Nice comprehensive article on the current state and recommendations for the treatment of panic disorder with and without the use of medication. On our web site is a link to Freedom from Fear that offers both a good diagnostic test and further information for patients or parishioners on this disorder.

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The Treatment of Panic Disorder

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Abstract and Introduction

Abstract

Purpose of Review: The aim of this article is to provide an updated review of studies and recommendations published from August 2003 to August 2004 on the treatment of panic disorder.
Recent Findings: Cognitive-behavioral psychotherapy remains the treatment of choice for panic disorder. Recent studies confirm selective serotonin reuptake inhibitors as the first-choice drugs in treating panic disorder. Recommendations for (adjunctive) high-potency benzodiazepines have been published. Psychoeducation and combined pharmacotherapy/psychotherapy improve treatment response. Optimal long-term treatment of panic disorder involves adequate medication and duration of treatment, since relapse is frequent.
Summary: Recent studies confirm that cognitive-behavioral therapy, alone or in combination with drug therapy, remains the treatment of choice for panic disorder. Long-term treatment is often necessary due to the chronicity of the illness.

Introduction

Panic disorder is a chronic and debilitating illness characterized by recurrent, unexpected panic attacks coupled with anticipatory anxiety. Agoraphobia is a frequent complication of panic disorder. Panic disorder is often comorbid with major depressive disorder (MDD) and mitral valve prolapse (MVP) frequently accompanies the disorder.

Swoboda *et al*.[1] showed that embarrassability and fear of negative evaluation are significantly higher in patients with agoraphobic avoidance than in patients with uncomplicated panic disorder and controls. Furthermore, women generally showed higher embarrassability scores than men. The authors concluded that heightened embarrassability is an important characteristic of patients suffering from panic disorder with agoraphobia (PDA).

Anxiety disorders such as panic disorder are risk factors for the first onset of MDD, severe impairment being the strongest predictor of MDD, as recently confirmed in a study by Bittner *et al*..[2]

In a 15-year follow-up study of 55 outpatients with panic disorder published by Andersch and Hetta,[3] complete recovery (no panic attacks and no longer on medication during the last 10 years) was seen in 18% of patients, and an additional 13% recovered but were still on medication. Fifty-one percent experienced recurrent anxiety attacks whereas 18% still met diagnostic criteria for panic disorder. The incidence of agoraphobia decreased from 69% to 20%. Patients with agoraphobia at admission tended to have a poorer long-term outcome according to daily functioning compared with patients without agoraphobia at admission, although both groups reported improved daily functioning at follow-up. Maintenance medication was common. No benzodiazepine abuse was reported. The authors concluded that panic disorder has a favourable outcome in a substantial proportion of patients. However, the illness is chronic and needs treatment.

Finally, Culpepper[4] proposed a review on the identification of panic disorder in primary care.

Treatment

A cost-effectiveness study conducted by Issakidis *et al*.,[5] that aimed to identify the averted burden and economic efficiency of current and optimal treatment for the major mental disorders, showed that evidence-based care for anxiety disorders (including panic disorder) would produce greater population health gain at a similar cost to that of current care, resulting in a substantial increase in the cost-effectiveness of treatment.

The most recent clinical practice guidelines for the treatment of panic disorder and agoraphobia were published by the Royal Australian and New Zealand College of Psychiatrists in December 2003.[6**] Treatment recommendations include education for the patient and significant others covering the nature and course of panic disorder and agoraphobia; an explanation of the psychopathology of anxiety, panic and agoraphobia; and rationale for the treatment, likelihood of a positive response, and expected time frame. Cognitive-behavior therapy (CBT) is more effective and more cost-effective than medication. Tricyclic antidepressants (TCAs) and serotonin selective reuptake inhibitors (SSRIs) are equal in efficacy and both are to be preferred to benzodiazepines. Treatment choice depends on the skill of the clinician and the patient's circumstances. Drug treatment should be complemented by behavior therapy. If the response to an adequate trial of a first-line treatment is poor, another evidence-based treatment should be used. A second opinion can be useful. The presence of severe agoraphobia is a negative prognostic indicator, whereas comorbid depression, if properly treated, has no consistent effect on outcome.

