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Recommendations for the Long-Term Treatment of Anxiety Disorders

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This reprint has been adapted from an academic supplement based on information presented at the World Council of Anxiety Meeting, held September 11, 2000, in Pisa, Italy.

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WCA Recommendations for the Long-Term Treatment of Anxiety Disorders

By Joseph Zohar, MD

Anxiety disorders represent a spectrum of conditions that collectively encompasses more than half of all psychiatric disorders. In addition to being highly prevalent, anxiety disorders are usually chronic conditions that can substantially impair a patient's quality of life. Affected individuals frequently present with atypical/subthreshold symptoms and often exhibit comorbidity, including comorbid psychiatric/medical disorders, thus hindering correct diagnosis. As the recognition and diagnosis of anxiety disorders has improved, the rate of medical office visits in which a diagnosis of anxiety is documented increased 1.4-fold in the United States between 1990 and 1997.[1] This higher rate of diagnosis not only reflects considerable personal suffering, but imposes a substantial economic burden on society. The annual cost of anxiety disorders in the US was estimated at more than $42 billion in 1990.[2]

The last decade has brought about effective new treatments, both in pharmacotherapy and psychotherapy. However, the difficulty of obtaining effective psychotherapy is a major limitation in its use. The majority of clinical trials of pharmacologic agents have focused on the acute treatment phase, and therefore less is known about the long-term management of anxiety disorders. (Please see the accompanying Table for a listing of drug-specific long-term pharmacotherapy treatment data). Questions remain regarding the length of time and dose of medication required during the maintenance phase.

To help close this information gap, the World Council of Anxiety (WCA) has prepared a series of articles based on their meeting held September 11, 2000 in Pisa, Italy. The articles provide a comprehensive, state-of-the-art review of the data on the effectiveness of long-term treatment for anxiety disorders. As few guidelines exist that offer recommendations for long-term treatment, this information may assist the practicing clinician in choosing the most appropriate long-term treatment options for each individual patient.

The five papers included in this supplement discuss the following anxiety disorders: obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, social phobia (social anxiety disorder), and generalized anxiety disorder.

Each article covers the following areas: clinical presentation; underlying biological substrates; clinical course, chronicity, and associated disability; diagnosis, including differential diagnosis; comorbidity and its complexity; acute to long-term treatment options, including pharmacotherapy, psychotherapy, and combination treatment; and at-a-glance tables of available treatment guidelines and trials.

In these five articles the authors review the available published literature on anxiety disorders, which was gathered by searching MEDLINE as of October 15, 2001. In developing these recommendations for the long-term treatment of anxiety disorders, the WCA relied on methodologically sound studies, ie, studies that were at least 24 weeks in duration and included a double-blind, randomized, placebo-controlled period. No open-label, naturalistic studies or case studies were considered for inclusion.

In addition to the published literature, studies described in congress abstracts from the following meetings held in 1999, 2000, and 2001 were included:

- American Psychiatric Association Annual Meeting, May 15–20, 1999, Washington, DC
- 11th World Congress of Psychiatry, August 6–11, 1999, Hamburg, Germany

TABLE. LONG-TERM RANDOMIZED CONTROLLED TREATMENT TRIALS OF PHARMACOTHERAPY FOR ANXIETY DISORDERS

Study Drug	Number of Studies	Authors	Year
Clomipramine	1	Katz et al[3]	1990
Fluoxetine	2	Tollefson et al[4]	1994
		Romano et al[5]	2001
Fluvoxamine	2	Cottraux et al[6]	1990
		Mallya et al[7]	1992
Sertraline	4	Greist et al[8]	1995
		Rasmussen et al[9]	1997
		Koran et al[10]	1999
		Bergeron et al[11]	2000
Citalopram	1	Lepola et al[12]	1998
Clomipramine	1	Fahy et al[13]	1992
Fluoxetine	1	Michelson et al[14]	1999
Paroxetine	2	Lydiard et al[15]	1998
		Lecrubier et al[16]	1997
Sertraline	1	Rapaport et al[17]	2001
Sertraline	2	Londborg et al[18]	2001
		Davidson et al[19]	2001
Clonazepam	1	Connor et al[20]	1998
Paroxetine	2	Hair et al[21]	2000
		Kumar et al[22]	1999
Sertraline	2	Walker et al[23]	2000
		Blomhoff et al[24]	2001
Clorazepate	1	Rickels et al[25]	1988
Venlafaxine extended-release	2	Allgulander et al[26]	2001
		Gelenberg et al[27]	2000
Paroxetine	1	Stocchi et al[28]	2001

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- 12th Congress of the European College of Neuropsychopharmacology, September 21–25, 1999, London, United Kingdom
- American Psychiatric Association Annual Meeting, May 13–18, 2000, Chicago, Illinois
- 22nd Collegium Internationale Neuropsychopharmacologicum Congress, July 9–13, 2000, Brussels, Belgium
- 13th Congress of the European College of Neuropsychopharmacology, September 9–13, 2000, Munich, Germany
- American Psychiatric Association Annual Meeting, May 5–10, 2001, New Orleans, Louisiana
- World Congress of Biological Psychiatry Biennial Meeting, July 1–6, Berlin, Germany

We hope that this supplement contributes to an increased awareness and understanding of anxiety disorders. Specifically, by helping clinicians and patients recognize the importance of extended treatment, we hope to improve the long-term management of anxiety disorders. CNS

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WCA Recommendations for the Long-Term Treatment of Obsessive-Compulsive Disorder in Adults

By John H. Greist, MD, Borwin Bandelow, MD, Eric Hollander, MD, Donatella Marazziti, MD, Stuart A. Montgomery, MD, David J. Nutt, MD, FRCP, FRCPsych, FMedSci, Ahmed Okasha, MD, PhD, FRCP, FRCPsych, FACP, Richard P. Swinson, MD, FRCPC, FRCPsych, DPM, and Joseph Zohar, MD

FOCUS POINTS

- Both psychotherapy and pharmacotherapy are recommended for the treatment of obsessive-compulsive disorder (OCD).
- Selective serotonin reuptake inhibitors (SSRIs) are considered first line in the pharmacotherapy of OCD.
- Acute and long-term efficacy has been shown with clomipramine, fluvoxamine, fluoxetine, and sertraline.
- Guidelines recommend maintenance pharmacological therapy for a minimum of 1–2 years.
- Despite the availability of SSRIs, many patients remain treatment-resistant or refractory.

ABSTRACT

What are the latest psychotherapeutic and pharmacotherapeutic treatment recommendations for obsessive-compulsive disorder (OCD)? OCD is a relatively common disorder with a lifetime prevalence of ~2% in the general population. It often has an early onset, usually in childhood or adolescence, and frequently becomes chronic and disabling if left untreated. High associated healthcare utilization and costs, and reduced productivity resulting in loss of earning, pose a huge economic burden to OCD patients and their families, employers, and society. OCD is characterized by the presence of obsessions and compulsions that are time-consuming, cause marked distress, or significantly interfere with a person's functioning. Most patients with OCD experience symptoms throughout their lives and benefit from long-term treatment. Both psychotherapy and pharmacotherapy are recommended, either alone or in combination, for the treatment of OCD. Cognitive-behavioral therapy is the psychotherapy of choice. Pharmacologic treatment options include the tricyclic antidepressant clomipramine and the selective serotonin reuptake inhibitors (SSRIs) citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. These have all shown benefit in acute treatment trials; clomipramine, fluvoxamine, fluoxetine, and sertraline have also demonstrated benefit in long-term treatment trials (at least 24 weeks), and clomipramine, sertraline, and fluvoxamine have United States Food and Drug Administration approvals for use in children and adolescents. Available treatment guidelines recommend first-line use of an SSRI (ie, fluoxetine, fluvoxamine, paroxetine, sertraline, or citalopram) in preference to clomipramine, due to the latter's less favorable adverse-event profile. Further, pharmacotherapy for a minimum of 1–2 years is recommended before very gradual withdrawal may be considered.

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INTRODUCTION

Obsessive-compulsive disorder (OCD) is a chronic, debilitating disorder that causes substantial distress and has a negative impact on an individual's relationships and ability to work. Early accounts of OCD date from the 15th century, when symptoms resembling those of OCD were reported in a treatise on witchcraft.[1] William Shakespeare wrote of Lady Macbeth's compulsive washing, "It is an accustomed action with her, to seem this washing her hands. I have known her continue with this for a quarter of an hour."[2]

EPIDEMIOLOGY

Epidemiologic studies have shown that the lifetime prevalence of OCD in the general population is between 1% and 3%,[3,4] making OCD the sixth most common psychiatric disorder in the United States.[5] The gender ratio has been found to be approximately equal,[4,6] although among childhood OCD cases, males predominate.[6] In this regard, OCD is different from other anxiety disorders, which are more prevalent in females than in males. More than 80% of individuals date the onset of symptoms before 18 years of age.[7]

CLINICAL PRESENTATION

OCD is characterized by a range of obsessions and compulsions that are remarkably heterogeneous but stereotypic across the affected population.[6] Obsessions are recurrent or persistent thoughts, images, or impulses that the patient considers inappropriate and, therefore, struggles to ignore or suppress. In an effort to relieve the anxiety caused by the presence and intensity of these obsessions, the person feels compelled to perform specific repetitive behaviors or mental acts called rituals.[8] The most common obsessions include contamination; pathological doubt; aggressive, sexual, or somatic repetitive intrusive thoughts; and the need for

These recommendations are based on proceedings from the World Council of Anxiety meeting held September 11, 2000, in Pisa, Italy, and on guidelines and articles published in the medical literature through October 15, 2001.

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symmetry and precision. The most common compulsions evoke rituals of cleaning, checking, and counting.[6]

Most patients will have several obsessions and corresponding compulsions, although one particular pattern (symptom type) may predominate.[9] In addition, at different points in the course of their illness, patients report different problems as most prominent.[9] The patient usually recognizes that the obsessions and compulsions are excessive or unreasonable, which results in substantial distress. The compulsions of OCD, as opposed to those of addiction, are not considered pleasurable. They merely relieve anxiety associated with the obsession, albeit temporarily.

UNDERLYING BIOLOGICAL SUBSTRATES

Neuroanatomical Changes

A wealth of information from brain-imaging studies has become available that complement research in other areas and suggest the existence of an abnormal functioning neural circuitry specific to OCD. Overall, brain-imaging research provides evidence that the underlying dysfunction is likely to involve the prefrontal cortex-basal ganglia thalamic circuitry rather than any single region of the brain.[10]

Neurobiological Changes

It appears that serotonin dysfunction is involved in OCD. Evidence from early neurobiological and brain-imaging studies implicates serotonin (5-HT) receptor dysfunction in the pathogenesis of the disorder.[11] There is also evidence for the possible roles of dopaminergic dysfunction,[12] other neuropeptide abnormalities,[13] and infective immunological mechanisms.[10,14]

The Role of Serotonin

During the 1980s, abnormality of the serotonergic system and, in particular, hypersensitivity of postsynaptic 5-HT receptors remained the leading hypothesis for the underlying pathophysiology of OCD.[11] Clinical studies have demonstrated that antiobsessional activity was a function of serotonin reuptake inhibition.[15] Further support is derived from studies of markers and biological probes and from behavioral responses to serotonergic challenge:

- Treatment response is correlated with decreased 5-hydroxyindolacetic acid (5-HIAA) levels in the cerebrospinal fluid of OCD patients.[16]
- Studies have demonstrated that platelet 5-HT transporter dysfunction, serotonin concentrations, and monoamine oxidase activity are correlated with symptom severity and response to selective serotonin reuptake inhibitor (SSRI) treatment.[17-19]
- Neuroendocrine challenge tests suggest that 5-HT_1 receptors may be altered in OCD.[10]
- Behavioral or physiological responses have been observed following challenge with metachlorophenylpiperazine, a serotonergic agonist.[11]

CLINICAL COURSE, CHRONICITY, AND ASSOCIATED DISABILITY

Most patients with OCD experience persistent symptoms throughout their lives and require long-term treatment. If untreated, the natural course of OCD is usually chronic and often severe enough to have a significant impact on the lives of patients and their families, friends, employers, and society.[20] SSRIs and clomipramine are the mainstay of pharmacologic treatment of OCD and have been shown to significantly improve symptom severity, quality of life (QOL), and functioning. However, as many as 40% to 60% of patients with OCD may not achieve an adequate response with SSRI or clomipramine monotherapy, and may require additional/alternative treatment approaches.[21]

Quality of Life

A survey of 701 OCD patients found that OCD had a significant impact on QOL measures: 58% reported lower academic achievement; 64% reported lower career aspirations; and 40% reported inability to work, with an average loss of 2 years of wages.[20,22] Further, 62% of subjects reported having fewer friends or difficulty maintaining relationships following onset of OCD, and the majority (92%) experienced lowered self-esteem.[20] Of note, 13% of respondents attempted suicide secondary to OCD.[20] With treatment, 62% had improved overall QOL and 43% showed improved ability to study or work.[22]

Cost Implications

The vast majority of costs associated with OCD are indirect, resulting from job loss, absenteeism, and early retirement.[20] Direct treatment costs are comparatively small in part because many OCD patients never seek treatment and some who do are incorrectly diagnosed and receive ineffective treatment. Since OCD frequently manifests during childhood or adolescence, the potential loss of income over a lifetime is significant.[20] As with other psychiatric disorders, OCD is associated with high healthcare costs in those who do seek treatment. A survey by Hollander and colleagues[22] found that OCD sufferers who have sought treatment spent $4,000/year on outpatient provider costs and $1,500 on medication (in 1995 dollars). Subjects averaged lifetime hospitalization costs of $12,500, and one in four were hospitalized for OCD, which extrapolates to $5 billion in lifetime hospital costs for the total United States OCD population.[20,22] Furthermore, 28% of this patient population have received inappropriate treatment, resulting in an additional annual cost of approximately $2.2 billion.[20,22]

DIAGNOSIS

Currently, there are two sets of diagnostic criteria used to define OCD: the World Health Organization *International Classification of Diseases*, Tenth Revision (*ICD-10*) criteria[23] and the American Psychiatric Association *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*) criteria.[24] The essential characteristic of OCD is the presence of recurrent obsessive thoughts and compulsive acts, which are severe and take up many hours of the day or cause significant distress or impairment to the individual. These obsessions and compulsions are at some point recognized by the patient as excessive or unreasonable behavior.

ICD-10 classifies OCD as a stand-alone disorder within neurotic, stress-related, and somatoform disorders, whereas *DSM-IV* classifies OCD as one of a group of anxiety disorders.

Misdiagnosis of Obsessive-Compulsive Disorder

Despite high prevalence rates, OCD is still underdiagnosed and undertreated in both children and adults.[10] A survey of 701 OCD patients showed, on average, a 17-year delay between onset of symptoms and commencement of appropriate treatment.[20,22] The average age of onset was determined as 14.5 years, with professional help sought at 25 years of age, correct diagnosis made at 30 years of age, and appropriate treatment given at 31.5 years of age. The reasons for these low rates of detection and diagnosis may include the following:

- Patients often conceal their symptoms, which they may perceive to be shameful, unique, or perverse.[8]
- Symptoms may overlap with those of other psychiatric disorders,[20] which can lead to misdiagnosis and inadequate and/or inappropriate treatment.
- Traditionally, there has been a perception among professionals that OCD is a treatment-resistant condition.[8]

Comorbidity

Various conditions are frequently encountered as comorbid disorders with OCD. The most common comorbidity is major depressive disorder (MDD)[25]; up to two thirds of OCD patients have a lifetime comorbid major depressive illness.[6] After MDD, the most prevalent lifetime comorbid diagnoses reported in patients with OCD are: simple phobia (22%), social phobia (18%), eating disorder (17%), alcohol dependence (14%), panic disorder (12%), and Tourette's syndrome (7%).[26]

TREATMENT OPTIONS

A growing body of evidence supports the efficacious use of the SSRIs fluvoxamine, paroxetine, sertraline, citalopram, and fluoxetine, and the tricyclic antidepressant (TCA) clomipramine, for the treatment of OCD. Cognitive-behavioral therapy (CBT) provides short- and long-term efficacious treatments for OCD without drug side effects. However, because CBT is not widely available, long-term pharmacotherapy is now the usual treatment for OCD. For OCD refractory to CBT and SSRIs, neurosurgical treatment is sometimes helpful. Efficacy of treatments are typically evaluated in clinical trials using the following rating instruments:

- Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)
- National Institute of Mental Health Global Obsessive-Compulsive Rating Scale (NIMH-OC)
- Behavioral Avoidance Test (BAT)
- Maudsley Obsessive-Compulsive Inventory (MOC)
- Clinical Global Impression Scales: Severity (CGI-S) and Improvement (CGI-I)
- Patient's Global Impression Scale (PGI) and PGI-Improvement
- Obsessive-Compulsive Inventory

The 10 item Y-BOCS is the most widely used rating scale for measuring changes in OCD symptoms during pharmacological treatment. The total Y-BOCS score gives the range of severity for patients who have both obsessions and compulsions (0–7=subclinical; 8–15=mild; 16–23=moderate; 24–31=severe; 32–40=extreme). For those with only obsessions or compulsions, half of these score ranges correlate reasonably well with these severity descriptors.

PHARMACOTHERAPY

Acute Treatment Trials

Tricyclic Antidepressants

A growing body of evidence supports the efficacy of the TCA clomipramine for the treatment of OCD. Clomipramine, fluvoxamine, and sertraline have received indications for treatment of OCD in children and adolescents. Clomipramine was the first agent approved for treatment of OCD by the US Food and Drug Administration. In two studies, clomipramine treatment for 10 weeks was associated with significantly greater reductions in OCD symptoms in nondepressed patients (mean Y-BOCS reduction of 38% and 44%) compared with placebo (mean Y-BOCS reduction of 3% and 5%).[27] Side effects most frequently associated with clomipramine treatment include anticholinergic effects (dry mouth, constipation), postural dizziness, somnolence, weight gain,[28] and cardiovascular adverse effects (increase in standing heart rate, decrease in standing systolic blood pressure).[27]

The efficacy of clomipramine in the treatment of OCD is linked to its potency for inhibition of synaptic serotonin reuptake. This feature differentiates clomipramine from other available TCAs, which have effects on both noradrenergic and serotonergic reuptake, but are much less potent than the SSRIs in serotonergic reuptake blockade. Studies comparing clomipramine with nortriptyline, amitriptyline, imipramine, and desipramine have shown that while these TCAs treat depression effectively, they do not appear to have a specific effect on the symptoms of OCD.[8,29]

Selective Serotonin Reuptake Inhibitors

Paroxetine, sertraline, citalopram, clomipramine, fluoxetine, and fluvoxamine have demonstrated acute efficacy in OCD treatment trials lasting 4–12 weeks.[30,31] Clomipramine and the SSRIs fluoxetine, fluvoxamine, paroxetine, and sertraline are approved by the FDA for the treatment of OCD. An indirect comparison of the FDA registration data for clomipramine, paroxetine, fluvoxamine, and sertraline, found clomipramine more effective and as well tolerated.[32] Head-to-head comparisons of SSRIs to clomipramine generally show SSRIs to be equally effective and better tolerated.[33-36] Some of these studies have flawed designs that put clomipramine at a distinct disadvantage. In the study by Bisserbe and colleagues,[33] for example, clomipramine was started at double the recommended starting dose and produced more early dropouts than found in other studies using the recommended dose.

Long-Term Treatment Trials

OCD is a chronic condition that can cause significant disability and often requires long-term management.[37]

Symptoms are likely to recur within a few weeks of discontinuation of therapy.[38] Because long-term maintenance treatment is frequently necessary, it is recommended that practitioners prescribe agents that have established acute and long-term efficacy and a good tolerability profile, such as SSRIs. Several randomized, controlled trials (24 weeks) have been reported for each of the pharmacologic agents approved for OCD treatment (Table).[39-47] These treatments will be discussed in order of their approval to market in the US.

Clomipramine

Katz and colleagues[39] assessed the efficacy of clomipramine in OCD in a randomized controlled trial lasting >1 year. Patients (N=263) were randomized to receive double-blind clomipramine (100–300 mg/day) or placebo for 10 weeks. Responders to therapy (n=124) were then entered into a double-blind extension period for an additional 52 weeks. In the initial 10-week phase of the study, patients receiving clomipramine had clinically and statistically significant reductions in global severity of OCD. Efficacy of clomipramine was maintained in the extension period. At the end of the extension trial, more than one-half of those patients who received clomipramine had benefited to such a degree that their OCD symptoms (as assessed by NIMH-OC and CGI) no longer caused a significant interference in their lives. A high incidence of medical problems (adverse events or concomitant illness) was noted in the clomipramine-treated group, with 22.7% of clomipramine-treated patients versus 0% of placebo patients discontinuing treatment due to adverse events during the extension study.

Fluoxetine

Following a 13-week double-blind, placebo-controlled trial of three fixed doses of fluoxetine (20, 40, and 60 mg/day) in 274 OCD subjects,[40] treatment responders (n=76) were continued on blinded treatment, while acute fixed-dose nonresponders (n=198) began an open-label trial on their maximally tolerated dose (up to 80 mg/day) for an additional 24 weeks.[48] In the blinded extension study, at the end of the treatment period all three doses of fluoxetine were associated with further Y-BOCS improvement from baseline. Mean decreases from baseline to endpoint within the treatment group were statistically significant for the 60-mg dose only (P=.022). In the open-label study, subjects benefited from dose titration, with two thirds achieving a clinical response during the subsequent 24 weeks and more robust results seen at either 60- or 80-mg/day doses. Fluoxetine was well tolerated in both extension studies: 6% of subjects treated with fluoxetine in the responder extension discontinued due to adverse events.

A further study assessed the efficacy and safety of fluoxetine versus placebo in preventing relapse of OCD during 1 year of treatment.[42] Patients (N=130) were treated with single-blind fluoxetine (20, 40, or 60 mg/day) for 20 weeks. Responders (n=71) were then randomized to continue double-blind treatment with fluoxetine or placebo. Patients who received fluoxetine had numerically lower relapse rates over 52 weeks compared with those who received placebo, although the difference was not significant. Kaplan-Meier 1-year relapse rates were 20.6% for fluoxetine and 31.6% for placebo (P=.137). Single-dose comparisons showed that patients who continued treatment with fluoxetine 60 mg/day had significantly lower rates of relapse than those who were switched to placebo (P=.041). Fluoxetine was well tolerated over the 52-week study period.

Fluvoxamine

The efficacy of long-term treatment with fluvoxamine in OCD has been studied in two trials.[42,43] The first study involved 60 outpatients diagnosed with OCD. A secondary diagnosis of MDD was allowed if it had been preceded by obsessive-compulsive symptoms. Patients were randomized to receive fluvoxamine (up to 300 mg/day) with antiexposure therapy (F), fluvoxamine with exposure therapy (Fe), or placebo with exposure therapy (Pe) for 24 weeks.[42] Fe and Pe were double-blind while F was single-blind. Comparison of Fe with Pe tested the effectiveness of fluvoxamine while holding exposure constant. All three groups showed improvement in rituals and depression from week 0 to week 24, with a numeric superiority for combined treatment at week 24. Follow-up at 48 weeks (weeks 24 through 48 being drug-free) showed no between-group difference in rituals or depression.

In the second study, 39 OCD patients were randomized to receive double-blind fluvoxamine (50–300 mg/day) or placebo for 10 weeks.[43] Patients who completed the 10-week study period were then eligible to enter an open-label extension phase of active fluvoxamine treatment for 8–52 weeks. Among the 28 completers of the 10-week study, mean improvement in Y-BOCS was significantly greater in the fluvoxamine group than in the placebo group (33%±30% versus 5%±18%, respectively; P=.025). Twenty-one patients entered an open-label extension for 8–52 weeks, of which nine completed the total 52 weeks of treatment. Patients who previously received active drug treatment during the initial phase were continued on the same dose, while patients who previously received placebo were switched to fluvoxamine (titrated up to a maximum of 300 mg/day). Fifty-seven percent (n=12) of patients responded or maintained response to fluvoxamine in the open-label extension. However, seven of nine patients reported recurrence of OCD symptoms within a few days to weeks following discontinuation of fluvoxamine. The most common side effects during long-term treatment were sedation, tiredness, and anorgasmia.

Sertraline

Sertraline has been extensively studied in the long-term treatment (up to 2 years) of OCD. Greist and colleagues[44] studied the efficacy of sertraline in a 1-year placebo-controlled randomized trial. The study began with a 12-week phase of fixed-dose sertraline treatment (50, 100, or 200 mg/day) or placebo, after which treatment responders (N=118, including placebo patients) were offered an additional 40 weeks of double-blind treatment at previously assigned doses. At the end of the study, the pooled sertraline group exhibited significantly greater improvement

than the placebo group on all efficacy measures (Y-BOCS, NIMH-OC, CGI-S, and MOC). Furthermore, pairwise analysis revealed a significant effect on all three investigator-rated scales for patients receiving 50 or 200 mg/day of sertraline; in the 100-mg/day group there was a significant effect on the NIMH-OC. Sertraline was well tolerated; during the initial phase, 10% of patients withdrew from the study due adverse events (compared with 6% of placebo-treated patients), and only an additional 4% of patients stopped treatment due to adverse events (versus 5% for placebo) during the 40-week continuation phase. At 1 year of randomized treatment, responders were then offered another year of sertraline treatment (50–200 mg/day) in an open-label extension study.[45] The 38 patients who completed a full 2 years of treatment with sertraline exhibited a mean improvement of 15.6 points on the Y-BOCS. Patients exhibited significant improvement in OCD symptoms during open sertraline treatment as assessed by Y-BOCS, NIMH-OC, and CGI-S ($P<.05$). Long-term sertraline treatment did not appear to be associated with the emergence, increased incidence, or increased severity of adverse events, or with clinically significant abnormalities in laboratory tests, vital signs, or electrocardiogram.

