Consensus Statement on Panic Disorder From the International Consensus Group on Depression and Anxiety

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Objective: To provide primary care clinicians with a better understanding of management issues in panic disorder and guide clinical practice with recommendations for appropriate pharmacotherapy. ***Participants:*** The 4 members of the International Consensus Group on Depression and Anxiety were James C. Ballenger (chair), Jonathan R. T. Davidson, Yves Lecrubier, and David J. Nutt. Four faculty invited by the chairman also participated: David S. Baldwin, Johan A. den Boer, Siegfried Kasper, and M. Katherine Shear. ***Evidence:*** The consensus statement is based on the 6 review papers that are published in this supplement and on the scientific literature relevant to these issues. ***Consensus Process:*** There were group meetings held during a 2-day period. On day 1, the group discussed each review paper and the chairman and discussant (Dr. Kasper) identified key issues for further debate. On day 2, the group discussed these key issues to arrive at a consensus view. After the group meetings, the consensus statement was drafted by the chairman and approved by all attendees. ***Conclusions:*** The consensus statement provides standard definitions for response and remission and identifies appropriate strategy for the management of panic disorder in a primary care setting. Serotonin selective reuptake inhibitors are recommended as drugs of first choice with a treatment period of 12 to 24 months. Pharmacotherapy should be discontinued slowly over a period of 4 to 6 months.

(J Clin Psychiatry 1998;59[suppl 8]:47–54)

Panic disorder is a disabling psychiatric condition, estimated to affect between 2% and 4% of the population at some time in their lives,[1–4] and it affects almost 2% of primary care attendees. Typically a disorder of young adults, panic disorder impairs the social, family, and working lives of sufferers at a time when they should make their greatest contribution to society. Frequent comorbid psychiatric conditions, most notably depression, complicate the clinical presentation, exacerbating individual disability and increasing the economic burden to society.

Panic disorder was the subject of the first meeting of the International Consensus Group on Depression and Anxiety. Our objective was to provide clinicians with a better understanding of the management of panic disorder by identifying what is known in the field and what requires further research. This article presents our views on the treatment of panic disorder based on our review of the available clinical evidence and sets out our clinical recommendations for the pharmacotherapy of panic disorder.

DEFINING PANIC DISORDER

Panic attacks are the core feature of panic disorder, but other symptoms (anticipatory anxiety and phobias) and functional ability in daily life must also be taken into consideration when defining the disorder. We can identify 5 domains in which improvement should be observed:

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Presented at the meeting "Focus on Panic Disorder: Antidepressants in Practice," January 15–16, 1998, in Bad Ragaz, Switzerland, held by the International Consensus Group on Depression and Anxiety. This Consensus Meeting was supported by an unrestricted educational grant from SmithKline Beecham Pharmaceuticals.

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1. Panic attacks, including limited-symptom attacks
2. Anticipatory anxiety
3. Panic-related phobias (including agoraphobia and body-sensation phobias)
4. Well-being/overall severity of illness
5. Disability in terms of work, social, and family impairment

We recognize the need to educate clinicians and their patients about the extent to which panic disorder can affect the daily lives of sufferers. When taking a patient's history, it is important for the clinician not only to identify specific phobias but also to explore the level of disability associated with symptoms. When assessing improvement in that patient's condition during treatment, the clinician should take account of all 5 domains affected by panic disorder.

RESPONSE AND REMISSION IN PANIC DISORDER

There is no definition of treatment response in the DSM classification of panic disorder; few investigators use rigorous methodologies for response with a standard time frame to ensure stability; and the most commonly used measure of response, endpoint Clinical Global Impressions scale (CGI) score, is inadequate in many ways. Definitions of remission are provided in the DSM classification, but remission is rarely defined by investigators and, when it is, there is no consistency of time frame, standardization of measures, or agreement on the symptom levels for full or partial remission.

