Panic disorder

Peter P Roy-Byrne, Michelle G Craske, Murray B Stein

Panic disorder is a common mental disorder that affects up to 5% of the population at some point in life. It is often disabling, especially when complicated by agoraphobia, and is associated with substantial functional morbidity and reduced quality of life. The disorder is also costly for individuals and society, as shown by increased use of health care, absenteeism, and reduced workplace productivity. Some physical illnesses (eg, asthma) commonly occur with panic disorder, and certain lifestyle factors (eg, smoking) increase the risk for the disorder, but causal pathways are still unclear. Genetic and early susceptibility factors also exist, but their exact nature and pathophysiological mechanisms remain unknown. Despite an imprecise, although increased, understanding of cause, strong evidence supports the use of several effective treatments (eg, pharmacological, cognitive-behavioural). The adaptation and dissemination of these treatments to the frontlines of medical-care delivery should be urgent goals for the public-health community.

Although panic disorder emerged as a diagnostic entity only 25 years ago with the publication of the Diagnostic and Statistical Manual of Mental Disorders (DSM) III,1 accounts of a clinically similar syndrome have appeared much earlier (eg, Da Costa’s soldiers heart,2 Wheeler’s neurocirculatory asthenia,3 and Lewis’s effort syndrome).4 Along with paroxysmal autonomic nervous system arousal and catastrophic cognitions, these descriptions highlighted symptoms of profound fatigue, which are not part of current diagnostic criteria. The military contexts in which these syndromes developed implicated a prominent role for stress and trauma, suggesting a possible area of causal overlap with post-traumatic stress disorder, another anxiety illness that often includes panic attacks. Of all the anxiety-related syndromes, panic disorder has been the most intensively studied during the past 25 years, has advanced our understanding of the psychology and neurobiology of anxiety, and has helped dispel the notion that anxiety is a trivial problem (ie, affecting worried yet well individuals) not needing definitive treatment.

Diagnosis and differential diagnosis

Although descriptions of panic disorder differ slightly between DSM III,1 DSM III R, and DSM IV,5 the essential elements of the syndrome are consistent with the International Classification of Diseases 10 (ICD-10) description. Currently, diagnosis requires the presence of recurrent panic attacks, along with any of the following: worry about the possibility of future attacks, development of phobic avoidance—ie, staying away from places or situations in which the individual fears could elicit a panic attack, where escape or obtaining help in the event of an attack would be unlikely or difficult (eg, driving on a bridge, sitting in a crowded movie theatre), or any other change in behaviour due to the attacks (eg, visits to the emergency room or doctor because of concerns about undiagnosed medical illness).4 Panic attacks are sudden, sometimes unexpected paroxysmal bursts of severe anxiety, accompanied by several physical symptoms (eg, cardiorespiratory, oto-neurological, gastrointestinal, or autonomic). Such attacks are often striking in their initial presentation, affect the individual’s function, and could be progressive and disabling, especially if complicated by agoraphobia (an extreme form of phobic avoidance).

Controversy continues about the nosological status of agoraphobia without panic attacks, which is rarely seen in clinical settings.7 Agoraphobia takes place before the onset of panic in almost a third of people with panic disorder, suggesting that not all agoraphobia is a consequence of panic.8 Moreover, some instances of agoraphobia without panic attacks might be causally distinct from agoraphobia with panic attacks, indicating the development of agoraphobic behaviour in response to a physical illness (eg, vestibular disease, postural instability due to Parkinson’s disease) that impairs an individual’s sense of competence or safety in doing everyday activities.9 Not all panic attacks are indicative of panic disorder. The same physical and cognitive symptom constellation can occur in individuals with specific phobias when exposed to the feared stimulus (eg, heights, snakes, spiders) or in those with social phobia who faced with situations where they might be scrutinised. The difference in such situations is that the individual is keenly aware of the source of their fearful sensations, whereas in panic disorder, these same types of sensations are unprovoked, unexplained, and often occur out of the blue. Panic

