Australian and New Zealand clinical practice guidelines for the treatment of panic disorder and agoraphobia

Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Panic Disorder and Agoraphobia

Background: The Royal Australian and New Zealand College of Psychiatrists is co-ordinating the development of clinical practice guidelines (CPGs) in psychiatry, funded under the National Mental Health Strategy (Australia) and the New Zealand Health Funding Authority.
Method: For these guidelines, the CPG team reviewed the treatment outcome literature, consulted with practitioners and patients and conducted a meta-analysis of recent outcome research.
Treatment recommendations: Education for the patient and significant others covering: (i) the nature and course of panic disorder and agoraphobia; (ii) an explanation of the psychopathology of anxiety, panic and agoraphobia; (iii) rationale for the treatment, likelihood of a positive response, and expected time frame.
Cognitive behaviour therapy (CBT) is more effective and more cost-effective than medication. Tricyclic antidepressants (TCAs) and serotonin selective reuptake inhibitors are equal in efficacy and both are to be preferred to benzodiazepines. Treatment choice depends on the skill of the clinician and the patient's circumstances. Drug treatment should be complemented by behaviour therapy.
If the response to an adequate trial of a first-line treatment is poor, another evidence-based treatment should be used. A second opinion can be useful. The presence of severe agoraphobia is a negative prognostic indicator, whereas comorbid depression, if properly treated, has no consistent effect on outcome.
Key words: agoraphobia, panic disorder, treatment outcomes.

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These guidelines, provided to promote good clinical care, are designed for mental health professionals trained to assess, diagnose and treat panic disorder (PD). Specialist clinicians should consider, but not be limited to, the treatments recommended. Panic disorder has been much studied in the past 30 years. The literature is extensive and there are numbers of systematic reviews of randomised controlled trials. There are aspects about which less is known and lower orders of evidence have been used. The levels of evidence can be used as a guide to the robustness of the evidence.

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Definitions and main features

Anxiety is a normal emotion that can be adaptive and aid performance. We all suffer from uncomfortable levels of anxiety at some time. In fact, 40% of young people have had at least one spontaneous panic attack [1], although they will not have repeated attacks and do not meet the criteria for PD (Table 1).

Panic attacks, the sudden experience of fear accompanied by symptoms of the 'flight or fight' response, occur in people with a range of anxiety, depressive and substance use disorders. The key feature of a panic attack that is part of PD is fear about the consequences of the attack. People with PD worry that the panics are evidence of something physically or mentally wrong with them that might lead to illness, loss of control or death.

Panic disorder is characterized by discrete periods of intense fear, with symptoms of the 'flight or fight' response. There is persistent concern about having another attack and worry about the consequences of that attack. Some attacks seem to come out of the blue, others are accompanied by a sense of impending doom and an urge to flee the situation. Agoraphobia may or may not be present (Table 2). Attacks that meet all other criteria but that have fewer than four somatic or cognitive symptoms are called *limited-symptom attacks* [2].

Agoraphobia is anxiety about and avoidance of places or situations from which escape might be difficult or help unavailable in the event of a panic attack. Such situations commonly include being alone, crowds, public transport, driving alone, and being on a bridge or in a lift. The DSM-IV criteria (Table 3) and the ICD-10 criteria are similar. In cases of agoraphobia without a history of panic, which do occur in the community [3] but are rare in clinical practice [4], situations are avoided for fear of uncomfortable symptoms, usually of anxiety.

Table 1. DSM-IV criteria for a panic attack

A discrete period of intense fear or discomfort, in which four (or more) of the following symptoms developed abruptly and reached a peak within 10 minutes:

Palpitations, pounding heart or accelerated heart rate
Sweating
Trembling or shaking
Sensations of shortness of breath or smothering
Feeling of choking
Chest pain or discomfort
Nausea or abdominal distress
Feeling dizzy, unsteady, lightheaded or faint
Derealization or depersonalization
Fear of losing control or going crazy
Fear of dying
Paresthesias (numbness or tingling sensations)
Chills or hot flushes

Epidemiology

Anxiety disorders are the most common mental disorders. In Australia 3.8% of adults met criteria for a DSM-IV anxiety disorder within the past month [5]. Anxiety disorders account for a quarter of the burden of disease attributed to mental disorders [6].