In the sertraline relapse-prevention study, adults with OCD who had responded to 52 weeks of open-label treatment with sertraline (50–200 mg/day) were randomized to 28 weeks of double-blind, placebo-controlled treatment (N=232).[49] Significantly fewer discontinuations due to relapse or insufficient clinical response occurred in sertraline-treated patients (9%) compared with placebo-treated patients (24%) during the placebo-controlled 28-week phase ($P=.004$). At the end of the randomized study, sertraline was found to be significantly superior to placebo in preventing an acute exacerbation of OCD (rates of exacerbation measured as 12% versus 35%, respectively; $P=.001$) and in maintaining improvements in Y-BOCS, NIMH-OC, CGI-S, and CGI-I scores.[47] Sertraline was also significantly superior to placebo in maintaining improvements in QOL, as measured by the patient-rated Quality of Life Enjoyment and Satisfaction Questionnaire. Sertraline was well tolerated; 13.3% of subjects discontinued the study due to adverse events during the open-label 52-week phase, while 5% of sertraline subjects and 11% of placebo subjects discontinued for these reasons during the 28-week double-blind phase.[47]

Few studies have directly compared different SSRIs in the treatment of OCD. In a 24-week study comparing sertraline (50–200 mg/day) and fluoxetine (20–80 mg/day) for the treatment of OCD,[50] equivalent and significant improvements ($P<.001$) in Y-BOCS and NIMH-OC scores were observed for both sertraline and fluoxetine. However, patients treated with sertraline were 42% more likely to have achieved a response by week 12 than those treated with fluoxetine. Moreover, sertraline treatment was associated with a higher percentage of patients in remission (CGI <2 and Y-BOCS <11) at weeks 12 ($P=.047$) and 24 ($P=.075$).

Paroxetine

There are no published data for the long-term treatment of OCD with paroxetine. A study was presented at the American College of Neuropsychopharmacology meeting in 2000, but citations are not permitted.

Citalopram

To date, only short-term, open-label trials of citalopram in OCD patients who did not respond to one or more SSRIs have been reported.[30,31]

Augmentation

There is insufficient systematic research on the use of pharmacologic augmentation for treatment-refractory OCD patients. Two placebo-controlled trials of lithium augmentation of SSRIs and three placebo-controlled trials of buspirone augmentation of SSRIs found lithium and buspirone to be no more efficacious than placebo. Greater efficacy was obtained by adding risperidone to an SSRI or clomipramine in patients who failed to respond to monotherapy in an open trial.[21] This result was corroborated in a double-blind, placebo-controlled trial.[46] In another trial, response to risperidone augmentation appeared to be influenced by symptom subtypes and comorbid conditions: patients with horrific mental imagery had the strongest and fastest response, and patients with comorbid psychotic disorders improved gradually over 2–3 weeks.[51] Risperidone was associated with a high rate of adverse events that led to discontinuation in 24% of patients.[21,52] Preliminary results of a double-blind, placebo-controlled crossover trial of risperidone (1 mg/day) versus haloperidol (2 mg/day) augmentation in SSRI-refractory OCD patients for 9 weeks suggest that patients show more clinical benefit with risperidone and improved performance on cognitive tasks.[53] Most patients were unable to tolerate haloperidol or experienced considerable side effects.

The addition of sertraline after 6 months of failed clomipramine treatment has been shown to improve patient response considerably.[54] A significant decrease in mean global Y-BOCS score was observed in patients treated with clomipramine and sertraline. Although increasing the dose of clomipramine was as effective as the addition of sertraline to the lower dose, there were increased side effects leading to higher rates of discontinuation.

Treatment of Comorbid Disorders

Depression and OCD

In the only double-blind study of sufficient size to assess the efficacy of antidepressants in the treatment of OCD with concurrent MDD, sertraline-treated patients were significantly better at endpoint on measures of OCD and MDD symptoms compared with those treated with desipramine (a norepinephrine reuptake inhibitor) after 12 weeks of treatment.[29] Sertraline-treated patients were also significantly more likely to achieve a robust improvement in OCD symptoms (40% reduction in baseline Y-BOCS). More patients receiving desipramine than sertraline discontinued treatment due to adverse events.

Tic Disorder and OCD

For OCD accompanied by a tic disorder, small doses of pimozide or haloperidol, in addition to the serotonergic drug, are associated with a higher therapeutic response.[55]

Schizophrenia and OCD

If a patient has both schizophrenia and OCD, the addition of antiobsessive treatment to the ongoing antipsychotic therapy may be useful.[56] This combination has been associated with a somewhat better outcome in some patients who are otherwise difficult to treat. The role of mixed dopaminergic and serotonergic blockers, such as risperidone, in this subset of patients has not been studied systematically. The pharmacologic profile of these medications and some open reports in this area suggest that this group of medications (ie, atypical neuroleptics) may be useful.

PSYCHOTHERAPY

Cognitive-Behavioral Therapy

CBT provides short- and long-term efficacious treatment for OCD and avoids drug side effects. However, because CBT is not widely available, long-term pharmacotherapy is now the usual treatment for OCD. The refinement (first described by Meyer in 1966[57]) of behavioral therapies such as exposure and ritual prevention therapy (the field has adopted "ritual prevention" as a clearer description of what is done rather than "response prevention") in the early 1970s

TABLE. LONG-TERM TREATMENT TRIALS OF PHARMACOTHERAPY FOR OCD

Authors (Year)	N	Study Drug	Comparator	Study design
Katz et al (1990)[39]	263 entered, 124 continued	Clomipramine	Placebo	RCT → RCT extension
Tollefson et al (1994)[40]	274 entered; 76 responders continued RCT; 198 switched to OL dose titration	Fluoxetine	Placebo	RCT fixed dose → RCT continuation or switch to OL dose titration
Romano et al (2001)[41]	130 entered OL; 71 responders randomized	Fluoxetine	Placebo	OL flexible dose → RCT
Cottraux et al (1990)[42]	60 entered	Fluvoxamine+ exposure therapy; fluvoxamine+ antiexposure therapy	Placebo+ exposure therapy	RCT
Mallya et al (1992)[43]	39 entered RCT; 21 continued OL treatment	Fluvoxamine	Placebo	RCT → OL
Greist et al (1995)[44]	325 entered; 118 continued	Sertraline	Placebo	RCT → RCT continuation
Rasmusson et al (1997)[45]	59 entered; continuation of Greist et al (1995)[44]	Sertraline		→ OL extension prior to 52-week RCT
Bergeron et al (2000)[46]	150 entered RCT	Sertraline	Fluoxetine	RCT
Koran et al (1999)[47]	649 entered; 224 randomized	Sertraline	Placebo	OL → RCT

OCD=obsessive-compulsive disorder; RCT=randomized controlled trial; wks=weeks; OL=off-label; NIMH-OC=National Institute of Mental Health Global Obsessive-Compulsive rating scale; PGI=Patient's Global Impression Scale; HDRS=Hamilton Depression Rating Scale; Y-BOCS=Yale-Brown Obsessive Compulsive Scale; CGI-S=Clinical Global Impression-Severity; AEs=adverse events; CGI-I=Clinical Global Impression-Improvement; BAT=Behavioral Avoidance Test;

resulted in the first empirically validated treatment for OCD.[58] Until that time, OCD was believed to be refractory to psychotherapy and carried a poor prognosis.[58] Treatments such as psychodynamic therapy, which focused on the meaning of obsessions and compulsions, had not been successful. The efficacy of exposure and ritual prevention, which focus on compulsive behaviors as treatment targets, has been well documented over the past 2 decades.[58]

Behavioral Therapy

Behavioral therapy (ie, exposure in vivo and ritual prevention in particular), if tolerable to patients, is one of the most effective therapies for OCD.[59] It involves exposing the person to a situation that provokes the ritual while asking the person to forgo ritualizing. Behavioral therapy may be of great benefit to the patient, resulting in the maintenance of a clinical response after therapy is discontinued.[60]

The reported success of behavioral treatments in significantly reducing OCD symptoms is 20% to 60% in eligible patients.[61] As with medication treatment, success depends, in part, on the clinical severity of the problem and whether the patient has a comorbid Axis I disorder and/or personality disorder. Patients with comorbid severe depression seldom respond to behavioral therapy alone.[60] The major obstacle to successful outcomes with behavioral therapy is poor compliance or adherence. About 15% of patients find the prospect

Study Duration	Main Efficacy Variables	Efficacy Outcome	Tolerability Outcome
10 wks+52 wks	NIMH-OC PGI HDRS score	>Placebo	Discontinuations due to medical problems in extension: 22.7% clomipramine; 0% placebo
13 wks RCT+ 24 wks OL	Y-BOCS CGI-S CGI-I PGI	>Placebo	5% of responders in RCT extension discontinued due to adverse events
20 wks OL+ 52 wks RCT	Y-BOCS CGI-S CGI-I PGI	No significant difference in relapse rate versus placebo overall (only significant for patients on a 60-mg/day dose at start of RCT)	No clinically significant differences in AEs, vital signs, or laboratory values between fluoxetine and placebo in 52-wk phase
24 wks	BAT target ritual score: time, discomfort, duration per day	=Placebo+exposure	7% of fluvoxamine-treated patients withdrew due to drug-related side effects
10 wks RCT+ 8–52 wks OL	Y-BOCS	57% of patients improved in OL trial	Most common adverse events were sedation, tiredness, anorgasmia
12 wks RCT+ 40 wks RCT continuation	Y-BOCS NIMH-OC CGI-S MOC	>Placebo (RCT continuation study)	No statistically significant differences between sertraline and placebo groups in incidence of vital sign or laboratory abnormalities during RCT continuation
52 wks OL extension	Y-BOCS NIMH-OC CGI-S CGI-I	Mean improvement of 15.6 points on Y-BOCS for patients completing 2 years of treatment	Sertraline was well tolerated; adverse events decreased during second year of treatment
24 wks	Y-BOCS NIMH-OC CGI-S CGI-I	=Fluoxetine	No statistically significant difference in incidence of adverse events
52 wks OL sertraline+ 28 wks RCT	Y-BOCS NIMH-OC CGI-S CGI-I Q-LES-Q	>Placebo	No statistically significant difference in incidence of adverse events, laboratory or vital sign abnormalities

MOC=Maudsley Obsessive-Compulsive Inventory; Q-LES-Q=Quality of Life Enjoyment and Satisfaction Questionnaire.

Greist JH, Bandelow B, Hollander E, et al. *CNS Spectrums.* Vol 8, No 8 (suppl 1). 2003.

of exposure and ritual prevention too frightening and refuse it outright.[60] Approximately 10% of patients who try behavioral therapy find that it engenders so much anxiety that they discontinue treatment.[60] However, the 75% adherence rate with behavior therapy is at least as high as that reported with pharmacotherapy, which should be continued for 1–2 years to reduce the risk of relapse that occurs rapidly with shorter durations of treatment. Patients with severe depression rarely respond to behavioral therapy alone and need direct intervention, such as antidepressants or electroconvulsive therapy.[60]

Relapse is reported in about 30% of behavioral therapy cases.[61] However, a maintenance program, following an intensive program of exposure and ritual prevention and cognitive therapy (CT), has proven effective in preventing relapse for up to 2 years posttreatment in a small population of patients.[62] Patients maintained their gains for the 2-year follow-up period on measures of anxiety associated with avoidance, obsessions, compulsions, and anxiety. Further, patients were able to effectively manage relapses without additional therapist intervention.[61]

Several meta-analyses have suggested behavioral therapy to be at least as effective as pharmacotherapy.[63-65] A single meta-analysis by Kobak and colleagues[58] found no significant difference between exposure and ritual prevention therapy and pharmacotherapy with SSRIs or clomipramine.

In a recent long-term, follow-up study of the effect of behavioral therapy with pharmacologic treatment in patients with OCD, Alonso and colleagues[66] observed greater, but not statistically significant, reductions in both Y-BOCS global (44%±27%) and obsessions subscale (41%±27%) scores in patients who completed behavioral therapy. However, these patients showed significantly greater improvement in the compulsions subscale (P=.01).

Cognitive Therapy

CT has also been found to be effective in treating patients with OCD. However, in research and clinical use, cognitive and behavioral techniques are almost always used in combination as CBT.[59] The general strategies of CBT are: consider the intrusive obsessional thoughts as stimuli; identify the distressing thoughts; challenge these automatic thoughts; and change these thoughts to nondistressing thoughts, while making sure the patient does not avoid the obsessive thoughts as such avoidance is a form of antiexposure which has been shown to worsen OCD. The underlying dysfunctional assumptions are also identified and challenged in therapy sessions and the patient continues these exercises as homework assignments.[65]

COMBINING PSYCHOTHERAPY AND PHARMACOTHERAPY

A meta-analysis by Kobak and colleagues[58] found that treatment with exposure and response prevention and an SSRI or clomipramine had a greater effect than either treatment alone, but the differences were not statistically significant. Most clinicians believe that a treatment approach combining exposure and ritual prevention and pharmacotherapy is the best course of action, although the limited availability of trained behavioral therapists makes this treatment difficult to administer on a large scale.[58]

OVERVIEW OF AVAILABLE TREATMENT GUIDELINES

Expert Consensus Guidelines for the treatment of OCD were published in 1997.[67] The recommended initial treatment of choice is either CBT alone or in combination with an SSRI or clomipramine. The likelihood that medication will be included in the recommendation depends on the severity of the OCD and the age of the patient. In mild OCD, CBT alone is the initial choice, as it is for younger patients. Combination treatment was rated best by experts in terms of efficacy, speed, durability, tolerability, and acceptability, suggesting that overall it may be the most successful treatment approach for the majority of patients.

In terms of psychotherapy, experts consider the combination of exposure and ritual prevention and CBT as the optimal behavioral therapy for OCD. Regarding pharmacotherapy, both SSRIs and clomipramine are the recommended treatment options, although the guidelines note that SSRIs are associated with fewer adverse events than clomipramine. If there is no response to first-line treatment with either an SSRI or CBT alone, a combination of both treatment strategies is the preferred option. If there is no response to combination therapy, switching SSRIs and continuing CBT is recommended. In patients with a partial response to combination therapy, switching SSRIs, providing more CBT, or possibly augmenting treatment with another medication is recommended.

Once patients have responded to acute-phase treatment for OCD, a maintenance phase of continued pharmacotherapy with monthly follow-up visits for a minimum of 3–6 months is recommended. It is highly recommended that pharmacotherapy be continued for extended periods of time. One or two years are often needed, and much longer periods are usually required most of the time. Booster CBT sessions may help reduce the risk of relapse while medication is being titrated downward and possibly withdrawn. Long-term or lifelong prophylactic maintenance medication is recommended after two to four severe relapses, or three to four mild-to-moderate relapses.

CONCLUSION

OCD is a common disorder that has a profound effect on patient QOL and is associated with significant impairment in social and occupational functioning. Both psychotherapy (ie, CBT) and pharmacotherapy, separately or in combination, are recommended to treat the symptoms of OCD. Pharmacotherapies that target serotonergic mechanisms-including clomipramine and the SSRIs sertraline, citalopram, fluoxetine, fluvoxamine, and paroxetine are recommended first-line treatment for OCD. The

SSRIs fluoxetine, fluvoxamine, and sertraline, and the TCA clomipramine, have demonstrated efficacy in published long-term treatment trials (6 months). Current guidelines recommend that pharmacotherapy of OCD be continued for a minimum of 1–2 years in treatment-responsive individuals. In the event of relapse due to treatment withdrawal, lifelong prophylactic maintenance medication may be necessary. Further studies are required to determine the optimal duration of long-term pharmacotherapy for OCD. Finally, despite the number of available treatments, many patients remain treatment-resistant and treatment-refractory. Additional research is needed to identify better treatment and management strategies for refractory OCD. CNS

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WCA Recommendations for the Long-Term Treatment of Panic Disorder

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FOCUS POINTS

- Selective serotonin reuptake inhibitors are currently the first-choice drugs in the treatment of panic disorder with or without agoraphobia.
- Paroxetine, sertraline, citalopram, clomipramine, alprazolam, fluoxetine, and clonazepam have an approved indication for panic disorder in Europe and/or the United States.
- Long-term pharmacologic treatment of panic disorder is safe and effective in accruing continued improvement, maintaining benefit, and preventing relapse.
- Cognitive-behavioral therapy, alone or in combination with drug therapy, is an effective treatment for panic disorder.

ABSTRACT

What are the symptoms of panic disorder and how is the disorder most effectively treated? One of the most commonly encountered anxiety disorders in the primary care setting, panic disorder is a chronic and debilitating illness. The core symptoms are recurrent panic attacks coupled with anticipatory anxiety and phobic avoidance, which together impair the patient's professional, social, and familial functioning. Patients with panic disorder have medically unexplained symptoms that lead to overutilization of healthcare services. Panic disorder is often comorbid with agoraphobia and major depression, and patients may be at increased risk of cardiovascular disease and, possibly, suicide. Research into the optimal treatment of this disorder has been undertaken in the past 2 decades, and numerous randomized, controlled trials have been published. Selective serotonin reuptake inhibitors have emerged as the most favorable treatment, as they have a beneficial side-effect profile, are relatively safe (even if taken in overdose), and do not produce physical dependency. High-potency benzodiazepines, reversible monoamine oxidase inhibitors, and tricyclic antidepressants have also shown antipanic efficacy. In addition, cognitive-behavioral therapy has demonstrated efficacy in the acute and long-term treatment of panic disorder. An integrated treatment approach that combines pharmacotherapy with cognitive-behavioral therapy may provide the best treatment. Long-term efficacy and ease of use are important considerations in treatment selection, as maintenance treatment is recommended for at least 12–24 months, and in some cases, indefinitely.

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INTRODUCTION

Panic disorder was first defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (*DSM-III*) in 1980.[1] Panic attacks are accompanied by distressing anticipatory anxiety and often agoraphobia. This disorder shows a chronic course associated with distress and disability. Patients with panic disorder report impairment in social, marital, and vocational functioning.[2] Panic disorder, which is frequently comorbid with other psychiatric disorders, is associated with increased medical resource utilization, premature mortality, and reduction in quality of life.[2] The dramatic presentation of panic disorder and the efficacy of both psychosocial and pharmacologic treatments have made it the focus of extensive treatment and nosologic research.[3]

CLINICAL PRESENTATION

Panic disorder is characterized by recurrent panic attacks, along with fearful anticipation of panic or the frightening consequences or implications of these attacks.[2,4] Panic attacks, presenting as sudden-onset episodes of intense fear or anxiety accompanied by rapidly peaking symptoms of cognitive and autonomic arousal,[2,4-6] occur at seemingly random intervals[7] and can occur during sleep.[8] Panic attacks can also occur in an attenuated form called limited-symptom episodes. Agoraphobia is a frequent complication of panic disorder.[4] The anticipation of panic attacks often leads to agoraphobic symptoms: anxiety about panic disorder symptoms appearing in situations where attacks previously occurred, or from which escape or getting help in the event of an attack may be difficult. Epidemiologic surveys suggest that approximately one third of patients with panic disorder develop comorbid agoraphobia,[9,10] in clinical samples this proportion is about 80%.[11] Panic disorder in the absence of agoraphobia is sometimes referred to as uncomplicated panic disorder.

The following five principal symptom domains of panic disorder have been identified: panic attacks, including limited-symptom episodes; anticipatory anxiety; panic-related phobias (including agoraphobia and body-sensation phobias); well-being/overall severity of illness; and functional disability (including work, social, and family functioning).

Symptoms of Panic Attacks

The symptoms of a panic attack include heart palpitations, pounding heart, or accelerated heart rate; sweating; trembling or shaking; sensations of shortness of breath or of being smothered; feeling of choking; chest pain or discomfort; nausea or abdominal distress; feeling dizzy, unsteady,

These recommendations are based on proceedings from the World Council of Anxiety meeting held September 11, 2000, in Pisa, Italy, and on guidelines and articles published in the medical literature through October 15, 2001.

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light-headed, or faint; derealization (feelings of unreality) or depersonalization (feeling detached from oneself); fear of losing control or of going crazy; fear of dying; paresthesia (numbness or tingling sensations); and chills or hot flashes.[5]

Data suggest the existence of a prodromal phase of panic disorder in some patients, ie, a time interval between the onset of prodromal symptoms and the onset of the characteristic manifestations of the fully developed illness.[8]

In addition to anticipatory anxiety, most patients with panic disorder present with somatic symptoms, especially cardiac, gastrointestinal, or neurologic complaints.[12]

DIFFERENTIAL DIAGNOSIS

Due to the presence of nonspecific somatic symptomatology, when establishing the diagnosis of panic disorder, physicians must consider other medical conditions, mental disorders, and physiologic causes that may mimic panic attacks. Misdiagnosis of patients with panic disorder is frequent and is associated with considerable economic and social impact.[13] Many of the symptoms of panic disorder are also cardinal features of cardiovascular diseases.[14] Patients with panic disorder may initially present to emergency care complaining of acute chest pain or other cardiovascular symptoms. Such patients then undergo costly, invasive cardiac testing.[14] At least one third of the 20% to 30% of patients who undergo angiography to evaluate chest pain are found to have normal coronary arteries.[15]

Although many patients with panic disorder are misdiagnosed as cardiac cases, there is some evidence that panic disorder may be linked with cardiovascular disease.[14] The prevalence of panic disorder in both cardiology outpatients and patients with documented cardiovascular disease ranges from 10% to 50%.[14] Men with panic disorder have been shown to have an excess number of deaths due to circulatory system disease.[16] The risk for stroke in individuals with a lifetime diagnosis of panic disorder could be higher than that for individuals with other psychiatric disorders or with no other psychiatric disorder.[16] Similarly, patients with panic disorder appear to be at greater risk for hypertension and myocardial infarction than individuals with no other psychiatric disorder.[17,18] In addition, there are preliminary data linking panic disorder to reduced heart rate variability, which may predispose persons with panic disorder to the development of malignant arrhythmias.[14]

Panic disorder also shares a number of symptoms with asthma, such as dyspnea, choking, sensations of being smothered, and chest pain. Respiratory factors of this type play an important role in panic disorder, and the majority of panic-disorder patients experience breathing-related problems. This makes diagnosing panic disorder in the presence of asthma a challenge. More than one in five individuals with asthma report having experienced panic attacks.[19]

Other Anxiety and Mood Disorders

Panic attacks may be experienced in several anxiety disorders, either as a response to specific triggers or as part of a complicated pattern of comorbid conditions. It is therefore important to determine whether panic attacks are not better accounted for by another anxiety disorder, such as social anxiety disorder (SAD), which occurs on exposure to feared social situations; specific phobia, which is limited to a single situation, eg, elevators; obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD); or generalized anxiety disorder (GAD). In addition, panic attacks may occur in the context of depressive and bipolar disorders.