Search strategy and selection criteria

We searched MEDLINE, PSYCHINFO, and the Cochrane Library from 1980, to September, 2005. We used search terms “panic disorder” and “phobic disorders” in combination with “diagnosis”, “epidemiology”, “genetics”, “neuroimaging”, “neurobiology”, “treatment”, “pharmacotherapy”, “psychotherapy”, “cognitive therapy”, and “behaviour therapy”. We focused on studies during the past 10 years but included seminal older publications. We also searched reference lists of these articles and selected relevant citations for inclusion. In addition to citing the original research articles in this Seminar, we make a point of citing review articles and book chapters that comprehensively cover their stated topics.
attacks can also take place in people with post-traumatic stress disorder, for whom exposure to reminders of a traumatic event can trigger attacks and can be especially difficult to discern as such, unless a careful history of previous traumatic experiences is recorded.

Because panic disorder mimics many medical conditions, patients often have increased use of health-care visits, procedures, and laboratory tests.24–26 Panic attacks can also be a symptom of common conditions such as hyperthyroidism, caffeine and stimulant use or abuse (eg, cocaine, metamfetamine), and occasionally in disorders such as phaeochromocytoma or partial complex seizures. The comorbidity of cardiovascular (eg, paroxysmal atrial tachycardia, mitral-valve prolapse), respiratory (eg, asthma and chronic obstructive pulmonary disease), and otological (eg, Meniere’s disease) disorders rises with panic disorder, but these conditions rarely are a direct cause of panic attacks.13

**Epidemiology**

For panic disorder, the National Comorbidity Survey-Replication (NCS-R) reports prevalence estimates of 2.7% at 12 months and 4.7% during lifetime.13,14 These rates are higher than those reported in the original NCS publication;21 in the older Epidemiological Catchment Area (ECA) study;26 in studies from the Ukraine (1-27% and 1-94%),17 Japan (0-5% at 12 months),18 and Germany (1-8% at 12 months);19 and in a compilation of cross-national surveys done at the same time as the ECA study.20 Although some investigators have suggested a trend of increasing prevalence over the past two decades,21 the varying prevalences in these contemporaneous international data strongly suggest differences in diagnostic methodology as well as variations in diagnostic criteria. Despite variability in prevalence, studies,13,15,16 including those across cultures, have shown consistently an excess of panic disorder in female individuals, a modal age of onset in late adolescence or early adulthood, and strong associations with both agoraphobia and major depression. Some evidence of a lower prevalence in older individuals could suggest decreasing severity21 to subclinical values, possibly due to age-related changes in key brain regions mediating anxiety responses.22

Panic disorder rarely occurs in clinical settings without other psychopathological comorbidity. Other axis I psychiatric disorders, especially major depression,5 bipolar illness,9 other anxiety disorders,26 and possibly alcohol abuse have been reported with an increased occurrence of panic disorder.27 Although panic could be the main illness in terms of temporal precedence in some circumstances, it might also be secondary and be seen as a severity marker of the comorbid illness.27 In children and adolescents, the disease tends to have a chronic course and is often comorbid with other anxiety, mood, and disruptive disorders.28 Data suggest that childhood panic,29 as well as its possible precursor, behavioural inhibition30 (which is also a risk factor for social anxiety disorder), are more common in the offspring of parents with panic disorder. Separation anxiety is specific to childhood panic and does not reliably develop into adult panic, although it is also more common in children who have parents with panic disorder than those who do not.31

Reports23 of an association between panic disorder and increased risk of lifetime suicide attempts have been attributed, in subsequent analyses and studies,27 to the comorbid conditions accompanying panic disorder, such as major depression, borderline personality, or alcohol abuse. However, an analysis of the NCS dataset suggest that, although the association between lifetime panic disorder and lifetime suicide attempts is eliminated after controlling for these other factors, more recent (12-month) disease remains significantly related to more recent (12-month) suicide attempts, even if comorbidity and a history of childhood abuse are accounted for.46 Furthermore, data from a prospective population-based survey in the Netherlands show a strong association between panic disorder (and anxiety disorders in general) and suicidal ideation and suicide attempts, even after adjustment for affective comorbidity and other suicide risk factors.46 Because of these observations, clinicians should be vigilant to the probability that their patients with panic disorder are at increased risk for suicide.

