Management of panic disorder in primary care

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Panic disorder is a common presentation in primary care and in recent years, evidence supporting the use of many drug treatments and psychotherapies has emerged. This article discusses the diagnosis and clinical assessment of panic disorder and examines the efficacy of the pharmacological and psychological treatment options available.

Advances in research in the fields of neuroscience and psychology have improved our understanding of anxiety. Several anxiety disorders have been identified, with distinct symptom patterns or triggers. These include panic disorder, social anxiety disorder (social phobia), post-traumatic stress disorder (PTSD), specific phobia and generalised anxiety disorder (GAD). Effective treatments for most of the anxiety disorders have been available for several decades. Over recent years, progress in the development and evaluation both of pharmacological treatments and psychological therapies has yielded a range of treatment options that can be tailored to the individual patient’s needs and preferences.

Panic disorder was first described in the 1960s when it was observed that patients with panic attacks responded to treatment with imipramine, while other anxious patients did not. Experimental models and paradigms in animals and humans have allowed the processes occurring during a panic attack to be linked to neurobiological changes. Evidence pointing to a role for brain neurotransmitters such as serotonin, gamma-aminobutyric acid (GABA) and noradrenaline has accumulated, and manipulation of these systems provides the rationale for drug therapy. Meanwhile in the field of psychotherapy, models of the panic attack, including those based on aberrant cognition or behaviour, have been developed and these form the basis of the most frequently used psychotherapeutic approaches, ie cognitive therapy, behavioural therapy and, combining both elements, cognitive behavioural therapy (CBT). Thus, for the patient presenting with anxiety symptoms in the form of panic attacks, a well-developed framework exists for diagnosis and effective treatment.

Recent epidemiological studies have suggested a lifetime prevalence in the population of 13% for panic attacks and 2% for panic disorder in accordance with Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria. Panic disorder

Figure 1. Symptom control at onset and withdrawal of treatment with SSRIs and benzodiazepines
and its associated symptoms are commonly seen in primary care. In a pan-European study of consecutive general practice attendees, a “panic syndrome” (having broader diagnostic criteria than panic disorder itself) was detected in 9.2% of women and 5.6% of men studied, with the figures for the UK slightly higher at 10.3% and 8.8%. For GPs, knowledge of how to identify panic disorder and initiate one of the many effective treatments is valuable, because if unrecognised, the disorder has the potential not only to impair quality of life through its disabling and unpleasant symptoms, but also to mimic several physical illnesses exposing the patient to avoidable investigations and procedures.

Diagnosis

A panic attack is a discrete period of fear or anxiety that has a rapid onset, reaches a peak within 10 minutes and in which at least four of 13 characteristic symptoms are experienced. Many of these symptoms involve bodily systems, such as racing heart, chest pain, sweating, shaking, dizziness, flushing, stomach churning, faintness, breathlessness, numbness/tingling, and sensations of choking. A common accompanying symptom is derealisation (a sense of the world feeling unreal), or depersonalisation (the sense of being disconnected from one’s personal identity). Further recognised panic attack symptoms involve fearful cognitions, such as the fear of losing control, going mad or dying.

Panic attacks may happen in the absence of any diagnosis, but can occur in several of the anxiety disorders and, indeed, in other psychiatric disorders. To make a diagnosis of panic disorder (see Table 1), further conditions must be met relating to attacks – they must be recurrent, and some should come on unexpectedly rather than being confined to predictable externally triggered situations. For example, a person who only ever has panic attacks when confronted by spiders would be diagnosed as having a specific phobia rather than panic disorder. The DSM-5 diagnostic system requires that at least one attack is followed by a month or more of either “anticipatory anxiety”, ie a persistent worry about having further attacks, or a maladaptive behavioural change such as avoiding certain activities or situations to reduce the likelihood of further attacks (which can lead to agoraphobia). Panic disorder should not be diagnosed where symptoms can be accounted for by a direct medical cause, eg hyperthyroidism, or panic-inducing substances, notably caffeine.