EPIDEMIOLOGY

General population surveys have estimated the lifetime prevalence of panic disorder to be between 1% and 4%.[3,10,20] A World Health Organization survey of 15 worldwide sites estimated the average current prevalence at 1.1%,[21] and the Epidemiologic Catchment Area study identified panic disorder in 1.4% to 8% of primary care patients.[12] Lifetime rates of uncomplicated panic disorder are considerably lower than rates of panic disorder complicated by comorbid psychiatric conditions.[22] Recurring panic attacks not meeting full diagnostic criteria for panic disorder also have a relatively high lifetime prevalence (3.6% in a study of 18,000 adults in the United States), and subsyndromal panic is associated with significant morbidity and disability as well.[23] The prevalence of panic disorder is greatest in the 25- to 44-year-old age group.[3] It is more prevalent in women than in men, by a factor of at least 2-fold.[3,10,20,24,25]

In clinical samples of patients with panic disorder, four of five typically also have agoraphobia,[11] whereas in samples of the general population, the proportion tends to be lower. In the US National Comorbidity Survey, 50% of survey respondents with panic disorder reported no symptoms of agoraphobia,[20] and in another, smaller community study in the US, the ratio was closer to 1:3.[9,23]

CLINICAL COURSE

The course of panic disorder is not uniform,[26] but typically follows a chronic, recurrent, and usually debilitating course, with relapses after remission.[2,27] The mean age of onset tends to be in early to middle adulthood (~20–30 years of age), though it can date back to childhood.[2,10,17,28] Patients with early-onset panic disorder have a longer duration of illness than later-onset patients and are more likely to have other psychiatric comorbidities.[29]

The course of illness of panic disorder appears to be different for men than it is for women. Men and women are equally likely to experience remission of panic disorder during naturalistic follow-up, but in a 5-year, prospective, follow-up study, the rate of symptom recurrence in women was nearly double the rate in men.[30]

Follow-up studies of up to 20 years' duration have demonstrated low rates of remission and poor long-term outcome, suggesting that full remission of panic disorder might occur in only 10% to 35% of patients who have undergone clinical treatment.[3,9,20,24,30-32] However, patient samples derived from treatment settings may constitute a

sample biased toward the more severely ill, who may have waited many years before receiving specialized clinical treatment.[23] A comparison of 1-month and lifetime prevalence data in epidemiologic studies suggests that the remission rate in general population samples may be greater. These studies show that at least 60% of those with panic disorder at some period of their lives did not experience symptoms in the month before being interviewed.[3,20,23,24]

Long duration of illness and agoraphobia at baseline, and not the severity and frequency of panic attacks, appear to predict an unfavorable course.[9,30,32] At 1 year, patients with uncomplicated panic disorder were more than twice as likely to achieve full remission than patients with panic disorder complicated by agoraphobia.[27]

SOCIAL AND HEALTH CONSEQUENCES

Panic disorder is associated with pervasive social and health consequences similar to or greater than those associated with major depression.[13,33] The often chronic course of panic disorder is associated with quality-of-life impairment,[34] as well as subjective poor physical and emotional health, substance abuse, increased likelihood of suicide attempts, lower educational achievement,[20] higher likelihood of unemployment and low work productivity,[34] impaired social and marital functioning, and financial dependency that cannot be attributable solely to comorbidity with other psychiatric disorders.[33]

Patients with panic disorder are particularly high users of healthcare services[12] and visit more specialists than patients with other anxiety disorders.[13] Studies suggest that approximately one third of patients with panic disorder visit three or more healthcare specialists per year.[13,35] Almost one fifth of patients with panic disorder had visited a general hospital emergency department and one in ten had been hospitalized at some point for anxiety complaints.[35] More than 40% of panic disorder patients use both psychiatric and medical services, compared with 4% of the general population.[33] Nearly 30% of patients with panic disorder have been assessed by a cardiologist or a neurologist or both.[35] They also see otolaryngologists, obstetricians-gynecologists, and urologists more frequently than subjects with other psychiatric disorders.[13]

SUICIDE

Panic disorder and panic attacks are associated with an elevated risk of suicidal ideation and suicide attempts. The lifetime rate of suicide attempts in patients with panic disorder is ~20%,[16,22,36,37] which is similar to that of subjects with major depression.[22] The comorbid conditions of depression, alcohol abuse, and personality disorders appear to be the main risk factors associated with risk of death from suicide attempts.[22,38]

In a clinical sample of 100 outpatients with panic disorder, Lepine and colleagues[39] found that 42% had a history of suicide attempts. Patients who had attempted suicide were significantly more likely to have suffered from a major depressive episode and alcohol or other substance abuse in their lifetime, compared with those who did not attempt suicide. Lecrubier and Ustun[21] showed that, among patients with comorbid panic disorder and depression, 43% had a history of suicide attempts.

COMORBIDITY

Panic disorder complicated by other psychiatric conditions is more common than panic disorder alone.[21] Patients with uncomplicated panic disorder represent fewer than one third of all patients with panic disorder,[22] and ~25% of patients with panic disorder complicated by other psychiatric conditions are likely to develop an additional first-onset disorder within 1 year of follow-up.[22] The presence of comorbidity results in more severe anxiety and depressive symptoms, higher rate of suicide attempts, higher frequency of other comorbid conditions, and poorer treatment response and compliance than in patients with panic disorder alone.[21] Comorbidity is also associated with worse outcomes on selected measures of symptomatic and functional impairment.[40]

There is an association between panic disorder and depression. Between one third and two thirds of patients with lifetime panic disorder have or have had at least one major depressive episode.[23,28,35,40,41] Patients with agoraphobia have rates of depression comparable to patients with uncomplicated panic disorder.[28] Patients with a longer duration of illness, low self-reported assertiveness, early-onset depression, melancholic depression, or family histories of anxiety or depression are more likely to experience recurrent depression.[28] Rates of panic disorder are also elevated in patients with bipolar disorder.[41,42]

In clinical populations, nearly one in three patients with panic disorder also meets the diagnostic criteria for social anxiety disorder.[43] This comorbidity is associated with an increased likelihood of developing major depression.[28] Other anxiety disorders associated with panic disorder include OCD, PTSD, and GAD; personality disorders and alcohol or other drug dependence or abuse also frequently complicate the clinical picture.

Although comorbidity of any type may occur in either men or women with panic disorder, there is a tendency toward higher comorbidity rates in women for specific phobia, GAD, manic-depressive episodes, and dysthymia. Men have a tendency for higher comorbidity rates for SAD and hypochondria, and are significantly more likely to have a history of alcohol dependence or abuse.[24]

PREDISPOSING FACTORS

Both heritable factors and stressful life events, particularly in early childhood, are conducive to onset of panic disorder.[7] Panic disorder is familial; it has its basis in an unusually sensitive fear network, with the central nucleus of the amygdala playing a significant role.[7] Disrupted emotional attachments with significant caregivers during childhood have been identified as a potential risk factor.[7] The onset of panic disorder may also be precipitated by exposure to drugs (eg, cocaine, marijuana, or amphetamines) or alcohol use or withdrawal.[44]

The pathophysiology of panic disorder and the neurobiologic basis of panic attacks have been the focus of much research. Some of the proposed hypotheses of neurobiologic dysfunctions involve the classic neurotransmitter systems, such as norepinephrine, γ-aminobutyric acid, serotonin, and the peptide cholecystokinin.[7,8,45-50]

ASSESSMENT

An extensive range of clinician-based and self-report rating scales have been used in selecting treatment options for panic disorder. Currently, the most frequently used measures are the panic diary (panic attack frequency), Clinical Global Impression (CGI) scale,[51] Hamilton Rating Scale for Anxiety (HAM-A),[52] Hamilton Rating Scale for Depression (HAM-D),[53] Marks-Sheehan Phobia Scale,[54] and the Panic Associated Symptom Scale.[55]

Several recently developed scales of panic disorder severity assess all five of the key domains that reduce quality of life in a single measure. Examples include the Panic Disorder Severity Scale (PDSS)[4] and the Panic and Agoraphobia (P & A) scale.[56]

TREATMENT OPTIONS

The main objectives of treatment are to reduce the number and intensity of panic attacks, reduce anticipatory anxiety, and treat any underlying depression or other psychiatric comorbidities associated with panic disorder. The long-term goal is sustained full remission.[4] Both pharmacologic and psychosocial therapies are effective.

PHARMACOTHERAPY

In 1962, Klein and Fink[57] described various patterns of behavioral response to imipramine in a group of 180 inpatients predominantly diagnosed with schizophrenia or affective disorders, one of which was a reduction in episodic anxiety response, including the cessation of panic attacks, in a subset of 14 patients. This initial observation led to evaluation of a number of agents to treat panic disorder, and tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and high-potency benzodiazepines (BZDs) have been found to be effective. Monoamine oxidase inhibitors (MAOIs) and reversible inhibitors of monoamine oxidase type A (RIMAs) have also shown efficacy in the treatment of panic disorder.

There are advantages and disadvantages to each of these classes of medications, and the choice of agent is determined by several factors, including side-effect profile, cost, comorbidities, history of past response or failure, and patient preference. Patients with panic disorder are disproportionately sensitive to the side effects of medications and typically require treatment initiation at lower doses than those used for patients with depression, although maintenance doses can be similar and may sometimes be higher.[58]

Acute Treatment Trials

Most research on the treatment of panic disorder has been conducted as relatively brief efficacy trials of 6–12 weeks.

Tricyclic Antidepressants

Imipramine is the most widely investigated TCA in the treatment of panic disorder, although it is not approved in the US for this indication. Several trials have compared imipramine with other therapeutic approaches in the acute treatment of panic disorder (eg, fluvoxamine,[58] alprazolam,[11,59-63] and cognitive-behavioral therapy [CBT][64]). Generally, these trials reported more side effects with imipramine than the comparator, including significant effects on a number of cardiovascular variables.[59-61]

Clomipramine has been evaluated in the treatment of panic disorder in short-term (6–12 weeks), placebo-controlled studies.[56,65-72] These studies have consistently shown clomipramine to be significantly more effective than placebo in treating panic disorder (assessed using a variety of measures). Clomipramine has also been compared with imipramine in several trials. In one, 59 patients with panic disorder (*Diagnostic and Statistical Manual of Mental Disorders*, Third Edition-Revised [*DSM-III-R*])[73] were randomly assigned to either clomipramine or imipramine at comparable, flexible dosages for 10 weeks at the beginning of a 2-year, nonblinded trial.[74] By 10 weeks, both drugs were equally effective in blocking panic attacks, alleviating phobic avoidance, and reducing nonspecific aspects of anxiety. However, during the first 2 weeks, clomipramine was significantly more effective than imipramine in its antipanic and antiphobic effects.[74]

Additionally, acute treatment with clomipramine (mean dose 109 mg/day) has been shown to be significantly superior to imipramine (mean dose 124 mg/day), as assessed by reduction in full panic attack frequency, total panic attack frequency, and anxiety between attacks.[72] No significant differences in efficacy were observed between clomipramine (100 mg/day) and lofepramine (140 mg/day) in the 6-week, placebo-controlled, acute phase of the Galway Study of Panic Disorder.[66]

TCAs were the first antidepressants widely used for panic disorder, and were considered first-line treatment for many years.[75] Although TCAs are effective in treating panic disorder, they have disadvantages: they are associated with anticholinergic and cardiovascular adverse effects that may affect patient compliance, and they are toxic in overdose. Because of the greater tolerability and comparable efficacy of newer classes of antidepressants, the TCAs are now generally reserved for second- or third-line use.

Selective Serotonin Reuptake Inhibitors

The SSRIs, either alone or in combination with BZDs, are the treatment of first choice for panic disorder with most clinicians worldwide.[75,76] They lack the serious side effects of TCAs and MAOIs and the dependence problems associated with BZDs.[77] The efficacy of SSRIs in the treatment of panic disorder has been well established in clinical trials.

Paroxetine was the first SSRI to receive US Food and Drug Administration approval for use in panic disorder, and acute-treatment trials have demonstrated its antipanic efficacy. In a placebo-controlled study of paroxetine in the treatment of panic disorder, evaluating fixed doses of 10, 20, or

40 mg/day over 10 weeks, the minimum dose of paroxetine that showed superiority over placebo was 40 mg/day. The 10- and 20-mg doses showed a tendency toward superiority over placebo but did not reach statistical significance. Adverse effects that were significant versus placebo included decreased libido and abnormal ejaculation, tremor, diarrhea, dry mouth, and dyspepsia.[78] In a 12-week, randomized, double-blind trial, Oehrberg and colleagues[79] randomized 120 patients to treatment with paroxetine (20, 40, or 60 mg/day) or placebo; standardized CBT was given to all patients. Patients who received paroxetine with CBT showed significantly greater improvement in panic attack frequency than those in the placebo group, and a greater percentage had a reduced number of panic attacks (1 or 0) in the final 3-week interval (36% versus 16%, respectively, at week 12; *P*=.024).

Paroxetine 20–60 mg was compared with clomipramine 50–150 mg over 12 weeks in a placebo-controlled study in 367 patients with *DSM-III-R*–defined panic disorder.[68] At the study endpoint (weeks 7–9, when at least 70% of the patients remained in each treatment group), paroxetine was significantly more effective than clomipramine (*P*=.041) or placebo (*P*=.004), based on the number of patients achieving no full panic attacks. A second short-term, placebo-controlled study assessed the relative efficacy of paroxetine (20–60 mg/day), clomipramine (50–150 mg/day), and CBT in 131 randomly assigned patients with *DSM-III-R*–defined panic disorder.[69] Paroxetine (mean dose 38.6 mg/day) was significantly more effective than placebo in reducing panic attacks (*P*=.01), agoraphobic complaints, anxiety, depression, and social dysfunction (*P*<.005). With the exception of scores on panic frequency, paroxetine also showed superiority over CBT on all rating scales (*P*<.05), but efficacy measures were not significantly different from those of clomipramine, with the exception of the CGI-Severity score, on which scores in the paroxetine group were higher (*P*<.001).

A recent 10-week, placebo-controlled pilot study evaluated the effects of combining paroxetine (10–50 mg/day) with a very brief form of CBT in 33 patients with *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*)[80]–defined panic disorder.[81] At week 10, the proportion of panic-free patients was significantly higher in the paroxetine- than in the placebo-treated group (80% versus 25%; *P*<.007), as was the proportion of patients who rated themselves as very much improved (60% versus 13%; *P*<.017).

Another SSRI marketed in the US for panic disorder is sertraline. In the first controlled study of sertraline in treating panic disorder, 178 subjects were randomly assigned to 12 weeks of sertraline (50, 100, or 200 mg/day) or placebo after a 2-week, single-blind, placebo lead-in.[82] In the pooled sertraline group (n=127), panic attacks decreased 65% from baseline versus 39% in the placebo group (n=44). All three sertraline groups demonstrated similar efficacy, although the reduction rate was greater among the lower-dose sertraline groups (71%, 83%, and 42% for 50 mg, 100 mg, and 200 mg, respectively). Adverse effects that were significant versus placebo included decreased libido and abnormal ejaculation, tremor, diarrhea, dry mouth, and dyspepsia.[78] There were no dose-related adverse events. Discontinuation rates were similar for sertraline and placebo.

In a randomized, double-blind, parallel-group, flexible-dose comparison of sertraline and placebo that began with a 2-week, single-blind placebo lead-in, 168 patients were randomly assigned to either sertraline or placebo for 10 weeks. Sertraline was initially given at 25 mg/day for 1 week followed by titration to 50–200 mg/day; mean dose at endpoint was 126 mg/day.[83] Sertraline was significantly more effective than placebo in decreasing the number of full and limited-symptom panic attacks: the mean number of attacks per week decreased 88% in the sertraline group versus 53% in the placebo group. The sertraline group also had higher scores on the Quality of Life Enjoyment and Satisfaction Questionnaire, patient global evaluation, CGI-Severity, and CGI-Improvement. Sertraline was well tolerated, with only 9% of subjects terminating treatment due to adverse effects.

In another study, 176 patients participated in a multiple-site trial using identical protocols with a flexible-dose design.[84] After 2 weeks of single-blind placebo treatment, subjects were randomized to 10 weeks of double-blind, flexible-dose treatment with sertraline (50–200 mg/day) or placebo. The sertraline group exhibited significantly greater improvement at endpoint (*P*=.01) than the placebo group in panic attack frequency. The active treatment group also realized significant improvement on the CGI-Improvement (*P*=.01) and CGI-Severity (*P*=.009), PDSS (*P*=.03), high end-state function assessment (*P*=.03), patient global evaluation rating (*P*=.01), and quality-of-life scores (*P*=.003). Adverse events were mild or moderate in both the sertraline and placebo groups.

Finally, in a pooled analysis of four double-blind, placebo-controlled studies (n=664) (two flexible-dose and two fixed-dose), sertraline was effective in treating panic disorder even in the presence of baseline clinical variables that have been associated with poor response, such as high panic severity, presence of agoraphobia, greater chronicity, and female gender. Endpoint reduction in panic attack frequency was similar across all comparisons (78% to 82%, with and without a poor prognostic variable) and also when three or more high-risk variables were combined.[85]

Fluvoxamine was the first SSRI to be evaluated in a double-blind study in patients with panic disorder.[75] In the 8-week study, 50 patients were randomized to fluvoxamine (mean dose 207 mg/day) or placebo.[86] Fluvoxamine was significantly more effective than placebo in the parameters of panic attack frequency (from week 3) and anxiety, depression, and disability (from week 6; assessed on the Clinical Anxiety Scale, the Montgomery-Asberg Depression Rating Scale [MADRS], and the Sheehan Disability Scale). Other placebo-controlled trials with fluvoxamine have demonstrated similar results.[58,87-89]

Fluvoxamine 150 mg/day was also compared with maprotiline 150 mg/day, a noradrenergic reuptake inhibitor, in a 6-week study in 44 patients with panic disorder.[48] The fluvoxamine

group had significant reductions in panic attack frequency, avoidance behavior, and depressive symptomatology, while maprotiline had virtually no effect on anxiety symptoms (assessed with HAM-A and State-Trait Anxiety Inventory). The therapeutic properties of fluvoxamine were apparent beginning at week 4. Another randomized, placebo-controlled trial compared fluvoxamine and imipramine over 8 weeks in 54 patients with *DSM-III-R*–defined panic disorder.[58] Fluvoxamine (mean dose at week 8:147 mg/day) was associated with significantly fewer panic attacks at week 8 than either imipramine or placebo ($P<.01$). However, no statistically significant differences in Clinical Anxiety Scale ratings among groups were noted at study endpoint.

Fluvoxamine has also been compared with CBT in patients with moderate-to-severe panic disorder,[87] and was found to be superior to CBT and to placebo on most outcome measures ($P<.05$), including number of panic attacks, global improvement, and depression (assessed by Clinical Anxiety Scale, CGI, and MADRS). Additionally, fluvoxamine produced improvement earlier than CBT. A subsequent 96-patient, randomized, 4-arm trial (fluvoxamine+exposure, placebo+exposure, CBT+exposure, and exposure alone) suggested that the combination of fluvoxamine with exposure was significantly superior to all other treatments in diminishing agoraphobic avoidance, the primary endpoint (assessed using an agoraphobia composite) over a 3-month period.[89] No differences in number of panic attacks were observed among the groups, probably due to the relatively low number of panic attacks at baseline.

A 10-week, randomized, placebo-controlled trial compared fluoxetine, 10 and 20 mg/day, and placebo in 243 patients with *DSM-III-R*–defined panic disorder.[90] Fluoxetine, 10 mg/day, had a statistically significantly greater reduction in total panic attack frequency than placebo ($P=.006$), and 20 mg/day had a statistically significantly greater improvement than placebo in a range of symptom domains, including anxiety phobia and depression.

A more recent, placebo-controlled trial in 25 patients with panic disorder who had failed to respond to an 8-week trial with fluoxetine 20 mg/day suggests that pindolol 2.5 mg TID has an augmenting effect on fluoxetine in patients with treatment-resistant panic disorder.[91] Pindolol is a β-blocker with intrinsic sympathomimetic activity. It was examined as a potential augmenting agent for refractory panic because it also blocks presynaptic 5-HT_{1A} and 5-HT_{1B} autoreceptors, potentially increasing synaptic serotonin. Patients were randomized to receive either pindolol or placebo in addition to continued treatment with fluoxetine 20 mg/day for 4 weeks; those randomized to fluoxetine+pindolol had significant improvements on a number of rating scales, including HAM-A, HAM-D, and CGI, compared with the fluoxetine+placebo group.

Currently, only one double-blind, placebo-controlled study of citalopram in panic disorder has been published.[70] A total of 475 patients (with *DSM-III-R* criteria for panic disorder) were randomized to 8 weeks of treatment with either placebo, citalopram, or clomipramine (60–90 mg/day). Citalopram at doses of 20, 30, 40, or 60 mg/day was significantly more effective than placebo in treating panic disorder, in both physicians' and patients' Global Improvement Scales, as well as MADRS and HAM-A total scores ($P<.005$). However, citalopram at 10–15 mg/day was no more effective than placebo. No significant differences in treatment effect between citalopram and clomipramine were reported.

Benzodiazepines

High-potency BZDs have been shown to be effective in rapidly decreasing panic symptoms in a number of trials. However, a drawback of long-term BZD use is the possibility of dependence and associated withdrawal symptomatology on discontinuation. One study showed that ~70% of patients who had panic disorder and were treated with alprazolam had a discontinuation syndrome, which usually involved anxiety and agitation, when they attempted to decrease the dosage.[92] The antidepressants have been shown to be more effective than the BZDs in treating concomitant depressive symptomatology and at least as effective in improving anxiety, agoraphobic avoidance, and overall improvement.[93]

Alprazolam is the most widely investigated BZD in the treatment of panic disorder. Phase I of the Cross-National Collaborative Panic Study (n=526) was an 8-week, placebo-controlled trial of flexible-dose alprazolam (2–10 mg/day; mean dose at week 8 was 5.7 mg/day).[94] Alprazolam was significantly more effective than placebo in reducing panic attack frequency, phobic fears, avoidance behavior, anxiety, and secondary disability (assessed by a range of measures).

Some of these patients (n=109) subsequently underwent a closely monitored placebo-controlled tapered reduction of study medication over 4 weeks, with further observation for another 2 weeks.[95] The alprazolam-treated group had significant relapse between the first and last week of taper, suggested by deterioration in measures of total panic attacks, freedom from panic attacks, anxiety on the HAM-A Scale, overall phobic state, and the Physician's Global Scale. By the last posttaper observation week, there were no significant differences between the two groups.

A wider dosage range of alprazolam was investigated in a 6-week, flexible-dose study that randomized 94 patients with defined panic disorder to either alprazolam 2 mg, alprazolam 6 mg, or placebo.[96] Both active-treatment groups improved significantly more than the placebo group on most outcome measures. The pattern of treatment response across measures suggested a dose effect, although only a few statistically significant differences between the 2- and 6-mg group were reported (eg, frequency of anticipatory episodes, $P<.03$; Work and Social Disability rating, $P<.01$).

Another study randomized 154 patients to 8 weeks of either alprazolam+exposure therapy, alprazolam+relaxation (a psychologic placebo), placebo+exposure therapy, or placebo+relaxation (double placebo), followed by complete taper of medication over weeks 8–16.[97] At week 8, patients were taking a mean of 4.8 mg/day alprazolam. Although

alprazolam was associated with significantly greater improvements than placebo in assessments of phobic fear and avoidance, work/social disability, and global improvement ($P<.05$) at week 8, after withdrawal of treatment, the alprazolam effect disappeared on every measure. During taper and treatment-free follow-up at 6 months, therapeutic gains after alprazolam were lost, while gains after exposure were maintained. The findings of this and other studies led investigators to conclude that relapse is a problem regardless of when alprazolam (or any other BZD) is stopped.[97]

Several short-term (≤9 weeks), placebo-controlled studies of clonazepam (at doses of 0.5–4 mg/day) have been reported.[98-101] These studies consistently showed clinically and statistically significant superiority of clonazepam over placebo in panic disorder as determined by various measures. As with alprazolam, the gradual tapering of clonazepam (in decrements of 0.25–0.5 mg/day every 3 days) was associated with some clinical worsening, particularly in number of panic attacks, but patients did not revert to their baseline condition.[99]

Results of a small (n=72), randomized, placebo-controlled, head-to-head, 6-week comparison of clonazepam and alprazolam showed comparable efficacy.[102] Both clonazepam and alprazolam were superior to placebo for the treatment of panic disorder, as reflected by changes in panic attack frequency, phobic distress, social and work disability, and global assessments of severity of illness and improvement. No significant differences between the two agents were observed.

In a number of short-term, comparative studies, other BZDs have shown significant antipanic effects. Diazepam (mean dose=44 mg/day),[103,104] adinazolam (mean dose=95.5 mg/day), and lorazepam (mean dose 6 to 7.5 mg/day)[105-107] all had similar overall efficacy to alprazolam and may provide effective treatment alternatives, although they are not currently approved in the US for this indication.

Monoamine Oxidase Inhibitors

MAOIs have not been systematically studied in panic disorder,[108] although at least one study predating the current diagnostic nomenclature and likely including a group of panic patients is consistent with a therapeutic effect.

Reversible Inhibitors of Monoamine Oxidase A

A few randomized, controlled trials have investigated the efficacy of RIMAs in panic disorder and report variable results.[109-113] RIMAs are distinguished from the older MAOIs by their selectivity and reversibility. The most widely studied RIMAs are moclobemide and brofaromine. Brofaromine is not available in the US and moclobemide is not approved for use in the US, although it is available in Canada and other countries.

Long-Term Treatment Trials

Several studies were conducted on the long-terms pharmacotherapy treatment for panic disorder, particularly with TCAs, SSRIs, and BZDs (Table).[114-118]

Tricyclic Antidepressants

Although not approved in the US for the treatment of panic disorder, imipramine has been studied in a number of long-term (≥6 months) efficacy trials (Table), generally with small numbers of patients. These studies have included examination of second-year maintenance and discontinuation of imipramine,[119] and comparisons of imipramine with alprazolam[26,61,120-122] and CBT.[64,123]

Long-term treatment of panic disorder with clomipramine was investigated in the Galway Study of Panic Disorder, in which 57 patients initially randomized to a 6-week, placebo-controlled trial of clomipramine versus lofepramine were followed for 6 months of open-label treatment.[66] Patients originally randomized to placebo were alternately reassigned to either lofepramine or clomipramine for this phase of the trial. Data collected at weeks 8, 12, and 24 indicated that patients initially assigned to clomipramine and lofepramine continued to improve and that the course of improvement was similar. Patients initially assigned to placebo and then randomized to either medication continued to show improvement on major efficacy measures and no significant differences across medications were reported.