Prevalence

Studies across the developed world indicate a lifetime prevalence of PD between 1.4% and 2.9%, with higher rates for women [7]. Panic disorder without agoraphobia typically presents with a more equal sex ratio [8] than does agoraphobia, where around three-quarters of sufferers are women [9,10]. The point-prevalence of the panic cluster of disorders in the Australian National Mental Health Survey was 0.7%, and the male : female ratio 1 : 2 [5]. In community samples, one-third to one-half of those diagnosed with

Table 2. DSM-IV criteria for panic disorder without agoraphobia

A. Both of the following:
- recurrent and unexpected panic attacks
- at least one of the attacks has been followed by one month (or more) of one (or more) of the following:
  – persistent concern about having additional attacks
  – worry about the implications of the attack or its consequences (e.g. having a heart attack, going crazy)
  – a significant change in behaviour related to the attacks

B. Absence of agoraphobia
C. The panic attacks are not due to the direct physiological effects of a substance or a general medication condition.
D. The anxiety or phobic avoidance is not better accounted for by another mental disorder, such as social phobia (e.g. avoidance limited to social situations because of fear of embarrassment); specific phobia (e.g. avoidance limited to single situation like elevators); obsessive-compulsive disorder (e.g. avoidance of dirt in someone with an obsession about contamination); post-traumatic stress disorder (e.g. avoidance of stimuli associated with a severe stressor); or separation anxiety disorder (e.g. avoidance of leaving home or relatives).

The DSM-IV criteria for panic disorder with agoraphobia are the same as above, except that agoraphobia is present.

Table 3. DSM-IV Criteria for agoraphobia

- 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 or panic-like symptoms. Agoraphobia fears typically involve characteristic clusters of situations that include being outside the home alone; being in a crowd or standing in line; being on a bridge; and travelling in a bus, train or car.
- The situations are avoided or else are endured with marked distress or with anxiety about having a panic attack or panic-like symptoms, or require the presence of a companion.
- The anxiety or phobic avoidance is not better accounted for by another mental disorder, such as social phobia (e.g. avoidance limited to social situations because of fear of embarrassment); specific phobia (e.g. avoidance limited to single situations like elevators); obsessive-compulsive disorder (e.g. avoidance of dirt in someone with an obsession about contamination); post-traumatic stress disorder (e.g. avoidance of stimuli associated with a severe stressor); or separation anxiety disorder (e.g. avoidance of leaving home or relatives).

PD also report agoraphobia [11]. The rate is higher in clinical samples.

Course and prognosis

Panic disorder begins between late adolescence and the mid-30s [3,7,11,12], although the first panic attack may have been experienced years earlier [9]. The course is usually chronic but will often wax and wane. Typically there is a substantial period between initial onset and presentation for treatment. But even when people do present, PD is both under-diagnosed and under-treated [13–15].

As with other anxiety disorders, stressful life events tend to precede the onset of PD [16,17]. It seems that it is not the stressful life events in themselves that are critical, but the negative interpretation of the consequent symptoms [18]. The frequency of panic attacks varies widely. One person housebound with agoraphobia might have only one panic attack in 12 months in which she anticipates collapse or death. Another person, not housebound, may have attacks of similar severity on a daily basis. Recurrent attacks may continue for years. There may be periods of full or partial remission, with no panics or only mild attacks with few symptoms. Panic disorder may be associated with minimal impairment in social or occupational functioning, or else with extreme impairment, as in severe agoraphobia.

Economic and social implications

The economic and social costs are considerable [13,19–21], and are greater than for schizophrenia or mood disorder. Anxiety disorders cost the US economy $US46.6 billion annually [22]. These costs are both direct (e.g. medical care, prescription drugs) and indirect (e.g. lost productivity).

In Western Australia, people with PD had significantly higher medical-use rates and incurred higher costs than either non-anxious controls or people with social phobia [23]. Over a 12-month period, they averaged a direct cost (including visits to primary care physicians, specialist consultations, diagnostic tests and ambulance and emergency department services) of $AU1118, compared with $99 for non-anxious age-matched controls.

Many people with PD do not seek treatment, and much of the economic cost is indirect (e.g. work disability and family dysfunction) [24,25]. A diagnosis of PD is associated with pervasive social and health consequences similar to or greater than those associated with depression [26,27].

Method

Key features of the development of this guideline have been: (i) a comprehensive review of relevant literature; (ii) meta-analysis of randomised controlled trials; (iii) development of evidence tables; (iv) initial drafting by a work group with clinical and research expertise; (v) patient review and input; and (vi) multiple drafting following widespread input.

Literature searches were of English language MEDLINE (1966–1999), PsychINFO (1984–1999), EMBASE (1988–1999) and the Cochrane Library (1966–1999). Key words for searches were: ‘clinical trial’; ‘controlled clinical trial’; ‘review’; ‘systematic review’; ‘meta-analysis’; ‘panic disorder’; ‘agoraphobia’; ‘psychotherapy’; ‘psychiatry’. Searches used extra key words such as: ‘assessment’; ‘comorbidity’; ‘outcome’; ‘course’; and ‘medical investigations’. Key texts and review articles were sourced

(e.g. *Treatments that work* [28]), and existing guidelines consulted.

An excellent meta-analysis conducted by Gould *et al*. [29] included 43 studies. Our meta-analysis focused on trials not included there or published subsequently. Of 137 studies identified, 58 were randomized placebo (psychological or pharmacological) controlled trials from which data could be coded. This and the Gould *et al*. meta-analysis provide the basis for our recommendations. While this guideline was in review, two more meta-analyses appeared; their results are noted. Evidence from the meta-analyses has been supplemented by lower-level evidence, including expert consensus, when more rigorous scientific evidence is lacking.