The patient’s history of physical symptoms and fearful cognitions must be taken carefully, as this leads to the diagnosis. Evidence may be gathered by asking the patient to keep a diary of anxiety symptoms, or by using questionnaires for self-rating, such as the Bodily Sensations Questionnaire. In previous classifications, agoraphobia (from the Greek “fear of the marketplace”) was regarded as being closely linked to panic disorder and described as a fear or avoidance of situations where a panic attack would be particularly distressing. For example, a person might avoid attending a concert where it would be difficult and disruptive to try to escape if a panic attack was imminent. Eventually the fear and avoidance might be so generalised that the patient may be afraid of going out at all. However, in DSM-5 the requirement for agoraphobia to be related exclusively to anticipation of panic attacks was removed. Although the long-established link between agoraphobia and panic disorder has been downgraded, the criteria still require fear or avoidance of situations due to thoughts about difficulties that might arise if “panic-like” symptoms were to occur.

The aetiology of panic disorder is not fully understood and is probably heterogeneous. Biological theories incorporate the faulty triggering of an inbuilt anxiety response, possibly a suffocation alarm. Evidence for this comes from biological challenge tests (lactate and carbon dioxide trigger panic in those with the disorder) and from animal experiments and neuroimaging studies in humans that show activation of fear circuits, such as that involving the periaqueductal grey (PAG) matter.

As in other anxiety disorders, evidence exists to suggest that aberrant immunological mechanisms may play a role in panic disorder but this area requires further investigation to see if preliminary findings on altered cortisol reactivity and cytokine concentrations may yield new insights for development of treatments or assessment of response.

The cognitive model of panic describes a vicious circle of a fearful interpretation of normal body symptoms leading to an anxiety response. For example, a person noticing their own heartbeat may misinterpret this normal perception as being evidence that there is a problem with the functioning of their heart, leading to fear that a serious cardiovascular issue may be about to emerge. The consequent increase in physical symptoms associated with this anxiety, eg breathlessness, tremor and stronger palpitations, may amplify the perception leading to a catastrophic panic attack. It stresses the predisposing role of

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**Table 1. Diagnostic features of panic disorder (DSM-5)**

- Recurrent panic attacks involving at least four symptoms (physical sensations such as racing heart, chest pain, sweating, trembling, choking, breathlessness, nausea, dizziness/lightheadedness, paraesthesias and hot flushes or cold chills, thoughts of derealisation/depersonalisation and fears, eg of ‘dying’ or ‘going mad’)
- Attacks reach a peak quickly and some are unexpected or spontaneous
- At least one attack followed by a month of persistent anxiety about having further attacks and/or a maladaptive change in behaviour related to the attack
- Attacks not explained by a medical condition or substance, eg caffeine
- When agoraphobia is present, fear or anxiety over at least six months, of two or more situations such as public transport, open or enclosed spaces, being in queues or crowds or being alone outside the home, in which developing ‘panic-like’ symptoms could be distressing, ie thoughts that escape might be difficult or help not available. The agoraphobic situations must be actively avoided or tolerated with intense fear or else require a companion to be present, and the fear, anxiety or avoidance must cause clinically significant distress and be out of proportion to the actual danger the situations pose

*Note: Unlike previous DSM classifications, agoraphobia can now be diagnosed irrespective of the presence of a diagnosis of panic disorder*
beliefs about the meaning of bodily sensations in the aetiology of the disorder.\(^7\) Exploration and challenge of this model forms the basis of cognitive therapy for panic disorder.

**Risk factors and clinical course**

Patients frequently have a family history of panic disorder or other anxiety and mood disorders. Epidemiological studies suggest a significant genetic contribution,\(^8\) although the specific genes implicated have not yet been identified. It is more common in females than males by a ratio of around 2:1. There is an association with “fearful spells” in childhood, and with sexual or physical abuse. Phobic symptoms commonly precede the panic attacks and onset of panic disorder may be triggered by a life event or a period of exposure to ongoing stress. Smoking, alcoholism and respiratory disorders are further known risk factors.

In a longitudinal study of individuals having an index episode of an anxiety disorder,\(^9\) 18% of those having panic disorder without agoraphobia at entry were still in their index episode of panic disorder after 12 years of follow-up. For panic disorder with agoraphobia, the figure was 48%, suggesting that the agoraphobia component is associated with chronicity. For comparison, the figures for social phobia and GAD were 37% and 58% respectively. However, among individuals who did achieve recovery, those with panic disorder, with or without agoraphobia, were more prone to subsequent relapse (56% and 58% respectively over the 12-year follow-up period) than were those with other anxiety disorders. The prognosis for panic disorder is worse in the presence of depression.\(^10\)