In a 3-year study, Lotufo-Neto and colleagues[124] also investigated recurrence and relapse rates following remission with clomipramine. Of the 81 patients treated for panic disorder with or without agoraphobia, 70% achieved full remission. Eighty-one percent of this sample had medication tapered off. From this group, 37% experienced relapse immediately, 43% experienced relapse over the course of 3 years, and 19% continued to be symptom-free.

Selective Serotonin Reuptake Inhibitors

The long-term efficacy of fluvoxamine in panic disorder was investigated in a naturalistic follow-up study of patients originally enrolled to a randomized 4-arm trial (fluvoxamine+exposure, placebo+exposure, CBT+exposure, and exposure alone).[125] Of the 76 patients who completed treatment in the original trial,[89] 71 (93%) were evaluated 2 years later. The treatment effect in the fluvoxamine+exposure group was maintained, but was no longer superior due to further improvements in the other groups. Most patients (77%) had received additional treatment during the follow-up. Forty-four percent of patients who had received fluvoxamine in the original study were still using it, although generally at a much lower dose (≤50 mg/day), and >50% of placebo-treated patients had received treatment with fluvoxamine at some point.

Paroxetine has been studied in both relapse prevention and long-term maintenance. Patients with panic disorder who had received fixed-dose paroxetine (10, 20, or 40 mg/day) in a 22-week, double-blind, placebo-controlled trial were immediately rerandomized to continue paroxetine or switch to placebo for an additional 12 weeks.[114] Relapse was defined as the return of panic attacks to a frequency equal to or greater than baseline, or an increase in the CGI-Severity scale of ≥2 points. Relapse rates were significantly higher in the group switched to placebo (11 of 37 patients) than in the group remaining on paroxetine (2 of 43 patients).

A 36-week paroxetine maintenance study[115] included 176 patients with *DSM-III-R* panic disorder who had

completed a 12-week, double-blind, randomized study of paroxetine, clomipramine, and placebo.[68] The primary endpoint was the final timepoint at which ≥70% of patients remained in the trial, which was at the eighth 3-week period (corresponding to week 24). At this time, the mean reduction relative to baseline in panic attack frequency was significantly greater for paroxetine than for placebo, but did not differ significantly from clomipramine. The proportion of patients free from panic attacks at week 24 did not differ significantly among the three groups.

Long-term treatment with sertraline in panic disorder has been demonstrated to be effective and well tolerated for up to 80 weeks in a large multicenter US study.[116] Patients with *DSM-III-R*–defined panic disorder, who had completed one of three 10-week randomized, double-blind, placebo-controlled studies, were entered into a 52-week, open-label, continuation phase with sertraline (25 mg/day for 1 week, 50 mg/day for week 2, and then optional titration up to 200 mg/day for the rest of the continuation phase). Of the 398 patients who entered the open continuation phase, 183 (46%) completed it and were rerandomized to an additional 28 weeks of double-blind, placebo-controlled treatment.[116] Continued improvement was shown on all efficacy measures during open sertraline treatment, with mean reductions of 44% in number of panic attacks, 46% in number of limited-symptom attacks, and 40% in amount of time spent worrying. In addition, there was a 46% reduction in the PDSS and a 29% reduction in both CGI-Improvement and CGI-Severity scores. At the end of the 28-week, double-blind phase, sertraline-treated patients were significantly less likely to discontinue treatment due to relapse or insufficient response (12%) than placebo-treated patients (24%).[116]

Sertraline's efficacy in panic disorder has also been shown in a study that examined clinical response and sexual functioning in a pooled analysis of panic-disorder patients.[126] Twelve-month data of completers were pooled from three studies with a 10-week placebo-controlled phase, followed by 52 weeks of open-label sertraline treatment. Sertraline-treated patients showed a marked improvement in symptoms of panic disorder. They had a 98% reduction in frequency of panic attacks, and 93% achieved remission (CGI-Improvement score of 1 or 2) or no full panic attacks after 12 months of treatment. Sexual functioning was affected in 22% of patients during the acute phase, and improved over time.

Arato and colleagues[127] have recently presented results of a multicenter, double-blind, randomized comparison of sertraline (50–100 mg) versus imipramine (100–200 mg) over 26 weeks in 138 patients with concomitant panic disorder and major depression. Both treatments were associated with a significant reduction in panic attacks and symptoms of depression, which resulted in improved quality of life. There were significantly fewer discontinuations due to adverse events in sertraline- versus imipramine-treated patients, and sertraline was better tolerated overall.

TABLE. LONG-TERM TREATMENT TRIALS OF PHARMACOTHERAPY FOR PANIC DISORDER[114-118]

Author (Year)	Patients (n)	Study Drug	Comparator(s)	Study Design
Fahy et al (1992)[66]	57	Clomipramine	Lofepramine Placebo (RCT phase only)	RCT → OL
Lydiard et al (1998)[114]	80	Paroxetine	Placebo	RCT → RCT
Lecrubier et al (1997)[115]	176	Paroxetine	Clomipramine Placebo	RCT
Rapaport et al (2001)[116]	183	Sertraline	Placebo	RCT → OL → RCT
Michelson et al (1999)[117]	88	Fluoxetine	Placebo	RCT → RCT
Lepola et al (1998)[118]	279	Citalopram	Clomipramine Placebo	RCT

* Patients rerandomized to active treatment or placebo.

RCT=randomized controlled trial; OL=open-label; wks=weeks; CGI=Clinical Global Impressions; HAM-A=Hamilton Rating Scale for Anxiety; HAM-D=Hamilton Rating Scale for Depression; MADRS=Montgomery-Asberg Depression Rating Scale; CGI-S=Clinical Global Impressions-Severity;

Saiz Ruiz and colleagues[128] gave sertraline to patients with panic disorder in the clinical setting. After 6 months of treatment, 89% of the 886 outpatients were free of panic attacks; discontinuation due to adverse events was observed in only 3.6% of patients.

In a long-term trial of fluoxetine, 88 patients who had responded to acute fluoxetine in a 10-week, placebo-controlled trial (CGI-Improvement score of 1 or 2) were subsequently randomized to continued fluoxetine or placebo for 24 weeks.[117] Patients who continued fluoxetine experienced improvement in panic-attack frequency and phobia rating scale score over the extension phase, whereas those switched to placebo experienced statistically significant worsening in HAM-A, HAM-D, and Symptom Checklist-90-Revised [SCL-90-R] rating scores. Overall relapse rates were low in both groups.

Roy-Byrne and colleagues[129] retrospectively examined a medical and pharmacy claims database to analyze use of emergency room and laboratory resources and costs for 120 patients with panic disorder who underwent SSRI treatment. The mean number of emergency room and laboratory visits and costs during the 6 months after therapy initiation were reduced compared with the 6 months prior to starting treatment. Sertraline reduced emergency room visits by 79.5% and costs by 85.2% (P<.05), while fluoxetine reduced visits by 25.0% and costs by 69.5% (P=not significant [NS]), and paroxetine reduced visits by 8.6% and costs by 30.8% (P=NS).

Citalopram has also shown efficacy in long-term treatment of panic disorder. Of 475 patients who completed 8 weeks of treatment with either placebo, citalopram (10–15, 20–30, and 40–60 mg/day), or clomipramine (60–90 mg/day),[70] 279 entered a double-blind continuation phase, and 179 completed the full 12 months.[118,129] All active medications were superior to placebo in preventing relapse in patients with panic disorder.[118] Response (defined as no panic attacks in the week before assessment) was significantly higher in the citalopram 20–30 mg and 40–60 mg groups than in the placebo group (P=.001 and P=.003, respectively). The lowest citalopram dose and clomipramine also demonstrated modest advantages over placebo (P<.05).[130] At all dosages, citalopram was more effective than placebo in controlling phobic symptoms (assessed using the Phobia Scale and SCL-90-R phobia-related factors); 20–30 mg was generally the most effective dosage. Alleviation of phobic symptoms tended to continue to increase toward the end of treatment.[131]

Benzodiazepines

In addition to the long-term alprazolam/imipramine comparisons noted above, a long-term comparison of alprazolam with clonazepam has also been published.[132] Patients originally randomized to treatment in a placebo-controlled trial comparing these two agents were reevaluated in a follow-up study ~1.5 years later, when 78% of patients remained on medication (the majority on BZDs). For those patients on BZDs, there was a significant worsening of global outcome

Study Duration	Main Efficacy Variables	Efficacy Outcome	Tolerability Outcome
6 wks RCT 18 wks OL	CGI HAM-A HAM-D MADRS	=Lofepramine	30% discontinuation
22 wks RCT 12 wks RCT*	CGI-S PAF	>Placebo	ND
36 wks RCT	PAF	>Placebo =Clomipramine	10% discontinuation
10 wks RCT 52 wks OL 28 wks RCT	PDSS CGI-I	>Placebo	10% OL; 3% 28 wks RCT discontinuation
10 wks RCT 24 wks RCT*	PAF HAM-A HAM-D SCL-90-R	>Placebo	ND
8 wks+ 46 wks	PAF SCL-90	>Placebo	ND

ND=no data; PAF=panic attack frequency; PDSS=Panic Disorder Severity Scale; SCL-90=Symptom Checklist-90-Revised; ND=no data.

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between endpoint and follow-up ($P<.05$), although the final clinical status remained significantly better than the pretreatment score ($P<.001$). There was no significant difference across groups in the number of patients free from panic at follow-up.

Monoamine Oxidase Inhibitors

No controlled long-term trials of MAOIs in the treatment of panic disorder have been published.

Reversible Inhibitors of Monoamine Oxidase A

Long-term efficacy data for RIMAs in panic disorder are limited.[109,113]

PSYCHOSOCIAL TREATMENT

Exposure

Exposure-based psychotherapy has been compared with medication in at least two controlled trials.[89,97] In a placebo-controlled comparison with alprazolam, 156 patients were randomized to 8 weeks of alprazolam+exposure therapy, alprazolam+relaxation (a psychologic placebo), placebo+exposure therapy, or placebo+relaxation (double placebo), followed by taper off medication over weeks 8–16.[97] All 4 treatment groups improved on panic measures, but on nonpanic measures, exposure had twice the effect of alprazolam at the end of treatment. During taper and treatment-free follow-up at 6 months, therapeutic gains after exposure were maintained, while gains after alprazolam were lost.

A randomized, 3-month, 4-arm trial (exposure+fluvoxamine, exposure+placebo, exposure+CBT, and exposure alone) with 96 patients showed that all four treatments were effective and resulted in a significant decrease in phobic avoidance.[89] Effectiveness of exposure therapy alone did not differ significantly from that of exposure+CBT or exposure+placebo, but was inferior to exposure+fluvoxamine.

Cognitive-Behavioral Therapy

Perhaps the most common nonpharmacologic therapy used in the management of panic disorder is CBT, and several studies have confirmed its effectiveness.[64,87,88,123] CBT is designed to help the patient understand the role of his or her cognitions in the development of panic and to accept a more benign interpretation of the bodily sensations.[87] The elements involved in CBT are diverse and can involve anxiety management skills, cognitive restructuring, and progressive exposure to panic attack triggers. Homework assignments form an important part of this approach.

There are numerous studies demonstrating the efficacy of CBT. In one of the largest placebo-controlled trials, Barlow and colleagues[64] found an equivalent response rate between medication and CBT, with a small advantage for imipramine by the end of the acute phase (12 weeks). However, at follow-up 6 months after treatment discontinuation, patients who had received CBT alone maintained their improvement significantly better (4% relapse) than those given imipramine (25% relapse), based on PDSS responder criteria.[64] An earlier, smaller study by Brown and Barlow[132] examined long-term outcome (24-month follow-up) of CBT in 63 patients. Many patients sought further treatment for panic during follow-up because of a less-than-adequate response to treatment; nevertheless, additional treatment did not result in further improvement.

Exercise

Regular aerobic exercise (eg, running) has also been evaluated as a nonpharmacologic approach to managing panic disorder in a 10-week, placebo-controlled comparison with clomipramine. Exercise was less effective than clomipramine, but more effective than placebo, in most primary and secondary outcome measures of efficacy, including the P&A scale, Fear Questionnaire, and CGI scores.[56,71]

COMBINATION THERAPY

The combination of medication and CBT, a treatment approach that is reviewed in some detail by Gelder,[133] may prove more effective than either treatment alone in the management of panic disorder.[134] Results from a limited number of studies support this approach, although more research is needed before definitive conclusions can be made about the relative benefits of combined treatment.

The addition of brief dynamic psychotherapy (15 weekly sessions) to treatment with clomipramine significantly reduced the subsequent relapse rate of panic disorder compared with clomipramine alone (20% versus 75%, respectively) during long-term follow-up.[135] Earlier trials have provided similar evidence for the efficacy of imipramine treatment combined with exposure therapy. A trial conducted in 62 chronically agoraphobic patients tested clinical measures of global severity, phobia, panic, anxiety, depression, and behavioral performance before treatment and at weeks 4, 8, and 12 of treatment. The combination of imipramine and exposure therapy was as effective as imipramine monotherapy, and more effective than exposure alone.[136] Another early trial in 76 agoraphobic women compared combined imipramine+group exposure in vivo treatment with combined placebo+group exposure in vivo treatment.[137] The imipramine+exposure group demonstrated significantly greater improvements than the placebo+exposure group in primary phobia, spontaneous panic, and global improvement.

Paroxetine has also been studied in combination with CBT. In a 12-week, randomized, double-blind trial by Oehrberg and colleagues,[78] discussed previously, 120 patients received CBT with either paroxetine or placebo. Significantly greater improvements were seen with paroxetine+CBT than with placebo+CBT.

More recently, a 10-week, placebo-controlled pilot study evaluated the effects of combining paroxetine (10–50 mg/day) with a very brief form of CBT in 33 patients with *DSM-IV* panic disorder.[80] Patients in both groups (ie, paroxetine+CBT and placebo+CBT) improved similarly and substantially on most measures during the 10 weeks of acute treatment. However, the proportion of panic-free patients was significantly higher in the paroxetine-treated

group than in the placebo group (80% versus 25%; *P*<.007), as was the proportion of patients who rated themselves as very much improved at week 10 (60% versus 13%; *P*<.017).

According to a recent randomized, placebo-controlled trial, combining imipramine with CBT also appears to be an effective approach to panic disorder, both acutely and in the long term.[64] This five-arm trial compared CBT only (n=77), imipramine only (n=83), CBT+imipramine (n=65), placebo only (n=24), and CBT+placebo (n=63) in patients with panic disorder. During the 12-week acute treatment phase, combined imipramine and CBT treatment resulted in limited benefit over monotherapy. By the end of the 6-month maintenance phase, the combined treatment was superior to CBT alone, CBT+placebo, and imipramine alone on PDSS measures.

OVERVIEW OF AVAILABLE TREATMENT GUIDELINES

Four sets of guidelines for the management of patients with panic disorder have been published. The most comprehensive are those from the American Psychiatric Association (APA) published in 1998.[134] These detailed guidelines aim to provide psychiatrists with recommendations on the overall care of patients with panic disorder, and were developed under the auspices of the Steering Committee on Practice Guidelines.

The guidelines note that both CBT and medication have been shown to be effective for panic disorder and also point out that there is no convincing evidence that one modality is superior for all patients or for particular patient subpopulations. They recommend that the choice of treatment should be based on individualized assessment of efficacy, benefit and risks of each modality, costs, and the patient's personal preferences.

The APA Guidelines also consider optimal length of treatment, and note that the acute phase of treatment with either CBT or medication generally lasts about 12 weeks. At this point, the patient should have markedly fewer and less intense panic attacks than before treatment (ideally no panic attacks), should worry less about panic attacks, and should experience minimal or no phobic avoidance. With CBT, the guidelines suggest that the frequency of visits is generally decreased after the acute phase of treatment and eventually discontinued within several months.

After successful acute treatment with medication, the patient should continue to receive drug therapy for a minimum of 12–18 months. Discontinuation should be attempted only if the patient experiences significant or full improvement. Patients who partially or fully relapse following drug discontinuation should resume medication immediately. They could benefit from prolonged treatment, although no specific length of time is given. Longer periods of initial treatment with medication may decrease the risk of relapse when medication is stopped.

The International Consensus Group on Depression and Anxiety published a consensus statement in 1998 to provide clinicians with a better understanding of management issues in panic disorder and to give clinical recommendations for treatment.[76] The statement is based on a series of six review articles, each of which focuses on a key area in the clinical management of panic disorder, and on the relevant scientific literature. The six areas covered in the reviews are:

(1) Response, remission, and relapse[4];
(2) Impact of comorbidity on treatment approach[138];
(3) Differential efficacy of drug treatments[93];
(4) Tolerability and safety of drug treatments[139];
(5) Clinical and preclinical mechanisms of drug treatment[45]; and
(6) Long-term treatment.[77]

The consensus statement recommends SSRIs as the first-choice drug type. It also notes that full remission of panic disorder will require a minimum of 9–12 months of treatment and that continued treatment for up to 1 year is effective in maintaining and improving acute response and preventing relapse. In terms of duration, the consensus statement recommends that treatment should continue for at least 12–24 months and should be discontinued only if the patient is not currently experiencing a stressful life event and full remission is maintained. Treatment should be continued in patients with persistent symptoms or a history of severe relapse.

Roy-Byrne and colleagues[140] developed guidelines for the family physician to improve the recognition and treatment of panic disorder in primary care. These guidelines briefly discuss diagnosis and the rationale for treatment of panic disorder and provide guidance on appropriate choices regarding treatment type, dosing, titration, side-effect management, maintenance therapy, and referral. A treatment algorithm assumes an 8-week period for initial treatment and recommends that patients continue pharmacotherapy for at least 1 year. In general, discontinuation should only be considered if there are no signs of symptomatology, serious medical illness, or major psychosocial stress.

The Ontario Program for Optimized Therapeutics offers guidelines for the primary care management of anxiety disorders in Canada.[141] They recommend CBT as first-line treatment for anxiety disorders if patient compliance is not an issue. For pharmacotherapy of anxiety disorder with or without agoraphobia, citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, and venlafaxine are all recommended as first-line treatments. The guidelines suggest initiating therapy at a low dose, with gradual upward titration until complete symptom remission is achieved. After 12 weeks of treatment, if response is apparent, pharmacotherapy should be maintained for at least 1 year; then if the patient maintains a full remission (no panic attacks), the clinician can consider stopping therapy gradually over 2–6 months. As relapse is common following discontinuation of medication, relapsing patients should begin taking medication again or be treated with CBT.

CONCLUSION

SSRIs are currently the drugs of first choice in the treatment of panic disorder with or without agoraphobia, and paroxetine, sertraline, citalopram, clomipramine, alprazolam, fluoxetine, and clonazepam are approved treatments for panic disorder in Europe and/or the US. Most randomized, controlled treatment trials of panic disorder are limited to ≤12 weeks of treatment. While the number of long-term studies is limited and often confined to naturalistic follow-up, currently available data suggest that the efficacy of studied drugs is maintained with continued treatment. Long-term data are available for all the medications that are approved for the treatment of panic disorder, except for the BZDs, which have only naturalistic long-term follow-up data. Available evidence suggests that long-term pharmacologic treatment of panic disorder is safe and effective in accruing continued improvement, maintaining benefit, and preventing relapse. In addition, CBT, alone or in combination with drug therapy, is also effective for the treatment of panic disorder. CNS

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WCA Recommendations for the Long-Term Treatment of Posttraumatic Stress Disorder

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FOCUS POINTS

- Posttraumatic stress disorder (PTSD) is a commonly unrecognized, chronic condition associated with significant disability, increased societal costs, and reduced productivity.
- Psychotherapy and pharmacotherapy, both separately and in combination, are useful in the treatment of PTSD.
- While the selective serotonin reuptake inhibitors sertraline, paroxetine, and fluoxetine have shown efficacy in acute treatment trials, sertraline is the only one for which long-term efficacy has been demonstrated.
- Current guidelines recommend that pharmacotherapy be continued in chronic PTSD for a minimum of 12–24 months and that maintenance cognitive-behavioral therapy sessions be provided as needed.

ABSTRACT

Posttraumatic stress disorder (PTSD) is a common and disabling condition. In addition to combat-related PTSD, the disorder occurs in civilians exposed to severe traumatic events, with the community prevalence rate for the combined populations reaching as high as 12%. If left untreated, PTSD may continue for years after the stressor event, resulting in severe functional and emotional impairment and a dramatic reduction in quality of life, with negative economic consequences for both the sufferer and society as a whole. Although PTSD is often overlooked, diagnosis is relatively straightforward once a triggering stressor event and the triad of persistent symptoms—reexperiencing the traumatic event, avoiding stimuli associated with the trauma, and hyperarousal—have been identified. However, comorbid conditions of anxiety and depression frequently hamper accurate diagnosis. Treatment for PTSD includes psychotherapy and pharmacotherapy. The latter includes selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, and monoamine oxidase inhibitors. Only SSRIs have been proven effective and safe in long-term randomized controlled trials. Current guidelines from the Expert Consensus Panel for PTSD recommend treatment of chronic PTSD for a minimum of 12–24 months.

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INTRODUCTION

The nonmedical literature has long documented symptoms of posttraumatic stress disorder (PTSD). For example, in the 17th century, Samuel Pepys recorded his flashbacks of the great fire of London. However, it was not until after the Vietnam War that PTSD received widespread recognition as an independent disorder, and only in 1980 was PTSD included in the official nomenclature.[1]

PTSD represents a pathological response after trauma. The disorder was originally thought to be primarily associated with war and combat, but studies conducted during the past several decades have revealed that PTSD can also arise after experiencing or witnessing a variety of severe traumatic events that involve actual or threatened death or serious injury to self or others. Such events include interpersonal violence (eg, physical/sexual abuse, physical assault, kidnapping, torture, military combat, terrorist attacks), man-made (eg, motor vehicle accidents), or natural (eg, fire) accidents or disasters.

EPIDEMIOLOGY OF POSTTRAUMATIC STRESS DISORDER

PTSD is one of the most common anxiety disorders, affecting 8% to 12% of the general population at some time during their lives.[2,3] While estimates for lifetime prevalence of exposure to a traumatic event vary widely—from 39% to 89%—PTSD develops in only 10% to 20% of people exposed to trauma.[2-4] The likelihood of developing PTSD following exposure to a traumatic event depends on a number of factors, including:

- *Type and severity of trauma.* Childhood abuse, rape, assaultive violence, and sudden unexpected death of a loved one are associated with high rates of PTSD in the community.[3] The National Comorbidity Survey (NCS) of the United States general population found that rape was associated with the highest likelihood of developing PTSD among both men and women.[2] Other traumas that the NCS associated with a high probability of developing PTSD included combat exposure, childhood abuse, sexual molestation, physical attack, and being threatened with a weapon.
- *Gender.* PTSD appears to be twice as common in women as in men,[2,3,5] even when controlling for the type of trauma exposure.[3] PTSD also lasts longer in women (median duration, 48.1 months versus 12.0 months in men)[3]

These recommendations are based on proceedings from the World Council of Anxiety meeting held September 11, 2000, in Pisa, Italy, and on guidelines and articles published in the medical literature through October 15, 2001.

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- *Factors surrounding the trauma*. Factors preceding trauma (eg, pre-existing depression or anxiety, family psychiatric history, early separation from parents[4]), factors during the trauma (eg, dissociation), and factors operating after the trauma (eg, lack of social support and additional life stress[6]), have an effect on development of PTSD.

CLINICAL PRESENTATION

Symptoms of PTSD are grouped into three clusters according to *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*) criteria[7]:

(1) *Re-experiencing*. This may involve persistent re-experiencing of the traumatic event, with flashbacks, intrusive thoughts, recurrent distressing recollections and dreams; having the feeling that the traumatic event is recurring; and psychological distress and physiological reactivity when exposed to reminders.

(2) *Avoidance/numbing*. Sufferers seek to avoid stimuli associated with the traumatic event including thoughts, conversations, people, and places. There may be inability to recall aspects of the traumatic event, markedly reduced interest in participating in once-typical activities, feelings of detachment or emotional numbing, or a feeling of reduced life expectancy.

(3) *Hyperarousal*. Persistent symptoms of hyperarousal are among the first symptoms experienced in PTSD. These may include sleep disturbance, hypervigilance, exaggerated startle response, irritability or outbursts of anger, and concentration difficulties.

UNDERLYING BIOLOGICAL ETIOLOGY

There is growing evidence that PTSD is not merely a normal response to an abnormal event, but is a medical disorder mediated by psychobiological dysfunction occurring after trauma. Specific neuroanatomical, biochemical, and psychological abnormalities have been found in patients with PTSD, and this work has provided a rationale for using particular interventions in the treatment of this disorder. Although there has been some variability in findings across studies, a useful basis has been laid from which future work can proceed.[8-11]

Neuroimaging techniques, for example, have shown several important changes in the brains of PTSD victims compared with controls. These include possible reductions in hippocampal volume, and functional changes in the amygdala, hippocampus, anterior paralimbic regions, and Broca's area.[12-15] Whether the structural hippocampal changes observed in PTSD patients predispose them to PTSD or if they are a direct effect of the disorder is still under investigation. However, the clinical relevance of this work is supported by data showing that reduced hippocampal volume is associated with severity of the traumatic exposure, symptoms, and cognitive problems. Similarly, the finding that neuronal circuits involved in fear conditioning overlap with those highlighted in functional imaging studies of PTSD provides a useful basis for future research on interventions to enhance fear extinction and decrease symptoms.

