacotherapy is that during maintenance treatment, further improvements can be seen (Ballenger, 2000; Lecrubier & Judge, 1997). However, many remitted patients discontinue antidepressant treatment. Studies investigating treatment adherence of anxiety disorder patients and, more specifically of panic disorder patients, reported that more than half of the patients are non-compliant or interrupt treatment within several months to years (Stein *et al.* 2006; Toni *et al.* 2004).

A crucial question is what is the optimal duration of pharmacotherapy that will allow patients to discontinue pharmacotherapy relatively safely (i.e. without a substantial risk for relapse), and not take medication longer than necessary. Research with regard to the optimum duration of pharmacotherapy is sparse; however, results so far do not indicate the existence of a 'safe' period to withdraw from medication. In a study conducted by Mavissakalian & Perel, (2002) the duration of treatment with imipramine following response was not associated with relapse: relapse occurred as frequently after 6 months of treatment as it did after 12–30 months of treatment (Mavissakalian & Perel, 2002). In addition, Choy and colleagues reported that even after 3 yr of sustained remission while taking medication, relapse occurs more often and earlier in those who discontinue medication compared to those who continue pharmacological treatment (Choy *et al.* 2007). However, because this is a naturalistic study, a firm causal relation cannot be presumed.

Given the limited empirical data available, international guidelines differ slightly in their recommendations on maintenance treatment. Whereas the guideline from the American Psychiatric Association refrains from recommendations (APA, 2009), most guidelines refer to expert consensus and suggest continuation for at least a year (Andrews, 2003; Bandelow *et al.* 2008; LSMRG, 2009), although a shorter period has also been suggested (Baldwin *et al.* 2005; CPA, 2006).

When medication is being discontinued, consensus advice is to taper down the medication gradually over weeks to months (APA, 2009; Andrews, 2003; Baldwin *et al.* 2005; LSMRG, 2009) to reduce the likelihood of discontinuation symptoms and to monitor for early signs of relapse.

To reduce the risk for relapse and optimize the long-term outcome in panic disorder, research on the optimal duration of pharmacotherapy should be conducted, as well as research on how to optimize treatment adherence. In addition, other lines of research may also be fruitful.

First, predictors for relapse should be identified, because those at the highest risk for relapse may

benefit most from long-term maintenance treatment, and it can be hypothesized that patients at the highest risk for relapse are better motivated for long-term maintenance treatment. In addition, costs of long-term maintenance treatment for those at highest risk to relapse may well be acceptable given the costs associated with recurrence of panic disorder.

Second, the question of whether maintenance treatment with lower dosages will suffice to maintain acute-phase improvements is worthy of further study, given previous results of a small study in which patients maintained their improvement when imipramine was continued at half the dosage (Mavissakalian & Perel, 1992), and studies indicating that the daily dosage of benzodiazepines can be reduced while remaining efficacious (Ballenger, 1991; Burrows *et al.* 1993; Pollack *et al.* 1986).

Third, providing psychotherapy to panic disorder patients may also be beneficial in enhancing the long-term outcome for several reasons, the most important reason being that the effects of CBT may be maintained over time (Bakker *et al.* 1998; Fava *et al.* 2001; Oei *et al.* 1999; Peter *et al.* 2008). In addition, some evidence indicates that a CBT relapse-prevention programme provided after acute-phase treatment prevents relapse in patients with panic disorder (Wright *et al.* 2000) and that adding brief psychodynamic psychotherapy to clomipramine treatment may reduce relapse rates in panic disorder (Wiborg & Dahl, 1996). Finally, a few studies have shown that CBT may also prevent relapse or worsening of panic in patients who discontinue pharmacological treatment (Bruce *et al.* 1999; Choy *et al.* 2007; Furukawa *et al.* 2007; Schmidt *et al.* 2002; Spiegel *et al.* 1994; Whittal *et al.* 2001).