General issues in treatment

Aims of treatment

Effective treatment has these goals: (i) control and cessation of panic attacks; (ii) control and cessation of fear-driven avoidance; and (iii) reduction in vulnerability to relapse.

Both psychological and pharmacological treatments can achieve the first two goals but there is no evidence that drugs are able to reduce vulnerability. Cognitive behavioural therapy can, through education about panic and the provision of skills to deal with anxiety, reduce the probability of relapse. Treatment of panic rarely requires hospitalization unless there is concurrent suicidal depression or substance use requiring detoxification. Panic disorder alone is not an indication for admission.

Assessment

As panic attacks may occur in a number of disorders apart from PD, a behavioural assessment facilitates thorough understanding [30]. The major differential diagnoses are panic attacks in the other anxiety disorders and in depression. If the panic attacks occur only in social situations and there is a fear of shame, this is consistent with social phobia. If the panic relates to obsessional fears in obsessive compulsive disorder (OCD), to situational fears in specific phobia, or is directly attributable to the physiological changes in drug withdrawal or depression (when attacks occur upon waking), the diagnosis is unlikely to be PD. The attacks relate to fear of the consequences of panic. People fear that they will have a heart attack, collapse, go mad or die. The situation that is feared, endured or avoided merely adds to the risk of not being able to escape or get help. The danger in a panic attack is the *danger to the self by the self.*

Once details of the panic and related avoidance have been established, the clinician should establish the onset and the course of the disorder, factors that maintain the problem, and coping strategies that have been successful in the past. It is important to enquire about past treatment, including response and attitude towards them. A psychiatric and medical history should be taken to determine whether there is concurrent depression or a physical basis for the symptoms [31,32]. The person's psychosocial circumstances should be established (e.g. family, partners, accommodation, education, occupation and social relationships). Disability should be established (What do the panics/agoraphobia stop you doing?). Assessment should consider cultural issues in the expression and experience of anxiety (see Appendix).

The consequences of panic must be identified. A common type is avoidance, with subtle strategies such as carrying medication or a mobile phone, or distracting oneself in the feared situation. Recognizing the link between panic attacks and avoidance facilitates CBT (e.g. 'I avoid crowded trains because the air may run out given that everyone is breathing it').Typical beliefs associated with PD include: 'I might have a heart attack'; 'I might lose control of myself'; 'I am going crazy'; and 'I might die'. People with PD also fear embarrassment but this is not a primary concern. The main worry is about what will happen to them as a result of their symptoms; the fear of bodily collapse is paramount.

The differential diagnoses in DSM-IV include medical conditions that can cause panic-like attacks such as hyperthyroidism, hyperparathyroidism, seizure disorders and cardiac conditions like arrhythmias. Onset after age 45 or the presence of neurological symptoms during a panic attack (e.g. vertigo, loss of consciousness, loss of bladder or bowel control, headaches, slurred speech or amnesia) suggest the possibility that a general medical condition/organic syndrome may be causing the panic-like symptoms. If the presentation is complex, conduct a thorough behavioural analysis and consider contacting other medical professionals regarding past investigations. Panic attacks can occur with most recreational drugs, especially as part of withdrawal. If symptoms persist after intoxication or withdrawal have ended, a primary diagnosis of PD should be considered.

Investigations

It is rare for people with a long history of PD to have an undiagnosed medical condition. Many have sought medical advice on numerous occasions and continue to do so despite negative tests. If a person presents in the early stages, and the history suggests a psychological

trigger, it is appropriate to begin treatment without first investigating. If after 6 weeks panic symptoms are still prominent and cannot be clearly explained by psychological factors, it is prudent to conduct special investigations to rule out a medical cause. Remember that PD and medical conditions can coexist. There is no diagnostic test specific to PD.

Concurrent disorders

Clinical studies indicate that the rate of major depression may be higher than 30% [14,33,34]. Panic disorder occurring only in the context of depression is excluded by the criteria (see DSM-IV), but having concurrent depression can result in a poorer response to treatment [34–40]. A history of other anxiety disorders is also common, particularly social phobia (21%), generalized anxiety disorder (56%) and OCD (24%) [9,41]. People with PD are more likely to abuse alcohol and sedative-hypnotics than the general population [42,43]. The effect of alcohol use both on the underlying psychiatric disorder and on the effectiveness of drug and psychological therapy is stressed in the literature [44]. The rate of Axis II disorders in those with PD varies widely between studies [45–48], and the effect on treatment outcome is unclear.

Suicide ideation is common and should be carefully assessed. The high rate of suicide attempts is not always reflected in completed suicides [49,50]. This may be related to the high level of comorbid major depression and the disinhibiting effects of substance abuse [33,51–53] and may not differ from other mental disorders [52], but PD in the young may be more serious [54].