Attempts to define subtypes of panic disorder, based on prominence of distinct symptom clusters (eg, dizziness, dyspnoea), have not shown consistent results.30 Panic disorder that occurs predominantly during sleep seems to share many characteristics with the daytime illness, and has a similar response to treatment.7 The course and outcome of panic disorder is consistent with decade-old reports emphasising the chronic effect of anxiety disorders. Only 30% of patients remit without subsequent relapse in a few years, although a similar proportion (35%) show notable improvement, albeit with a waxing and waning course.33,34 However, a study35 showed that naturalistic prognosis in panic disorder, especially in the absence of agoraphobia, is better than that of generalised and social anxiety disorders, which tend to be much more chronic.36 The number of individuals with continued poor response could be related to low community rates of receiving evidence-based treatment, with many patients receiving inappropriate or inadequate treatment.47 Many epidemiological studies have investigated risk factors for panic disorder. As with most psychiatric disorders, a stress-diathesis model is commonly used to explain the genesis and maintenance of the disorder. Twin studies suggest heritability of about 40%, with contributions from common (ie, familial) environmental effects (<10%) and unique environmental effects (>50%).43 Data have suggested that early life trauma or maltreatment44 is an important risk factor, along with an anxious temperament that is characterised by neuroticism45 and anxiety sensitivity.46 Stressful life events probably contribute to the timing of onset as well as to the maintenance
of the disorder.  

Cigarette smoking and nicotine dependence in adolescence have been implicated as risk factors for later onset of panic disorder, although the cause of this association has been questioned.  

**Cause and pathological change**

**Genetic susceptibility**

Panic disorder, similar to other psychiatric disorders, is thought to be complex with many genes conferring vulnerability through unknown pathways. Panic might exist in many distinct genetic forms, each with a different set of genes, or it could exist in one form with an underlying set of genes that reflect a broad vulnerability to panic and anxiety. Evidence has supported a specific type of panic disorder associated with bladder problems (possibly urinary interstitial cystitis) that is linked to locus q32–33 on chromosome 13. An association study also related this same chromosomal region to panic disorder, irrespective of associated features. A subtype of bipolar illness associated with panic attacks has been linked to a locus on chromosome 18 and might show clinical differences from other forms of bipolar illness (i.e., rapid mood switching and increased familial risk for affective illness), although these findings are neither consistent nor robust. The exact genes, gene products, or functions related to the genetic regions implicated in both these phenotypes of panic disorder remain unknown.

Finally, a genome-wide scan of an Icelandic cohort revealed linkage on chromosome 9q31, which has also been linked to cigarette smoking. This common region is notable because of the previously reported association between teenage smoking and adult risk of panic disorder, and could constitute another possible phenotype of the disorder.

Other studies have focused on genes judged to have functional importance in anxiety pathophysiology. A genome-wide scan implicated regions on chromosome 1, consistent with QTL (quantitative trait loci) studies linking anxiety to this locus in both healthy human beings and mice and to chromosome 11p at a marker for the cholecystokinin-B (CCK-B) receptor gene, consistent with the known ability of CCK to precipitate panic attacks in some individuals with panic disorder. However, not all studies have shown an association between the CCK-B gene and the disorder. Finally, both association studies and linkage studies have implicated the adenosine 2A receptor gene in panic disorder, consistent with the anxiogenic effects of caffeine (a known antagonist of this receptor) and with the finding that allelic variations in the gene have been associated with caffeine-induced anxiety.

Association studies of genes in neurotransmitter systems thought to be associated with fear and anxiety (e.g., norepinephrine and serotonin) have produced inconsistent, often non-replicated results. The most consistent data implicate the gene for 22q11 catechol-o-methyltransferase (COMT) that codes for the enzyme responsible for norepinephrine metabolism. Linkage and association studies have implicated this region of chromosome 22. By contrast, two association studies have failed to link the norepinephrine transporter to panic disorder and most studies of serotonin-related genes have been negative, including the serotonin-transporter-promoter region previously linked to anxiety states in general, the serotonin 1A receptor, and the serotonin 2C receptor. Only one study has shown an association between the serotonin 2A receptor gene and panic disorder.