**Panic disorder and other medical conditions**

The relationship with other medical disorders is complicated and requires careful assessment. The somatic symptoms of a panic attack can mimic a range of conditions including asthma, congestive cardiac failure, angina, cardiac arrhythmia, benign positional vertigo and thyroid abnormalities. One study found panic disorder in over 10 per cent of patients referred to a cardiology clinic with palpitations.\(^11\) However, patients may have both cardiac disease and panic disorder, and investigations such as an ECG should be considered, particularly if dizziness, syncope or persistent tachycardia is present. There are reported associations of panic disorder with hypertension, mitral valve prolapse, exercise avoidance, thyroid disease, temporal lobe epilepsy and migraine; and with use of alcohol, amphetamines, benzodiazepines, cannabis and cocaine.\(^12\)

**Clinical assessment and psychoeducation**

Diagnosis of panic disorder is made from the history, although further investigation of somatic symptoms may be appropriate. Panic attacks, their constituent symptoms, frequency and occurrence with and/or without situational triggers should be noted. Fearful cognitions can be unearthed by a process of ‘Socratic questioning’, i.e. persistent, inquisitive interrogation until the root cause of the problem is uncovered. The patient may deny or avoid disclosing their central fears. An assessment of functional impairment should be made, with enquiries about avoidance of situations in which attacks may be embarrass-
### Selective serotonin reuptake inhibitors (SSRIs)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Acute panic attack</th>
<th>Acute panic disorder</th>
<th>Long-term panic disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
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<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Escitalopram</td>
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<td>✓</td>
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</tr>
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</tr>
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</tr>
<tr>
<td>Paroxetine</td>
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<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Sertraline</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>✓</td>
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### Serotonin noradrenaline reuptake inhibitors (SNRIs)

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<tbody>
<tr>
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### Tricyclic antidepressants

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</tr>
<tr>
<td>Imipramine</td>
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### Other antidepressants

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<th>Long-term panic disorder</th>
</tr>
</thead>
<tbody>
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<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Moclobemide</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>✓</td>
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<td>✓</td>
</tr>
<tr>
<td>Reboxetine</td>
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### Benzodiazepines

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<th>Long-term panic disorder</th>
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<tbody>
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<td>Alprazolam</td>
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<td>✓</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Diazepam</td>
<td>✓</td>
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<td>✓</td>
</tr>
<tr>
<td>Lorazepam</td>
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### Others

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<th>Acute panic disorder</th>
<th>Long-term panic disorder</th>
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</thead>
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<tr>
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<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Risperidone</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Pindolol (as adjunct to fluoxetine)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

* Comparator-controlled study only

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**Drugs used in depression**

Given the various issues with benzodiazepines, the reuptake blocking drugs that are familiar as treatments for depression, especially the selective serotonin reuptake inhibitors (SSRIs) and the serotonin-noradrenaline reuptake inhibitor (SNRI) venlafaxine, are generally considered to be the preferred drug treatments in panic disorder. As with mood disorders, the onset of clinical response typically occurs after at least two weeks (see Figure 1). The exact mechanism of these drugs’ action is not known, but one possibility is via enhancement of serotonergic tone to modulate GABA input to the PAG matter.

Patients with panic disorder sometimes seem to be especially sensitive to drug side-effects. When prescribing any of the reuptake inhibitor drugs, it is wise either to start with low doses and titrate upwards slowly, or at least to explain that typically some excess anxiety may be expected in the first few days of treatment before the therapeutic effect becomes established, in a phenomenon known as the ‘jitteriness/anxiety syndrome’. In describing this possibility, patients can be reassured that the emergence of such symptoms should not be misinterpreted as the drug being unlikely to help in the longer term.

Among the many reuptake inhibitors that have been studied in randomised controlled trials (RCTs) in panic disorder, the six SSRI drugs and the SNRI venlafaxine are considered the first-line treatments. In the UK, only the SSRIs citalopram, escitalopram and paroxetine hold a specific licence for panic disorder, but there is adequate data from placebo-controlled RCTs to establish the efficacy of all six drugs in the class.