Current treatment evidence

We offer recommendations about psychological and pharmacological treatments when there is consistent evidence of efficacy from three or more randomised controlled trials from more than one research group. Two statistics summarize the overall treatment effect (Table 4).

The *number needed to treat* (NNT) is an estimate of the number of people who would need to be treated for one of them to achieve designated treatment success. In this guideline, NNT is based on the percentage of people who are panic-free at the end of active treatment. For example, a pooled NNT of 3 means that a clinician needs to treat three people to achieve panic-free status in one. Thus an NNT of 2 is better than a NNT of 6.

The *effect size* (ES) illustrates the extent of improvement in the average patient. It is the difference between the treatment and control group expressed in standard deviation units, thereby allowing comparisons across different outcomes and treatments. An ES of 1.0 indicates that the average treated person would be better than 86% of untreated patients.

Levels of evidence for various treatments are specified in roman numerals before the reference numbers. For example, [I] [29] means that the level of evidence is 1, and the reference corresponding is 29.

Beneficial interventions

Cognitive behaviour therapy (CBT)

Acute management

Cognitive behavioural thereapy is the most consistently efficacious treatment for PD, according to three

Table 4. Effect sizes (ES) and number needed to treat (NNT) at post-treatment and follow-up for the Gould et al. *meta-analysis and our meta-analysis*

	Post-treatment				Follow-up			
	Drug therapies	95% CI†	Psych. therapies	95% CI†	Drug therapies	95% CI†	Psych. therapies	95% CI†
Gould *et al.* (1995)	0.47	0.38–0.54	0.68	0.58–0.78	0.01	–	0.74	–
CPG analysis: all measures‡	0.40	0.27–0.52	0.61	0.35–0.87	0.00	0.27–0.27	0.57	0.24–0.91
CPG analysis: revised all measures§	0.43	0.30–0.55	0.59	0.34–0.83	0.00	0.27–0.27	0.65	0.31–1.00
CPG analysis: NNT	6	5–7	3	3–5	6	4–4	3	3–5

†Confidence interval; ‡measures from which ESs were calculable–the decision rule used by Gould *et al.* §excludes measures not directly related to panic and agoraphobia (e.g. personality and depression). ES estimator method = Glass' Delta. Effect sizes for our guideline combined a random effects model.

meta-analyses [I] [2,29,55–58]. The elements included in most trials are psychoeducation, anxiety management (control of hyperventilation and relaxation), cognitive therapy, and *in vivo* and interoceptive exposure. Cognitive behavioural thereapy showed the strongest ESs in both systematic reviews, as well as the greatest percentage of people who were panic-free at the end of treatment (74.3%). Dropout rates were low [I] (56%)[29]; (11.7%) [56].

Although *in vivo* exposure alone may be helpful [I] [59], it is not the treatment of choice [I] [56,60]. Interoceptive exposure is an important treatment, but we cannot conclude that it is superior to *in vivo* exposure or can replace it [I] [61–63]. Cognitive therapy without behavioural techniques showed a strong effect in our meta-analysis, although further investigation with larger sample sizes is required before recommending it as the sole treatment [I] [56].

A variety of delivery methods for CBT have been researched. Brief cognitive therapy, with only 6.5 h of therapist time, has been shown to be as efficacious as standard CBT (12 – 15 h) [II] [64]. In two trials, self-help books were as efficacious as group CBT, with gains maintained at 6-month follow-up; this presents a potentially cost-effective option [II] [65,66]. Telephone-administered exposure instructions have been shown to be an effective alternative for people who are not willing to be treated outside their home [II] [67,68], although it is probably best reserved for those who would otherwise not receive treatment. A related approach, CBT with reduced therapist contact (some by telephone), has proved to be viable and cost-effective [II] [69]. Computer-assisted therapy may be a useful treatment approach [II] [70].

Cost analysis conducted in the US has shown that imipramine and group CBT are the lowest cost interventions [I] [29]. Cognitive behavioural therapy had slightly better efficacy and a higher rate of tolerability (retention) than imipramine, and so appears to be the most cost-effective and tolerable treatment available.

Harms

In our meta-analysis, dropouts for *in vivo* exposure alone (21.3%) were higher than for either cognitive therapy alone (1.8%) or combined CBT (11.8%) [56]. We identified no adverse events. A disadvantage of CBT is that therapists need training [71] and there is a dearth of trained CBT clinicians. Generic counselling is less effective than properly conducted CBT [72].

Maintenance and long-term management

Most courses of CBT include one or more follow-up sessions. Manuals which are personalized during the sessions can be a useful continuing resource for self-treatment. Evidence is accumulating that CBT better prevents relapse [II] [73–76] than medication [I] [29]. Cognitive behavioural therapy confers skills, and this new knowledge produces future benefits that may not always be enhanced by additional treatment [77]. In a study of routine functioning, benefits were maintained at 2-year follow-up [II] [78]. This is an important finding, for patients with comorbid depression or personality disorders were not excluded, as in many randomised controlled trials.