Several of these negative studies have compared panic disorder with and without agoraphobia and have shown some positive findings for the agoraphobia subgroup, although with variable and inconsistent data. These investigations have been restricted because we do not know enough about the pathophysiology of panic disorder, nor are we yet able to identify the most heritable phenotypes of the illness. However, the failure to replicate genetic associations is not a problem for panic disorder only, and shows inherent difficulties in the extant association approaches to complex genetic diseases.

Genome-wide association methods will be used to study panic disorder further, complemented by the scrutiny of gene-environment interactions.

**Neurobiological processes**

Since Ferris Pitt’s observation that hyperosmolar sodium lactate provoked panic attacks in patients with panic disorder but not in controls, several compounds with disparate mechanisms of action (e.g., caffeine, isoproterenol, yohimbine, carbon dioxide, and CCK) have shown similar abilities to provoke panic in patients but not in controls (and in some instances, not in patients with other anxiety or mood disorders without panic attacks). Although these approaches did not improve biological understanding of panic, many of these findings can now be subsumed by more general cognitive-behavioural theories of panic disorder, or by current neural systems models for panic disorder that emphasise the amygdala and related structures as part of a dysfunctional anxiety assessment and response system (figure 1).

Changes in these neural circuits of patients with panic disorder include: reduced volumes in amygdala and temporal lobe, lowered amounts of creatine and phosphocreatine metabolites in the medial temporal lobe, and decreased cerebral glucose metabolism in amygdala, hippocampus, thalamus, and brain-stem areas. A reduced orbitofrontal blood flow that predicts panic response to doxapram, a respiratory stimulant, also accords with the braking action of this area on amygdala activity. Many of these findings are not necessarily specific to panic disorder, and also occur in various combinations in other anxiety disorders such as post-traumatic stress disorder and social anxiety.

Finally, several but not all studies have shown reductions in benzodiazepine-receptor density in perihippocampal and amygdala areas. These findings are consistent with evidence that, compared with controls,
patients with panic disorder are less sensitive to the effects of infused benzodiazepines, have lower concentrations of cortical γ-aminobutyric acid (GABA) at baseline, and show smaller decreases in cortical GABA in response to benzodiazepine challenge. One study showed reductions in 5HT1a receptor concentrations, consistent with animal knockout models of this same receptor resulting in pathological anxiety and changes in GABA, thereby establishing a link with the two neurochemical systems that mediate the effects of the two major classes of anti-panic drugs (ie, serotonin-reuptake-inhibitor [SSRI] antidepressants and benzodiazepines).

Psychopathological processes

Psychosocial risk factors
Factors that increase the salience of bodily sensations are central to the onset of panic disorder. One such factor is anxiety sensitivity, the belief that anxiety could cause deleterious physical, social, and psychological consequences that extend beyond any immediate physical discomfort during a panic attack. Anxiety Sensitivity Index values predict the onset of panic attacks in adolescents, university students, and community sample groups, even after previous depression is controlled for, and also predict spontaneous panic attacks and worry about panic during 5 weeks of basic military training, even after history of panic attacks and trait anxiety are controlled for. However, anxiety sensitivity accounts for less of the variance in panic disorder onset than neuroticism, or proneness to have negative emotions in general.

Anxiety sensitivity could be acquired insidiously from a lifetime of direct aversive experiences (ie, personal history of severe illness or injury), vicarious observations (ie, severe illnesses or death among family members), informational transmissions (ie, parental warnings), or parental reinforcement of attention to somatic symptoms and parental modelling of distressed reactions to bodily sensations. Finally, panic attacks themselves increase anxiety sensitivity. The peak in prevalence between ages 15 and 19 years possibly occurs because of the added salience of bodily cues at that stage of psychosocial development, due to sexual development and hormonal changes.

Maintenance of panic
Acute fear of fear that develops after initial panic attacks is attributed to two factors. The first factor, interoceptive conditioning or conditioned fear of internal cues (eg, raised heart rate), occurs when early somatic components of the anxiety response cause pronounced bursts of anxiety or panic. In this model, slight changes in bodily functions that patients might not be conscious of can elicit conditioned fear and panic because of previous pairings with the terror of panic, and could contribute to the unexpected quality of panic. Such changes in bodily function might result from subclinical cardiorespiratory or vestibular dysfunction. However, whether the interoceptive conditioning model can be tested is unknown.