The most frequent longer term side-effects of SSRIs are tiredness, weight gain, abdominal distress and sexual dysfunction. In terms of differentiating between SSRIs, the propensity for adverse effects, withdrawal issues and drug interactions may guide the prescriber in selecting a specific drug. In recent years, regulatory bodies have highlighted evidence that citalopram has been associated with a slightly elevated risk of QTc prolongation at higher doses, which may indicate an increased risk of cardiac arrhythmia. Any association of escitalopram with arrhythmia appears to be less robust. Meanwhile, paroxetine is associated with difficult withdrawal in a sizeable proportion of cases. Fluoxetine (CYP3A4 and CYP2D6), paroxetine (CYP2D6) and fluvoxamine (CYP3A4 and CYP1A2) are all cytochrome P450 enzyme inhibitors and hence increase the risk of drug interactions. Among the SSRIs, sertraline or escitalopram are therefore often seen as a good place to start in the absence of other persuasive factors.

Venlafaxine also has a well-developed evidence base and is sufficiently different pharmacologically from the SSRIs that if SSRIs are either ineffective or not tolerated, a logical step is to switch to venlafaxine with its additional noradrenergic reuptake inhibition. Note that there is no randomised trial evidence to support the use of other commonly prescribed SNRIs such as duloxetine and desvenlafaxine (the latter is not available in the UK).

A further step after SSRIs and/or venlafaxine is to switch to the noradrenaline-serotonin-receptor blocking drug mirtazapine, which has evidence of effectiveness in panic disorder.

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**Table 2.** Randomised controlled trial evidence for drug treatment of panic attacks and panic disorder as indicated. Drugs in red are considered first-line treatments. Drug trials for acute treatment were double-blind with placebo control except where marked by the * symbol. Trials for long-term treatment (six months – three years) are in most cases open follow-up phases of double-blind trials. [Derived from: Baldwin DS, et al. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. J Psychopharmacol 2014;28:403–39.][1]
derived from a randomised comparator trial where it was as effective as fluoxetine. One area that has yet to receive adequate attention is whether enhanced efficacy could be anticipated if mirtazapine is used in combination with SSRIs or SNRIs rather than as monotherapy. Evidence for mirtazapine augmenting SSRIs or SNRIs does exist in depression so this strategy is certainly acceptable where panic disorder and depression are co-morbid.

Beyond mirtazapine, the remaining antidepressant drugs with known efficacy in panic disorder all belong to less widely used classes, which may not be as familiar to the majority of prescribers. These drugs can be divided into three categories. First, tricyclic antidepressants; clomipramine and imipramine are supported by good RCT data. These are also serotonin and noradrenaline reuptake blockers, with additional blockade of histamine, serotonin and acetyl choline receptors. They are licensed in some European countries, although not in the UK, but due to their association with anticholinergic side-effects and toxicity in overdose they are seen as less desirable options than the newer drugs discussed above, and are usually reserved for treatment-resistant cases. Lofepramine, which is also a serotonin/noradrenaline reuptake blocker, has evidence of equivalence to clomipramine from a randomised comparator trial.

Second, the selective noradrenergic reuptake inhibitor reboxetine has proven efficacy although it too tends to provoke adverse effects similar to the anticholinergic effects of tricyclic antidepressants.

Third, there is also placebo-controlled RCT evidence for using the monoamine oxidase inhibitor (MAOI) drug phenelzine and evidence from comparator-controlled RCTs to support moclobemide, the reversible inhibitor of monoamine oxidase A. Since moclobemide is less likely to provoke the well-known and dangerous ‘cheese reaction’ toxicity characteristically occurring when a person taking one of the original, or ‘irreversible’, MAOIs ingests foods containing tyramine (although some dietary restrictions still apply), moclobemide may be seen as a useful option in treatment-resistant cases.

**Gabapentin and pregabalin**

There are several other drugs outside the antidepressant type that have evidence of efficacy, either as monotherapy or as augmentation strategies. Gabapentin, which is thought to modulate glutamate neurotransmission, has some evidence of being effective in monotherapy, which is stronger for more severe cases. Evidence for gabapentin’s successor drug pregabalin is very limited, being confined to an uncontrolled open trial of continuation therapy in a population with panic disorder, GAD or social anxiety disorder, which suggested efficacy over a 12-month period. This evidence is clearly inadequate to recommend pregabalin in non-co-morbid panic disorder. However, with several randomised trials demonstrating efficacy specifically in GAD and one in social anxiety disorder, pregabalin may have a role to play where panic disorder and either GAD or social anxiety disorder are present co-morbidly.