In addition to these structural and functional brain changes, neuroendocrinological alterations have been associated with PTSD[8] and it has been suggested that the disorder is characterized by decreased serum cortisol due to increased hypothalamic-pituitary-adrenal (HPA) axis negative feedback.[8,15] This line of argument suggests that the nature of HPA dysfunction seen in PTSD differs significantly from that seen in depression, supporting the specificity of the neurobiology of PTSD. There has been interest in the use of cortisol release factor antagonists for mood and anxiety disorders, and future work in this area may ultimately lead to novel interventions for the treatment of PTSD.

Possible evidence of serotonergic dysregulation in PTSD includes frequent symptoms of aggression, impulsivity, depression, suicidality, and the demonstrated clinical efficacy of selective serotonin reuptake inhibitors (SSRIs).[16] Possible evidence of adrenergic and noradrenergic dysregulation includes exaggerated startle response, exaggerated increases in heart rate and blood pressure on exposure to reminders of the traumatic event, and elevated 24-hour urine catecholamine excretion.[17] Psychotropic medications with prominent actions on noradrenaline that have been used for the treatment of PTSD include clonidine, propranolol, prazosin, tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). The dopamine system may also play an important role in PTSD, and the role of new-generation antipsychotics in PTSD is receiving increased attention.

CLINICAL COURSE, CHRONICITY, AND ASSOCIATED DISABILITY

Once PTSD develops, it is typically chronic (lasting >3 months) and recurrent. In the NCS, ~25% of untreated patients recovered over the course of 12 months and 40% recovered by 24 months; however, 50% still met criteria for PTSD 6 years after the event.[2]

If left untreated, PTSD can result in:

- Significant functional and emotional impairment
- Dramatic reduction in the patient's quality of life
- Predisposition to other psychiatric and physical illnesses
- Significantly increased likelihood of suicide attempts, hospitalization, and alcohol dependence or abuse[2,18-20]
- Higher healthcare utilization and costs

Patients with PTSD exhibit varying degrees of functional impairment.[21] Nevertheless, assessments of quality of life and functioning have shown that, in general, PTSD significantly affects an individual's well-being and quality of life, particularly physical health and functioning, and role functioning at home, work, or school.[22] PTSD is more strongly associated with suicidal behavior than are most other anxiety disorders. Among individuals with PTSD, the reported rate of attempted suicide is 19%, which is comparable with that seen in depression.[23]

With regard to the significant cost burden to both the individual and society in terms of lost earnings and associated healthcare costs, general population research in the US estimates that 38% of people with PTSD are in treatment in a given year, which is comparable to rates among people with major depression (36%) but higher than those seen in other anxiety disorders (23%) or substance use disorders (23%).[24]

In 1998, the cost of anxiety disorders in the US was estimated at $63 billion. PTSD and panic disorder were associated with the highest rates of service use.[25] Furthermore, PTSD is associated with an estimated 3.6 days of work impairment per month, translating into an annual productivity loss in the US in excess of $3 billion.[24]

DIAGNOSIS

Currently, there are two sets of diagnostic criteria used to define PTSD: (1) the World Health Organization *International Classification of Diseases*, Tenth Revision (*ICD-10*) criteria[26] and (2) the American Psychiatric Association *DSM-IV* criteria.[7] While not identical, the *ICD-10* and *DSM-IV* criteria are generally in agreement. For example, *ICD-10* concurs with *DSM-IV*[27] that the essential feature of PTSD is the development of characteristic symptoms following exposure to an extreme traumatic stressor, with the subject's response involving intense fear, helplessness, or horror. Both sets of diagnostic criteria identify exposure to a traumatic event followed by the PTSD symptoms of re-experiencing, avoidance, and hyperarousal.

DSM-IV criteria specify that the duration of illness must exceed 1 month before a diagnosis can be given. In addition, diagnosis requires that the symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. Further, *DSM-IV* defines PTSD as either chronic or acute, depending on whether symptoms last for >3 months or <3 months, respectively.

Despite their similarities, the *ICD-10* criteria for PTSD are less rigid than those of *DSM-IV* in the following ways[26]:

- Symptoms are not required to cause clinically significant distress.
- Symptoms indicating numbing of responsiveness are not emphasized.
- Only one symptom of avoidance needs to be present compared to a minimum of three avoidance symptoms in *DSM-IV*.
- There is no differentiation between acute and chronic PTSD.

COMORBIDITY

PTSD is associated with an increased risk of comorbid anxiety disorders, depression, and substance abuse. The risk of developing comorbid disorders appears to be related to the severity of trauma and consequent complexity of the PTSD reaction.[24] Population studies have shown that >80% of people with PTSD also have a history of at least one other psychiatric disorder, including[24]:

- Comorbid major depression—increased likelihood is 7-fold for men and 4-fold for women.
- Generalized anxiety disorder—increased likelihood is 6-fold for men and 3-fold for women.
- Panic disorder—increased likelihood is 4-fold for men and 3-fold for women.

In addition, individuals with PTSD are 8 (women) and 14 (men) times more likely to have three or more psychiatric disorders than those without PTSD.[2]

TREATMENT OPTIONS

The goals of PTSD treatment are to reduce core symptoms, comorbidity, and disability; improve quality of life; and prevent recurrent episodes.

Current treatment approaches involve psychotherapy, pharmacotherapy, or a combination of both. Successful treatment for PTSD should demonstrate effects across the spectrum of PTSD symptom clusters. A number of rating instruments are used to assess the severity of PTSD symptoms and determine the efficacy of treatments in clinical trials, including:

- Clinician-Administered PTSD Scale, Part 2 (CAPS-2)[28]
- Clinical Global Impression (CGI) scales: CGI–Severity (CGI-S) and Improvement (CGI-I)[29]
- Impact of Event Scale–Revised (IES)[30]
- Davidson Trauma Scale (DTS)[31]
- Treatment Outcome PTSD Scale (TOP-8)[32]
- Mississippi Scale for Combat-Related PTSD (self-rating)[33,34]

PHARMACOTHERAPY

SSRIs have been recommended as the first-line medications of choice for the treatment of PTSD.[35,36] Sertraline, paroxetine, and fluoxetine have demonstrated effectiveness and tolerability in randomized, controlled acute treatment trials. Sertraline, however, is the only treatment for which long-term efficacy (up to 1 year) has been demonstrated. Other pharmacologic agents, including TCAs and MAOIs, have been studied in trials of PTSD patients. Early studies of TCAs suggested their efficacy in the treatment of PTSD in combat veterans, but these studies were small and did not use clinician-rated PTSD scales.[37,38] MAOIs may be effective, but side effects, potentially dangerous interactions, and the need for dietary restrictions may limit their use in clinical practice.[39]

In some studies of combat-related PTSD, medication has not proven effective.[40] The following fundamental differences between combated-related and civilian PTSD may lead to differences in clinical trial data[41]:

- Differential nature of the traumatic stress in combat versus civilian settings.
- Differences in the clinical presentation of PTSD (eg, markedly greater baseline severity in veteran study participants compared with civilian subjects).
- Increased longitudinal comorbidity of combat-related PTSD (eg, increased occurrence of alcoholism, substance abuse, medical comorbidity).

- Gender-specific neurobiological factors that may render SSRIs more effective in women than in men.
- Psychosocial context of the illness in the military veteran setting (eg, ongoing monetary support for combat-related PTSD diagnosis).

Acute Treatment Trials

Selective Serotonin Reuptake Inhibitors and Serotonin Norepinephrine Reuptake Inhibitors

Sertraline was the first drug approved by the US Food and Drug Administration for the treatment of PTSD, and was subsequently approved in many other countries. Sertraline has demonstrated acute efficacy in the treatment of PTSD in two large multicenter trials, as well as in smaller studies in specific PTSD patient populations.[41-45]

Davidson and colleagues[42] randomized 208 patients (predominantly civilians) to receive either sertraline (50–200 mg/day) or placebo for 12 weeks. All patients had a baseline total severity score ≥50 on CAPS-2. The primary efficacy measures were total scores on CAPS-2, IES, and CGI. Sertraline was superior in significantly reducing total CAPS-2 (P=.003), and IES (P=.02) scores, and improving CGI-S, CGI-I (P<.001), and DTS (a secondary outcome parameter; P=.002) scores. An intent-to-treat (ITT) endpoint analysis demonstrated a 60% responder rate for sertraline versus 38% for placebo (P=.004). Sertraline was well tolerated, and reported adverse events were consistent in frequency and type with the previously established safety profile.

In a second trial, Brady and colleagues[43] randomized 187 patients (mostly civilians) to receive either sertraline (50–200 mg/day) or placebo for 12 weeks. As in the Davidson study,[42] all patients had a baseline total severity score ≥50 on CAPS-2; the primary efficacy measures were total CAPS-2, IES, and CGI scores. The researchers found that sertraline was superior to placebo in significantly reducing total CAPS-2 (P<.05) starting from week 2, and improving CGI-I, CGI-S (P≤.02) and DTS (P=.003) scores. Sertraline was also associated with significantly greater improvements (P=.004) in quality-of-life scores compared with placebo. In addition, sertraline treatment was associated with a similar magnitude of improvement in the avoidance/numbing, arousal, and re-experiencing/intrusion clusters, with improvements in the first two being significantly greater with sertraline than with placebo. Sertraline was well tolerated, with insomnia being the only adverse event reported significantly more often with sertraline than with placebo.[43]

In a 10-week, double-blind, pilot study, 42 Israeli military veterans were randomized to receive either a flexible dose of sertraline (50–200 mg/day) or placebo.[41] Responder rates for completers were 53% for sertraline and 20% for placebo based on CGI-I criteria (P=.057), and 41% for sertraline and 20% for placebo based on combined CGI-I and CAPS-2 reduction criteria (P=.28). Sertraline treatment was well tolerated, with a 13% discontinuation rate due to adverse events. Additional adequately powered controlled trials are needed to confirm these results within the military veteran population.

The short-term efficacy of fluoxetine has been demonstrated in three randomized controlled trials (RCTs) of 5 and 12 weeks' duration. In a preliminary 5-week study of 64 randomized subjects (men and women; military veterans and civilians), 47 subjects completed the trial.[40] Among completers, CAPS-2 score was significantly reduced from baseline for fluoxetine-treated patients (average dose, 40 mg/day) versus placebo. Improvements were predominantly seen in the numbing and hyperarousal symptom clusters. Civilian trauma patients demonstrated significant improvement versus placebo, whereas those with combat-related trauma did not.

A further 12-week study compared fluoxetine with placebo in 53 civilians with PTSD.[46] A statistically significant number of patients in the fluoxetine group compared with the placebo group (85% versus 62%, respectively, P<.06) were classified as responders at week 12 weeks based on the Duke Global Rating (DUKE) criterion of 1 or 2 (much or very much improved). Using the more stringent criterion of a DUKE score of 1 (very much improved), response rates were lower (59% for fluoxetine and 19% for placebo, P<.0005).

A recent double-blind, placebo-controlled study of fluoxetine for the treatment of PTSD was conducted mainly in areas affected by war.[47] Patients were randomized to 12 weeks of treatment with either fluoxetine (n=226; 20–80 mg/day) or placebo (n=75). Compared with placebo, fluoxetine was associated with a significantly greater reduction in baseline TOP-8 score (P=.006), as well as significantly higher response rates (P=.02) and significantly greater improvement on most secondary measures, including CAPS-2 (P=.021), the Hamilton Rating Scale for Anxiety (HAM-A) (P=.001), and the Montgomery-Asberg Depression Rating Scale (P<.001). Fluoxetine treatment significantly reduced PTSD symptoms compared to placebo. There were no significant differences in the number of patients reporting adverse events between groups.

Paroxetine is approved in the US and several other countries for the treatment of PTSD. A recent fixed-dose, placebo-controlled trial examined the efficacy and safety of paroxetine in the treatment of 551 patients with chronic PTSD (*DSM-IV* and CAPS-2 score ≥50).[48] Patients were randomly assigned to placebo (n=186), paroxetine 20 mg/day (n=183), or paroxetine 40 mg/day (n=182) for 12 weeks. Paroxetine-treated patients in both dosage groups showed significantly greater improvements compared with placebo-treated patients in both CAPS-2 total score and rate of response for global improvement on the CGI scale. Paroxetine treatment also led to significant improvement over placebo on all three PTSD symptom clusters (re-experiencing, avoidance/numbing, hyperarousal), social and occupational impairment, and comorbid depression. Both doses of paroxetine were well tolerated in this study.[48]

Ruggiero and colleagues[49] conducted a flexible-dose trial of paroxetine for the treatment of chronic PTSD. In this double-blind, placebo-controlled study, 307 subjects were randomly assigned to receive paroxetine (20–50 mg/day) or placebo for 12 weeks. Primary efficacy variables included change from baseline to endpoint in CAPS-2 total score and the proportion of responders on CGI-I. Other outcome measures included change from baseline in CAPS-2; total scores on TOP-8, DTS, and the Sheehan Disability Scale; and the proportion of patients achieving response and remission. PTSD symptoms were significantly more reduced on both primary and secondary outcome measures in the paroxetine group (n=151) than in the placebo group (n=156). CAPS-2 total score was significantly more improved in the paroxetine group compared with the placebo group from week 8 ($P<.05$) on, and significantly more paroxetine-treated patients achieved response ($P<.001$) by week 12. Treatment was well tolerated, with the frequency and type of adverse events corresponding to the known safety profile of paroxetine.

To date, only open-label studies of citalopram, fluvoxamine, nefazodone, and venlafaxine have been reported.

Tricyclic Antidepressants

Early studies of TCAs suggested efficacy in the treatment of PTSD in combat veterans.[37,38] The effectiveness of TCAs, however, may be offset by the significant incidence of adverse events, risk for overdose, and poor compliance rates.

An 8-week study of amitriptyline versus placebo in war veterans (N=46) found amitriptyline (mean dose=169 mg/day) superior to placebo in completers (n=33) based on IES, CGI, Hamilton Rating Scale for Depression, and HAM-A scores.[37] There are no published studies showing efficacy in trials >12 weeks.

Monoamine Oxidase Inhibitors

Phenelzine has demonstrated efficacy in the treatment of PTSD in a small 8-week study comparing the effects of phenelzine (n=19) with the TCA imipramine (n=23) and placebo (n=18).[50] PTSD symptoms, as assessed by improvement in IES score from baseline, were significantly reduced in the phenelzine (44%) and imipramine (25%) treatment groups, while there was some reduction with placebo (5%). The intrusion (but not avoidance) subscale of the IES showed significant improvement; initial mild to moderate depressive symptoms did not significantly improve. At endpoint, CGI-I showed similar improvement with both imipramine and phenelzine (65% and 68%, respectively), while 28% of the placebo group was rated as improved.

Two RCTs have studied the effects of the selective reversible MAOI brofaromine on PTSD. A 12-week study, comprised mostly of combat veterans, did not demonstrate any significant differences between brofaromine and placebo on PTSD-specific measures (CAPS-2),[51] although it did show greater efficacy on the CGI-I.[52] In a 14-week European study, the drug effect was more robust on the civilian population CGI-I.[57] However, the manufacturer terminated further clinical development of brofaromine based on the results of depression trials, and it is no longer available.[52]

Other Agents

Buspirone, a 5-HT_{1A} partial agonist, has shown limited benefit in treating hyperarousal symptoms of PTSD in an open-label study. Several benzodiazepines have been studied in small-scale, short-term clinical trials. However, the lack of demonstrated efficacy and difficulties associated with discontinuation of treatment limit the use of these drugs in PTSD.[54-56]

Mood stabilizers may be particularly effective as single or adjunctive medication for the explosive behavior common in PTSD.[57] The anticonvulsants carbamazepine and sodium valproate have shown positive results in small, open-label trials in combat veterans. Another anticonvulsant, lamotrigine (up to 500 mg/day), has been examined in a small (N=15), 12-week, double-blind, placebo-controlled pilot study of civilians with PTSD.[58] The response rate in patients receiving lamotrigine was twice as high compared with patients receiving placebo (50% versus 25%, respectively), as assessed by the DUKE. Lamotrigine demonstrated greater efficacy for the re-experiencing and avoidance/numbing symptom clusters. Further large, double-blind RCTs are required to confirm the usefulness of lamotrigine as a primary or adjunctive treatment for patients with PTSD.

Long-Term Treatment Trials

Very few trials have investigated whether long-term pharmacologic treatment of PTSD is efficacious and safe. Only sertraline has been studied for up to 1 year, in both continuation and relapse-prevention design studies (Table[59,60]). In the continuation trial, 249 outpatients with PTSD who completed one of two 12-week, randomized, double-blind studies of sertraline and placebo were eligible to enter a 24-week open-label trial of sertraline (50–200 mg/day).[59] Significant improvement with sertraline was observed both in patients who had received sertraline and in those who had received placebo in the 12-week feeder studies. At endpoint, patients in the 24-week open-label study showed significant and substantial improvement ($P<.05$) from baseline on CAPS-2, CGI-S, CGI-I, and IES. The data indicated that 92% of patients who responded to acute-phase treatment with sertraline sustained their initial response. Furthermore, 54% of patients who failed to respond to acute treatment with sertraline were converted to responders in the continuation phase.[63] Sertraline was well tolerated, with discontinuation due to adverse events observed in only 8.6% of patients.

In a relapse-prevention design study, 96 outpatients who had completed and responded to 24 weeks of open-label continuation treatment with sertraline[59] were randomized to receive sertraline (50–200 mg/day) or placebo for an additional 28 weeks.[60,61] Kaplan-Meier analyses were used to estimate time to relapse, rates of relapse or discontinuation due to clinical deterioration, and acute exacerbations. Patients who continued sertraline treatment for a further 28 weeks maintained their improvements. The proportion of patients who relapsed on sertraline (5%) was

significantly lower (P=.02) than the proportion of patients who relapsed on placebo (26%): patients receiving placebo were 6.4 times as likely to experience a relapse as patients receiving sertraline. Patients receiving placebo also relapsed or discontinued due to clinical worsening significantly earlier than patients receiving sertraline. Mean changes in secondary endpoints on CAPS-2, CGI-I, CGI-S, and IES were significantly different between the two groups. Sertraline's ability to sustain improvements was comparable across all three core PTSD symptom clusters. Sertraline was well tolerated, with no treatment-emergent, treatment-related adverse events observed at a rate ≥10%.

Changes in quality of life and psychosocial functioning across 64 weeks (12-week double-blind acute phase followed by a 24-week open-label continuation phase and a 28-week double-blind relapse-prevention phase) of sertraline treatment (50–200 mg/day) were also examined.[62] Patients were assessed using the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), and the Medical Outcomes Study 36-Item Short Form. At the end of 12 weeks, 58% of sertraline responders had achieved a Q-LES-Q total score within 10% of community norms. Continuation treatment for 24 weeks led to an additional 20% improvement in quality of life and functional measures. Overall, sertraline treatment resulted in sustained and progressive improvement in quality of life and functional measures during >12 months of treatment.

PSYCHOTHERAPY

Psychotherapy is recommended as a first-line treatment for mild and sometimes moderate PTSD and in combination with pharmacotherapy in more severe cases.[35] Cognitive-behavioral therapy (CBT), including exposure therapy, anxiety management, and cognitive therapy, focuses on the traumatic event and is effective in the management of PTSD.[23] CBT is generally short term, averaging 8–12 sessions held once or twice a week.[36] To alleviate such symptom subsets as anger and interpersonal problems, long-term supportive therapies are recommended for prolonged, complex, and intractable PTSD.[23]

Exposure Therapy

Exposure therapy is designed to help the patient confront certain situations, people, objects, memories, or emotions that have become associated with the stressor and now evoke an unrealistically intense fear. This can be done either by repeated emotional recounting of the traumatic experiences until they no longer provoke high stress, or by confrontations with the actual triggers that are now safe but are being actively avoided by the patient.

Several studies have investigated the effects of exposure therapy in veterans from the Vietnam War with PTSD.[63] These studies indicated that exposure therapy was effective in reducing PTSD symptoms in this population, but therapeutic effects were modest.[64] In a study by Foa and colleagues[65] comparing the effect of exposure therapy with stress inoculation therapy in female assault victims, exposure therapy, stress inoculation therapy, and a combination of the two all reduced the severity of PTSD and depression to a similar extent while a wait-list control group saw no improvement. These effects were maintained at 6- and 12-month follow-up. In the more rigorous ITT analysis, however, exposure therapy was superior to the other treatments in improving posttreatment anxiety and global social adjustment, and had larger effect sizes on PTSD severity, depression, and anxiety.

Anxiety Management

Anxiety management (or stress inoculation training) teaches a set of skills that help the patient cope with stress, including relaxation training, breath training, positive thinking, assertiveness training, and negative-thought stopping. As described in the preceding section on exposure therapy, Foa and colleagues[65] found that anxiety management was as effective as exposure therapy at reducing the severity of the symptoms of PTSD, although results in

TABLE. LONG-TERM TREATMENT TRIALS OF PHARMACOTHERAPY FOR PTSD

Authors (Year)	N	Study Drug	Comparator	Study Design	Study Duration
Londborg et al (2001)[59]	249	Sertraline	None	RCT→ OL	12-wk RCT acute phase + 24-wk OL continuation phase
Davidson et al (2000)[60]	96	Sertraline	Placebo	OL→RCT	12-wk RCT acute phase + 24-wk OL continuation phase + 28-wk RCT relapse-prevention phase

PTSD= posttraumatic stress disorder; RCT=randomized controlled trial; OL=open-label; wk=week; CAPS-2=the Clinician-Administered PTSD Scale, Part 2; CGI=Clinical Global Impression–Improvement; CGI-S=Clinical Global Impression–Severity; IES=Impact of Event Scale–Revised.

the intent-to-treat sample indicated that exposure therapy was more effective.

Cognitive Therapy

Cognitive therapy aims to help modify unrealistic assumptions, beliefs, and automatic thoughts that lead to disturbing emotions. The goal of cognitive therapy is to teach patients to identify their own particular illogical and unrealistic thought processes and adopt more realistic responses that will generate more balanced emotions.

In one study of victims of mixed traumas with PTSD, 10 weekly sessions of prolonged exposure were compared with cognitive restructuring, a combination of the two therapies, and relaxation control.[66] Exposure therapy and cognitive restructuring singly or combined improved symptoms of PTSD markedly, but the two therapies were no more effective when combined. At 6-month follow-up, the group that received exposure therapy alone seemed to maintain its gains to a greater extent than the group that received cognitive therapy alone.

OVERVIEW OF AVAILABLE TREATMENT GUIDELINES

Relatively few guidelines on the treatment of PTSD have been published.[35,36] Practice Guidelines from the International Society for Traumatic Stress Studies recommend SSRIs as first-line treatment for PTSD in civilians[36]; evidence for their use in veterans is difficult to interpret due to the severity and chronicity of PTSD in the veteran cohorts tested thus far. In addition, the guidelines strongly recommend the use of some form of exposure therapy in the treatment of PTSD.

In 1999, over 100 psycho- and pharmacotherapy experts were surveyed, resulting in publication of the Expert Consensus Guidelines for the treatment of PTSD.[35] These guidelines recommend psychotherapy as a first-line treatment for mild PTSD or a combination of psycho- and pharmacotherapy for patients with more severe or chronic problems. In terms of pharmacotherapy, SSRIs are the first-line choice regardless of the type of symptom that is most prominent. If the patient responds only partially, treatment may be augmented with the addition of another medication or combined with psychotherapy. The most highly recommended adjunctive medication is a mood stabilizer. For patients not responding to the maximum tolerated dose of the initial treatment, switching to a different SSRI or other medication, or different psychotherapy, is recommended. Regarding treatment duration, continuing medication for at least 12 months is recommended before dose tapering can be considered. In chronic PTSD with residual symptoms, treatment for at least 24 months is recommended before considering treatment withdrawal.