Tricyclic antidepressants (TCAs)

Acute management

Two meta-analyses showed no significant difference in outcome between TCAs and benzodiazepines (BZDs). Tricyclic antidepressants showed a higher dropout rate (25.4%) than BZDs (13.1%) [I] [29,79]. In our meta-analysis TCAs were the pharmacological treatment with the strongest ES across a range of measures, and showed similar efficacy to CBT [I] [56]. Seven of the eight available meta-analyses show imipramine to be effective [I] [59]. The optimal dose was 100–225 mg daily, and benefit was obvious within 8–12 weeks. Clomipramine (a TCA with serotonin reuptake inhibitory effects) has been found to be beneficial [I, II] [80] at doses of 50–100 mg for 6–12 weeks. The evidence about desipramine is equivocal. In a 12-week randomised controlled trial, desipramine was not shown to be more helpful than placebo [II] [81], although a less well-controlled study showed it to be as beneficial as fluoxetine [82].

Harms

Many patients on TCAs drop out (a quarter in our meta-analysis) due to side-effects [I, II] [79,83]. Anticholinergic effects are frequently associated with imipramine and clomipramine. In one review, 43% reported such effects, including dry mouth, excessive sweating, constipation, blurred vision, urinary retention and mydriasis [II] [84].

Maintenance and long-term management

Maintenance treatment with a constant dose of imipramine over a year has a protective effect against relapse in patients who showed good initial response to the drug [II] [85]. A relapse rate of more than a third within the first year of imipramine discontinuation was reported in the same study. Similarly, a group maintained on a constant dose of imipramine or alprazolam

did slightly better on symptom measures than a placebo group, although less than 40% in both groups continued medication [II] [83]. Relapses usually occur 4–6 months after discontinuation [II] [85]. One trial found that after 6 months on imipramine, relapse can be prevented for up to an additional year by maintenance on half the original dose [86]. Paucity of long-term data precludes recommendations about long-term management with TCAs but expert consensus suggests 12 months of medication and then tapered withdrawal.

Serotonin selective reuptake inhibitors (SSRIs)

Benefits

Evidence for efficacy is conflicting. One meta-analysis found SSRIs (including paroxetine, fluvoxamine, zimelidine, and clomipramine) more effective than low dose, but no high dose, imipramine and clonazepam [I] [57]. The Gould *et al*. meta-analysis was conducted before evidence about SSRIs accumulated. In our meta-analysis, SSRIs were modestly useful, with less demonstrated efficacy than imipramine and alprazolam [I] [56]. They were less beneficial than CBT. Two subsequent meta-analyses [58,87] concluded that SSRIs were equal to TCAs but were better tolerated, although onset of benefit was slower. There are no data on the optimum length of treatment following initial response.

Harms

The main side-effects of SSRIs include headaches, irritability, nausea and other gastrointestinal complaints, insomnia, sexual dysfunction, increased anxiety, drowsiness and tremor. A withdrawal syndrome caused by abrupt discontinuation of SSRIs [88] may occur. In our meta-analysis a large proportion (26%) of those taking SSRIs dropped out of treatment [I].

Specific SSRIs

Fluvoxamine At least six double-blind, placebo-controlled trials show this to be a useful treatment, with similar benefits to clomipramine [II] [89–92]. A dose of 100–200 mg is recommended. Negative trials exist [II] [93]. The side-effect profile is similar to that of other SSRIs [92], and commonly includes sleepiness, sweating, diarrhea and nausea [94].

Fluoxetine There is evidence of efficacy at a daily dose of 5–20 mg [II] [95,96]. In one trial comparing 10 and 20 mg, 20 mg was associated with greater improvement, though the difference was not large compared with placebo [96]. There is more anxiety, nervousness and agitation in the initial weeks of treatment than with other drugs in this class [92]. Hostility is a possible side-effect [I] [97].

Paroxetine Four double-blind, placebo-controlled clinical trials have demonstrated efficacy in short-term treatment [II] [98–100]. Clear superiority over placebo and equivalent effectiveness to clomipramine were observed, and a threshold dosage of 40 mg/day is recommended [101]. One double-blind trial compared paroxetine plus cognitive therapy to placebo plus cognitive therapy [II] [100]. Significantly, more patients in the paroxetine group achieved a 50% reduction in panic frequency. Paroxetine reduces the number of panic attacks and prevents relapse for up to 9 months [II] [99,102]. It has a similar side-effect profile to other SSRIs, most notably nausea and sweating, and there is a problem with discontinuation.

Sertraline Two randomised, double-blind, placebo-controlled trials [II] [103,104] found sertraline to be superior to placebo at 50, 100 and 200 mg, with no difference in the efficacy of different doses [II] [103]. Since the difference from placebo on many measures was not significant in one of these trials [104], more trials are needed. In one trial, a third dropped out because of adverse experiences or insufficient response [92,104,105].