Self-help and Psychoeducation

Self-help and psychoeducation have been identified as effective methods for delivering treatment and remain an essential component of effective treatment of panic disorder.

Baillie and Rapee[7] have developed a prognostic scale which predicts who will recover from panic attacks and who will require more assistance. The prognostic scale may be used to guide the choice of psychoeducation, self-help or face-to-face therapy as the first step in stepped care.

Self-directed treatment with brief therapist contact may also be a viable option for many people with panic disorder. In a study conducted by Hecker *et al*.,[8] 28 individuals with panic disorder were provided with a copy of 'Mastery of Your Anxiety and Panic II' and received either four sessions of group CBT or one meeting with a therapist plus three telephone calls. A higher percentage of participants in the telephone condition achieved high end-state functioning status

following treatment compared with those who participated in group CBT (72% versus 24%), but this difference disappeared at 6 months following treatment (45% versus 55%).

A computer-aided CBT self-help system for anxiety and depressive disorders has been developed by Marks and his team and is described by Marks *et al*.[9] and Gega *et al*..[10] Self-exposure therapy for panic/phobia cut clinician time per patient by 73% without losing efficacy when guided mainly by a computer rather than entirely by a clinician. The systems were accessible at home. Initial brief screening by a clinician can be done by phone, and if patients get stuck they can obtain brief live advice from a therapist on a phone helpline. In an open study by Kenwright and Marks,[11] 10 people with phobia or panic disorder who could not travel repeatedly to a therapist accessed a computer-aided exposure self-help system (FearFighter) at home on the Internet with brief therapist support by telephone. They improved significantly, and their outcome and satisfaction resembled those in patients with similar disorders who used FearFighter in clinics with brief face-to-face therapist support. Such clinician-extender systems offer hope for enhancing the convenience and confidentiality of guided self-help, reducing the per-patient cost of CBT, and lessening the stigma.

Cognitive-behavioral Psychotherapy

The American National Institute of Health recommended CBT programs as the treatment of choice for panic disorder. CBT therapy has demonstrated efficacy both in the acute and long-term treatment of panic disorder. The following studies have been published during the review period.

Group Therapy. Dannon *et al*.[12] evaluated the effectiveness of group CBT in the treatment of panic disorder, comparing the treatment outcome with paroxetine pharmacotherapy. Treatment with group CBT alone for the acute phase of panic disorder appeared to be equally efficacious to treatment with paroxetine alone.

Virtual Reality. Virtual reality-based treatments may increase the availability of CBT programs for panic disorder. Virtual reality has several advantages compared with conventional techniques. One of the essential components in treating these disorders is exposure. In virtual reality the therapist can control the feared situations at will and with a high degree of safety for the patient as it is easier to grade the feared situations. Another advantage is that virtual reality is more confidential and less time consuming because treatment takes place in the therapist's office. Considering the large number of situations and activities that agoraphobic patients try to avoid, virtual reality can save a significant amount of time and money. Another advantage is that virtual reality offers a more natural setting for interoceptive exposure than the consultation room in treating PDA because bodily sensations can be elicited while the patient is immersed in virtual reality agoraphobic situations. Finally, virtual reality exposure can be a useful intermediate step for those patients who refuse in-vivo exposure because the idea of facing real agoraphobic situations is too aversive for them. In an article by Botella *et al*.,[13] a program developed for PDA is summarized and compared with in-vivo exposure. The findings support the efficacy and effectiveness of virtual reality for the treatment of PDA. A system that allows the patient to continue a psychological virtual reality treatment from his or her home PC as complementary therapy is described by Alcaniz *et al*..[14]

Cognitive-behavioral Therapy by Videoconference. Delivering psychotherapy by videoconference may also significantly increase the accessibility of empirically validated treatments. A study conducted by Bouchard *et al*.[15] with 21 patients compared the effectiveness of CBT for PDA when the therapy is delivered either face to face or by videoconference. None of the comparisons with face-to-face psychotherapy suggested that CBT delivered by videoconference was less effective. The participants reported the development of an excellent therapeutic alliance in videoconferencing as early as the first therapy session.