The consensus group arrived at the following proposals for defining response and remission in panic disorder:

Response: a stable, clinically significant improvement (usually occurring after 4 to 8 weeks of treatment) such that the patient no longer has the full range of symptoms, but continues to show more than minimal symptoms

Full remission: almost complete resolution of symptoms across the 5 domains of panic disorder maintained for a period of at least 3 months

Standard definition of the terms commonly used to describe the course of panic disorder would provide clinicians with a consistent frame of reference, similar to that used to describe the time course in depression, and facilitate comparisons between clinical studies. In the experience of the consensus group, full remission as defined above will require at least 9 to 12 months of treatment intervention: 6 to 9 months for the initial response and consolidation of that response, and 3 months to demonstrate stable and almost complete resolution of symptoms and thus meet the criterion for full remission.

CLINICAL IMPACT OF COMORBIDITY IN PANIC DISORDER

Patients with panic disorder often suffer from other psychiatric disorders at the same time.[1,5] Depression is the psychiatric condition most frequently associated with panic disorder; around two thirds of panic patients will also experience a major depressive episode.[6,7] Anxiety disorders that commonly occur with panic disorder are obsessive-compulsive disorder, posttraumatic stress disorder, and social phobia. The latter is the most prevalent of the anxiety disorders; more than 40% of patients with panic disorder also meet diagnostic criteria for social phobia.[8,9] Personality disorder and alcohol dependence are other important, but less common, comorbid conditions.

Comorbidity has a detrimental effect on the course and outcome of panic disorder.[10–12] Compared with patients who have panic disorder alone, comorbid patients take longer to respond to treatment. They are less likely to obtain full remission of their symptoms during treatment and are more likely to seek medical help for these symptoms.

When panic disorder and depression occur together, patients experience more severe symptoms of anxiety and depression and more severe impairment in their daily activities than patients with a single psychiatric disorder. Most importantly, we recognize that comorbidity with depression radically increases the risk of suicide attempts in patients with panic disorder.[13,14]

Clinical Recommendations

Depression and panic disorder frequently occur in the same patient. When the clinician detects depression in a patient with panic disorder, it is a signal for the need to follow that patient closely, since the risk of attempted suicide is radically increased. As time to response is prolonged when there is comorbid depression, the clinician must carefully monitor treatment to ensure that an optimal response is achieved.

MEASURING IMPROVEMENT IN PANIC DISORDER

Response and remission in panic disorder are defined with reference to improvement across the 5 principal domains affected by the disorder. Many different instruments exist to assess symptoms, impairment, and functional disability in panic disorder (see the article by Shear, this supplement). These may be used in combination to measure improvement and assess treatment outcome, but a single instrument that combines assessment of all 5 domains is recommended.

The Panic Disorder Severity Scale (PDSS) is an instrument modeled on the Yale-Brown Obsessive Compulsive Scale. It is a single measure of the 5 principal domains in panic disorder and has good psychometric properties[15]

unlike the commonly used global measure, the CGI. We recommend consideration of the PDSS as the appropriate rating scale in panic disorder and a potential instrument for future quality research in panic disorder and even in clinical practice.

Research Need: The PDSS is a new instrument, and further research is needed to (1) validate its use in the long-term follow-up of patients and (2) determine scores in a normal population and in a primary care setting.

THE CLINICAL IMPLICATIONS OF PANIC ATTACKS

Most clinical opinion has been that panic attacks are clinically significant and predictive of significant future morbidity only when the sufferer meets diagnostic criteria for panic disorder. Recent research[16] on the impact of psychiatric disorders in both community and primary care settings challenges this view and indicates that the simple occurrence of panic attacks has an important predictive value.

The occurrence of even an isolated panic attack is a powerful marker for the presence of other psychiatric symptoms. In a primary care population,[16] 99% of individuals with a panic attack during the previous month had other psychiatric symptoms, and around 90% met diagnostic criteria for a full psychiatric disorder, principally depression, panic disorder, or another anxiety disorder (WHO study, see article by Lecrubier, this supplement). A lifetime history of panic attacks is also predictive of both future panic disorder and depression in the majority of cases.[16]

Clinical Recommendations

A single panic attack is a signal to the clinician that a patient is almost certainly suffering from other psychiatric symptoms and probably has a full psychiatric disorder. This signal should not be ignored, because it is a reliable marker for significant depressive and anxiety difficulties, the most common psychiatric disorders in primary care. Although frequently seen in a primary care setting, panic attacks are also often missed, because sufferers tend to focus primarily on their physical symptoms, such as hyperventilation and chest pain. They should be questioned about psychological symptoms to see whether they have experienced the sudden overwhelming episode of anxiety that is characteristic of panic attacks.