Optimal approach to pharmacotherapy in treatment-refractory patients

Despite the availability of treatments with reported efficacy, a substantial number of panic disorder patients do not respond, or only respond partially to treatment. For example, Pollack *et al.* (2007*b*) reported response rates between 70% and 80% and remission rates around 45% during the acute treatment of panic disorder with venlafaxine, thereby underscoring the need for additional treatment strategies to achieve full remission. There are, however, few data to guide clinicians in next-step treatment strategies (Ipser *et al.* 2006). The approach to treatment-refractory patients may consist of optimizing the current treatment, switching to another agent or treatment modality, or augmentation.

Optimizing treatment

With regard to optimizing the current pharmacotherapy, it may be useful to investigate whether the patient is adhering to the treatment regimen, given the high rates of non-compliance with pharmacological treatment. In addition, it should be noted that during maintenance treatment, further improvements may occur (Ballenger, 2000; Lecrubier & Judge, 1997). With regard to the dosage, assessing the blood level in imipramine treatmemt may be helpful (Mavissakalian & Perel, 1995). By contrast, a small study reported that an increased dosage of a SSRI was no more effective than continuing the previous dosage (Simon *et al.* 2009*b*), a finding that is in line with recent research on the absence of additional effects when increasing the SSRI dose in depressed patients (Ruhe *et al.* 2009).

Switching

Switching within or between classes of pharmacological agents seems a reasonable option. Based on safety and tolerability issues described above, we propose the following steps: SSRI or venlafaxine, another SSRI or venlafaxine, clomipramine or imipramine, benzodiazepine, MAOI. Switching to another treatment modality with proven efficacy in treating panic disorder, such as CBT, is also a reasonable option. CBT is effective in panic disorder (Furukawa *et al.* 2007), and positive effects have been reported for CBT in studies with panic disorder patients who failed to respond adequately to pharmacological treatment (Rodrigues *et al.* 2011).

In addition, a wide range of other pharmacological agents has been suggested for the treatment of panic disorder. These include SNRIs other than venlafaxine (Blaya *et al.* 2007; Simon *et al.* 2009*a*), the selective noradrenergic reuptake inhibitor reboxetine (Bertani *et al.* 2004; Dannon *et al.* 2002; Seedat *et al.* 2003; Versiani *et al.* 2002), GABAergic treatment including vigabatrin and tiagabine (Pande *et al.* 2000; Zwanzger & Rupprecht, 2005; Zwanzger *et al.* 2009*a*), the reversible MAOI moclobemide (Kruger & Dahl, 1999; Loerch *et al.* 1999; Ross *et al.* 2010; Tiller *et al.* 1999; Uhlenhuth *et al.* 2002), other antidepressants including mirtazapine, buproprion, trazodone (APA, 2009), anticonvulsants (Mula *et al.* 2007; Papp, 2006), the antipsychotic olanzapine (Hollifield *et al.* 2005), and antihypertensives (APA, 2009). None of these agents can be considered as first-line options for the pharmacological treatment of panic disorder because they are insufficiently investigated or because results were inconsistent. To determine their role in treating panic

disorder, randomized controlled trials of sufficient sample sizes are needed to verify results and to compare both efficacy and tolerability with more established treatments. A clinician could potentially consider prescribing these agents in treatment-refractory patients, prioritizing those agents for which there is the most data on efficacy and tolerability.

The agents for which there is most data on efficacy and tolerability are the SNRIs milnacipran and duloxetine and the selective noradrenergic reuptake inhibitor reboxetine. This is not surprising given the efficacy of the SNRI venlafaxine in the treatment of panic disorder and the noradrenergic role in the pathophysiology of panic disorder. Small open-label studies showed positive results for the SNRIs milnacipran (Blaya *et al.* 2007) and duloxetine (Simon *et al.* 2009*a*). Reboxetine has been investigated in several small studies. In a single-blind, cross-over study, reboxetine was as effective as citalopram with regard to panic, although less effective than citalopram with regard to co-occurring depressive symptoms (Seedat *et al.* 2003). In a single-blind randomized trial ($n = 68$), paroxetine showed larger effects on panic attacks than reboxetine, but no differences were found on anticipatory anxiety and avoidance (Bertani *et al.* 2004). In a double-blind randomized, controlled trial reboxetine was more effective compared to a placebo group (Versiani *et al.* 2002). Finally, in a small open-label study, reboxetine showed positive effects for patients who had not responded to a SSRI (Dannon *et al.* 2002). Given these preliminary results, both these SNRIs and reboxetine might be an option when prescribing off-label agents in treatment-refractory patients.