Pharmacotherapy

Recently, pharmacological treatment guidelines for panic disorder have changed as newer treatment options have become available. In a review, Bruce *et al*.[16**] examined how the use of psychotropic drugs has shifted over the course of 10 years to determine if prescribing patterns have changed to reflect these revised treatment guidelines. Despite efforts aimed at increasing the use of SSRIs in patients with panic disorder, only a modest increase in their use was found. Treatment patterns for psychotropic drugs appear to have remained stable over the past decade, with benzodiazepines being the most commonly used medication for panic disorder. Recommendations to use SSRIs to treat panic disorder are not being followed.

Selective Serotonin Reuptake Inhibitors. SSRIs have emerged as the first-choice treatment as they have a beneficial side-effect profile, are relatively safe (even if an overdose is taken), and do not produce physical dependency. Paroxetine, sertraline, citalopram and fluoxetine have an approved indication for panic disorder in Europe and the USA.

Paroxetine. A 3-year naturalistic outcome study by Dannon *et al*.[17] of 143 patients observed the course of illness in panic disorder patients receiving long-term versus intermediate-term paroxetine treatment. This enabled comparison of the relapse rates and side-effect profile after long-term paroxetine treatment between patients with panic disorder and PDA and to observe paroxetine's tolerability over a 24-month period. In this study, the extension of paroxetine maintenance treatment from 12 to 24 months did not seem to further decrease the risk of relapse after medication discontinuation. Twenty-four month paroxetine treatment was accompanied by sexual side effects and weight gain similar to those observed during a 12-month treatment.

A preliminary report by Yeragani *et al*.[18] showed that paroxetine decreases respiratory irregularity of linear and nonlinear measures of respiration in patients with panic disorder. Yeragani also stated that paroxetine appears to be safer in regards to cardiovascular effects compared with nortriptyline.[19]

Kjernisted and Bleau[20] emphasized in a recent review that in the management of panic disorder, paroxetine and venlafaxine XR doubled the percentage of patients who were panic free compared with placebo.

Finally, a controlled-release formulation of paroxetine has recently been developed. Bang and Keating[21] emphasized that recipients of controlled-release paroxetine experienced significantly less nausea than recipients of immediate-release paroxetine in the first week of treatment.

Sertraline. In a study conducted by Bandelow *et al*.[22*] adult outpatients with panic disorder with or without agoraphobia were randomly assigned in double-blind fashion to 12 weeks of treatment with flexible doses of sertraline (titrated up to 50-150 mg/day; *n* = 112) or paroxetine (titrated up to 40-60 mg/day; *n* = 113). Sertraline and paroxetine had equivalent efficacy in panic disorder, but sertraline was significantly better tolerated and was associated with significantly less clinical worsening during taper than paroxetine. A letter by Sheikh *et al*.[23] reports a preliminary open-label trial of sertraline for panic disorder in older adults.

Escitalopram. A randomized, double-blind, placebo-controlled trial of 366 participants (128 escitalopram patients, 119 citalopram patients, and 119 placebo patients) conducted by Stahl *et al*.[24] showed that escitalopram is efficacious, safe, and well tolerated in the treatment of panic disorder. The rate of discontinuation for adverse events was 6.3% for escitalopram, 8.4% for citalopram, and 7.6% for placebo.

Other Antidepressants. Reversible monoamine oxidase inhibitors and TCAs have also shown antipanic efficacy. Clomipramine is approved for panic disorder. In a study by Mavissakalian[25]

comparing imipramine with sertraline in panic disorder, greater early improvement was seen with imipramine but no enduring differences beyond week 8 of treatment. Side effects were higher for imipramine.