When the patient presents with a panic attack in primary care, the physician should probe for other symptoms and assess the level of impairment in the patient's social and working life associated with these symptoms. The important value of the panic attack as a signal for other psychopathology reduces the need for differential diagnosis of depression and anxiety disorders: the simple coexistence of a panic attack and disabling psychiatric symptoms indicates the need for therapeutic intervention. (For a discussion of the appropriate management of patients, see later sections.)

Research Need: Longitudinal follow-up of patients who present with a panic attack has shown that 50% will suffer an episode of major depression within 1 year.[16] The question is whether early intervention will prevent the development of depression and whether treatment should be continued for 1 year, 2 years, or longer. The study should be conducted with a serotonin selective reuptake inhibitor because of their high tolerability, which encourages good compliance (see recommendation on appropriate pharmacotherapy).

Further studies are needed in primary care to replicate the finding on the predictive value of panic attacks reported in the WHO study.

MANAGEMENT OF PANIC DISORDER

The consensus panel recognizes that, on rare occasions, panic attacks are indicative of an underlying medical condition. The possibility of a medical disorder can generally be excluded by the history and routine physical and laboratory examination of the patient. No further investigation is warranted unless this initial assessment indicates a suspected condition, for example, a possible cardiac problem.

Education about the nature of panic disorder is an important first step in patient management. Patients must understand that panic attacks are common and disabling but that panic disorder is treatable and they will improve if effective medication is continued at an appropriate dosage for an appropriate length of time. Phobias are an inherent feature of panic disorder, and clinicians must explain to patients the value of reexposure to phobic situations.

As for any psychiatric disorder, patients require psychological support in addition to effective medication. The possibility of combining specialized psychotherapy with pharmacotherapy might be considered, when this option is available. One of the most important messages to clinicians is to initiate effective medication promptly. While it is important to explore life issues and precipitating events, symptom control is of paramount importance.

To provide guidance on pharmacotherapy in panic disorder, we considered the following questions:

1. On what basis should choice be made?
2. How should the drug of choice be used?
3. For how long should treatment be continued?

CHOICE OF PHARMACOTHERAPY IN PANIC DISORDER

The choice of treatment in panic disorder should be decided in the context of an informed discussion with the pa-

Table 1. Comparison of the Effective Therapeutic Classes by Agent, Based on Published Data*

	SSRIs					TCAs			Benzodiazepines	
Area of Comparison	Citalopram[a]	Fluoxetine	Fluvoxamine	Paroxetine[a]	Sertraline[a]	Clomipramine	Imipramine	Lofepramine	Alprazolam	Clonazepam
Efficacy in panic disorder[b]	●	#	◗	●	#	●	●	◗	●	●
Efficacy in reducing panic attacks to zero[b]										
Short-term studies	●		◗	●		●	●	◗	●	●
Long-term studies				●		●	●		●	#
Efficacy data for all 5 domains (panic attacks, anxiety, phobias, well-being, disability)[b]			◗	●		●	●		●	
Onset of action (wk)	4	4	4	4	4	6	8	6	1	1
Efficacy in comorbid conditions[b]										
Depression	●	●	●	●	●	●	●	●		
OCD	#	●	◗	●	●	●				
Once-daily dosing[b]	●	●		●	●	●				
Good tolerability[b]	●	#	◗	●	#				●	●
Safety[c]										
In overdose	?	■	■	■	■				■	■
In driving		■		■	■					
Risk of dependence									■	■
Ease of withdrawal[d]	○	○	○	○	○	○	○	○		
Pharmacokinetics[c]										
Lack of active metabolites			■	■					■	■
Half-life greater than 1 day	■	■								?

