# Panic disorder

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**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 experiential 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.**

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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,[5] and DSM IV,[6] 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).[6] Panic attacks are sudden, sometimes unexpected paroxysmal bursts of severe anxiety, accompanied by several physical symptoms (eg, cardiorespiratory, otoneurological, 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 when 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.[10,11] 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.[12]

## 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;[15] in the older Epidemiological Catchment Area (ECA) study;[16] 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,[15,16,20] 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 severity[22] to subclinical values, possibly due to age-related changes in key brain regions mediating anxiety responses.[23]

Panic disorder rarely occurs in clinical settings without other psychopathological comorbidity. Other axis I psychiatric disorders, especially major depression,[15] bipolar illness,[24] other anxiety disorders,[25] and possibly alcohol abuse have been reported with an increased occurrence of panic disorder.[26] 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 inhibition[30] (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]

Reports[32] of an association between panic disorder and increased risk of lifetime suicide attempts have been attributed, in subsequent analyses and studies,[33] 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.[34] 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.[35] 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.[36] Panic disorder that occurs predominantly during sleep seems to share many characteristics with the daytime illness, and has a similar response to treatment.[37] 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.[38,39] However, a study[40] 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.[40] 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.[41]

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%).[42] Data have suggested that early life trauma or maltreatment[43] is an important risk factor, along with an anxious temperament that is characterised by neuroticism[44] and anxiety sensitivity.[45] Stressful life events probably contribute to the timing of onset as well as to the maintenance

of the disorder.[46,47] 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.[48]

## Cause and pathological change

### Genetic susceptibility

Panic disorder, similar to other psychiatric disorders,[49] 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)[50] that is linked to locus q32–33 on chromosome 13.[51] An association study[52] 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[53] and might show clinical differences from other forms of bipolar illness (ie, rapid mood switching[54] and increased familial risk for affective illness[55]), 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,[56] which has also been linked to cigarette smoking.[57] This common region is notable because of the previously reported association between teenage smoking and adult risk of panic disorder,[48,58] 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[59] implicated regions on chromosome 1, consistent with QTL (quantitative trait loci) studies linking anxiety to this locus in both healthy human beings and mice[60] 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.[61] However, not all studies have shown an association between the CCK-B gene and the disorder.[62] Finally, both association[63] and linkage[64] 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.[65]

Association studies of genes in neurotransmitter systems thought to be associated with fear and anxiety (eg, 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[66] and association studies[67] have implicated this region of chromosome 22. By contrast, two association studies have failed to link the norepinephrine transporter to panic disorder[68] and most studies of serotonin-related genes have been negative, including the serotonin-transporter-promoter region previously linked to anxiety states in general,[69] the serotonin 1A receptor,[70] and the serotonin 2C receptor.[70] Only one study has shown an association between the serotonin 2A receptor gene and panic disorder.[70]

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.[71,72] Genome-wide association methods[72] 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,[73] several compounds with disparate mechanisms of action (eg, 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).[74] 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).[75]

Changes in these neural circuits of patients with panic disorder include: reduced volumes in amygdala[76] and temporal lobe;[77] lowered amounts of creatine and phosphocreatine metabolites in the medial temporal lobe;[78] and decreased cerebral glucose metabolism in amygdala, hippocampus, thalamus, and brain-stem areas.[79] A reduced orbitofrontal blood flow that predicts panic response to doxapram,[80] 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.[81]

Finally, several[82,83] but not all[84] studies have shown reductions in benzodiazepine-receptor density in peri-hippocampal and amygdala areas. These findings are consistent with evidence that, compared with controls,