The second factor is catastrophic misappraisals of bodily sensations (eg, imminent death or loss of control), which can operate subconsciously (eg, during panic attacks when sleeping or when specific catastrophic thoughts are not recalled) but mostly are consciously accessible even if panic attacks are perceived as unexpected. Although the theoretical validity of this factor has been questioned, catastrophic misappraisals could become conditioned stimuli that trigger panic (figure 2).

Functional neuroimaging data suggest that a specific brain region, the insular cortex, could mediate heightened anxiety sensitivity. Insular cortex activation, while monitoring the heartbeat, is associated with some bodily awareness; activation of this region during risky decision-making correlates with both harm avoidance and neuroticism, and anticipation of emotionally aversive stimuli activates the right insular cortex. These data herald much closer ties between the psychological and biological theories of panic disorder.

Treatment

Pharmacotherapy
Since Donald Klein first described the efficacy of the tricyclic antidepressant imipramine for blocking panic
attacks in 1964,\textsuperscript{109} many studies have recorded the efficacy of most antidepressants in panic disorder. Benzodiazepines are another effective medication currently available. Other treatments with theoretically relevant mechanisms of action (eg, corticotropin-releasing-factor receptor-1 antagonists) are still in development. The aim of pharmacotherapy is not only to prevent the occurrence of panic attacks, but also to reduce or eliminate associated anticipatory anxiety, phobic avoidance, and other symptoms due to comorbid conditions such as major depression.

Currently, SSRIs are the preferred treatment for panic disorder, on the basis of many positive placebo-controlled, randomised trials supporting the efficacy of six different drugs—fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, and escitalopram.\textsuperscript{110} Meta-analyses and reviews focusing on several of these agents have reported medium to large effect sizes compared with placebo. Most trials have been short term, although several have examined and confirmed longer-term efficacy of up to 1 year.\textsuperscript{115} These compounds are also effective for associated mood and other anxiety disorders. Therapeutic response in panic disorder is a class effect, which is common to all the SSRIs, with no evidence of differential efficacy within the class. Although relevant differences exist in side-effect profiles, drug interactions, and half-life, differences in cost due to availability of the generic forms of these substances (fluoxetine, paroxetine, sertraline, and citalopram are currently available in the USA) are probably much more important.

Placebo-controlled trials\textsuperscript{116} also support the efficacy for an extended-release form of venlafaxine in panic disorder. Either efficacy findings are absent (eg, for duloxetine, mirtazapine, nefazodone) or evidence indicates a low efficacy (eg, for trazodone,\textsuperscript{117} bupropion)\textsuperscript{118} for other second-generation antidepressants. The older class of tricyclic antidepressants, although associated with more side-effects,\textsuperscript{119} includes drugs that are both less expensive and similarly effective than newer classes of antidepressants, with many studies indicating efficacy for imipramine, desipramine, clomipramine, nortriptyline, and amitriptyline,\textsuperscript{120} and six older pre-DSM III studies\textsuperscript{121} showing efficacy of monoamine oxidase (MAO) inhibitors in the phobic anxiety of individuals with panic-like symptoms. These compounds, especially MAO inhibitors, can be useful in treatment-refractory patients.

Benzodiazepines are very effective against panic disorder, work rapidly (within days to 1 week), are better tolerated than the very tolerable SSRIs, and have many generic versions that are available.\textsuperscript{122} But they are restricted by their narrow range of efficacy across disorders (panic disorder, social anxiety disorders, and generalised anxiety disorder; but not obsessive-compulsive disorder, post-traumatic stress disorder, or major depression), the risk of physiological dependence and withdrawal, and the risk of abuse. Because many patients do not respond fully to SSRIs, the coprescription of benzodiazepines to anxious patients treated with antidepressants is very common.\textsuperscript{123} Although guidelines from the UK National Institute of Clinical Excellence (NICE)\textsuperscript{124} suggest that long-term use of benzodiazepines is contraindicated, many North American psychiatrists still think that exaggerated fear about their abuse potential restricts use to the detriment of patients who could benefit from long-term treatment.\textsuperscript{125} Adjunctive treatment with a benzodiazepine can be given to achieve a rapid reduction in panic attacks during the several weeks needed for an SSRI to take effect.\textsuperscript{126} No controlled data strongly support anecdotal reports of the efficacy of various anxiolytic drugs for panic disorder, and controlled studies have failed to support the efficacy of buspirone\textsuperscript{127} and β blockers.\textsuperscript{128}