<table>
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<tr>
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<tbody>
<tr>
<td>Speed of onset</td>
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<td>Fast</td>
</tr>
<tr>
<td>Onset worsening</td>
<td>Sometimes</td>
<td>No</td>
</tr>
<tr>
<td>(jitteriness/anxiety</td>
<td></td>
<td></td>
</tr>
<tr>
<td>syndrome)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrawal worsening</td>
<td>Discontinuation syndrome</td>
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</tr>
<tr>
<td>(common if stopping</td>
<td>common if stopping</td>
<td></td>
</tr>
<tr>
<td>paroxetine abruptly,</td>
<td>paroxetine abruptly,</td>
<td></td>
</tr>
<tr>
<td>rare with other</td>
<td>rare with other SSRIs</td>
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</tr>
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<td>Yes</td>
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<tr>
<td>Alcohol interaction</td>
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<td>Yes</td>
</tr>
<tr>
<td>Therapeutic tolerance</td>
<td>Rare</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Treat associated</td>
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<td>Yes, but more limited</td>
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<td>depression</td>
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<tr>
<td>Safe in substance</td>
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<td>No</td>
</tr>
<tr>
<td>abusers</td>
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**Table 3. Comparison of attributes of SSRIs and benzodiazepines in the treatment of panic disorder**

**Antipsychotics**

Good-quality evidence for antipsychotic monotherapy is relatively sparse, with only risperidone (a serotonin/dopamine-receptor blocker) demonstrating equivalence to an SSRI in a randomised trial. Quetiapine and olanzapine have a more limited evidence base, relying on open studies. Evidence to support antipsychotic augmentation of SSRIs (for risperidone, aripiprazole and olanzapine) is also restricted to open studies.

**Benzodiazepines**

The benzodiazepines lorazepam, clonazepam, diazepam and alprazolam also have evidence of efficacy for panic disorder in RCTs. There is high-quality evidence for clonazepam not only as monotherapy but also as an adjunct to SSRIs. Benzodiazepines have an advantage over other drugs of being able to provide relief and remission more rapidly. However, what must be considered alongside this strong evidence base are the problems of the class being associated with tolerance and difficult withdrawal. Most specialists are willing to prescribe benzodiazepines for short periods for certain patients who have no history of substance misuse, especially where the patient feels that the impact of their panic attacks is so great that rapid relief is required. However, they will normally continue to explore and utilise other treatment strategies – both pharmacological and psychological – aiming to provide remission through these approaches and avoiding the possibility of exposing the patient to the potential problems of longer term benzodiazepine use. Benzodiazepines may also have a useful role if given on or soon after initiating antidepressants if the jitteriness/anxiety syn-
Panic disorder

A further strategy is to provide a small supply of benzodiazepines, eg clonazepam, as a ‘rescue medication’, which can be carried by the patient to be taken only in case of onset, or anticipated onset, of a severe panic attack on an as-needed basis. The authors have observed in their clinical practice that some patients report that the mere existence of the tablet as a means to head off an attack has had an empowering effect, enabling them to face situations that they would otherwise have avoided. This can be very important in overall outcome, as fear of facing panic-inducing situations significantly limits behavioural interventions to improve panic. Also, restricting the actual administration of the drug to incidences where a panic attack is either expected or the symptoms have just been perceived to be starting, may allow the problems of tolerance and withdrawal phenomena to be avoided.

The question of allowing regular benzodiazepines to be continued for more than four weeks is more controversial; for example, the BNF advises avoiding prolonged use. This standpoint is based on the judgement that the potential for tolerance (with possible dose escalation), difficult withdrawal and side-effects such as sedation, increased rate of motor vehicle accidents and, in older patients, increased risk of falls, fractures and possibly cognitive impairment represent too great a burden of risk in relation to the therapeutic effect, which is less well characterised beyond four weeks. In contrast, a recent expert consensus statement advises that, providing the question of dose reduction is discussed with the patient from time to time, long-term benzodiazepine use can be an acceptable strategy in panic disorder if a benzodiazepine has delivered relief where other treatments have failed, and where dose escalation has been avoided. It should be noted that observational studies of benzodiazepines in panic disorder usually find reduced rather than increased usage over time, suggesting tolerance is not a major factor in this patient population.

Other drug strategies
A further strategy having good-quality trial evidence is the augmentation of fluvoxetine with pindolol, an antihypertensive drug that has both beta-receptor blocking and serotonin-modulating properties. Sodium valproate has also been evaluated in several small open trials with some evidence of effect, and may be worth trying either as monotherapy or in combination with antidepressants when other strategies have failed.