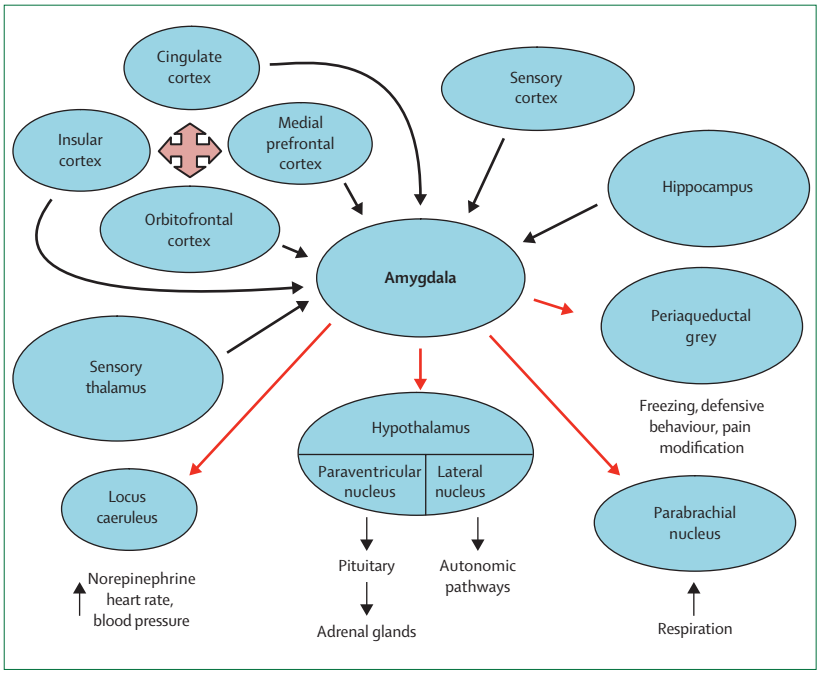


***Figure 1:*** **Proposed neural circuitry of panic**
The amygdala has a crucial role as an anxiety way-station that mediates incoming stimuli from the environment (thalamus and sensory cortex) and stored experience (frontal cortex and hippocampus; dark arrows), which affects the anxiety and panic response by stimulating various brain areas responsible for key panic symptoms (red arrows). The periaqeductal gray in the midbrain could be especially important for mediating panic-anxiety. Drug treatments can target all parts of this system, affecting amygdala and frontal-lobe interpretation of stimuli, or output effects. Cognitive-behavioural treatment affects the frontal-lobe areas, especially in the medial prefrontal cortex, which is known to inhibit input to the amygdale by using a braking action.

patients with panic disorder are less sensitive to the effects of infused benzodiazepines,[85] have lower concentrations of cortical γ-aminobutyric acid (GABA) at baseline,[86] and show smaller decreases in cortical GABA in response to benzodiazepine challenge.[87] One study[88] showed reductions in 5HT1a receptor concentrations, consistent with animal knockout models of this same receptor resulting in pathological anxiety and changes in GABA,[89] 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,[90] 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,[91] university students,[92] and community sample groups,[93] even after previous depression is controlled for,[91] and also predict spontaneous panic attacks and worry about panic during 5 weeks of basic military training,[94] even after history of panic attacks and trait anxiety are controlled for.[94] 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),[95] or parental reinforcement of attention to somatic symptoms and parental modelling of distressed reactions to bodily sensations.[96,97] Finally, panic attacks themselves increase anxiety sensitivity.[98,99] 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.[100]

#### *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.[101] In this model, slight changes in bodily functions that patients might not be conscious of[102,103] can elicit conditioned fear and panic because of previous pairings with the terror of panic,[101,104] and could contribute to the unexpected quality of panic.[103] 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),[105] 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).[101]

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;[106] activation of this region during risky decision-making correlates with both harm avoidance and neuroticism,[107] and anticipation of emotionally aversive stimuli activates the right insular cortex.[108] 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,[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.[110] Meta-analyses and reviews[111–114] 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.[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, setraline, and citalopram are currently available in the USA) are probably much more important.

Placebo-controlled trials[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,[117] bupropion)[118] for other second-generation antidepressants. The older class of tricyclic antidepressants, although associated with more side-effects,[113] 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,[110] and six older pre-DSM III studies[110] 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.[119] 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.[119] Although guidelines from the UK National Institute of Clinical Excellence (NICE)[120] 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.[121] Adjuvant treatment with a benzodiazepine can also be given to achieve a rapid reduction in panic attacks during the several weeks needed for an SSRI to take effect.[122] No controlled data strongly support anecdotal reports of the efficacy of various anticonvulsant drugs for panic disorder, and controlled studies have failed to support the efficacy of buspirone[123] and β blockers.[124]

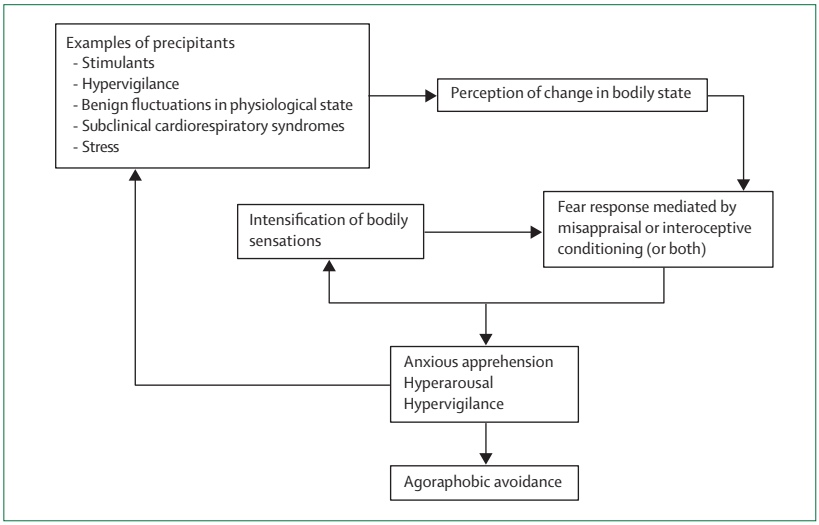


*Figure 2:* **Cognitive factors that initiate and maintain panic attacks**

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.[110] Additionally, SSRIs, serotonin-noradrenaline-reuptake inhibitors (SNRIs), tricyclic antidepressants, and benzodiazepines are associated with a time-limited withdrawal syndrome (much worse for benzodiazepines),[125] 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,[126] and in augmenting the anti-panic effects of brief CBT.[127]

### 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%)[114] and 0·90.[128] CBT for panic disorder is effective in comorbid conditions and could also improve the outcome of comorbid conditions.[129] Although the nature of the evidence is robust, such approaches are underused in the USA, compared with drug treatment.[130] Despite increasing interest in CBT for anxiety and depression in the UK,[131] similar underuse to that in the USA also exists.[132] 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.[133] Several studies[134] 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.[135]