Many studies show clearly that discontinuation of medication results in relapse in a substantial proportion of patients, with rates of 25–50% recorded within 6 months, depending on study design.\textsuperscript{129} Additionally, SSRIs, serotonin-noradrenaline-reuptake inhibitors (SNRIs), tricyclic antidepressants, and benzodiazepines are associated with a time-limited withdrawal syndrome (much worse for benzodiazepines),\textsuperscript{130} which could be an interoceptive stimulus that promotes or contributes to panic disorder relapse.

No placebo-controlled studies have yet been done to validate the effectiveness of switching agents within or between antidepressant classes in patients who do not respond to treatment, or the effectiveness of augmenting SSRIs with benzodiazepines, other antidepressants, or atypical neuroleptic substances in patients who respond partly. Cognitive-behavioural treatment (CBT) could be used for individuals who do not do well on pharmacotherapy. Two controlled studies have shown that paroxetine is more effective than placebo in non-responders to CBT,\textsuperscript{131} and in augmenting the anti-panic effects of brief CBT.\textsuperscript{132}

\textbf{Figure 2: Cognitive factors that initiate and maintain panic attacks}

- Examples of precipitants
  - Stimulants
  - Hypervigilance
  - Benign fluctuations in physiological state
  - Subclinical cardiorespiratory syndromes
  - Stress

- Perception of change in bodily sensations
- Fear response mediated by misappraisal or interoceptive conditioning (or both)
- Anxious apprehension
- Hyperarousal
- Hypervigilance
- Agoraphobic avoidance
Psychological-behavioural treatment

CBT is the most widely studied and validated psychotherapeutic treatment for panic disorder, and is effective given individually or in a group. Two large meta-analyses reported large effect sizes of 1.55 (response of 63%) and 0.90. CBT for panic disorder is effective in comorbid conditions and could also improve the outcome of comorbid conditions. Although the nature of the evidence is robust, such approaches are underused in the USA, compared with drug treatment. Despite increasing interest in CBT for anxiety and depression in the UK, similar underuse to that in the USA also exists. Low rates of use are probably due to: public unfamiliarity with the nature and efficacy of CBT relative to medication; restricted access to specialty mental-health treatment and to professionals who are familiar with its efficacy and delivery; and little training and familiarity with CBT for many mental-health professionals who currently treat patients with panic disorder.

CBT is based on both the interoceptive conditioning and cognitive theories. The two major forms of CBT developed for panic disorder have been Barlow and Craske’s panic control treatment, and Clark’s cognitive therapy for panic. Both treatments emphasise components of psychoeducation about panic, to correct misconceptions regarding panic symptoms; cognitive restructuring, to identify and correct distortions in thinking; and interoceptive exposure to feared bodily sensations (eg, palpitations, dyspnoea, dizziness) and in-vivo exposure to feared situations (eg, unfamiliar areas, driving), to obtain corrective information that disproves fearful misappraisals and to lessen fear responding. Retraining of breathing to help patients cope with their panic and anxiety has been found to be unnecessary. Several studies indicate the effectiveness of applied relaxation that incorporates exposure to feared stimuli. Delivery of CBT by alternative routes such as computers and the internet might be effective.

Other psychotherapeutic treatments often used by clinicians for panic disorder are not well supported by rigorous empirical study, which include insight-oriented therapies, relaxation training without exposure, stress management, hypnosis, and eye-movement desensitisation and reprocessing therapy (EMDR).