*Table developed by the Consensus Group and includes data from references 17–35.
[a]SSRIs licensed for use in panic disorder.
[b]Efficacy and tolerability data from placebo-controlled studies: ● = large studies of over 100 patients; ◗ = small studies involving less than 100 patients; # = open, or nonpublished placebo-controlled data; blank = no published placebo-controlled data.
[c]Safety and pharmacokinetic data from published studies: ■ = the drug meets the criteria; ? = equivocal data; blank = not meeting criteria.
[d]○ = no addiction or dependence problems, but tapering of dose recommended; blank = not meeting criteria.

tient. The determinants of choice are clinical efficacy, tolerability and safety, comorbidity, relapse prevention, ease of use, and pharmacologic differences.

Clinical Efficacy

The consensus group considered the quality of clinical evidence available for the current therapeutic options in panic disorder: serotonin selective reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), benzodiazepines, β-blockers, and anticonvulsants (see the article by den Boer, this supplement).

Multicenter placebo-controlled trials provide strong evidence for the clinical efficacy of agents in each of the 3 therapeutic classes: SSRIs,[17–23] TCAs,[20,21,24–28] and benzodiazepines.[24,27–35] For the SSRIs, there is strong, well-controlled published data for paroxetine and also for fluvoxamine (see Table 1).

There are controlled data for the efficacy of MAOIs, although the quality of evidence is less extensive than that for SSRIs, TCAs, or benzodiazepines.[36]

There is only a single trial to support the efficacy of β-blockers, and the consensus group concluded that they should be considered an ineffective therapeutic option in panic disorder. The quality of evidence for anticonvulsants is also considered limited, and recommended use of valproate is confined to treatment-resistant patients at this point.

From our review of the clinical literature (see the article by den Boer, this supplement), we conclude that two thirds or more of patients with panic disorder treated with an SSRI, TCA, or benzodiazepine show a clinical improvement across the 5 principal domains (panic attacks, general anticipatory anxiety, agoraphobia and other phobias, well-being, and disability). Efficacy is broadly comparable across these 3 medication classes. However, when panic disorder is associated with depression or with another anxiety disorder such as obsessive-compulsive disorder, serotonergic antidepressants are a more effective therapeutic choice than benzodiazepines.

Tolerability and Safety

Patients with panic disorder are particularly sensitive to physical symptoms and to medication effects. Clinicians must initiate treatment at low doses and inform patients that some medications can cause physical effects, such as jitteriness, which resemble untreated anxiety symptoms.

From our review of the clinical literature (see the article by Baldwin, this supplement), we reached the following conclusions on the comparative tolerability of benzodiazepines, TCAs, and SSRIs:

1. Benzodiazepines are generally well tolerated, although they can cause unwanted sedative effects,

poor coordination, and memory problems. More importantly, benzodiazepines potentiate the effects of alcohol, and their prolonged use is associated with the risk of dependence and therefore potential difficulties with withdrawal symptoms.

2. TCAs are associated with poor tolerability (primarily through their anticholinergic effects), weight gain, or carbohydrate craving, and they have the potential to cause seizures. Concerns about the safety of TCAs, often related to their cardiac effects, are particularly pertinent to their use in the medically ill or to overdosage in suicidal patients.
3. SSRIs have an improved tolerability over traditional TCAs; most side effects resolve over time, and safety in the medically ill and with overdoses has been established. Some SSRIs, most notably fluoxetine, may cause initial jitteriness.

Treatment-emergent sexual dysfunction has been reported with all 3 therapeutic classes. Interference with normal sexual function is an important side effect reported relatively frequently with the SSRIs and needs close attention from clinicians.[37,38] These effects tend to be noticed more during treatment with SSRIs than with other therapy probably because the SSRIs cause so few other side effects. Evaluation of the literature indicates that sexual dysfunction is equally prevalent during treatment with TCAs or benzodiazepines.

Absence of behavioral toxicity, as it applies to driving ability, is an important consideration for the patient, to maintain a normal active daily life. SSRIs do not impair driving ability, whereas there is good evidence that the use of TCAs and benzodiazepines is associated with an increase in road traffic accidents.[39]

Clinical recommendations. Patients with panic disorder and a recent history of alcoholism should, except in some instances, not be prescribed benzodiazepines. Patients who have panic disorder and a history of suicidal ideation or temporal lobe epilepsy should not be prescribed TCAs. SSRIs are a particularly appropriate choice of treatment for patients with panic disorder who also have concomitant depression, high suicidality, or concomitant medical illness. (See Table 1 for comparative efficacy of SSRIs, TCAs, and benzodiazepines in panic disorder, when alone or comorbid with other psychiatric conditions.)