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[136] 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.[136] 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[137,138] 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[138] showed similar but marginal advantages of the combination treatment in the acute phase. The meta-analysis data also accord with another study,[139] 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.[120] 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 benzodiazapines (0·40), although patients samples might not be the same across all the studies in the meta-analyses.[113,140] 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,[10] 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).[10] 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,[141] which is currently recommended for major depression.[142] 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.[142] 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.[130,143] 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).[144]

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 emphasised a primary role for the primary-care physician, with support from a mental-health provider to deliver medications (effect size 0·42–0·69),[145] to manage care in general,[146] or provide CBT specifically adapted for that setting; this approach has been shown to be effective (0·23–0·51)[147] and cost-effective.[148] 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.[149]

## Prevention

Because the onset of panic disorder peaks late in adolescence, prevention efforts could be best directed at or before this critical developmental period. In a study,[150] 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,[151] 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.[148] 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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**References**

1 American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 3rd edn. Washington, DC: American Psychiatric Association, 1980: 230–32.

2 Wooley CF. Jacob Mendez DaCosta: medical teacher, clinician, and clinical investigator. *Am J Cardiol* 1982; **50:** 1145–48.

3 Wheeler EO, White PD, et al. Neurocirculatory asthenia, anxiety neurosis, effort syndrome, neurasthenia; a 20 year follow-up study of 173 patients. *J Am Med Assoc* 1950; **142:** 878–89.

4 Nixon PG. The grey area of effort syndrome and hyperventilation: from Thomas Lewis to today. *J R Coll Physicians Lond* 1993; **27:** 377–83.

5 American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 3rd edn revised. Washington, DC: American Psychiatric Association, 1987: 235–40.

6 American Psychiatric Association. DSM-IV diagnostic and statistical manual of mental disorders, 4th edn. Washington, DC: American Psychiatric Association, 1994.

7 Wittchen HU, Reed V, Kessler RC. The relationship of agoraphobia and panic in a community sample of adolescents and young adults. *Arch Gen Psychiatry* 1998; **55:** 1017–24.

8 Bienvenu OJ, Onyike CU, Stein MB, et al. Agoraphobia in adults: incidence and longitudinal relationship with panic. *Br J Psychiatry* 2006; **188:** 432–38.

9 Lang AJ, Stein MB. Anxiety disorders. How to recognize and treat the medical symptoms of emotional illness. *Geriatrics* 2001; **56:** 24–27.

10 Roy-Byrne PP, Stein MB, Russo J, et al. Panic disorder in the primary care setting: comorbidity, disability, service utilization, and treatment. *J Clin Psychiatry* 1999; **60:** 492–99.

11 Katon W. Panic disorder and somatization. Review of 55 cases. *Am J Med* 1984; **77:** 101–06.

12 Simon NM, Fischmann D. The implications of medical and psychiatric comorbidity with panic disorder. *J Clin Psychiatry* 2005; **66** (suppl 4)**:** 815.

13 Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005; **62:** 617–27.

14 Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005; **62:** 593–602.

15 Kessler R, Stang P, Wittchen H, Ustun B, Roy-Byrne P, Walters E. Lifetime panic-depression comorbidity in the National Comorbidity Survey. *Arch Gen Psychiatry* 1998; **55:** 801–08.

16 Eaton WW, Anthony JC, Romanoski A, et al. Onset and recovery from panic disorder in the Baltimore Epidemiologic Catchment Area follow-up. *Br J Psychiatry* 1998; **173:** 501–07.

17 Bromet EJ, Gluzman SF, Paniotto VI, et al. Epidemiology of psychiatric and alcohol disorders in Ukraine: findings from the Ukraine World Mental Health survey. *Soc Psychiatry Psychiatr Epidemiol* 2005; **40:** 681–90.

18 Kawakami N, Takeshima T, Ono Y, et al. Twelve-month prevalence, severity, and treatment of common mental disorders in communities in Japan: preliminary finding from the World Mental Health Japan Survey 2002–2003. *Psychiatry Clin Neurosci* 2005; **59:** 441–52.

19 Goodwin RD, Faravelli C, Rosi S, et al. The epidemiology of panic disorder and agoraphobia in Europe. *Eur Neuropsychopharmacol* 2005; **15:** 435–43.

20 Weissman MM, Bland RC, Canino GJ, et al. The cross-national epidemiology of panic disorder. *Arch Gen Psychiatry* 1997; **54:** 305–09.

21 Goodwin RD. The prevalence of panic attacks in the United States: 1980 to 1995. *J Clin Epidemiol* 2003; **56:** 914–16.

22 Sheikh JI, Swales PJ, Carlson EB, Lindley SE. Aging and panic disorder: phenomenology, comorbidity, and risk factors. *Am J Geriatr Psychiatry* 2004; **12:** 102–09.

23 Charney DS, Woods SW, Krystal JH, Nagy LM, Heninger GR. Noradrenergic neuronal dysregulation in panic disorder: the effects of intravenous yohimbine and clonidine in panic disorder patients. *Acta Psychiatr Scand* 1992; **86:** 273–82.

24 Goodwin RD, Hoven CW. Bipolar-panic comorbidity in the general population: prevalence and associated morbidity. *J Affect Disord* 2002; **70:** 27–33.

25 Goisman RM, Goldenberg I, Vasile RG, Keller MB. Comorbidity of anxiety disorders in a multicenter anxiety study. *Compr Psychiatry* 1995; **36:** 303–11.