Drugs having negative trial evidence
Some drugs have been reported to be ineffective in RCTs for the acute treatment of panic disorder as monotherapy; these include buspirone, trazodone, carbamazepine, tiagabine and propranolol. The dopamine/noradrenaline reuptake blocker bupropion has evidence of effect in an open trial but was ineffective in an RCT.

Longer term drug treatment
Long-term treatment efficacy of maintenance therapy over six months to three years has been established through open follow-up of placebo-controlled randomised trials for several drugs, notably the SSRIs citalopram, paroxetine, fluoxetine and fluvoxamine, and the tricyclics clomipramine and imipramine. Moclobemide has similar evidence from a comparator randomised trial. Sertraline was as effective as imipramine in an RCT lasting six months. The benzodiazepines alprazolam and clonazepam have also shown to be effective in long-term treatment of two and three years respectively, although as discussed in the section above, the pros and cons of embarking on benzodiazepine treatment beyond four weeks must be considered carefully.

SSRIs, venlafaxine and imipramine have additionally been reported to outperform placebo in preventing relapse in discontinuation studies (randomised trials conducted in patients who have achieved remission, with some participants allocated to either continue the medication they responded to or to switch to placebo). Patients who are responding well to an antidepressant at 12 weeks should generally have it continued for at least six months. When stopping, the antidepressant should be tapered off to reduce the likelihood of a discontinuation reaction (especially with paroxetine and venlafaxine). Despite careful treatment, a significant number of patients will experience a recurrence, and may require long-term maintenance therapy.

Psychological treatments
Evidence exists for several forms of psychotherapy in panic disorder, including CBT, its constituent components of cognitive therapy and behavioural therapy, ‘third wave’ CBT techniques (which include mindfulness-based approaches), as well as psychodynamic therapy, psychoeducation and supportive therapy. A recent Cochrane review, using the network meta-analysis technique, has examined evidence on these various psychotherapeutic approaches for panic disorder. CBT has the most extensive evidence base and there was some lower grade evidence to suggest that CBT, along with psychodynamic therapy and the nonspecific modality of supportive therapy, were superior to the remaining approaches. For many prescribers, the reported value of supportive therapy, which is not directly tailored to panic disorder per se but requires the more general skills of empathic listening and direction, is of interest as this approach can easily be adopted when seeing the patient to review their progress and adjust medications.

The combination of antidepressant medication with psychotherapy has been reported in a meta-analysis to have superior efficacy over psychotherapy alone and over antidepressants alone, both during the acute treatment phase and subsequent continuation phase. More controversially, the same paper suggested that overall, psychotherapy alone (as well as combination treatment) may be a preferable first-line strategy to antidepressants alone. This was based on analyses of relapse rates 6–24 months after treatment discontinuation, ie stopping antidepressants and/or ceasing psychotherapy sessions, which indicated that: (a) patients who had been treated with the combination were less likely than those who had received antidepressants to suffer relapse in this period; and (b) no dif-
ference emerged between patients who had had the combination and those who had received psychotherapy alone. However, the ‘combination vs antidepressants only’ analysis identified five trials where comparison of relapse rate after treatment discontinuation was possible, three of which employed tricyclic antidepressants and one moclobemide – none of which are considered to be first-line drug treatments for panic disorder.\textsuperscript{13,14} Three of the five trials employed CBT as the psychotherapy, the superiority of combination treatment over antidepressants after discontinuation in these three meta-analysed together being marginal (p=0.05).

The only trial to report a significant difference between combination therapy and antidepressants alone after discontinuation\textsuperscript{24} actually used psychodynamic therapy. The authors of this trial acknowledged that because both groups had medication managed by a GP but the combination group additionally had psychotherapy delivered by expert therapists at a centre of excellence while those allocated to medication only had no additional input, results could be subject to an ‘expectation bias’. Participants in the latter group were fully aware they had missed out on receiving the psychodynamic therapy and may have been subsequently undermined by this disappointment.

The high likelihood of bias in this key study, the predominant use of second-line antidepressants in the trials identified and the marginal outcome if only the trials employing CBT are considered, means that the suggestion that this evidence supports the use of psychotherapy as the first-line treatment over antidepressants\textsuperscript{24} should be viewed with caution. The British Association for Psychopharmacology guidelines published in 2014\textsuperscript{13} advise that antidepressants and psychotherapy are each considered first-line treatments, providing that access to staff with appropriate training and supervision in the psychotherapy modality chosen is available.