Comorbidity

Comorbidity complicates the treatment of panic disorder, increasing the need for higher doses and a longer duration of treatment or additional pharmacotherapy. Simple panic disorder can be managed adequately at a primary care level, but the consensus group takes the view that patients with a comorbid disorder often require specialist care. Antidepressant therapy is indicated for the many patients who have panic with concurrent depression, and we recommend an SSRI as the first-line choice (see later section: "How to treat with appropriate drug therapy"). We believe that SSRIs should also be the preferred therapeutic option for panic disorder comorbid with other anxiety disorders (e.g., obsessive-compulsive disorder) or alcoholism.

Relapse Prevention

Panic disorder is a chronic and recurring condition requiring long-term management. We recognize that there are limited data on the clinical efficacy of long-term treatment (see article by Davidson, this supplement) but from these data we conclude that SSRIs are generally preferable to TCAs or benzodiazepines. Data on the long-term efficacy of SSRIs, which are available for paroxetine, indicate that continued treatment for up to 1 year is effective in maintaining and extending short-term improvements and in preventing relapse of panic disorder.

Ease of Use

As with other chronic illnesses, a simple dosing regimen is an important factor in encouraging compliance with medication so that an optimal response to treatment is obtained. With the exception of fluvoxamine, the SSRIs can be administered in a once-daily dosing regimen, and dose-finding studies have been published for paroxetine[22] and for citalopram.[23] Clomipramine can be administered as a single dose, once daily at bedtime, whereas multiple doses are used for the other TCAs studied in panic disorder, imipramine and lofepramine. Multiple daily dosing is also a requirement for benzodiazepines.

Pharmacologic Differentiation

The clinical relevance of pharmacologic differences within a therapeutic class relate to patient response, side effects, and switching treatment. SSRIs, for example, have differences in the relative inhibition of serotonin and norepinephrine reuptake, receptor subtype affinity, and pharmacokinetics (see article by Nutt, this supplement). By analogy with depression, when a patient with panic disorder fails to respond to treatment with one SSRI, a therapeutic trial of another SSRI is generally indicated (see later section: "How to treat with appropriate drug therapy"). It should be remembered that switching treatment (or discontinuing abruptly after a serious adverse event) can be problematic when the elimination half-life of the SSRI is long and there are active metabolites, as in the case of fluoxetine.

Research Need: Clinical trials have assessed the effect of switching from one SSRI to another in depressed patients unresponsive to treatment. Comparable data are needed on the effect of switching

SSRI therapy in patients with panic disorder who are initial nonresponders.

Treatment of choice. The consensus group recommends that the first-line treatment for panic disorder be an SSRI. Most of the published evidence in support of this recommendation at this point is the well-controlled scientific data on paroxetine[19–22] and fluvoxamine.[17,18] Paroxetine was the first SSRI with adequate data to gain a license for the treatment of panic disorder, and, importantly, there is clinical evidence for its efficacy not only in comorbid depression but also in the anxiety disorders frequently comorbid with panic disorder, such as obsessive-compulsive disorder.

HOW TO TREAT WITH APPROPRIATE DRUG THERAPY

Initiation of Treatment

Treatment of panic disorder should start with a low dose of an SSRI. The dose should be gradually titrated upward until it is the same or higher than that used to treat depression. In published clinical trials of paroxetine, treatment was started with a dose of 10 mg/day and gradually increased to 40 mg/day, the recommended dosage for the treatment of panic disorder.

Concomitant use of a benzodiazepine for a limited period (less than 8 weeks) may help to initiate treatment with SSRIs in some patients.

Maintenance Dose

Limited evidence from naturalistic studies of antidepressants and benzodiazepines indicate that once a patient is in full remission, the dose of therapy may be lowered slowly and the response to treatment maintained.

Research Need: Controlled studies are needed to examine whether the dose of antidepressant therapy can be reduced during long-term treatment and to what extent, while still maintaining wellness.