26 Zimmermann P, Wittchen HU, Hofler M, Pfister H, Kessler RC, Lieb R. Primary anxiety disorders and the development of subsequent alcohol use disorders: a 4-year community study of adolescents and young adults. *Psychol Med* 2003; **33:** 1211–22.

27 Kessler RC, Stang PE, Wittchen HU, Ustun TB, Roy-Byrne PP, Walters EE. Lifetime panic-depression comorbidity in the National Comorbidity Survey. *Arch Gen Psychiatry* 1998; **55:** 801–08.

28 Biederman J, Faraone SV, Marrs A, et al. Panic disorder and agoraphobia in consecutively referred children and adolescents. *J Am Acad Child Adolesc Psychiatry* 1997; **36:** 214–23.

29 Biederman J, Petty C, Faraone SV, et al. Parental predictors of pediatric panic disorder/agoraphobia: a controlled study in high-risk offspring. *Depress Anxiety* 2005; **22:** 114–20.

30 Rosenbaum JF, Biederman J, Hirshfeld-Becker DR, et al. A controlled study of behavioral inhibition in children of parents with panic disorder and depression. *Am J Psychiatry* 2000; **157:** 2002–10.

31 Aschenbrand SG, Kendall PC, Webb A, Safford SM, Flannery-Schroeder E. Is childhood separation anxiety disorder a predictor of adult panic disorder and agoraphobia? A seven-year longitudinal study. *J Am Acad Child Adolesc Psychiatry* 2003; **42:** 1478–85.

32 Weissman MM, Klerman GL, Markowitz JS, Ouellette R. Suicidal ideation and suicide attempts in panic disorder and attacks. *N Engl J Med* 1989; **321:** 1209–14.

33 Vickers K, McNally RJ. Panic disorder and suicide attempt in the National Comorbidity Survey. *J Abnorm Psychol* 2004; **113:** 582–91.

34 Goodwin RD, Roy-Byrne P. Panic and suicidal ideation and suicide attempts: results from the National Comorbidity Survey. *Depress Anxiety* 2006; **23:** 124–32.

35 Sareen J, Cox BJ, Afifi TO, et al. Anxiety disorders and risk for suicidal ideation and suicide attempts: a population-based longitudinal study of adults. *Arch Gen Psychiatry* 2005; **62:** 1249–57.

36 Goodwin RD, Hamilton SP, Milne BJ, Pine DS. Generalizability and correlates of clinically derived panic subtypes in the population. *Depress Anxiety* 2002; **15:** 69–74.

37 Craske MG, Lang AJ, Mystkowski JL, Zucker BG, Bystritsky A, Yan-Go F. Does nocturnal panic represent a more severe form of panic disorder? *J Nerv Ment Dis* 2002; **190:** 611–18.

38 Katschnig H, Amering M. The long-term course of panic disorder and its predictors. *J Clin Psychopharmacol* 1998; **18:** 6–11S.

39 Roy-Byrne PP, Cowley DS. Course and outcome in panic disorder: a review of recent follow-up studies. *Anxiety* 1995; **1:** 151–60.

40 Bruce SE, Yonkers KA, Otto MW, et al. Influence of psychiatric comorbidity on recovery and recurrence in generalized anxiety disorder, social phobia, and panic disorder: a 12-year prospective study. *Am J Psychiatry* 2005; **162:** 1179–87.

41 Wang PS, Berglund P, Kessler RC. Recent care of common mental disorders in the United States : prevalence and conformance with evidence-based recommendations. *J Gen Intern Med* 2000; **15:** 284–92.

42 Hettema JM, Neale MC, Kendler KS. A review and meta-analysis of the genetic epidemiology of anxiety disorders. *Am J Psychiatry* 2001; **158:** 1568–78.

43 Stein MB, Walker JR, Anderson G, et al. Childhood physical and sexual abuse in patients with anxiety disorders and in a community sample. *Am J Psychiatry* 1996; **153:** 275–77.

44 Roth M. Agoraphobia, panic disorder and generalized anxiety disorder: some implications of recent advances. *Psychiatr Dev* 1984; **2:** 31–52.

45 McNally RJ. Anxiety sensitivity and panic disorder. *Biol Psychiatry* 2002; **52:** 938–46.

46 Watanabe A, Nakao K, Tokuyama M, Takeda M. Prediction of first episode of panic attack among white-collar workers. *Psychiatry Clin Neurosci* 2005; **59:** 119–26.

47 Roy-Byrne PP, Geraci M, Uhde TW. Life events and the onset of panic disorder. *Am J Psychiatry* 1986; **143:** 142–47.

48 Isensee B, Wittchen HU, Stein MB, Hofler M, Lieb R. Smoking increases the risk of panic: findings from a prospective community study. *Arch Gen Psychiatry* 2003; **60:** 692–700.

49 Kendler KS. "A gene for...": the nature of gene action in psychiatric disorders. *Am J Psychiatry* 2005; **162:** 1243–52.

50 Weissman MM, Gross R, Fyer A, et al. Interstitial cystitis and panic disorder: a potential genetic syndrome. *Arch Gen Psychiatry* 2004; **61:** 273–79.

51 Hamilton SP, Fyer AJ, Durner M, et al. Further genetic evidence for a panic disorder syndrome mapping to chromosome 13q. *Proc Natl Acad Sci USA* 2003; **100:** 2550–55.