Citalopram A double-blind, placebo and clomipramine-controlled, parallel group, 8-week study with a large sample size found citalopram superior to placebo [II] [106]. The most advantageous benefit/risk ratio was at a dose of 20–30 mg/day. Side-effects are similar to other SSRIs [II] [106].

Interventions with a trade-off between benefits and harms

Literature that would allow the calculation of the number needed to harm could not be found.

High-potency benzodiazepines (BZDs)

Acute management

In both our meta-analysis and that of Gould *et al.* BZDs were found to have a small to moderate effect [I] (ES = 0.39; ES = 0.40) [29,56]. They have often been found to have similar efficacy to TCAs, although in our meta-analysis they were less effective [I] [60]. They were found to be more tolerated than TCAs, with fewer dropouts [I] [79]. The BZD with the most data is alprazolam, although controlled trials of diazepam, lorazepam, andinazolam and clonazepam suggest similar benefits [II] (e.g. 107–110). Alprazolam works in the range of

4–15 mg given for 4–15 weeks. Even with a slow taper, relapse rates of 50% or higher following discontinuation are typical [II] [111,112].

Harms

BZDs carry a risk of iatrogenic dependence as well as industrial and road traffic accidents [113,114]. They have been found to cause impairment in attention, concentration and short-term memory up to 24 weeks following withdrawal [II] [115,116]. Rebound anxiety on withdrawal has been reported in 15–30% of patients [113,117,118]. Side-effects include sedation or drowsiness (38–75%), memory impairment (up to 15%) [II] [119], unsteadiness, slurring of speech, occasional forgetfulness, irritability and reduced motivation [120]. Other adverse reactions to alprazolam (4–21%) include amnesia, aggression and mood changes [121,122]. Hostility occurred in 10% of one group receiving alprazolam [123]. The attrition rate is lower for BZDs than for TCAs [II] [124,110]. In our meta-analysis 12.8% of patients taking BZDs dropped out [I] [56], and higher rates than this have been reported [125]. Benzodiazepines should be avoided in late pregnancy and while breast-feeding [126]. The most common and serious interaction with other medications is enhancement of alcohol and augmentation of opiate-induced euphoria [127].

Maintenance and long-term management

There is concern that maintenance alprazolam might lead to dependence, withdrawal, continued treatment and further dependence [128], and it is not recommended for long-term use. A number of studies have found that people find it difficult to withdraw from alprazolam, with most suggesting that up to half are unable to discontinue within a month [128,129]. Only 27–47% of patients are off high-potency BZDs 12–30 months later [130–132]. In one study most remained in need of their drug 2 years after initial treatment [133]. Common symptoms of withdrawal are nervousness, irritability, sleep difficulties, loss of appetite, tremor, myalgia and, in rare cases, seizures [128,134]. Propranolol, buspirone and clonidine have been reported to be ineffective or of modest efficacy in attenuating BZD withdrawal syndrome [128], but carbamazepine may assist [II] [128,135,136].

If BZDs are prescribed, alprazolam should be continued for six symptom-free months, with a slow taper between 6 and 12 months after remission [V] [137,118]. A threefold increase in successful discontinuation from high-potency BZDs occurs when CBT is incorporated into the process (see below for discussion of combined treatments) [138].

Interventions likely to be beneficial

For the following sections, evidence is not categorized into acute, maintenance and long-term treatment as there is insufficient information available at this stage.

Monoamine oxidase inhibitors (MAOIs)

Only early open-label studies are available. Both studies on RIMAs, one a double-blind comparison of brofaromine and clomipramine [II] [139] and the other an open study of brofaromine [III] [140], showed antipanic and antiphobic value.

Applied relaxation

This may be a useful treatment [II] [141,142]. One trial showed similar efficacy to cognitive therapy, with 65% in the applied relaxation group and 74% in the cognitive therapy group panic-free at the end of 12 sessions [II] [142]. Results were maintained 1 years later. It should be noted that cognitive therapy did not involve traditional cognitive restructuring, but superficial techniques such as distraction [143]. Negative trials exist.

Interventions of unknown efficacy

Other drugs

There is insufficient information to recommend nefazodone, moclobemide or venlafaxine [144–146]. None of the following has been found to be useful: buspirone [II] [147,148]; beta blockers such as propanolol [149,143]; BZDs such as flurazepam, temazepam and triazolam; and bupropion [31].

Client-centred therapy

A randomised controlled trial of client-centred therapy compared to insight-orientated therapy plus exposure found improvement in both groups [II] [150]. The combined group was superior in the first 6-month follow-up period, but there were no differences at 1 year.

Psychodynamic therapy

Adding 15 weekly sessions of dynamic psychotherapy to treatment with clomipramine reduced the relapse rate over 9 months [III] [151] after clomipramine was withdrawn. Long-term psychodynamic therapy may be of value when there are comorbid personality disorders.

Eye movement desensitization and reprocessing

Compared to wait-list control, any short-term benefits had dissipated 3 months after treatment, suggesting that this is not a treatment of choice for long-term control [II] [152].