CONCLUSION

PTSD is a commonly unrecognized, chronic condition that has a profound effect on the quality of life of the individual sufferer. In addition, PTSD is associated with significant disability, increased healthcare utilization and costs, and reduced productivity. Psychotherapy and pharmacotherapy, both separately and in combination, are recommended to treat the symptoms of PTSD. The SSRIs sertraline, paroxetine, and fluoxetine have demonstrated their efficacy in the treatment of PTSD in randomized acute treatment trials. Sertraline is the only SSRI for which long-term efficacy has been demonstrated in both continuation and relapse-prevention trials. Despite the lack of long-term RCTs, current guidelines from the Expert Consensus Panel for PTSD recommend that pharmacotherapy be continued in chronic PTSD for a minimum of 12–24 months and that for CBT, "booster sessions" should be provided as needed.[35] Further research is needed to optimize the treatment of the sub-groups of PTSD patients who do not respond to initial treatment with an SSRI or CBT. Additional long-term RCTs are also required to provide further clarification of the most appropriate treatment strategies for patients suffering from PTSD. CNS

Main Efficacy Variables	Efficacy Outcome	Tolerability Outcome
CAPS-2 CGI-I CGI-S IES	92% of acute-phase responders maintained response during continuation phase 54% of patients who failed to respond to acute phase treatment with sertraline converted to responders	8.6% of patients discontinued due to adverse events adverse events: upper respiratory tract infection, (24.2%), headache (22.7%), ejaculatory failure in males (17.6%), insomnia (17.2%), diarrhea (16.4%), nausea (2.5%), malaise (10.9%), fatigue (10.9%), dry mouth (10.9%), dizziness (10.2%)
12-wk study: CAPS-2 CGI-I CGI-S IES 28-wk study: all above plus time to and rate of relapse	>Placebo	No treatment-emergent, treatment-related adverse events at a rate ≥10% for sertraline-treated patients

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WCA Recommendations for the Long-Term Treatment of Social Phobia

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FOCUS POINTS

- Selective serotonin reuptake inhibitors are the drugs of first choice in the treatment of social phobia, paroxetine being the only one approved by the Food and Drug Administration for this indication.
- Sertraline, clonazepam, phenelzine, and moclobemide have also been studied in long-term randomized clinical trials.
- Cognitive-behavioral therapy has demonstrated efficacy in randomized clinical trials but has limited availability
- Current guidelines recommend that pharmacotherapy be continued for a minimum of 12 months after symptoms end.
- More controlled research is needed on the relative and combined short- and long-term efficacy of pharmacologic and psychologic treatment for social phobia.

ABSTRACT

What is the best approach for treating patients with social phobia (social anxiety disorder) over the long term? Social phobia is the most common anxiety disorder, with reported prevalence rates of up to 18.7%. Social phobia is characterized by a marked and persistent fear of being observed or evaluated by others in social performance or interaction situations and is associated with physical, cognitive, and behavioral (ie, avoidance) symptoms. The onset of social phobia typically occurs in childhood or adolescence and the clinical course, if left untreated, is usually chronic, unremitting, and associated with significant functional impairment. Social phobia exhibits a high degree of comorbidity with other psychiatric disorders, including mood disorders, anxiety disorders, and substance abuse/dependence. Few people with social phobia seek professional help despite the existence of beneficial treatment approaches. The efficacy, tolerability, and safety of the selective serotonin reuptake inhibitors (SSRIs), evidenced in randomized clinical trials, support these agents as first-line treatment. The benzodiazepine clonazepam and certain monoamine oxidase inhibitors (representing both reversible and nonreversible inhibitors) may also be of benefit. Treatment of social phobia may need to be continued for several months to consolidate response and achieve full remission. The SSRIs have shown benefit in long-term treatment trials, while long-term treatment data from clinical studies of clonazepam are limited but support the drug's efficacy. There is also evidence for the effectiveness of exposure-based strategies of cognitive-behavioral therapy, and controlled studies suggest that the effects of treatment are generally maintained at long-term follow-up. In light of the chronicity and disability associated with social phobia, as well as the high relapse rate after short-term therapy, it is recommended that effective treatment be continued for at least 12 months.

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INTRODUCTION

Social phobia (social anxiety disorder) is a chronic and highly prevalent disorder that is often associated with significant psychosocial impairment.[1] Although highlighted as a substantial public health problem by many researchers,[2,3] social phobia remains widely underrecognized and undertreated.[4] Very little had been known about cultural differences in the prevalence of social phobia, but increased cross-cultural awareness and information regarding prevalence, presentation, and diagnosis of the disorder are now becoming available.[5]

Only a small proportion of people with social phobia seek professional treatment.[6-9] The reason for this is unclear, but theories suggest that the fear of social situations extends to help-seeking situations,[10] or that affected individuals do not define their anxiety as an illness.[6] Among patients with symptoms of social phobia, those with agoraphobia appear to be the most likely to seek treatment,[6] perhaps because symptoms of agoraphobia may be more easily recognized as deviations from normal behavior. Interestingly, patients with social phobia are more likely to be recognized by their primary care physician if they have a comorbid condition such as major depression.[11]

CLINICAL PRESENTATION AND DIAGNOSIS

Social phobia is characterized by a marked and persistent fear of being observed or evaluated by others in social performance or interaction situations.[12,13] The individual fears acting in a way that will cause him or her to be humiliated or embarrassed, or exhibit anxiety symptoms, and consequently seeks to avoid situations where close scrutiny, whether real or

These recommendations are based on proceedings from the World Council of Anxiety meeting held September 11, 2000, in Pisa, Italy, and on guidelines and articles published in the medical literature through October 15, 2001.

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imagined, might take place. The majority of patients with social phobia experience onset in childhood or adolescence,[6,14] a critical time in terms of social and academic development. Onset at this impressionable age contributes to the significant interference of this disorder in the patient's personal, academic, and professional life.

The key diagnostic criteria for social phobia in both the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*)[12] and the *International Classification of Diseases*, Tenth Revision (*ICD-10*)[13] are mostly similar but have the following differences:

(A) The *DSM-IV*[12] requires the presence of significant interference with the patient's normal routine, occupational (or academic) functioning, or social activities/relationships, while the *ICD-10*[13] cautions against the use of lifestyle impairment as a diagnostic criterion because of its dependence on the social environment, which may be influenced by culture and differ according to the social situation[15];

(B) The *ICD-10*[13] recognizes specific physical symptoms (eg, blushing), while the *DSM-IV*[12] refers to anxiety symptoms that may take the form of a panic attack;

(C) The *ICD-10*[13] diagnosis requires one of the following symptoms: persistent fear of social situations, fear of humiliation, or avoidance of social situations, while *DSM-IV* criteria[12] stipulate that all three symptoms be present.

SYMPTOMS

Social phobia is characterized by the presence of physical, cognitive, and behavioral (avoidance) symptoms. The physical symptoms may resemble anxiety attacks and include blushing, sweating, shaking, palpitations, nausea, diarrhea, and speech block.[16,17] Increased heart rate and blood pressure are also associated with social phobia when subjects are exposed to their feared stimuli.[17] Maladaptive thoughts about social situations are important cognitive symptoms.[16]

Significant functional impairments are associated with social phobia, particularly in the areas of partner and family relationships, education, and career development.[1,15,18-20] People with social phobia have been reported to achieve lower-than-average educational levels and have less stable employment histories compared with the general population.[19,20] Most of these patients have lower socioeconomic status, with >70% falling into the lower half of the population in terms of socioeconomic achievement.[17] Furthermore, suicidal ideation has been shown to occur more frequently in people with social phobia than in the general population.[21] In one study, an increase in the number of suicide attempts was observed in patients with social phobia and a comorbid condition such as depression.[21]

SUBTYPES

Two subtypes of social phobia are recognized: a nongeneralized (discrete/specific) form and a generalized form,[12,16] although the *ICD-10* does not differentiate between the two.[13] The nongeneralized form usually involves fear of public performance (eg, public speaking), when scrutiny by others may be possible.The generalized subtype, found in ~50% of lifetime cases of social phobia, is more severe and complex, and is characterized by strong fear and avoidance of multiple social interactional and performance situations.[10] The generalized form of social phobia is usually more functionally disabling, familial, and longer lasting than the nongeneralized, specific subtype; there is a lesser chance of spontaneous recovery with this subtype and it is associated with a higher risk of comorbidity and impairment.[3,22]

Findings from a large community survey (N=1,956) indicate that delineation of the two subtypes appears to be somewhat arbitrary[1] because a continuum of severity associated with a greater number of feared situations and greater disability is seen with social phobia. There is currently no definitive threshold demarcating the two subtypes, though a preliminary receiver operating characteristic analysis[23] suggests that a cut score of 60 on the Liebowitz Social Anxiety Scale (LSAS) may be a useful method for identifying the generalized subtype, with a sensitivity of 73% and a specificity of 74%.

DIFFERENTIAL DIAGNOSIS

While differentiating social phobia from other anxiety disorders can be difficult, the context of the symptoms provides important diagnostic clues. The differentiation of social phobia from normal shyness is a qualitative and quantitative issue related both to the type of fear and avoidance behavior and the level of distress and impairment associated with social fears.

The most difficult differential diagnostic consideration is the potential confusion with panic disorder with or without agoraphobia.[17] Several features are common to social phobia and panic disorder: individuals with either disorder may experience panic attacks, comorbid depression, distress in social situations, substance abuse, and suicidal ideation.[23] However, a diagnosis of panic disorder requires a history of unexpected panic attacks that do not occur exclusively in social situations.[12] It is also helpful for a clinician to ask patients what they fear in a given situation. Generally, patients with social phobia fear humiliation and embarrassment, while those with panic disorder fear the potential medical consequences of their panic attack symptoms.[17] In addition, the mean age of onset is younger for social phobia (15.6 years; standard deviation [SD]=9.9) than for panic disorder (29.57 years; SD=9.5).[23,24] Response to deliberate provocation, course, and response to treatment, as well as six specific symptoms (palpitations, chest pains, tinnitus, blurred vision, headaches, fear of dying, dry mouth) also help to distinguish between the two disorders,[24-26] as does the presence of flushing and tremor in some cases.[27]

Social phobia commonly overlaps with avoidant personality disorder (APD). The *DSM-IV* indicates that APD should also be considered as an additional diagnosis in persons with generalized social phobia; the two diagnostic groups do not appear to differ qualitatively in any significant way.[12,28]

Other potential differential diagnoses for social phobia are described in a review by Moutier and Stein[28] and include major depression with social withdrawal, generalized anxiety disorder, obsessive-compulsive disorder, body dysmorphic disorder, medical conditions such as Parkinson's disease, and paranoid symptoms in psychoses (the feeling of being observed by others).

Differences in the phenomenology of anxiety symptoms may also come with age (eg, elective mutism in children or adolescents)[29,30] and culture (eg, in the Japanese culture, "taijin kyofusho," which is a fear of offending or hurting others through one's awkward social behavior or an imagined physical defect).[31,32]

EPIDEMIOLOGY

Estimates of the prevalence of social phobia have recently been refined by large-scale epidemiological studies of psychiatric disorders, which have found the disorder to be common within the community.[1,33] Social phobia is the most prevalent of the anxiety disorders[34] and, according to the US National Comorbidity Survey, is the third most common psychiatric disorder after major depression and alcohol dependence.[35] However, it remains underrecognized and undertreated.[4] Because only a small proportion of people with social phobia seek treatment,[6] it is unlikely that those treated are representative of the majority of people affected by the disorder.[1]

Previously, the reported prevalence of social phobia ranged from 1.9% to 18.7%, as a result of differing diagnostic thresholds and variations in the stringency of the definitions of distress and impairment.[1,3,6,7,22,36] Most early studies were based on *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (*DSM-III*)[37] criteria assessed with the Diagnostic Interview Schedule (DIS), which covered only three social fear situations; estimates of prevalence from these studies are therefore regarded as somewhat conservative.[1] This underestimation was corrected in the successor to the DIS, the Composite International Diagnostic Interview (CIDI) of the World Health Organization (WHO), which includes a wider range of social situations and therefore yields considerably higher estimates.[6,7]

In epidemiological samples, there is a higher prevalence of social phobia in females than in males, but in clinical samples the gender distribution is equal, perhaps due to selection and/or recognition bias in clinical settings.[3,8] Rates of social phobia are consistently higher in younger- versus older-age cohorts and are inversely associated with socioeconomic status.[1,3,8]

Recent cohorts have reported a higher lifetime prevalence of generalized social phobia than in the past.[9,38] Current estimates place the point prevalence of social phobia at 4% to 6% and the lifetime risk between 7% and 13%.[39] People with social and economic advantages (eg, white, educated, married status) appear to be at greater risk for social phobia; this finding is not explained by increased comorbidity with other mental disorders.[38]

CLINICAL COURSE

Natural course studies show that the onset of social phobia typically occurs in the early teenage years,[3,10] although affected individuals who seek treatment frequently wait until later in life to do so.[2,9] Social phobia tends to follow a chronic course and demonstrates high levels of comorbidity with other anxiety, mood, and substance abuse disorders. It has been hypothesized that social phobia increases the risk for onset of secondary mood disorders.[40] Therefore, a relationship can be expected between primary social phobia and the subsequent onset, course, and severity of secondary disorders. This, in turn, is a strong predictor of the chronicity of social phobia[9,41] The US National Comorbidity Survey (NCS)[40] showed that ~27% of patients who have lifetime major depression, 29% patients with dysthymia, and 47% patients with bipolar disorder, also have social phobia. Additionally, 34% of patients with social phobia, compared with about 15% patients without social phobia, have a mood disorder.

The combination of high prevalence, early onset, and a chronic lifetime course, as well as risks of comorbidity, underdiagnosis, and low probability of treatment, make social phobia important from a public health perspective.[2,3,17] Social phobia is associated with lost wages, reduced productivity, increased disability, and lower quality-of-life indices.[29] Individuals with generalized social phobia earn salaries 19% lower than those without the disorder.[42] The costs of these impairments are not restricted to individual patients but also affect employers, health insurance providers, and the national economy.[43,44]

NEUROBIOLOGICAL BASIS

Social phobia is poorly understood from a neurobiological perspective. Although selective serotonin reuptake inhibitors (SSRIs) are successfully as pharmacologic treatment, it is unknown whether this condition—and therefore the success of treatment with SSRIs—is associated with alteration of serotonin (5-HT) neurotransmission.[45] Researchers have recently begun to explore the underlying neurobiology of the disorder, employing various approaches, including assessment of central neurotransmitter function, response to chemical and neuroendocrine challenges, and functional neuroimaging.[44,46-48] Current neurobiological evidence, however, suggests that there are abnormalities in the dopamine and serotonin systems of these patients.[49,50]

COMORBIDITY

Mood and Anxiety Disorders

Individuals with social phobia are at increased risk for other psychiatric disorders, with mood disorder (particularly major depression) being the most common other lifetime diagnosis.[2,8,45] Epidemiological and clinical samples suggest that more than one third of people with social phobia report a lifetime mood disorder (34% in the NCS,[2] 35% in a clinical study by Stein and colleagues,[51] and as high as 83% in a study by van Ameringen and colleagues[52]). Social phobia also exhibits a high degree of comorbidity with other anxiety

disorders,[33] particularly with panic disorder and generalized anxiety disorder, with a reported lifetime prevalence of 50% and 32%, respectively, in one clinical sample.[52]

In both clinical and epidemiological samples, social phobia occurs prior to any episode of mood or other anxiety disorder in the majority of individuals,[2,40,52] although this observation should be treated with caution as it is based on retrospective analyses. It suggests, however, that in most individuals there is a window of opportunity to treat social phobia prior to the onset of a secondary mood or anxiety disorder.[40]

Substance Abuse Disorders

Individuals affected by social phobia may self-medicate with alcohol or other substances to relieve their anxiety.[21] Substance and alcohol abuse are more common lifetime diagnoses in these individuals than in the general population.[45] In patients with social phobia, the incidence of alcoholism has been reported to range from 14% to 40%.[53] Although the relationship between alcohol dependence and social phobia is complex, many patients must drink before entering social situations. Social phobia has also been found to be associated with heavy smoking and nicotine dependence in both cross-sectional retrospective and prospective-longitudinal analyses.[54,55] Additionally, the failure rate of smoking cessation (89%) is higher in individuals with social phobia than in the general population.[55]

TREATMENT OPTIONS

Increased awareness of social phobia has led to a delineation of disease subtypes and research on its treatment.[16] A number of treatment approaches have been demonstrated to be beneficial for social phobia, including pharmacotherapy, psychotherapy, or a combination of both.

The rating instruments most commonly used to assess treatment effects in published pharmacologic studies of social phobia include the LSAS,[56] the Brief Social Phobia Scale (BSPS),[57,58] and the Fear Questionnaire (FQ)[59]

PHARMACOTHERAPY

Although a number of pharmacologic agents have been investigated in the treatment of social phobia, very few are currently licensed for this indication and most prescribing is off-label.[60] The current body of knowledge on pharmacotherapeutic intervention is based predominantly on short-term clinical trials investigating the generalized subtype of social phobia.

Acute Treatment Trials

Selective Serotonin Reuptake Inhibitors

Clinical trials have demonstrated the efficacy, tolerability, and safety of SSRIs in social phobia and consistently support their use as first-line treatment.[16]

In an early double-blind crossover study,[61] 12 outpatients were randomly assigned to 10 weeks of sertraline (50–200 mg/day, flexible dosing) and 10 weeks of placebo. The results indicated that sertraline was effective and well tolerated.[61]

Paroxetine was the first SSRI to gain approval for the treatment of social phobia (May 1999) and is approved for this indication in 35 countries, including Canada, Germany, the US, and the United Kingdom. Evidence of paroxetine's effectiveness first arose from open-label studies.[62,63] Subsequently, three 12-week, double-blind, placebo-controlled, flexible-dose trials consistently demonstrated that paroxetine (20–50 mg/day) is both effective and well tolerated in the acute treatment of social phobia.[64-66] The first involved 183 participants, the second included 92 participants, and the third included 290 subjects, demonstrating paroxetine's efficacy in a total of 565 participants. Of the 183 patients for whom efficacy data were available in a study by Stein and colleagues,[64] 55% of those receiving paroxetine versus 22% of patients taking placebo were responders (based on Clinical Global Impression-Improvement scale [CGI-I] score <2 [much or very much improved]) at the end of 12 weeks of treatment (P=.001). In addition, mean change from baseline on the LSAS was significantly greater (P<.001) in paroxetine-treated patients (30.5±2.66) than in placebo-treated patients (14.5±2.63). Paroxetine treatment also resulted in significant improvement in five of six secondary efficacy measures and did not cause any unusual adverse events. At study endpoint, the mean dose of paroxetine was 36.6±12.1 mg. The results of a fourth 12-week study in which 384 patients were randomized to fixed-doses of paroxetine found comparable CGI-I responder rates on the 20- (45%), 40- (47%), and 60-mg dose (43%).[67] The higher response rates when flexible doses of paroxetine were employed (in the range of 50% to 55%) suggest that even though no dose-response group effect was observed, many individual patients apparently benefit from the ability to titrate to higher doses.

Sertraline is also FDA approved for the treatment of social phobia (February 2003). After an early sertraline crossover study by Katzelnick and colleagues,[61] subsequent evidence of sertraline's efficacy in the treatment of generalized social phobia was supported by findings from a 20-week, double-blind, placebo-controlled study involving 204 patients.[68] At the end of the study, significantly more patients randomized to sertraline (50–200 mg/day) were responders based on CGI-I criteria. In addition, significantly greater reductions were reported in the MFQ social phobia subscale (MFQ-SP) and BSPS among sertraline-treated patients. It was observed that 53% (71/203) of sertraline-treated patients and 29% (20/203) of placebo-treated patients were responders at endpoint. Thirty percent of sertraline-treated patients compared with 13% of placebo-treated patients showed marked clinical improvement. The sertraline group demonstrated mean reductions of 32.6% and 34.3% in the MFQ-SP and BSPS, respectively, compared with reductions of 18.8% and 18.6% for the placebo group. Overall, sertraline was well tolerated with no differences in discontinuation rates compared with placebo-treated patients.

These results were confirmed by findings from a randomized, double-blind, placebo-controlled trial of flexible-dose

sertraline (50–200 mg) in patients with moderate-to-severe generalized social phobia, as evidenced by a baseline LSAS score of 91, which is the highest among published data seen in SSRI trials.[69] Sertraline was shown to be highly efficacious and well tolerated. At last-observation-carried-forward endpoint, sertraline-treated patients showed significantly higher CGI-I response rates than placebo-treated patients (47% versus 26%; *P*<.001), as well as greater decreases in mean LSAS total score (-31 versus -21). At week 12, the mean change in LSAS total score was significantly greater in the sertraline group than in the placebo group (-34 versus -23; *P*<.001), as was the percentage of CGI-I responders (56% versus 29%; *P*<.01). Sertraline was also superior to placebo on such secondary efficacy measures as the BSPS and Hamilton Anxiety and Depression rating scales, and on quality of life and functional measures, including the Quality of Life, Enjoyment, and Satisfaction Questionnaire and the Sheehan Disability Inventory.

Finally, a third placebo-controlled trial[70] examined the efficacy of sertraline (50–150 mg/day for 24 weeks) with or without exposure therapy in 387 patients in the general practice setting. This trial confirmed the efficacy of sertraline over placebo (*P*<.001) in the treatment of generalized social phobia.[70]

Fluvoxamine (100–300 mg/day) has also been shown to be effective, safe, and generally well tolerated in the short-term pharmacologic management of social phobia in a number of randomized, double-blind, placebo-controlled trials.[71,72] In each trial, there was a significantly higher proportion of responders in the fluvoxamine group than in the placebo group, with statistically significant effects seen on social phobia and psychosocial disability rating scales at 12-week trial endpoints.

The efficacy of citalopram in social phobia has not been well documented. Case series[73-75] indicate that citalopram may be effective at doses of 20–40 mg/day, but controlled trials are needed to confirm these data. Similarly, findings from a number of small, short-term, open-label trials of fluoxetine (up to 80 mg/day) have suggested potential efficacy in social phobia,[76-78] but no double-blind studies have been published.

Reversible Inhibitors of Monoamine Oxidase Type A

Four placebo-controlled studies of moclobemide, a reversible inhibitor of monoamine oxidase type A (RIMA), achieved varied results (reviewed in van der Linden and colleagues[79]). Moclobemide 600 mg/day has been reported to yield a 52% response rate (*P*=.0022 versus placebo) in a severely affected subset of patients compared with response rates of 37% for 300 mg/day moclobemide (*P*=.2016 versus placebo) and 30% for placebo,[80] and has shown superiority versus placebo beginning at week 4 in a trial by Versiani and colleagues.[81] However, these positive effects have not been supported by findings from other placebo-controlled studies.[82,83] A large (N=523) multicenter study showed that 35% of subjects taking the highest dose of moclobemide (900 mg/day) and 33% of placebo-treated patients were CGI-I responders after 12 weeks of treatment.[84] An even smaller clinical effect (CGI-I responder rates of 17.5% for moclobemide versus 13.5% for placebo; *P*=not significant) was observed by Schneier and colleagues.[83]

Phenelzine and moclobemide were compared in a double-blind, placebo-controlled, parallel-group trial that enrolled 78 patients with social phobia and lasted more than 24 weeks.[83] Patients were treated for 8 weeks initially (mean dose at end of the first phase was 580.7 mg/day for moclobemide and 67.5 mg/day for phenelzine), after which nonresponders (as measured by CGI) were withdrawn from the study. The efficacies of moclobemide and phenelzine were statistically comparable for most outcome measures and significantly superior to placebo from week 4 onward. Moclobemide was tolerated much better than phenelzine and had fewer and milder side effects than monoamine oxidase inhibitors (MAOIs).[84]

Brofaromine is another RIMA that has been studied in the treatment of social phobia. In a 12-week, double-blind, placebo-controlled trial in 30 patients with *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition-Revised (*DSM-III-R*)[85] social phobia, brofaromine (150 mg/day) led to "clinically relevant improvement" in 80% of patients.[86] Significant improvement was observed in social phobia, phobic avoidance, general anxiety, and interpersonal sensitivity measures in brofaromine- but not placebo-treated patients.

In another 12-week, double-blind, placebo-controlled study of brofaromine 150 mg/day administered to 77 patients with a *DSM-III-R* diagnosis of social phobia, 78% of brofaromine-treated patients were CGI-I responders compared with 23% of placebo-treated patients.[87] Significant improvement with brofaromine treatment compared with placebo was also observed on the LSAS and the Montgomery-Asberg Depression Rating Scale. However, brofaromine has been withdrawn from the worldwide market and is currently unavailable.

Monoamine Oxidase Inhibitors

A number of studies have demonstrated the superior efficacy of MAOIs (phenelzine,[88,89] tranylcypromine[90]) in treating generalized social phobia. However, because of significant adverse events and interactions, these agents are generally reserved for patients who are refractory to other treatment options.[91]

The efficacy of the irreversible, nonselective MAOI phenelzine (up to 90 mg/day) was first indicated in 1985 by results from a small open-label pilot study.[92,93] The first published placebo-controlled study that evaluated phenelzine for social phobia compared pharmacotherapy with phenelzine or alprazolam with cognitive-behavioral group therapy (CBGT) in 65 patients.[94] All treatments, including pill placebo, were associated with substantial improvements in patients with severe and chronic social phobia; self-directed exposure was strongly encouraged among all participants, which probably contributed to this observation. Although all treatments significantly improved symptoms of social phobia and a trend toward greater efficacy with phenelzine was observed, the results did not favor any one treatment.

Phenelzine 15–90 mg/day was subsequently shown to be effective in a 12-week placebo-controlled trial enrolling 133 patients, which also compared treatment with cognitive-behavioral therapy (CBT).[88] At endpoint, phenelzine was associated with superior response rates (Social Phobic Disorders Severity and Change Form) compared with placebo (65% versus 33%, respectively; $P<.005$) and greater change on dimensional measures (Anxiety Disorders Interview Schedule-Revised, Clinician's Severity Rating, and LSAS). Response to phenelzine was more evident than response to CBT after 6 weeks (35% versus 59%, respectively; $P<.03$) and was superior at 12 weeks on several measures (LSAS social avoidance and social fear), although both treatments were more efficacious than control conditions (pill placebo or placebo attention treatment).