52 Schumacher J, Abou Jamra R, Becker T, et al. Investigation of the DAOA/G30 locus in panic disorder. *Mol Psychiatry* 2005; **10:** 428–29.

53 MacKinnon DF, Xu J, McMahon FJ, et al. Bipolar disorder and panic disorder in families: an analysis of chromosome 18 data. *Am J Psychiatry* 1998; **155:** 829–31.

54 MacKinnon DF, Zandi PP, Gershon ES, Nurnberger JI Jr, DePaulo JR Jr. Association of rapid mood switching with panic disorder and familial panic risk in familial bipolar disorder. *Am J Psychiatry* 2003; **160:** 1696–98.

55 MacKinnon DF, Zandi PP, Cooper J, et al. Comorbid bipolar disorder and panic disorder in families with a high prevalence of bipolar disorder. *Am J Psychiatry* 2002; **159:** 30–35.

56 Thorgeirsson TE, Oskarsson H, Desnica N, et al. Anxiety with panic disorder linked to chromosome 9q in Iceland. *Am J Hum Genet* 2003; **72:** 1221–30.

57 Gelernter J, Liu X, Hesselbrock V, Page GP, Goddard A, Zhang H. Results of a genomewide linkage scan: support for chromosomes 9 and 11 loci increasing risk for cigarette smoking. *Am J Med Genet B Neuropsychiatr Genet* 2004; **128:** 9410–11.

58 Breslau N, Klein DF. Smoking and panic attacks: an epidemiologic investigation. *Arch Gen Psychiatry* 1999; **56:** 114–17.

59 Gelernter J, Bonvicini K, Page G, et al. Linkage genome scan for loci predisposing to panic disorder or agoraphobia. *Am J Med Genet* 2001; **105:** 548–57.

60 Fullerton J, Cubin M, Tiwari H, et al. Linkage analysis of extremely discordant and concordant sibling pairs identifies quantitative-trait loci that influence variation in the human personality trait neuroticism. *Am J Hum Genet* 2003; **72:** 879–90.

61 van Megen HJ, Westenberg HG, Den Boer JA, Kahn RS. The panic-inducing properties of the cholecystokinin tetrapeptide CCK4 in patients with panic disorder. *Eur Neuropsychopharmacol* 1996; **6:** 187–94.

62 Hamilton SP, Slager SL, Helleby L, et al. No association or linkage between polymorphisms in the genes encoding cholecystokinin and the cholecystokinin B receptor and panic disorder. *Mol Psychiatry* 2001; **6:** 59–65.

63 Deckert J, Nothen MM, Franke P, et al. Systematic mutation screening and association study of the A1 and A2a adenosine receptor genes in panic disorder suggest a contribution of the A2a gene to the development of disease. *Mol Psychiatry* 1998; **3:** 81–85.

64 Hamilton SP, Slager SL, De Leon AB, et al. Evidence for genetic linkage between a polymorphism in the adenosine 2A receptor and panic disorder. *Neuropsychopharmacology* 2004; **29:** 558–65.

65 Alsene K, Deckert J, Sand P, de Wit H. Association between A2a receptor gene polymorphisms and caffeine-induced anxiety. *Neuropsychopharmacology* 2003; **28:** 1694–702.

66 Hamilton SP, Slager SL, Heiman GA, et al. Evidence for a susceptibility locus for panic disorder near the catechol-O-methyltransferase gene on chromosome 22. *Biol Psychiatry* 2002; **51:** 591–601.

67 Domschke K, Freitag CM, Kuhlenbaumer G, et al. Association of the functional V158M catechol-O-methyl-transferase polymorphism with panic disorder in women. *Int J Neuropsychopharmacol* 2004; **7:** 183–88.

68 Lee YJ, Hohoff C, Domschke K, et al. Norepinephrine transporter (NET) promoter and 5'-UTR polymorphisms: association analysis in panic disorder. *Neurosci Lett* 2005; **377:** 40–43.

69 Sand P, Lesch KP, Catalano M, et al. Polymorphic MAO-A and 5-HT-transporter genes: analysis of interactions in panic disorder. *World J Biol Psychiatry* 2000; **1:** 147–50.

70 Inada Y, Yoneda H, Koh J, et al. Positive association between panic disorder and polymorphism of the serotonin 2A receptor gene. *Psychiatry Res* 2003; **118:** 25–31.

71 Ioannidis JP, Trikalinos TA, Ntzani EE, Contopoulos-Ioannidis DG. Genetic associations in large versus small studies: an empirical assessment. *Lancet* 2003; **361:** 567–71.

72 Hirschhorn JN, Daly MJ. Genome-wide association studies for common diseases and complex traits. *Nat Rev Genet* 2005; **6:** 9510–18.

73 Pitts FN Jr, McClure JN Jr. Lactate metabolism in anxiety neurosis. *N Engl J Med* 1967; **277:** 1329–36.

74 Krystal JH, Deutsch DN, Charney DS. The biological basis of panic disorder. *J Clin Psychiatry* 1996; **57** (suppl 10)**:** 23–31.

75 Gorman JM, Kent JM, Sullivan GM, Coplan JD. Neuroanatomical hypothesis of panic disorder, revised. *Am J Psychiatry* 2000; **157:** 493–505.