Other treatment modalities with insufficient evidence to date can also be considered in treatment-refractory patients. It should be stressed that, given the design and size of the studies, these results should be viewed as preliminary. Risk-benefit ratios should be taken into account. Options include repetitive transcranial magnetic stimulation and aerobic exercise. Repetitive transcranial magnetic stimulation has shown some beneficial effects for panic disorder in several small and open studies (Pigot *et al.* 2008; Zwanzger *et al.* 2009*b*). With regard to aerobic exercise, it was found that subsequent to exercise, panic disorder patients had less frequent panic when challenged with carbon dioxide (Esquivel *et al.* 2008) or cholecystokonin tetrapeptide (CCK-4) compared to controls who had no exercise or only very light exercise (Strohle *et al.* 2009). In an earlier study aerobic exercise indeed reduced panic symptoms, but later and less effectively than medication (Broocks *et al.* 1998). Results of a recent randomized controlled trial of aerobic exercise in panic disorder patients were disappointing (Wedekind *et al.* 2010).

Augmentation

Pharmacological treatment can be augmented by the use of additional medications, or by other treatment modalities. The incremental efficacy of combined psychotherapy (most often CBT) and antidepressant treatment was investigated in a Cochrane review including 21 trials in panic disorder (Furukawa *et al.* 2007). The authors concluded that in the short term, combined therapy was superior to medication alone, as well as to psychotherapy alone. These findings were irrespective of the kind of antidepressant (TCA *vs.* SSRI), irrespective of the presence of agoraphobia, and irrespective of the presence of comorbid depression. Six months after terminating treatment, combination therapy was more effective than medication alone, but was as effective as psychotherapy alone. This finding should be interpreted with some caution, given the naturalistic nature of the follow-up period, with a substantial proportion of patients receiving treatment of some kind (Furukawa *et al.* 2007). Insufficient data are available to determine whether combining benzodiazepines and psychotherapy is beneficial or not (Watanabe *et al.* 2007).

Augmenting benzodiazepines to antidepressant treatment is an option as this appeared equally effective compared to adding CBT to antidepressants in panic disorder. However, it should be noted that effects of both strategies were small in this study (Simon *et al.* 2009*b*). In addition, augmentation of antidepressants with an antipsychotic has been suggested for refractory panic disorder patients (Hoge *et al.* 2008; Saito & Miyaoka, 2007; Sepede *et al.* 2006; Simon *et al.* 2006). Risk-benefit ratios should be carefully considered given the adverse effects of antipsychotics. D-cycloserine, a partial agonist of the *N*-methyl-D-aspartate glutamergic receptor, has recently received attention because it may enhance fear extinction during exposure therapy (Hofmann, 2007). A small ($n = 31$) randomized, double-blind, placebo-controlled trial in which interoceptive exposure was augmented with either low doses of D-cycloserine or placebo showed that panic disorder patients who received D-cycloserine had better outcomes, both at post-treatment, and at 1-month follow-up (Otto *et al.* 2010).

Conclusion

Panic disorder is a prevalent and disabling disorder that can be treated effectively. However, only a

minority of those suffering from panic disorder appear to be adequately treated. The first-line pharmacotherapy for panic disorder has been SSRIs for some time, and there is now sufficient evidence to indicate that the SNRI venlafaxine should also be considered as a first-line agent. Less is known about how improvements can be maintained and how relapses can be prevented in patients who have responded well to medication in the acute phase. In general, however, most treatment recommendations are conservative, advising at least a year of antidepressant treatment. Similarly, relatively little is known about how best to manage treatment-refractory panic disorder. Nevertheless, current options include a range of switching and augmentation strategies. Further research comparing these options is needed.

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