Results of a multiphase, placebo-controlled, comparative trial (N=74) of phenelzine (up to 90 mg/day) and the β-blocker atenolol (up to 100 mg/day) in patients with *DSM-III* social phobia were described in a series of reports by Liebowitz and colleagues.[89,95,96] The overall CGI-I responder rate at 8 weeks for phenelzine was 64%, superior to both atenolol (30%) and placebo (23%). Patients who responded to treatment at the end of 8 weeks were continued on the same dosage in an 8-week double-blind maintenance phase. At the end of 16 weeks, phenelzine was still significantly superior to placebo. Patients with generalized social phobia constituted 76% of the sample and were preferentially responsive to phenelzine.

Benzodiazepines

Although only limited studies have been conducted to date,[97-99] benzodiazepines, such as clonazepam, have been reported to be effective in the treatment of social phobia. Benzodiazepines are not recommended as first-line agents because they do not also treat associated comorbid conditions, such as major depression and obsessive-compulsive disorder, and because of tolerability/dependence issues. Benzodiazepines may, however, benefit patients who are refractory to other treatments, and they may be useful as augmenting agents.[17,91] However, benzodiazepines may be associated with long-term dependence.[17,91]

In a 10-week double-blind pilot study enrolling 75 patients with social phobia, clonazepam (2.4 mg/day mean maximum dose at endpoint) was reported to yield a 78% CGI-I responder rate compared with a 20% response rate with placebo ($P=.0001$).[98] Although unsteadiness and dizziness were reported, clonazepam was generally well tolerated. In a 2-year follow-up of 56 patients (75%), subjects initially treated with clonazepam were reported to exhibit significantly less severe social phobia scores (LSAS, FQ, and Sheehan Disability Scale [SDS]) compared with placebo subjects, suggesting evidence of long-term benefit.[100]

In the only double-blind, placebo-controlled trial of alprazolam,[94] the response rate was only 38% compared with 69% for phenelzine, 24% for CBT, and 20% for placebo ($P<.09$).

Other Medications

Tricyclic antidepressants, shown to be effective in other anxiety disorders, have not been extensively investigated in social phobia in double-blind, placebo-controlled trials.[15] The efficacy of imipramine in social phobia was not supported by a small, 8-week, open-label study (N=15).[101] A number of other agents, including venlafaxine[102-104] and mirtazapine,[105] are in the early stages of evaluation for the treatment of social phobia.

β-blockers (eg, atenolol), sometimes used in clinical practice for the treatment of social phobia, may be effective for performance anxieties, such as public speaking fears.[19] However, they do not appear to have efficacy in generalized social anxiety disorder and are not indicated for its treatment.[16,106-107] A small (N=16) placebo-controlled trial did not reveal any additional benefits from the adjunctive use of propranolol in individuals with social phobia who underwent a 4-week course of social skills training.[108] Furthermore, a study comparing the efficacy of either phenelzine or the cardioselective β-adrenergic blocker atenolol with placebo in 74 patients with *DSM-III* social phobia found that while phenelzine was significantly more effective than atenolol and placebo, atenolol was not significantly more effective than placebo.[96]

Finally, the results of a 12-week, follow-up, double-blind, placebo-controlled study[109] of a small (N=21) open-label trial did not confirm the previously observed modest efficacy of the azaspirone anxiolytic buspirone in the treatment of social phobia.[110]

Anticonvulsants are also being evaluated for the treatment of social phobia. The safety and efficacy of gabapentin was evaluated in a randomized, double-blind, placebo-controlled trial in which 69 patients received either gabapentin (900–3,600 mg/day) or placebo for 14 weeks.[111] Patients treated with gabapentin showed a significant reduction in social phobia symptoms, as assessed by LSAS total score ($P<.05$), compared with placebo-treated patients. The treatment effects of gabapentin appeared to be dose-dependent and no serious adverse events were noted. In an 11-week double-blind study of pregabalin, a follow-up compound to gabapentin that is in development,[112] 135 patients were randomized to either low- (150 mg/day; n=42) or high-dose (600 mg/day; n=46) pregabalin or placebo (n=46). Efficacy was assessed primarily as change in LSAS score from baseline to endpoint, and high-dose pregabalin (600 mg/day) significantly improved LSAS score and several secondary efficacy measures between week 1 and week 11.

Long-term Treatment Trials

Few studies have investigated the efficacy and safety of long-term treatment of social phobia with agents that have shown short-term efficacy (Table).[70,81,99,113-115]

Selective Serotonin Reuptake Inhibitors

Sertraline is the only SSRI to gain approval for the long-term treatment of social phobia (February 2003). The long-term safety and efficacy of sertraline treatment for social phobia was demonstrated in a 24-week, double-blind, placebo-controlled relapse prevention study.[114] Fifty patients with generalized social phobia who had responded to

20 weeks of flexible-dose sertraline (50–200 mg/day) in this relapse prevention study were then randomly assigned to sertraline or placebo for another 24 weeks.[68] An additional 15 patients who had responded in the placebo arm of the original trial also continued to receive double-blind placebo treatment in the continuation study. At endpoint, significantly fewer (4% [1/25]) patients in the sertraline-continuation group than the placebo-switch group (36% [9/25]) had relapsed (P=.01). Mean rating scale scores (Clinical Global Impression-Severity [CGI-S], BSPS, and MFQ-SP) continued to improve in the sertraline-continuation group but deteriorated in both the placebo-switch and placebo-responder groups. This study suggests that sertraline treatment lasting up to 11 months effectively prevents relapse and the reemergence of social phobia symptoms. Long-term sertraline treatment was well tolerated in this study.

Paroxetine's potential to prevent relapse in social phobia was studied in a 23-week trial by Stein and colleagues.[63] The researchers treated 36 subjects with open-label paroxetine (10–50 mg/day) for 11 weeks. Of the 23 responders (CGI), 16 agreed to enter a double-blind placebo-switch phase for an additional 12 weeks. Only one of the eight patients who continued on paroxetine relapsed, compared with five of eight patients switched to placebo. Although these results suggest an advantage for paroxetine, the small sample size does not allow for definite conclusions.

Maintained efficacy of paroxetine in the long-term treatment of social phobia has also been demonstrated in a 36-week study which assessed the potential for relapse after medication discontinuation.[114] After a 12-week, single-blind acute phase, during which 380 patients with *DSM-IV* social phobia were treated with paroxetine (20–50 mg), 323 patients whose CGI-S score had decreased by at least two points were randomized in double-blind fashion to an additional 24 weeks of treatment with paroxetine or placebo. At endpoint, the relapse rate was significantly lower in the paroxetine group than in the placebo group (14% versus 39%; P<.001). Paroxetine was well tolerated for the duration of the study.

Continuing improvements in patients' symptoms and disabilities have been reported in a long-term, open-label extension of the first randomized, double-blind, placebo-controlled study of paroxetine in social phobia.[64,115] Ninety patients who had completed 12 weeks of treatment with paroxetine or placebo (Phase 1) received open-label paroxetine treatment for 24 weeks (Phase 2) followed by a 16-week double-blind re-randomization phase (Phase 3) with paroxetine or placebo. The number of paroxetine responders increased from 55% (50/91) at the end of Phase 1 (compared with 23.9% [22/92] in the placebo group [odds ratio 3.88; 95% confidence interval, 2.81-5.36])[59] to 89% (57/64) after 24 weeks of open-label paroxetine treatment (Phase 2).

TABLE. LONG-TERM TREATMENT TRIALS OF PHARMACOTHERAPY FOR SOCIAL PHOBIA

Authors (Year)	N	Study Drug	Comparator(s)	Study Design
Walker et al (2000)[113]	50	Sertraline	Placebo	RCT
Blomhoff et al (2001)[70]	387	Sertraline	Exposure therapy Placebo	RCT
Hair et al (2000)[114]	323	Paroxetine	Placebo	OL, RCT
Kumar et al (1999)[115]	90	Paroxetine	Placebo	RCT, OL, RCT
Connor et al (1998)[99]	56	Clonazepam	Placebo	OL, RCT 20-wk RCT
Versiani et al (1992)[81]	45	Phenelzine Moclobemide	Placebo	RCT

RCT=randomized controlled trial; OL=off-label; wk=week; CGI-S=Clinical Global Impression-Severity; CGI-I=Clinical Global Impression-Improvement; MFQ=Marks Fear Questionnaire; MFQ-SP=Marks Fear Questionnaire-Social Phobia subscale; BSPS=Brief Social Phobia Scale; SPS=Social Phobia Scale; LSAS=Liebowitz Social Anxiety Scale; SADS=Social Anxiety and Distress Scale; SDS=Sheehan Disability Scale; MSPS-S=Marks-Sheehan Main Phobia Severity Scale.

Concomitant with this finding was a continuing improvement in LSAS score and corresponding improvements in disability. Long-term treatment with paroxetine (up to 9 months) was well tolerated.

Monoamine Oxidase Inhibitors and Reversible Inhibitors of Monoamine Oxidase Type A

Phenelzine and moclobemide were compared in a double-blind, placebo-controlled, parallel-group trial that enrolled 78 patients with social phobia and lasted more than 24 weeks.[81] Patients were treated initially for 8 weeks (mean doses at end of the first phase: 580.7 mg/day moclobemide and 67.5 mg/day phenelzine), after which CGI-I nonresponders were withdrawn from the study. All other patients (n=45) continued with the same treatment for an additional 8 weeks (mean doses at end of the second phase: 582.3 mg/day moclobemide and 69.3 mg/day phenelzine), after which placebo responders and relapsers (in any group) were withdrawn from the study. In the final phase of the trial, one half of the responding patients continued on active treatment while the other half were switched to placebo. At week 4 and onward, both phenelzine and moclobemide were clinically and statistically more effective than placebo. At week 16, 82% of moclobemide- and 91% of phenelzine-treated patients were almost asymptomatic (based on changes in CGI-I, SDS, and Social Phobia Scale [SPS] scores) compared with 43% in the placebo group (statistical significance not reported). However, moclobemide was tolerated much better than phenelzine. All patients withdrawn from active treatment at week 16 had relapsed by week 24 (mean score on all parameters had increased).

The only other published long-term clinical trial data on MAOIs and RIMAs in social phobia come from open-label studies of tranylcypromine[90] and moclobemide.[85] A follow-up study of moclobemide examined its efficacy in the long-term treatment of social phobia. A total of 93 outpatients suffering from severe generalized or circumscribed social phobia were initially treated with moclobemide. Responders (59/93) continued treatment for 2 years, entered a 1-month drug-free period, and then completed another 2-year moclobemide treatment period. During the drug-free period, 88% of patients deteriorated. However, all patients responded again in the next 2-year period. A post-study follow-up at 6–24 months found that 63.2% of patients were almost asymptomatic or had only mild symptoms.

Benzodiazepines

Long-term treatment data from clinical studies of clonazepam are limited to the findings of a small study assessing whether clonazepam could safely and effectively be administered over a period of ~11 months.[99] In the first 6 months of the trial, 56 patients received open-label clonazepam treatment (up to 2.5 mg/day), which was associated with significant decreases in a number of social and disability assessment

Study Duration	Main Efficacy Variables	Efficacy Outcome	Tolerability Outcome
20-wk RCT and then 20-wk re-randomized	CGI-S MFQ-SP BSPS	>Placebo	4% discontinuation
24-wk RCT	CGI-S CGI-I SPS MFQ	>Placebo	Well tolerated
12-wk OL 24-wk RCT	CGI-S	>Placebo	Well tolerated
12-wk RCT 24-wk OL 16-wk RCT	LSAS CGI-I SADS SDS	>Placebo	Well tolerated
24-wk OL	CGI-S CGI-I BSPS MSPS-S	>Placebo	12% discontinuation
24-wk RCT	CGI-I SDS SPS	>Placebo	Side effects more frequent and severe in phenelzine group than in other two groups

Note: Venlafaxine extended release (XR) has since been approved for use in the United States for the treatment of social phobia.

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scores. Patients who responded to treatment were subsequently randomized to receive either continuation treatment with clonazepam for another 5 months (n=17) or undergo discontinuation treatment (using a slow-taper method) with a double-blind placebo substitution (n=19). Relapse rates were 0% and 21.1% in the continuation and discontinuation groups, respectively, and were significant using Kaplan-Meier survival analysis with extended time to relapse for continuation treatment ($P<.05$). The results of clinical efficacy scales at endpoint suggested a modest but statistically significant difference in favor of continuing treatment over tapered withdrawal, supportive of benefit for long-term clonazepam treatment in social phobia.

PSYCHOTHERAPY

A number of psychotherapeutic treatment modalities have been investigated for the treatment of social phobia, including exposure therapy, cognitive therapy, interpersonal psychotherapy, group social skills training, and supportive therapy.

The maintenance and treatment-free follow-up phases (each lasting 6 months) of the trial by Heimberg and colleagues[88] provide a valuable perspective of long-term treatment outcome with CBGT versus phenelzine.[116] There was a trend for greater relapse with phenelzine than with CBGT during treatment-free follow-up, despite the fact that phenelzine-treated patients showed greater improvement upon entering the maintenance phase of the study and, among nonrelapsing completers, greater improvement at endpoint. Thus, the authors suggest that CBGT may lead to a greater likelihood of maintaining response after treatment has terminated than does phenelzine, perhaps due to the coping skills explicitly provided by CBT. It should be noted, however, that these data are based on a very small sample size (N=28) in the follow-up phase.[116]

Sympathetic Block

Surgical sympathectomy has been suggested to relieve symptoms of social phobia, especially blushing, and might conceivably be a viable alternative when more conservative treatments prove to be insufficient after prolonged attempts. A prospective, uncontrolled study enrolling 260 patients with *DSM-IV* social phobia indicated that a reversible bilateral sympathetic block helps relieve the physical signs of social phobia, such as hand or facial sweating, blushing, and rapid heartbeat, as well as reduce other social phobia symptoms, such as avoidance behavior.[14] Patient satisfaction with the procedure was reported to exceed 90%. However, proper controlled studies are still needed to verify these results.

Cognitive-Behavioral Therapy/Exposure Therapy

The efficacy of CBT in social phobia has been demonstrated in several controlled trials (using waiting lists or other therapies as controls) and meta-analyses.[117] However, in spite of its proven efficacy in treating this disorder, CBT is not readily available, primarily for reasons of cost and shortages in appropriately trained therapists. CBT targets the avoidance-learning and negative cognitive patterns associated with social phobia by exposing the patient to the feared situation. Various treatment programs, including education and exposure instructions, have been developed.[118]

Many experts consider exposure to feared stimuli, objects, and situations to be an essential component of effective treatment for phobic disorders.[119] Although exposure can be conducted in the patient's imagination or in vivo (ie, real-life exposure to the actual situation), studies show that in vivo exposure is more effective.[119] Once exposure is initiated, cognitive restructuring can provide patients with a context in which to interpret their experiences during exposure practices.[119]

A study designed to determine the necessity for the cognitive-restructuring component of CBGT compared the therapy to an exposure-based treatment without formal cognitive restructuring. Both methods were superior to a wait-list control, with some advantage of exposure therapy over CBGT.[120] Two controlled studies have reported some advantage of combining exposure and cognitive therapy over the separate treatments.[121,122] A more recent trial compared 27 social phobia patients receiving CBT (individual cognitive therapy followed by group social skills training) with 28 patients receiving supportive therapy (ST).[123] Sustained improvement was observed in both groups at follow-up (up to 72 weeks) but overall, CBT was more effective than ST in improving social phobia measures.

As mentioned earlier, Gelernter and colleagues[94] compared CBGT with phenelzine, alprazolam, and pill placebo in 65 patients who were given directions for self-directed exposure to feared stimuli, and reported a substantial improvement in all treatment groups. However, the sample size in this study was probably too small (eg, 13 evaluable patients in the phenelzine group) to detect differences among treatments. A study by Heimberg and colleagues[88] that enrolled 133 patients compared CBGT, educational supportive group therapy, phenelzine, and pill placebo. CBGT was found to be superior to pill placebo and educational group therapy, but slightly inferior to phenelzine on some measures.

COMBINED PHARMACOLOGY AND PSYCHOTHERAPY

In a long-term study of social phobia, 387 patients meeting *DSM-IV* criteria for generalized social phobia in a primary care setting were randomized to sertraline with and without exposure therapy.[70] Patients were randomized to one of four groups: sertraline 50–150 mg+exposure therapy, sertraline alone, placebo+exposure therapy, or placebo alone for 24 weeks. Response rates (defined as CGI-S score ≤3, CGI-I score ≤2, and ≥50% reduction in the self-assessed SPS) in the four groups were 46%, 40%, 33%, and 24%, respectively.[70] Differences in the sertraline-alone and sertraline+exposure groups over the placebo-alone group were statistically significant ($P<.001$), and exposure therapy alone was also statistically better than placebo ($P=.04$). Although

no significant difference was observed between patients who received exposure therapy versus those who did not (P=.140), the addition of exposure therapy to sertraline resulted in a trend toward significance (P=.059).

A recent article[124] provides 24 weeks of additional follow-up evidence to the long-term sertraline versus exposure therapy study. This study represents the largest reported sample that evaluates the maintenance of treatment effect post-discontinuation. The study found an advantage for exposure therapy alone compared to sertraline in terms of response maintenance. Despite the large sample size, interpretation of the results is complicated by the difficulty of conducting such an ambitious long-term treatment and follow-up study in the primary care setting. Specifically, treatment assignment was not blinded, 19% of patients in the exposure therapy group were treated with SSRIs during follow-up, there was significantly greater attrition in the exposure-alone group (n=11) compared to the sertraline-alone group (n=10), and finally, relapse was not formally assessed. For these reasons, whether the modest advantage of exposure therapy is a genuine treatment effect is uncertain and awaits confirmation by additional studies.

The relative efficacies of clonazepam and CBGT in the treatment of social phobia have also been compared. In a 12-week trial, patients were randomly assigned to clonazepam or CBGT. All patients improved significantly, with little difference between the two treatment groups.[125]

OVERVIEW OF AVAILABLE TREATMENT GUIDELINES

Several publications have included guidelines and recommendations for the treatment of social phobia,[79,126,127] but the most comprehensive recent treatment guidelines are included in a consensus statement by the International Consensus Group on Depression and Anxiety.[16] The guidelines recommend SSRIs as first-line therapy and suggest that treatment may have to be continued for several months to consolidate response and achieve full remission. They also suggest that if treatment is effective it should be continued for a minimum of 12 months. Long-term treatment is indicated if symptoms are unresolved, the patient has a comorbid condition or history of relapse, or there was an early onset of social phobia.

The consensus group highlights the fact that there are insufficient clinical data on which to base a recommendation for the management of patients who fail to respond to an SSRI and calls for further research on the effectiveness of augmentation therapy with clonazepam or switching to alternative treatment.

The guidelines also highlight evidence for the effectiveness of exposure-based strategies of CBT in social phobia, but note that this evidence comes from relatively small trials. The consensus group notes the need for comparative studies of psychosocial treatment and pharmacotherapy, as well as studies evaluating their combined efficacy.

CONCLUSION

Social phobia is a complex syndrome that often begins during adolescence and has a chronic, unremitting course. Social phobia is a chronic illness associated with significant levels of distress and social and occupational disability. Its detrimental effects may be compounded by frequently present comorbid psychiatric conditions, such as depression, substance abuse, and other anxiety disorders. Although social phobia has been identified as the most prevalent of the anxiety disorders, it is still poorly recognized in clinical practice. However, it is receiving more attention with the increasing availability of effective treatments, particularly with the evidence that is accumulating for the efficacy and safety of SSRIs in long-term treatment. Recognition and treatment of social phobia not only benefits the patient's quality of life, but also decreases the social burden that this disorder places on society.

Based on available data, SSRIs are the drugs of choice in social phobia. While only paroxetine has a Food and Drug Administration-approved indication for social phobia, other drugs appear to be widely used off-label. Sertraline, paroxetine, clonazepam, phenelzine, and moclobemide have each been studied in long-term randomized clinical trials, and moclobemide has an indication for social phobia in several European countries. In addition, although CBT has demonstrated efficacy in randomized clinical trials, it has limited availability.

Discontinuation of effective short-term therapy frequently results in relapse. Consequently, serious consideration must be given to long-term treatment for a minimum of 12 months. Future controlled trials of long-term treatment are needed, including comparisons of pharmacotherapy, psychotherapy, and combination trials, to further clarify the most appropriate treatment strategy for this illness. CNS

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WCA Recommendations for the Long-Term Treatment of Generalized Anxiety Disorder

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FOCUS POINTS

- Both pharmacotherapy and, to a lesser extent, psychotherapy have shown benefit in the acute treatment of generalized anxiety disorder (GAD).
- Buspirone, venlafaxine, and paroxetine are approved for the treatment of GAD.
- Although benzodiazepines are commonly used for the acute treatment of GAD, their use may be limited due to adverse effects, withdrawal symptoms, development of tolerance, and high relapse rates upon discontinuation.
- More research is needed to determine the usefulness of the selective serotonin reuptake inhibitors in the treatment of GAD, and the best approach for the long-term treatment of the disorder.

ABSTRACT

What are the current recommendations for the long-term treatment of generalized anxiety disorder (GAD)? GAD is a common disorder with a lifetime prevalence of 4% to 7% in the general population. GAD is characterized by excessive, uncontrollable worry or anxiety about a number of events or activities that the individual experiences on more days than not over a 6-month period. Onset of GAD symptoms usually occurs during an individual's early twenties; however, high rates of GAD have also been seen in children and adolescents. The clinical course of GAD is often chronic, with 40% of patients reporting illness lasting >5 years. GAD is associated with pronounced functional impairment, resulting in decreased vocational function and reduced quality of life. Patients with GAD tend to be high users of outpatient medical care, which contributes significantly to healthcare costs. Currently, benzodiazepines and buspirone are prescribed frequently to treat GAD. Although both show efficacy in acute treatment trials, few long-term studies have been performed. Benzodiazepines are not recommended for long-term treatment of GAD, due to associated development of tolerance, psychomotor impairment, cognitive and memory changes, physical dependence, and a withdrawal reaction on discontinuation. The antidepressant venlafaxine extended-release (XR) has received approval for the treatment of GAD in the United States and many other countries. Venlafaxine XR has demonstrated efficacy over placebo in two randomized treatment trials of 6 months' duration as well as in other acute trials. Paroxetine is the first of the selective serotonin reuptake inhibitors (SSRIs) to receive US approval for the treatment of GAD. Paroxetine demonstrated superiority to placebo in short-term trials, and investigations into the use of other SSRIs are ongoing. This suggests that other SSRIs, and serotonin and noradrenaline reuptake inhibitors, are likely to be effective in the treatment of GAD. Of the psychological therapies, cognitive-behavioral therapy (CBT) shows the greatest benefit in treating GAD patients. Treatment gains after a 12-week course of CBT may be maintained for up to 1 year. Currently, no guidelines exist for the long-term treatment of GAD.

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INTRODUCTION

Generalized anxiety disorder (GAD) is a common, disabling psychiatric condition characterized by persistent, excessive worry and anxiety about events of daily life. GAD is marked by the duration, frequency, and intensity of anxiety of a feared event being far out of proportion to the actual likelihood or impact of the event.[1] The sufferer is unable to control the worry, which is accompanied by various symptoms, such as restlessness, fatigability, difficulty concentrating, muscle tension, irritability, sleep disturbances, and gastrointestinal distress. Affected individuals experience significant disability in work and social functioning.

GAD is frequently associated or comorbid with other mental disorders, such as major depression, dysthymia, panic disorder, and agoraphobia.[2] The mean age of onset of GAD appears to be in the late teens or early twenties.[3] The course of illness is usually chronic, with the severity of symptoms fluctuating over the patient's lifetime.

The diagnosis of GAD was first introduced in 1980 by the American Psychiatric Association in the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition (*DSM-III*).[4] Prior to 1980, GAD and panic disorder were conceptualized as the core components of anxiety neurosis. The recognition that GAD and panic, although co-occurring, are sufficiently distinct to be considered independent disorders led to their separation in *DSM-III*.[5]

Early clinical studies evaluating GAD, as described by *DSM-III*, found that the disorder usually occurred in the

These recommendations are based on proceedings from the World Council of Anxiety meeting held September 11, 2000, in Pisa, Italy, and on guidelines and articles published in the medical literature through October 15, 2001.