76 Massana G, Serra-Grabulosa JM, Salgado-Pineda P, et al. Amygdalar atrophy in panic disorder patients detected by volumetric magnetic resonance imaging. *Neuroimage* 2003; **19:** 80–90.

77 Uchida RR, Del-Ben CM, Santos AC, et al. Decreased left temporal lobe volume of panic patients measured by magnetic resonance imaging. *Braz J Med Biol Res* 2003; **36:** 925–29.

78 Massana G, Gasto C, Junque C, et al. Reduced levels of creatine in the right medial temporal lobe region of panic disorder patients detected with (l)H magnetic resonance spectroscopy. *Neuroimage* 2002; **16:** 836–42.

79 Sakai Y, Kumano H, Nishikawa M, et al. Cerebral glucose metabolism associated with a fear network in panic disorder. *Neuroreport* 2005; **16:** 927–931.

80 Kent JM, Coplan JD, Mawlawi O, et al. Prediction of panic response to a respiratory stimulant by reduced orbitofrontal cerebral blood flow in panic disorder. *Am J Psychiatry* 2005; **162:** 1379–81.

81 Kent JM, Rauch SL. Neurocircuitry of anxiety disorders. *Curr Psychiatry Rep* 2003; **5:** 266–73.

82 Bremner JD, Innis RB, White T, et al. SPECT [I-123]iomazenil measurement of the benzodiazepine receptor in panic disorder. *Biol Psychiatry* 2000; **47:** 96–106.

83 Malizia AL, Cunningham VJ, Bell CJ, Liddle PF, Jones T, Nutt DJ. Decreased brain GABA(A)-benzodiazepine receptor binding in panic disorder: preliminary results from a quantitative PET study. *Arch Gen Psychiatry* 1998; **55:** 715–20.

84 Brandt CA, Meller J, Keweloh L, et al. Increased benzodiazepine receptor density in the prefrontal cortex in patients with panic disorder. *J Neural Transm* 1998; **105:** 1325–33.

85 Roy-Byrne PP, Cowley DS, Greenblatt DJ, Shader RI, Hommer D. Reduced benzodiazepine sensitivity in panic disorder. *Arch Gen Psychiatry* 1990; **47:** 534–38.

86 Goddard AW, Mason GF, Almai A, et al. Reductions in occipital cortex GABA levels in panic disorder detected with 1h-magnetic resonance spectroscopy. *Arch Gen Psychiatry* 2001; **58:** 556–61.

87 Goddard AW, Mason GF, Appel M, et al. Impaired GABA neuronal response to acute benzodiazepine administration in panic disorder. *Am J Psychiatry* 2004; **161:** 2186–93.

88 Neumeister A, Bain E, Nugent AC, et al. Reduced serotonin type 1A receptor binding in panic disorder. *J Neurosci* 2004; **24:** 589–91.

89 Sibille E, Pavlides C, Benke D, Toth M. Genetic inactivation of the Serotonin (1A) receptor in mice results in downregulation of major GABA(A) receptor alpha subunits, reduction of GABA(A) receptor binding, and benzodiazepine-resistant anxiety. *J Neurosci* 2000; **20:** 2758–65.

90 Reiss S. Pavlovian conditioning and human fear: an expectancy model. *Behavior Therapy* 1980; **11:** 380–96.

91 Hayward C, Killen JD, Kraemer HC, Taylor CB. Predictors of panic attacks in adolescents. *J Am Acad Child Adolesc Psychiatry* 2000; **39:** 207–14.

92 Maller RG, Reiss S. Anxiety sensitivity in 1984 and panic attacks in 1987. *J Anxiety Disorders* 1992; **6:** 241–47.

93 Ehlers A. A 1-year prospective study of panic attacks: clinical course and factors associated with maintenance. *J Abnorm Psychol* 1995; **104:** 164–72.

94 Schmidt NB, Lerew DR, Jackson RJ. The role of anxiety sensitivity in the pathogenesis of panic: prospective evaluation of spontaneous panic attacks during acute stress. *J Abnorm Psychol* 1997; **106:** 355–64.

95 Craske MG, Rowe MK. Nocturnal panic. *Clin Psychol Sci Pract* 1997; **4:** 153–74.

96 Watt MC, Stewart SH. Anxiety sensitivity mediates the relationships between childhood learning experiences and elevated hypochondriacal concerns in young adulthood. *J Psychosom Res* 2000; **49:** 107–18.

97 Watt MC, Stewart SH, Cox BJ. A retrospective study of the learning history origins of anxiety sensitivity. *Behav Res Ther* 1998; **36:** 505–25.

98 Schmidt NB, Lerew DR, Joiner TE Jr. Prospective evaluation of the etiology of anxiety sensitivity: test of a scar model. *Behav Res Ther* 2000; **38:** 1083–95.

99 Weems CF, Hayward C, Killen J, Taylor CB. A longitudinal investigation of anxiety sensitivity in adolescence. *J Abnorm Psychol* 2002; **111:** 471–77.

100 Buchanan CM, Eccles JS, Becker JB. Are adolescents the victims of raging hormones: evidence for activational effects of hormones on moods and behavior at adolescence. *Psychol Bull* 1992; **111:** 62–107.

101 Bouton ME, Mineka S, Barlow DH. A modern learning theory perspective on the etiology of panic disorder. *Psychol Rev* 2001; **108:** 4–32.