Managing Side Effects

Patients with panic disorder are sensitive to the physical side effects of treatment. An important strategy in managing side effects is to inform the patient about potential physical effects, providing reassurance that the incidence will generally decrease as treatment is continued. Lowering the dose can reduce the side effect burden. On the rare occasions that it is needed, adjunctive therapy may be prescribed to counteract or reduce side effects, for example, benzodiazepines to manage agitation, 5-HT_2 receptor antagonists for sexual dysfunction, and 5-HT_3 receptor antagonists for nausea.

Research Need: (1) More research is needed on the clinical relevance of tolerability issues, especially over the long-term, since this is the principal difference between medications and between pharmacotherapy and psychological treatments of panic disorder. (2) We need to formally study the common practice of combining benzodiazepines with antidepressants to determine whether it is a strategy to avoid or embrace.

Managing Nonresponders

If a patient fails to respond to an adequate trial of therapy with an SSRI at the maximum tolerated dose (see next section: "Duration of treatment"), the appropriate choice of second-line therapy will depend on the clinical situation of nonresponse. We advise the following management strategy:

1. Second-line treatment: If the SSRI was well tolerated, with some evidence of response, try treatment with another SSRI. If tolerability was an issue, switch to a benzodiazepine or a TCA.
2. Third-line treatment: Try treating the patient with an MAOI. In the United States, no reversible MAOIs are available, so a traditional MAOI or valproate is often utilized.

Research Need: There has been no formal study of the most appropriate choice of therapy for the patient with panic disorder who fails to respond to a therapeutic trial of an SSRI. In fact, there are almost no studies to permit development of an algorithm of first, second, and third choices.

DURATION OF TREATMENT

An adequate trial of therapy requires 8 to 12 weeks of treatment, although further improvement, notably in disability, can be gained when treatment is continued for 12 or more months.

When to Stop Treatment

If treatment is effective and full remission maintained, consideration can be given to stopping treatment after 12 to 24 months, provided that the patient is not currently experiencing a stressful life event. As for all psychoactive medication, discontinuation of treatment should be slow (4 to 6 months), tapered, planned, and individualized. Clinicians should prepare their patients for what to expect during treatment discontinuation and offer reassurance and psychological support.

Research Need: Optimal length of treatment before discontinuation and appropriate taper rate need to be determined.

When Not to Stop Treatment

Treatment should be continued in patients with substantial residual pathology in any of the 5 domains, comorbid conditions, a history of severe relapse or high levels of

stress in their lives due to important lifestyle changes such as getting married. Patients may be concerned about continuing treatment and should be reassured that panic disorder is a condition that often requires long-term treatment.

Clinical Recommendations

The consensus group recommends that 12 months be the usual minimal duration of effective treatment of panic disorder with the therapy of choice being an SSRI. If the patient maintains a full remission for 12 to 24 months, the clinician can consider stopping treatment, which should be tapered slowly over a period of 2 to 6 months. If there are any persistent symptoms, in particular phobic symptoms, treatment should be continued. An important message for primary care physicians and their patients is that panic disorder is a chronic and disabling condition that often requires treatment over several years.

CLINICAL GUIDELINES FOR PRIMARY CARE MANAGEMENT OF PANIC DISORDER

The consensus group agreed on the following key clinical points:

1. Establish the diagnosis by conducting an appropriate, but limited, medical workup
2. Educate patients about the disorder
3. SSRIs are the drugs of first choice (for quality of evidence, see Table 1)
4. Start treatment with a low dose, for example, paroxetine 10 mg, and increase the dose slowly, as tolerated, to the target dose, for example, paroxetine 40 mg
5. Manage side effects successfully to allow continuation of treatment
6. The treatment goal is full remission across the syndrome: panic attacks, anxiety, phobias, well-being, and disability
7. When panic is comorbid or response is incomplete, consider referral to an anxiety disorder specialist
8. Continue effective treatment for 12 to 24 months and consider stopping only when the patient is well and in a stable life situation
9. Discontinue treatment slowly over 4 to 6 months
10. Inform patients not to stop medication abruptly without consulting their physician

Drug names: clomipramine (Anafranil), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), paroxetine (Paxil).

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