Comparative and combination treatments

A meta-analysis of 21 randomised trials that included more than 1700 patients with panic disorder with or without agoraphobia clearly showed that the combined treatment of antidepressants and psychotherapy (behaviour, CBT, and other) was more effective than antidepressant alone (relative risk 1.24 [95% CI 1.02–1.52]) and than psychotherapy alone (1.16 [1.03–1.20]) in the acute phase. After treatment was discontinued, patients who had received combined treatment continued to benefit compared with those who had received medication only (1.61 [1.02–1.30]), but did no better than those who had received psychotherapy only (0.96 [0.79–1.16]). Although the analysis did not show heterogeneity in psychotherapies, relative risks differed among them; CBT seemed to be most effective (combined treatment was not significantly better than CBT alone). Although two large trials suggested that, after medication was discontinued, patients who had received medication with CBT actually fared worse than those who received CBT only, these provocative findings need further replication before it can be definitively said that avoidance of concurrent prescription of anti-panic treatment is required to optimise the long-term effects of CBT. A large study examining the effects of CBT combined with benzodiazepines showed similar but marginal advantages of the combination treatment in the acute phase. The meta-analysis data also accord with another study, which compared the effects of 1 year of clomipramine and psychodynamic therapy with clomipramine only; patients receiving the combination treatment had improved outcomes at 6 months after treatment was discontinued.

After discontinuation, CBT effects are generally more durable than those of medication, as seen in NICE guidelines. Meta-analyses show that cognitive-behavioural treatments yield larger effect sizes (averaging over all dependent variables; mean 0.88–0.90) than antidepressants (0.40–0.55) or benzodiazepines (0.40), although patients samples might not be the same across all the studies in the meta-analyses. Thus, the evidence base is not yet mature enough to yield firm recommendations on whether most patients with panic disorder should begin with medication, CBT, or combination treatment. But inclusion of CBT at some point during treatment will probably enhance long-term wellbeing.

Challenges for treatment delivery

Most patients with panic disorder are treated in the primary-care setting, which is not surprising, since the physical symptoms of panic disorder can drive patients to seek care for what they perceive as a physical ailment (eg, in the emergency room). Difficulties in the diagnosis of panic disorder in this setting argue for the possible value of population-based screening for the disorder in primary care, which is currently recommended for major depression. Panic disorder is associated with severe disability and work impairment in patients receiving primary care, even if the effects of comorbid physical and depressive illness are accounted for. The quality of primary care given to patients with panic disorder (and other anxiety disorders) is not the best; only 19–40% of patients are estimated to receive the minimum standards accepted for evidence-based treatment. In addition to detection and diagnosis difficulties, many other barriers to care exist, including uncertainty about where to seek help, insufficient organisation of primary care to treat chronic disease, and problems with insurance coverage and concerns about cost of care (especially in the USA).
New approaches are needed to overcome these barriers and to improve delivery of health care for patients with panic disorder. Some models of care have emphasized a primary role for the primary-care physician, with support from a mental-health provider to deliver medications (effect size 0.42–0.69), to manage care in general, or provide CBT specifically adapted for that setting; this approach has been shown to be effective (0.23–0.51) and cost-effective. Other promising approaches that could supplement care provided by primary-care physicians, or that might be used alone for some patients, include self-help treatments for which computer (internet-based) delivery approaches are being increasingly proposed.

Prevention
Because the onset of panic disorder peaks later in adolescence, prevention efforts could be best directed at or before this critical developmental period. In a study, individuals presenting to the emergency room with panic attacks were assigned to 1 h of contact with a clinician from whom they received reassurance or exposure instruction. The exposure group improved on all measures of anxiety and panic after 6 months, compared with controls. 40% of the sample group met criteria for panic disorder, so this investigation was not a pure prevention study. In another study, university students with at least one panic attack in the past year and moderate anxiety sensitivity were assigned to be put on a waiting list or to undergo a 5-h, cognitive-behavioural workshop. 6 months later, 13-6% of controls developed panic disorder, compared with 1-8% of individuals in the workshop group. Increased research into methods for the detection and identification of individuals at risk of panic disorder (eg, children of patients with the disorder or behaviourally inhibited children) will be crucial.

Conflict of interest statement
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