\textbf{Biological treatments}

The noninvasive brain stimulation technique, repetitive transcranial magnetic stimulation (rTMS), has preliminary evidence of efficacy in open-label trials for people with panic symptoms. Furthermore, there is some evidence of effectiveness in panic disorder co-morbid with depression through a case series, but a trial examining its effectiveness as an adjunct to SSRIs in panic disorder was negative.

\textbf{Conclusion}

Panic disorder is common and frequently presents in primary care or general medical settings. In recent years, robust evidence supporting the use of numerous drug treatments has emerged, and for several compounds the evidence has been extended to demonstrate long-term efficacy. For most cases, the preferred drug treatment strategy is to start with an SSRI antidepressant or the SNRI venlafaxine. If neither are successful, the prescriber may consider progressing through the various classes of drugs used in depression that have randomised trial evidence (including mirtazapine, reboxetine, certain tricyclic antidepressants and moclobemide), and other drugs with an evidence base such as gabapentin, risperidone, pindolol augmentation of SSRIs and possibly sodium valproate.

Benzodiazepines are also effective, but the issues of ‘if and when’ they should be introduced, given the many concerns associated with their longer term use, may provide challenges for the prescriber, especially when faced with a patient who is eager to access the rapid relief they can provide. Where benzodiazepines are judged to be appropriate, the prescriber must decide whether they should be given only pro re nata (when required; such as the ‘rescue medication’ approach), as a regular but short-term prescription, or occasionally (in circumstances discussed earlier) as a longer-term regular prescription.

In addition, various psychotherapies, most notably CBT, but also supportive therapy and psychodynamic therapy, have an established evidence base, and using psychotherapy together with antidepressants may be more effective than either psychotherapy or antidepressants alone. Diagnosis and effective treatment is essential to prevent or reduce the many adverse consequences of this potentially disabling anxiety disorder.

\textbf{References}


**Declaration of interests**

None declared.

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**POEMs**

**Antipsychotics worsen symptoms in patients with delirium who receive palliative care**

**Clinical question:**
Do antipsychotic drugs improve symptoms of distress associated with delirium in patients receiving palliative care?

**Bottom line:**
For hospitalised patients with acute delirium and symptoms of distress who are receiving palliative care, the use of risperidone or haloperidol at conservative oral doses worsens symptoms and may shorten overall survival. (LOE = 1b)

**Reference:**

**Study design:** Randomised controlled trial (double-blinded). 
**Funding source:** Government. 
**Allocation:** Concealed. 
**Setting:** Inpatient (ward only).

**Synopsis:**
These researchers enrolled 247 hospitalised patients who were receiving palliative care and had delirium-related symptoms of distress. Patients were randomised, using concealed allocation, to receive either oral risperidone, haloperidol, or placebo for 72 hours for the management of these symptoms. There were slightly more than 80 patients in each of the three arms. The initial dose for both risperidone and haloperidol was 1mg, with maintenance doses of 0.5mg every 12 hours titrated to a maximum dosage of 4mg daily. Patients older than 65 years received half this dosage. All patients also received nonpharmacologic measures for delirium treatment, as well as treatment for reversible precipitants of delirium. Subcutaneous midazolam was given as needed for patients who required immediate intervention for safety or distress. Delirium symptom scores were obtained every eight hours using the three items on the Nursing Delirium Screening Scale that are considered measures of distress (inappropriate behaviour, inappropriate communication, and illusions/hallucinations). Each item was scored from 0 to 2, based on the presence and intensity of the symptom, for a total score of 0 to 6. The primary outcome was the average of the last two delirium symptom scores on day 3 of treatment. The three study groups had similar delirium symptom scores at baseline. The mean age in each group was 75 years and almost 90% of patients had cancer. Analysis was by intention to treat.

Overall, patients who received haloperidol and patients who received risperidone had significantly higher delirium symptom scores at day 3 as compared with those who received placebo by an average of 0.48 and 0.24, respectively. Both intervention groups also required more rescue midazolam than did the placebo group. Finally, the haloperidol group was noted to have decreased overall survival compared with the placebo group (hazard ratio 1.73; 95% CI 1.20–2.50; p=0.003). The authors suggest that this may be due to prolonged delirium or longer exposure to antipsychotics. Survival was also decreased in the risperidone group, though this did not reach statistical significance.