102 Block RI, Ghoneim MM, Fowles DC, Kumar V, Pathak D. Effects of a subanesthetic concentration of nitrous oxide on establishment, elicitation, and semantic and phonemic generalization of classically conditioned skin conductance responses. *Pharmacol Biochem Behav* 1987; **28:** 7–14.

103 Craske MG, Lang AJ, Rowe M, et al. Presleep attributions about arousal during sleep: nocturnal panic. *J Abnorm Psychol* 2002; **111:** 53–62.

104 Barlow DH. Anxiety and its disorders: the nature and treatment of anxiety and panic. New York, NY: Guilford Press, 1988.

105 Clark DM. A cognitive approach to panic. *Behav Res Ther* 1986; **24:** 461–70.

106 Critchley HD, Wiens S, Rotshtein P, Ohman A, Dolan RJ. Neural systems supporting interoceptive awareness. *Nat Neurosci* 2004; **7:** 189–95.

107 Paulus MP, Rogalsky C, Simmons A, Feinstein JS, Stein MB. Increased activation in the right insula during risk-taking decision making is related to harm avoidance and neuroticism. *Neuroimage* 2003; **19:** 1439–48.

108 Simmons A, Matthews SC, Stein MB, Paulus MP. Anticipation of emotionally aversive visual stimuli activates right insula. *Neuroreport* 2004; **15:** 2261–65.

109 Klein DF. Delineation of two drug-responsive anxiety syndromes. *Psychopharmacologia* 1964; **17:** 397–408.

110 Roy-Byrne PP, Cowley D. Pharmacologic treatments for panic disorder, generalized anxiety disorder, specific phobia and social anxiety disorders. In: PE N, Gorman J, eds. A guide to treatments that work. New York: Oxford University Press, 2002: 337–65.

111 Otto MW, Tuby KS, Gould RA, McLean RY, Pollack MH. An effect-size analysis of the relative efficacy and tolerability of serotonin selective reuptake inhibitors for panic disorder. *Am J Psychiatry* 2001; **158:** 1989–92.

112 Boyer W. Serotonin uptake inhibitors are superior to imipramine and alprazolam in alleviating panic attacks: a meta-analysis. *Int Clin Psychopharmacol* 1995; **10:** 45–49.

113 Bakker A, van Balkom AJ, Spinhoven P. SSRIs *vs* TCAs in the treatment of panic disorder: a meta-analysis. *Acta Psychiatr Scand* 2002; **106:** 163–67.

114 Mitte K. A meta-analysis of the efficacy of psycho-and pharmacotherapy in panic disorder with and without agoraphobia. *J Affect Disord* 2005; **88:** 27–45.

115 Pollack MH, Allgulander C, Bandelow B, et al. WCA recommendations for the long-term treatment of panic disorder. *CNS Spectrums* 2003; **8:** 17–30.

116 Bradwejn J, Ahokas A, Stein DJ, Salinas E, Emilien G, Whitaker T. Venlafaxine extended-release capsules in panic disorder: flexible-dose, double-blind, placebo-controlled study. *Br J Psychiatry* 2005; **187:** 352–59.

117 Charney DS, Woods SW, Goodman WK, et al. Drug treatment of panic disorder: the comparative efficacy of imipramine, alprazolam, and trazodone. *J Clin Psychiatry* 1986; **47:** 580–86.

118 Sheehan DV, Davidson J, Manschreck T, Van Wyck Fleet J. Lack of efficacy of a new antidepressant (bupropion) in the treatment of panic disorder with phobias. *J Clin Psychopharmacol* 1983; **3:** 28–31.

119 Bruce SE, Vasile RG, Goisman RM, et al. Are benzodiazepines still the medication of choice for patients with panic disorder with or without agoraphobia? *Am J Psychiatry* 2003; **160:** 1432–38.

120 NICE NCG. Anxiety: mangement of anxiety (panic disorder, with or without agoraphobia, and generalised anxiety disorder) in adults in primary, secondary and community care. London: National Collaborating Centre for primary care, 2004.

121 American Psychiatric Association. Practice guideline for the treatment of patients with panic disorder. Work Group on Panic Disorder. American Psychiatric Association. *Am J Psychiatry* 1998; **155** (suppl): 1–34.

122 Goddard AW, Brouette T, Almai A, Jetty P, Woods SW, Charney D. Early coadministration of clonazepam with sertraline for panic disorder. *Arch Gen Psychiatry* 2001; **58:** 681–86.

123 Sheehan DV, Raj AB, Harnett-Sheehan K, Soto S, Knapp E. The relative efficacy of high-dose buspirone and alprazolam in the treatment of panic disorder: a double-blind placebo-controlled study. *Acta Psychiatr Scand* 1993; **88:** 1–11.

124 Noyes R Jr, Anderson DJ, Clancy J, et al. Diazepam and propranolol in panic disorder and agoraphobia. *Arch Gen Psychiatry* 1984; **41:** 287–92.

125 Rickels K, Schweizer E, Weiss S, Zavodnick S. Maintenance drug treatment for panic disorder. II Short- and long-term outcome after drug taper. *Arch Gen Psychiatry* 1993; **50:** 61–68.

126 Kampman M, Keijsers GPJ, Hoogduin CAL, Hendriks G-J. A randomized, double-blind, placebo-controlled study of the effects of adjunctive paroxetine in panic disorder patients unsuccessfully treated with cognitive-behavioral therapy alone. *J Clin Psychiatry* 2002; **63:** 772–77.