Clinical applications of monoamine oxidase inhibitors, including panic disorder, were addressed in a recent article by Riederer *et al*..[26]

Benzodiazepines. High-potency benzodiazepines, essentially alprazolam, clonazepam, and lorazepam, are effective in treating panic disorder and panic attacks with or without agoraphobia and as add-on therapy to SSRIs in the treatment of panic disorder. Benzodiazepines act rapidly and are well tolerated, but their use presents clinical issues such as dependence, rebound anxiety, memory impairment, and discontinuation syndrome, as reviewed in a recent article by Chouinard.[27]

Due to the release of new formulations of two high-potency benzodiazepines, Moroz[28*] published a review on recent clinical results.

Clonazepam. Clonazepam has recently become available in a lyophilized wafer that disintegrates when exposed to saliva and enhances ease of administration without altering its pharmacology, as shown by bioequivalence studies. Two US multicenter trials carried out in the 1990s, among others, have provided strong confirmatory evidence for the use of clonazepam in panic disorder. Other recently published data on clonazepam pertain to its use as augmentation therapy with SSRIs and in the prevention of recurrences of MDD.

Rosenbaum[29] reports that in response to the apparent problematic pharmacokinetics of alprazolam, members of the Massachusetts General Hospital psychiatry department pursued investigation that ultimately established the antipanic efficacy of clonazepam.

Alprazolam. A new, extended-release formulation of alprazolam now allows for once-daily rather than three or four times daily dosing. With extended release, the blood drug concentrations of alprazolam remain within the therapeutic window for several hours, which should reduce fluctuation in therapeutic effect and curb the clock-watching phenomenon between doses.

An exhaustive review of the literature by Verster and Volkerts[30*] showed that alprazolam is significantly superior to placebo, and at least equally effective in the relief of symptoms as TCAs, such as imipramine. However, SSRIs appear to be superior to both sets of drugs. Therefore, alprazolam is recommended as a second-line treatment option, when SSRIs are not effective or well tolerated. Alprazolam may impair performance in a variety of skills: this behavioral impairment limits the safe use of alprazolam in patients routinely engaged in potentially dangerous daily activities, such as driving a car.

Other Pharmacological Treatments: Clonidine. Valenca *et al*.[31] reported that clonidine can be effective in the treatment of respiratory panic disorder. This drug may play a role in relieving symptoms of anxiety due to noradrenergic hyperactivity in these patients.

Physical Treatments

Physical treatments such as exercise and slow-breathing techniques were addressed in two recent articles.

Exercise. The results of a study conducted by Broman-Fulks *et al*.[32] indicate that both high and low-intensity exercise reduced anxiety sensitivity, a known precursor to panic attacks and panic disorder. However, high-intensity exercise caused more rapid reductions and produced more

treatment responders. Only high-intensity exercise reduced fear of anxiety-related bodily sensations.

Respiratory Feedback. Training patients to change their breathing patterns is a common intervention, but breathing has rarely been measured objectively in assessing the patient or monitoring therapy results. Meuret *et al*.[33] reported a new breathing training method that makes use of respiratory biofeedback to teach individuals to modify four respiratory characteristics: increased ventilation (respiratory rate × tidal volume), breath-to-breath irregularity in rate and depth, and chest breathing.

Integrated Treatment

An integrated treatment approach that combines pharmacotherapy with CBT may provide the best treatment. Characteristics that led psychiatrists to make a decision about intensive treatment of patients with PDA with CBT alone, CBT plus a high-potency benzodiazepine or CBT combined with a benzodiazepine and an antidepressant (in this case fluoxetine) were analysed by Starcevic *et al*..[34*] Psychiatrists generally used combination treatments in patients with more severe PDA. CBT alone was a more likely choice for dominant anxiety-related cognitive phenomena. Patients with prominent panic attacks and somatic symptoms were more likely to be treated with CBT plus a benzodiazepine, while those who also had significant depressive symptoms and higher disability levels were more likely to receive CBT plus a benzodiazepine plus an antidepressant. Patients in all three treatment groups showed significant reduction in symptoms during intensive treatment and reached similar end states.