Hypnosis

There is no evidence that hypnosis is useful [153].

Interventions likely to be ineffective or harmful

Antipsychotics

There is no evidence that conventional antipsychotics have a role, and the risk of side-effects outweighs any potential benefit [31].

Clonidine

Limited evidence suggests unsuitability [III] [154,155].

Is combining two forms of treatment better?

CBT and medication

Cognitive behavioural therapy before and during drug discontinuation improves maintenance of treatment effects in patients initially treated with medication [III] [138,112]. The opposite approach (adding medication to CBT) possibly provides short-term treatment gains but may reduce the long-term benefits of CBT [156]. In six of eight studies examining imipramine plus exposure, there was no greater benefit from the combination than from imipramine alone [I] [29]. Clinical observation suggests that the use of alprazolam during CBT, especially during later sessions, undermines the value of CBT [157]. Use of BZDs during CBT has been associated with poorer outcome at both 3- and 24-month follow-up [77], possibly because they prevent the evocation of anxiety necessary for emotional processing [157]. There are no data to support the use of BZDs as occasion requires instead of CBT to cope with acute panic attacks. State-dependent learning or attributing gains to drugs can lessen the efficacy of CBT. There are insufficient data to evaluate the combination of CBT and SSRIs, other TCAs or MAOIs.

Overview of outcome

Research on long-term outcome shows that although improvement is common with either CBT or medication, many people remain symptomatic [II] [77,130,158–160]. The rate of relapse following discontinuation of drugs is high [III] [161]. In one study only a quarter discontinuing antidepressants sustained remission for 2 years or longer [162]. In a long-term follow-up study of 367 patients treated with drugs, over half continued to have occasional panic attacks, 40% still experienced avoidance and half were still taking medication [163].

The goal of treatment should be the disappearance of residual and subclinical panic and agoraphobic avoidance [142]. Long-term course is improved by CBT [74,75,165,166]. Follow-up studies indicate that at 15–24 month follow-up, about 85% are panic-free but 30–50% have residual avoidance. Follow-up data for CBT and for drug therapy should be interpreted cautiously, as studies are naturalistic [167]. Increase in benefit by combining antidepressants and CBT has not been demonstrated, and combination with BZDs may worsen end-state functioning [167,168].

Psychological treatments

The average duration of CBT was 10 weeks and the average pharmacological trial was 8 weeks. Some CBT trials included a follow-up period of up to a year (mean 29 weeks) whereas only one pharmacological trial incorporated follow-up. Average dropout rates were lower for CBT (12%) than for medication (21%). Both *in vivo* exposure and cognitive therapy showed a strong effect on reducing frequency of panic attacks [I] [29,56].

Pharmacological treatments

Tricyclic antidepressants and SSRIs were the most beneficial, while BZDs were moderately so [I] [56]. A number of trials show that relapse following discontinuation of medication is common.

How do effective treatments compare? (i) Most patients show a positive response to either drugs or CBT. (ii) The number needed to treat to get one person panic free is 3 for CBT and 6 for medication. (iii) Cognitive behavioural therapy exerts a more enduring effect than medication. (iv) Dropout rates for medication are higher than for CBT.

Methodological concerns

Reduction in panic and phobic symptoms have been reported in agoraphobic patients receiving 2 weeks of placebo [169]. The placebo response was not transient, and a quarter of patients showed marked response after 10 weeks. In an 8-week trial, 70% of those receiving an active agent (alprazolam or imipramine) and 50% of the

placebo group were panic-free [124]. One explanation for the small difference between placebo and active treatment response may be that trials exclude those likely to have a complicated disorder [170].

People with PD are vigilant to changes in their bodies. They fear side-effects of medications, particularly since these may resemble symptoms of anxiety from which they are trying to escape. It is essential to educate the patient about side-effects and to caution against random changes in medication. In particular, response to SSRIs may show an increase in anxiety that peaks over the first week and then subsides. Follow the dose rule, 'start low and go slow'.

It is not advisable to discontinue medication after control of panic until avoidance behaviour has been overcome. Cessation of medication used to manage anxiety can cause rebound anxiety, a discontinuation syndrome or relapse. All medications should be tailed off gradually, over at least 4 weeks and longer for BZDs. During discontinuation, patients should be encouraged to increase the use of relaxation strategies, continue exercise and avoid stimulant drugs (such as caffeine and nicotine).

Cost-effectiveness of treatment

Cognitive behavioural therapy is the most cost-effective treatment available in Australia and the finding is similar to that of Gould *et al*. based on US data [29]. Cost-analysis compared imipramine, clomipramine, paroxetine and individual CBT (all provided by a psychiatrist).

The cost alternatives of various treatments were calculated by adding medication cost and cost in psychiatrists' time to diagnose and treat a person for 12 months. At 1 year the cost of CBT is less than that of average drug therapy (CBT becomes cheaper than paroxetine at 8 months, clomipramine at 11 months and imipramine at 13 months). During the second and subsequent years the superiority of CBT increases whether or not drugs are continued. If the drugs are continued, then their costs continue. If they are not, then relapse occurs in about half of those withdrawn from drugs, and the net benefit due to drug therapy declines. Relapse is not associated with CBT follow-up, at least for the first 5 years, so there is no change to cost or benefit.