127 Stein MB, Norton GR, Walker JR, Chartier MJ, Graham R. Do SSRIs enhance the efficacy of very brief cognitive behavioral therapy for panic disorder? A pilot study. *Psychiatr Res* 2000; **94:** 191–200.

128 Westen D, Morrison K. A multidimensional meta-analysis of treatments for depression, panic, and generalized anxiety disorder: an empirical examination of the status of empirically supported therapies. *J Consult Clin Psychol* 2001; **69:** 875–99.

129 Tsao JCI, Mystkowski J, Zucker B, Craske MG. Effects of cognitive-behavioral therapy for panic disorder on comorbid conditions: Replication and extension. *Behav Ther* 2002; **33:** 493–509.

130 Young AS, Klap R, Sherbourne CD, Wells KB. The quality of care for depressive and anxiety disorders in the United States. *Arch Gen Psychiatry* 2001; **58:** 55–61.

131 Bower P, Gilbody S. Stepped care in psychological therapies: access, effectiveness and efficiency. Narrative literature review. *Br J Psychiatry* 2005; **186:** 11–17.

132 Bebbington PE, Brugha TS, Meltzer H, et al. Neurotic disorders and the receipt of psychiatric treatment. *Psychol Med* 2000; **30:** 1369–76.

133 de Beurs E, Lange A, van Dyck R, Koele P. Respiratory training prior to exposure in vivo in the treatment of panic disorder with agoraphobia: efficacy and predictors of outcome. *Aust N Z J Psychiatry* 1995; **29:** 104–13.

134 Arntz A, van den Hout M. Psychological treatments of panic disorder without agoraphobia: cognitive therapy versus applied relaxation. *Behav Res Ther* 1996; **34:** 113–21.

135 Carlbring P, Nilsson-Ihrfelt E, Waara J, et al. Treatment of panic disorder: live therapy *vs* self-help via the Internet. *Behav Res Ther* 2005; **43:** 132–33.

136 Furukawa TA, Watanabe N, Churchill R. Psychotherapy plus antidepressant for panic disorder with or without agoraphobia: systematic review. *Br J Psychiatry* 2006; **188:** 305–12.

137 Barlow DH, Gorman JM, Shear MK, Woods SW. Cognitive-behavioral therapy, imipramine, or their combination for panic disorder: a randomized controlled trial. *JAMA* 2000; **283:** 2529–36.

138 Marks IM, Swinson RP, Basoglu M, et al. Alprazolam and exposure alone and combined in panic disorder with agoraphobia. A controlled study in London and Toronto. *Br J Psychiatry* 1993; **162:** 776–87.

139 Wiborg IM, Dahl AA. Does brief dynamic psychotherapy reduce the relapse rate of panic disorder? *Arch Gen Psychiatry* 1996; **53:** 689–94.

140 Gould RA, Otto M, Pollack M. A meta-analysis of treatment outcome for panic disorder. *Clin Psychol Review* 1995; **15:** 819–44.

141 Roy-Byrne PP, Katon W, Cowley DS, et al. Panic disorder in primary care: biopsychosocial differences between recognized and unrecognized patients. *Gen Hosp Psychiatry* 2000; **22:** 405–11.

142 Pignone MP, Gaynes BN, Rushton JL, et al. Screening for depression in adults: a summary of the evidence for the US Preventive Services Task Force. *Ann Intern Med* 2002; **136:** 765–76.

143 Stein MB, Sherbourne CD, Craske MG, et al. Quality of care for primary care patients with anxiety disorders. *Am J Psychiatry* 2004; **161:** 2230–37.

144 Craske MG, Edlund MJ, Sullivan G, et al. Perceived unmet need for mental health treatment and barriers to care among patients with panic disorder. *Psychiatr Serv* 2005; **56:** 988–94.

145 Roy-Byrne PP, Katon WJ, Cowley DS, Russo J. A randomized trial of collaborative care for patients with panic disorder in primary care. *Arch Gen Psychiatry* 2001; **58:** 869–76.

146 Rollman BL, Belnap BH, Reynolds CF, Schulberg HC, Shear MK. A contemporary protoclol to assist primary care physicians in the treatment of panic and generalized anxiety disorders. *Gen Hosp Psychiatry* 2003; **25:** 74–82.

147 Roy-Byrne PP, Craske MG, Stein MB, et al. A randomized effectiveness trial of cognitive-behavioral therapy and medication for primary care panic disorder. *Arch Gen Psychiatry* 2005; **62:** 290–98.

148 Katon W, Russo J, Sherbourne C, et al. Incremental cost-effectiveness of a collaborative care intervention for panic disorder. *Psychol Med* 2006; **36:** 353–63.

149 Proudfoot J, Ryden C, Everitt B, et al. Clinical efficacy of computerised cognitive-behavioural therapy for anxiety ad depression in primary care: randomised controlled trial. *Br J Psychiatry* 2004; **185:** 46–54.

150 Swinson RP, Soulios C, Cox BJ, Kuch K. Brief treatment of emergency room patients with panic attacks. *Am J Psychiatry* 1992; **149:** 944–46.

151 Gardenswarz C, Craske MG. Prevention of panic disorder. *Behav Ther* 2001; **32:** 725–37.