Long-term Treatment

The World Council of Anxiety (WCA) recently published recommendations for the long-term treatment of panic disorder.[35**] Long-term pharmacological treatment is safe and effective in accruing continued improvement, maintaining benefit and preventing relapse. Long-term efficacy and ease of use are therefore important considerations in treatment selection, as maintenance treatment is recommended for at least 12-24 months, and in some cases, indefinitely.

Long-term management of panic disorder is also described in a recent review by Doyle and Pollack,[36] showing that available pharmacotherapies as well as CBT have clear efficacy for the acute and long-term treatment of panic disorder, but many patients remain symptomatic despite their routine application.

In a 3-year follow-up study of 326 patients, Toni *et al*.[37] examined the relationships between long-term treatment response, side effects and drug discontinuation in panic disorder. A total of 179 patients interrupted pharmacological treatment. Among them, 26.8% were not traceable; 36.9% had deemed further contact with the psychiatrist unnecessary because of remission. Other reasons for interruption were ineffectiveness (18.4%), side effects (10.6%) and personal reasons (7.3%). Patients who interrupted pharmacological treatment because of symptom remission remained in the study for a longer period than those patients who interrupted their treatment because of inefficacy. The study showed that a high percentage of patients who have achieved symptom remission tend to default from further treatment. Adherence to long-term treatment with antidepressants was predicted by severe and long-lasting symptomatology.

Comorbid Tobacco or Cannabis Use

Smoking is specifically associated with panic disorder and not more generally associated with other anxiety disorders, as proven by another recent study by McCabe *et al*..[38] In a Russian sample,[39] the combination of high levels of anxiety sensitivity and smoking predicted

agoraphobic avoidance. Daily smoking may be a causal factor in panic disorder and agoraphobia, conditions that could be preventable by smoking cessation, as suggested in an article by Breslau *et al*..[40]

Acute cannabis use can also be associated with the onset of panic attacks and panic disorder. In a study by Tournier *et al*.[41] no evidence was found for an anxiolytic or anxiogenic effect of cannabis in daily life. This finding does not support the hypothesis that patients with high levels of anxiety use cannabis as a means of self-medication. The association between agoraphobia and cannabis use in daily life may be explained by anticipatory anxiety secondary to previous cannabis-induced panic-like symptoms. In a recent study, Dannon *et al*.[42] showed that panic disorder which develops after cannabis use stays responsive to pharmacotherapy.

Dental Implications

An article by Friedlander *et al*.[43] suggests that because there is a connection between panic attacks and MVP, the dentist needs to consult with the patient's physician to determine the presence of MVP and whether there is associated mitral valve regurgitation. Patients with MVP and accompanying mitral valve regurgitation require prophylactic antibiotics when undergoing dental procedures known to cause a bacteremia and heightened risk of endocarditis.

Conferences

The 1st International Conference on Panic Attacks[44] focused on the diversity of treatments and theories in this complex condition. Abstracts are available online (http://anxiety-panic.com/conference/). The second conference took place in October 2004.

Conclusion

Panic disorder is a chronic, disabling condition that is often associated with a need for long-term clinical treatment. Effective treatment methods are CBT, TCAs and SSRIs as first-line drug treatments, as well as high-potency benzodiazepines as second-line treatment. Cognitive-behavioral methods may be more effective in the long term than medication. Long-term pharmacological treatment, however, remains safe and effective in accruing continued improvement, maintaining benefit and preventing relapse.

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Abbreviation Notes

CBT = cognitive-behavioral therapy; MDD = major depressive disorder; MVP = mitral valve prolapse; PDA = panic disorder with agoraphobia; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

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