If one takes the number to treat to produce one panic free person, then the cost (in 2003 figures) is $A9000 for imipramine, $A10 500 for clomipramine, $A10 000 for paroxetine and $A6500 for CBT. On the basis of cost and efficacy, CBT clearly surpasses medication. However, effectiveness in practice is another issue since it is always less than efficacy; clinician competence and patient adherence erode potential effectiveness of a proven treatment. It would not be surprising if effectiveness were half that of the efficacy demonstrated in research.

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Appendix

Outcome measurement

Outcome measurement in PD is controversial. There are no guidelines for clinicians in practice. Both self-report and clinician-rated measures should be included, regardless of whether measurement is part of a research study or of routine care [171].

Structured diagnostic interviews are necessary only for difficult cases and research purposes. The most valid choice is the revised Anxiety Disorders Interview Schedule (ADIS-R) [70]. For a broader assessment, the (computerized) Composite International Diagnostic Interview [172,173] is appropriate, and for general disability, the SF-12 is a brief, widely used measure with good psychometric properties [174].

For assessing the specific features of PD, a range of measures with sound psychometric properties is available [9,171,175 for reviews]. The Panic and Agoraphobia Scale [176] is a short clinician- or patient-rated scale that includes a global severity score as well as five subscales (panic severity, frequency and duration; phobia avoidance; anticipatory anxiety; disability and health-related worries).

For measuring agoraphobic avoidance behaviour, both alone and when accompanied by a person, the Mobility Inventory for Agoraphobia [177] is apt. For panic-related symptom assessment, the Panic Attacks Symptom Questionnaire [178] has psychometric data. The Agoraphobic Cognitions Questionnaire [179] and the Body Sensations Questionnaire [179] are recommended for assessing panic-related cognitions.

Assessment for special groups

Culture (including a person's language) is an important determinant in the manifestation of illness [180]. Only by understanding the cultural context [181–183] can behaviours, feelings and thoughts be accurately interpreted. What is 'normal' in one setting may not be in another. Clinicians should understand a person's cultural perspective and curb the effect of their own preconceptions. Anxiety symptoms are articulated in culture-specific idioms [184] that include 'fright' disorders, problems associated with 'nerves' and a range of somatic expressions.

A cultural formulation should be routine [185]:

- Identification of the patient's culture, including language and spiritual/religious affiliation, and multicultural identity;
- Cultural explanations of the illness (i.e. idioms of distress, explanatory models, experience with popular and professional sources of care);
- Factors related to the psychosocial environment and functioning (e.g. cultural influences on stressors, social support and stigma);
- Cultural aspects of the relationship between patient and clinician.

Cognitive behaviour therapy

Cognitivie behavioural therapy derives from separate strands of psychological knowledge about behaviour and cognitive or thinking style. A more complete description will be found at http://www.gpcare.org Behavioural interventions focus on changing emotional distress and disturbed behaviour by modifying behaviour, e.g. by the use of reinforcement and exposure to the feared situation. Cognitive interventions modify attitudes and beliefs – the way people think and appraise themselves, the world and their future. Cognitive techniques include problem solving strategies but the core elements focus on learning ways of identifying and changing faulty thinking and assumptions and on replacing them with more adaptive patterns.

Cognitive approaches

People with anxiety disorders imagine the worst when confronted with a situation in which they are fearful. This thinking generates anticipatory anxiety, increases avoidance, and raises anxiety on exposure to the feared situation. The therapist helps the person to examine the thoughts that trigger and accompany anxiety symptoms, to put the fear into perspective and to replace these thoughts with more realistic thinking. For example, a person experiencing a panic attack is encouraged to challenge their catastrophic thinking ('I'm having a heart attack') with more realistic thoughts ('I'm probably not having a heart attack, I'm panicking. It feels bad now but it will soon pass').

Exposure-based approaches

Avoidance enables phobic behaviour to persist. As long as the agoraphobic person avoids being in a place where they might panic and not be able to escape, the phobia persists. The avoidance is rewarded as they do not have to experience the anxiety associated with the feared situation. Furthermore, they never test the reasonableness of that fear since they are never in a situation long enough to learn that they might be able to cope. The principle of graded exposure is for the person to face a graded set of fearful situations from least to most challenging. Each level is repeated until the person is able to remain in the situation without (or with only mild) discomfort. The most effective exposure is prolonged, not short, *in vivo* not fantasy, and regularly repeated.

Clinicians using exposure-based treatment for PD will need training and help to devise treatment. Much exposure work is done through self-directed homework. The clinician also needs to apply CBT skills, with the intervention itself and when giving advice. Treatment manuals for patient use are available at http://www.crufad.org [9].