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presence of another comorbid anxiety or mood disorder. Some investigators suggested that GAD might be better conceptualized as a prodrome, residual, or severity marker than as an independent disorder.[5] This view subsequently became invalid due to changes that were made in the revised criteria of *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition-Revised[6] (duration requirement extended from 1 month to 6 months) and *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*)[7] (change in the definition of excessive worry and the required number of associated psychological symptoms).[5]

DIAGNOSIS

Diagnosis of GAD can be made using either *DSM-IV*[7] or *International Classification of Diseases*, Tenth Revision (*ICD-10*)[8] criteria. By definition, GAD is a chronic disorder (Table 1[9]). The essential feature of GAD is excessive anxiety or worry (apprehensive expectation) about a number of events or activities, which occurs during a majority of the days within a period ≥6 months.[7] The anxiety and worry are accompanied by at least three additional symptoms from a list that includes restlessness, being easily fatigued, difficulty in concentrating, irritability, muscle tension, and disturbed sleep.[7]

Three major changes in the diagnostic criteria for GAD were made in the *DSM-IV*[6,7]:

- The definition of excessive anxiety and worry was simplified
- A new criterion was added, stating that the worry must be difficult to control
- The associated symptom criterion was focused, deleting most of the previous autonomic symptoms and leaving only the symptoms that reflect hypervigilance and motor tension (ie, restlessness and difficulty in concentrating)

DIFFERENTIAL DIAGNOSIS

Due to the frequent overlap of anxiety and somatic symptoms across different diagnostic syndromes, a variety of psychiatric diagnoses should be considered in patients presenting with GAD symptoms. These include social phobia, depression, substance abuse, and personality disorders.

GAD must be distinguished from an anxiety disorder due to a general medical condition—the diagnosis of which is based on history, laboratory findings, or physical examination—or a substance-induced anxiety disorder in which a substance is judged to be etiologically related to the anxiety disorder.[7] When another Axis I disorder is present, an additional diagnosis of GAD should be made only when the focus of anxiety and worry is unrelated to the other disorder, not restricted, for example, to panic attack (panic disorder), being embarrassed in public (social phobia), or being contaminated (obsessive-compulsive disorder [OCD]).

EPIDEMIOLOGY

The definition of GAD has changed considerably over the last 2 decades, and as a consequence, most epidemiological data were obtained on different patient populations. General United States population surveys show that GAD has a lifetime prevalence of 4% to 7% and a 1-year prevalence of 1% to 4%.[2,10,11] Using strict *DSM-IV* criteria, a national survey of more than 4,000 people in Germany found 12-month prevalences of GAD and major depressive disorder (MDD) to be 1.5% and 8.3%, respectively.[11,12] Higher rates of GAD were found in women (2.7%) and the elderly (2.2%).[11] In addition, GAD has been found to be more common among people of low socioeconomic status (SES), racial/ethnic minorities, and unmarried persons.[5]

CLINICAL PRESENTATION

The critical feature of GAD is excessive anxiety or worry occurring consistently on most days over a period ≥6 months. The individual finds these concerns, which may often be related to common events or activities, difficult to control.[1] Worries may be related to job and career, finances, health of friends and family, safety of children, everyday chores, or time management. The extent of worry is in excess of the actual likelihood or impact of the event being targeted.

TABLE 1. *DSM-IV* CRITERIA FOR THE DIAGNOSIS OF GAD[9]

DSM-IV
Excessive anxiety and worry
Difficult to control
Several subjects
Symptoms occur more days than not for 6 months
Significant distress or social impairment
At least three ancillary symptoms
Ancillary Symptoms
Restlessness/mental tension
Fatigability
Poor concentration
Irritability
Muscle tension
Sleep disturbance
Exclusions
Focus of anxiety/worry not another disorder (eg, panic)
Not part of mood disorder, psychotic disorder, or pervasive developmental disorder
Not substance related
Not organic

DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; GAD=generalized anxiety disorder.

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CLINICAL COURSE, CHRONICITY, AND ASSOCIATED DISABILITY

The clinical course of GAD is chronic and may be either constant or fluctuating, with spontaneous improvements and relapses. The mean age of onset appears to be in the late teens to early twenties,[3] although the onset of the disorder may be prepubertal. In the Epidemiological Catchment Area (ECA) study, the usual duration of illness was 6–10 years, with 40% reporting duration of illness >5 years.[10] For currently active cases of GAD, the mean duration of illness to date was reported as 8.5 years.[10]

GAD is a disabling clinical condition that results in significant impairments in terms of work productivity, resulting in days where a sufferer is limited or even completely unable to perform everyday activities, and reductions in quality of life and well-being.[12] The NCS found that the majority of individuals with GAD reported substantial interference with their lives (49%), high probability of seeking professional help for GAD symptoms (66%), and the taking of medications for relief of GAD symptoms (44%).[2,13]

Medically, 35% of subjects with GAD from the ECA sample reported that their physical health was only fair to poor.[10] This was also reflected in the high utilization of healthcare resources by patients with GAD. In one outpatient setting, a 20% lifetime prevalence of GAD was found among high users of medical care.[14]

Few studies have been published concerning the socioeconomic impact of GAD. In the ECA survey, 38% of subjects characterized their emotional health as only fair to poor, 27% reported currently receiving disability payments due to their anxiety, and approximately one half of the subjects were gainfully employed.[10] A diagnosis of GAD was associated with three times the likelihood of working at a low occupational level, and more than twice the likelihood of earning an annual salary <$10,000.[10] Souêtre and colleagues[15] have evaluated the direct and indirect costs associated with GAD and GAD comorbid with other psychiatric and somatic disorders in ~1,000 patients observed in the ambulatory care setting. Total direct and indirect costs associated with GAD were estimated at $733/patient for a 3-month period. This included costs of hospitalization, use of outpatient services, and lost days of work. For patients with GAD comorbid with other psychiatric disorders, the total costs rose to $1,208/patient for the 3-month period. Relative use of medical services varied between the two groups. Hospitalization accounted for 35% of the total costs and for over 53% of direct healthcare costs in patients with comorbid GAD, decreasing to 22% and 32%, respectively, in patients with no comorbidities.[15] GAD was associated with lost productivity, with patients estimated to lose an average of 45 work days/year due to the disorder, increasing to 57 work days/year for patients with a concomitant comorbid disorder.[15] The prevalence of absenteeism from work was higher for patients with comorbidities (34% versus 27%; $P<.05$). Absenteeism from work accounted for 34% and 31% of total costs for patients with and without comorbidities, respectively. A study conducted in France showed that GAD results in a substantial loss of productivity even in the absence of a comorbid psychiatric disorder.[16]

GAD has a pronounced negative effect on quality of life and is associated with significant psychosocial impairment, although not as much as is observed in patients suffering from major depression or panic disorder.[17] A German national survey of over 4,000 subjects found that on quality-of-life measures (Short Form-36) for subscales of general health, mental health, role limitations due to emotional health, and vitality, mean scores were significantly lower among subjects with GAD than among subjects with MDD.[11] For patients with comorbid GAD and MDD, mean scores on subscales for general health, mental health, social functioning, and vitality were significantly lower than in patients with MDD alone.

COMORBIDITY OF GENERALIZED ANXIETY DISORDER

Symptoms of anxiety may appear across many psychiatric diagnoses. Perhaps as a result of this phenomenon, the diagnosis of GAD is often noted as comorbid with other psychiatric disorders, including posttraumatic stress disorder, OCD, panic disorder (or social phobia), and mood disorders. Approximately 25% to 30% of patients with GAD present with comorbid depression, and 20% to 30% of patients with depression meet the diagnostic criteria for GAD.[18,19] In a national survey in Germany of the patients who met the *DSM-IV* diagnostic criteria for 12-month GAD, 41% had comorbid current MDD, while 59% had comorbid 12-month MDD.[12] Furthermore, it has been reported that up to 56% of all 12-month GAD cases fulfill the criteria for another anxiety disorder[11] Up to 50% of patients with GAD may have a coexisting personality disorder diagnosis, and as many as 80% of those with treatment-resistant GAD may have this condition.[18]

In a naturalistic sample of slightly less than 1,000 patients observed in the ambulatory care setting and diagnosed with GAD, 60% were experiencing one or more symptoms of comorbidity.[15] Addictive patterns (including alcoholism) were found to be the most prevalent type of psychiatric comorbidity (25%), followed by depressive symptoms (23%) and phobic symptoms (16%). For medical comorbidities, gastroenterological and gynecological symptoms were the most prevalent (15% and 10%, respectively).[15]

UNDERLYING BIOLOGICAL SUBSTRATES

Neuroanatomical changes

Brain-imaging studies have demonstrated that the pathogenesis and control of fear and anxiety involve the frontal cortex, medial temporal lobe, and limbic system.[20] Positron emission tomography data from patients with GAD suggest that cerebral metabolism is increased in the right temporal and frontal cortex and decreased in the basal ganglia and white matter.[21] Benzodiazepine receptor density in the left temporal pole was significantly decreased among patients with GAD, in line with results obtained in patients with panic disorder.[20]

NEUROBIOLOGICAL CHANGES

The pathogenesis and control of anxiety appears to involve several neurotransmitters including excitatory amino acids (eg, glutamate), inhibitory amino acids (eg, γ-aminobutyric acid [GABA]), and monoaminergic neurotransmitters (eg, serotonin [5-HT], dopamine, and norepinephrine).[22]

Benzodiazepine anxiolytic medications act mainly by potentiating GABA neurotransmission through the $GABA_A$ receptor subtype. Increased GABA neurotransmission suppresses neuronal firing, thus inhibiting or regulating other neurotransmitters in limbic areas, including 5-HT, noradrenaline ([NA], norepinephrine), and dopamine.[22] Noradrenergic cell bodies in the locus ceruleus have high concentrations of GABA receptors. The beneficial effects of benzodiazepines may be mediated, in part, through GABA-facilitated reductions in NA activity.[22,23]

The role of 5-HT in anxiety is supported by its modulatory effects on the locus ceruleus and its dense downstream projections into the amygdala.[22] Frontal-lobe feedback systems to limbic structures may also be serotonin sensitive. Norepinephrine turnover is also implicated, and the interactions of these two closely linked systems appear to be reciprocal.[22] Buspirone (a $5\text{-}HT_{1A}$ receptor partial agonist), venlafaxine, (which acts mainly through serotonin reuptake inhibition but may also have noradrenaline reuptake inhibition at higher doses), and some of the SSRIs have demonstrated efficacy in the treatment of GAD.

TREATMENT OPTIONS

A number of clinical trials have demonstrated the benefit of anxiolytic medication therapy and some psychotherapies in the acute treatment of GAD patients. Pharmacologic therapies include benzodiazepines, buspirone, and antidepressants. The psychological therapy that has shown greatest benefit is cognitive-behavioral therapy (CBT).

The rating instruments most commonly used to assess treatment effects in published pharmacological studies of GAD include:

- Hamilton Rating Scale for Anxiety (HAM-A)[24]
- Clinical Global Impression–Severity (CGI-S) and Improvement scales[25]

PHARMACOTHERAPY

In a 1997 survey, 34% of 51 internationally recognized experts selected benzodiazepines as the first-line therapy for GAD.[26] This percentage had decreased from the 41% measured in a survey 5 years earlier, but nonetheless showed that despite other available treatment options, benzodiazepines remained a popular choice of initial therapy, probably due to their rapid onset and good efficacy.[27] Buspirone was the preferred first-line treatment option for 15% of responders in both 1992 and 1997, while use of selective serotonin reuptake inhibitors (SSRIs) had increased from 2% to 19%. In 1999 and 2000, venlafaxine extended release (XR) and paroxetine were approved in the US for the treatment of GAD. The use of tricyclic antidepressants (TCAs) decreased from 20% to 15%.[26]

Acute Treatment Trials

Benzodiazepines

Benzodiazepines have been commonly used as the first-line acute treatment for GAD. Various benzodiazepines have been shown to be equally effective in the short-term treatment of GAD (eg, diazepam, clorazepate, alprazolam, lorazepam).[28] However, as a consequence of the changing definition of GAD over the past 2 decades, therapeutic data with benzodiazepines have been collected on different patient populations. None of the benzodiazepines has demonstrated efficacy in patient populations selected using either *ICD-10* or *DSM-IV* criteria.

Benzodiazepines exert their effects by enhancing GABA activity through interaction with the benzodiazepine–$GABA_A$ receptor complex.[29] Treatment with benzodiazepines may cause clinically significant sedation, as well as attentional, psychomotor, cognitive, and memory effects. Tolerance to most of these adverse events has been noted in patients treated with stable doses of benzodiazepines for longer than 6–8 weeks[17]; however, it is possible that some attentional and psychomotor impairment may persist.

Although benzodiazepines are effective in treating anxiety symptoms, their use is limited by several factors related to long-term use.[30] Physical dependence with long-term use and the withdrawal syndrome that develops upon drug discontinuation are key concerns. Withdrawal symptoms (eg, nervousness, insomnia, restlessness, lethargy, nausea, depression) appear within 6–12 hours and peak within 2–4 days of stopping a short-half-life benzodiazepine (eg, alprazolam or lorazepam), before subsiding in 2–3 weeks.[17] Discontinuation of high-potency, short-half-life benzodiazepines may cause the most severe withdrawal symptoms (eg, nervousness, insomnia, restlessness, lethargy, nausea, depression). Patients with a previous history of alcohol or substance abuse may be more prone to withdrawal effects.[31] Studies of the long-term efficacy of benzodiazepines have reported the development of tolerance or loss of effect over time in the treatment of anxiety.[30] Additionally, a high relapse rate (65%) is observed in the 6-month period following benzodiazepine discontinuation after short-term treatment.[30] However, Rickels and colleagues[32] demonstrated that clorazepate efficacy could be maintained over 6 months.

Although observed principally in persons who abuse other drugs and not in long-term GAD users, benzodiazepines also have the potential for recreational abuse.[17] Seizures can be precipitated by abrupt withdrawal of high doses of benzodiazepines.

Benzodiazepines also may have additive effects due to pharmacodynamic interactions when used concomitantly with central nervous system depressants, including alcohol.[33]

Azapirones

Azapirones, which act as partial agonists at the $5\text{-}HT_{1A}$ receptor level, were developed in an attempt to produce

effective antianxiety agents with no abuse potential, although only one, buspirone, made it to market. Advantages of azapirones include no withdrawal reaction, no potentiation of alcohol or other sedative hypnotics, and a lack of abuse potential.[34] A disadvantage is the relatively gradual onset of action (2 weeks). Side effects most frequently reported include gastrointestinal symptoms (appetite disturbances and abdominal complaints) and dizziness.

Buspirone was approved in the US as a treatment for symptoms of GAD in 1986. In most other countries where buspirone is licensed, it is for the treatment of anxiety but not for the treatment of GAD. Buspirone, in addition to its 5-HT_{1A} activity, has an affinity for dopamine D_2 receptors.[1] Buspirone has been shown in some studies to be equally effective as such benzodiazepines as diazepam, clorazepate, alprazolam, and lorazepam in treating GAD, while other studies failed to show superiority over placebo.[35] Although buspirone has consistently demonstrated a reduction in anxiety symptoms, it has not been shown to be effective in reducing the severity and frequency of panic attacks.[35] Buspirone is also more effective than placebo in improving anxiety and depressive symptoms in GAD patients with concurrent depressive symptoms.[36] Prior benzodiazepine treatment (within 4 weeks to 5 years) has a negative impact on buspirone treatment outcome, with increased rates of treatment discontinuation, adverse-event reports, and reduced response rates.[37]

Since buspirone was evaluated as a treatment for GAD using *DSM-III* criteria, which required only a 1-month duration of anxiety symptoms, few data on the efficacy of buspirone in subjects with chronic symptoms of anxiety are available.[28]

Tricyclic Antidepressants

Imipramine has shown some efficacy in the treatment of GAD. An 8-week study of 230 patients with *DSM-III* GAD compared the efficacy of imipramine with diazepam, trazodone, and placebo. By Week 3, all three active drugs produced comparable improvement. However, by Week 8, only imipramine, not placebo, had sustained significant improvement across all efficacy measures, including HAM-A total score, CGI-S, the Covi anxiety scale, and the patient-rated Hopkins Symptom Checklist ($P<.01$).[38] Significantly more side effects were elicited by imipramine and trazodone (mean maximum daily doses, 143 and 255 mg, respectively) than by diazepam (26 mg/day) or placebo. Imipramine was more effective in treating the psychic symptoms of anxiety, while diazepam appeared to be more effective in alleviating somatic symptoms. Another 6-week, double-blind, parallel-design study of 60 patients with GAD found imipramine to be more effective than alprazolam in attenuating psychic symptoms, such as dysphoria and negative anticipatory thinking, but less effective than alprazolam in attenuating somatic symptoms.[39]

Serotonin and Noradrenaline Reuptake Inhibitors

In 1999, venlafaxine XR, a serotonin and noradrenaline reuptake inhibitor (SNRI), became the first antidepressant to be approved for the treatment of GAD in the US. The XR formulation of venlafaxine was developed to allow for prolonged duration of absorption and once-daily dosing, with the potential of an improved side-effect profile.[40]

The efficacy of venlafaxine XR has been investigated in five outpatient placebo-controlled studies, which showed a consistent pattern of improvement in the treatment of GAD.[41] Four of these studies demonstrated a statistically superior improvement compared with placebo.[40-44]

In an 8-week randomized study of 365 GAD patients without comorbid MDD, venlafaxine XR (75 or 150 mg/day) was significantly more effective than placebo at week 8, as assessed by the HAM-A and patient-rated Hospital Anxiety and Depression Scale (HADS).[42] Venlafaxine XR 75 mg/day was superior to buspirone at weeks 3, 4, and 8, as assessed by CGI-S scores. Discontinuation rates due to adverse events were 22% for venlafaxine XR 75 mg/day, 28% for venlafaxine 150 mg/day, 15% for buspirone, and 10% for placebo.[42]

In contrast to the older TCAs, venlafaxine XR generally has a more favorable adverse-event profile and greater tolerability.[43] In short-term treatment with venlafaxine XR, the most common adverse events (occurring in ≥10% of patients and at least twice the frequency found with placebo) are nausea, somnolence, dry mouth, dizziness, sweating, constipation, and anorexia.[43]

Selective Serotonin Reuptake Inhibitors

Paroxetine was the first SSRI to receive approval for the treatment of GAD in the US (2001) and is the only SSRI to date for which there are published results of randomized short-term efficacy trials. In an 8-week study, 81 *DSM-IV*-diagnosed patients with GAD were randomized to receive paroxetine (20 mg/day), imipramine (50–100 mg/day), or 2´-chlorodesmethyldiazepam, a standard benzodiazepine (3–6 mg/day).[45] Significant improvement in anxiety ratings was observed after 2 weeks of treatment in all three groups. At study endpoint, the response rates, as assessed by ≥50% improvement in baseline HAM-A total score, were 68% in the paroxetine group, 72% in the imipramine group, and 55% in the 2´-chlorodesmethyldiazepam group. The most frequently reported adverse events for each drug were nausea (paroxetine); drowsiness (2´-chlorodesmethyldiazepam); and dry mouth, drowsiness, and constipation (imipramine).

Subsequently, three placebo-controlled, 8-week studies further evaluated paroxetine in the treatment of GAD.[46,47] A large US multicenter, fixed-dose study evaluated the efficacy of paroxetine (20 and 40 mg/day) in 566 patients with GAD.[48] Both doses of paroxetine showed a statistically significant reduction from baseline on both HAM-A total score and the patient self-rated Sheehan Disability Scale over placebo ($P<.001$) at week 8.

The other two studies were flexible-dose studies using paroxetine 20–50 mg/day.[46,47] In the first study, paroxetine-treated patients experienced a statistically significant improvement over placebo-treated patients in HAM-A score at weeks 6 and 8 ($P=.041$ and $P=.008$, respectively).[47] In the second study, paroxetine treatment resulted in a

statistically significant reduction in HAM-A score compared with placebo in the intent-to-treat observed-case data set ($P<.05$).[47] The safety profile was similar to that seen for paroxetine studies in depression and other anxiety disorders.[47]

Long-Term Treatment Trials

Few trials have studied the long-term (≥6 months) treatment of GAD (Table 2).[32,49-51] Venlafaxine has been studied in only two 6-month efficacy trials. The first was a randomized, double-blind, parallel-group, flexible-dose comparison of venlafaxine XR (75–225 mg/day) with placebo in 251 patients with GAD without MDD.[49] Anxiety scores were significantly improved by venlafaxine XR compared with placebo from week 1 or 2 through week 28 on all primary efficacy measures, including HAM-A total, HAM-A psychic anxiety factor, and CGI scale scores. The most common treatment-emergent adverse event was nausea, followed by somnolence and dry mouth.

In the second study, 544 patients were randomized to receive a fixed dose of venlafaxine XR (37.5, 75, or 150 mg/day) or placebo.[40,50,52] In a last-observation-carried-forward analysis, all three doses of venlafaxine XR resulted in statistically significant decreases from baseline on all primary efficacy variables (HAM-A total, HAM-A psychic anxiety factor, CGI). Moreover, as assessed by decreases in HAM-A total scores, the highest dose (150 mg/day) of venlafaxine XR was superior to the lowest dose (37.5 mg/day), from 3–6 months of treatment. Discontinuation of therapy with venlafaxine XR occurred mainly at the beginning of treatment; the adverse events most commonly leading to discontinuation were nausea, headache, dizziness, sweating, and insomnia.[52]

Paroxetine has also been assessed for the treatment of GAD in a 32-week multicenter relapse prevention study, which included an 8-week, single-blind, flexible-dose (20–50 mg/day) treatment period followed by a 24-week double-blind phase with patients randomized to either paroxetine (20–50 mg/day, patients maintained at dose taken in single-blind phase) or placebo.[51] Paroxetine treatment resulted in significantly fewer relapsed patients compared to placebo (10.9% versus 39.9%, respectively), and time to relapse for patients on placebo was 4.7 times more than for paroxetine-treated patients. The proportion of patients achieving remission (HAM-A total score ≤7) at the end of the single-blind phase was 42.5% and increased in the double-blind phase to 73%, compared with 34% for patients on placebo at the end of this phase. During the double-blind phase, a significant decrease in HAM-A scores was also noted in paroxetine-treated patients compared to those given placebo. An improvement in functional disability was observed in patients treated with paroxetine, and overall, paroxetine was well tolerated.

A prospective, double-blind study compared clorazepate (a benzodiazepine with a long half-life) with buspirone treatment in 134 patients with GAD.[32] The primary objective of this study was to assess the results of treatment withdrawal. Patients were treated with therapeutic doses of clorazepate (7.5–60 mg/day) or buspirone (5–40 mg/day) for 6 months before therapy was abruptly withdrawn. Both treatments demonstrated effective control of symptoms during the trial. There was a significant increase in symptom severity consistent with withdrawal reaction (five or more new symptom complaints on the Physician Checklist of Withdrawal Symptoms) for the clorazepate group (72%) but not the buspirone group (9%) ($P<.001$). There was no evidence of tolerance development with either drug during 6 months of treatment; improvement in HAM-A assessed after 1 month of treatment was maintained for the next 5 months in both groups. The most common adverse events reported with clorazepate were drowsiness, fatigue, and lack of coordination; with buspirone, adverse events were lightheadedness, dizziness, and insomnia. During the course of the study, significantly more patients discontinued treatment with buspirone (45%) than with clorazepate (26%). In practice, most clinicians taper benzodiazepines slowly.

TABLE 2. LONG-TERM TREATMENT TRIALS OF PHARMACOTHERAPY FOR GAD

Authors (Year)	N	Study Drug	Comparator	Study Design	Study Duration (Weeks)
Gelenberg, et al (2000)[49]	251	Venlafaxine XR	Placebo	RCT	28
Allgulander, et al (2001)[50]	541	Venlafaxine XR	Placebo	RCT	24
Rickels, et al (1988)[32]	134	Clorazepate	Buspirone	RCT	24
Stocchi, et al (2001)[51]	363	Paroxetine	Placebo	RCT	24

GAD=generalized anxiety disorder; XR=extended release; RCT=randomized controlled trial; HAM-A=Hamilton Rating Scale for Anxiety; CGI=Clinical Global Impression.

PSYCHOTHERAPY

Reviews of randomized clinical trials suggest that CBT is better than no treatment, broadly equivalent to medication, and more efficacious than other psychotherapies, with clinically significant improvement occurring in 50% to 70% of cases.[53,54] On average, if psychological therapy is given, about 60% of patients will show some form of significant improvement at 6-month follow-up, but only 40% will have recovered in terms of State-Trait Anxiety Inventory–Trait subscale scores.[55] However, this figure may overestimate the effects of short-term psychotherapy since many patients will likely have received medication or additional psychotherapy during the follow-up period.

Analysis of six randomized controlled trials comparing various psychological therapies in treating patients with GAD suggests that CBT is the most effective therapy and results in significant improvements for 50% to 60% of treated patients.[55] The trials employed various treatment modalities including behavioral therapy, cognitive therapy (or combination of both), nondirective (ND) therapy, applied relaxation (AR), self-control desensitization, analytical psychotherapy, or anxiety management training. Importantly, only one trial, which compared cognitive therapies to behavioral therapies, employed a wait-list control group.

Cognitive-Behavioral Therapy

The aim of CBT is to alleviate the suffering and interference caused by a disorder by helping the patient recognize and alter patterns of distorted thinking and dysfunctional behavior. The effect size of CBT over that of the waiting list was 1.22 based on HAM-A scores and 2.48 compared to pre-treatment within-group scores.[56]

Some studies suggest that treatment gains following CBT may be maintained for up to 1 year, whereas response after medication discontinuation is attenuated.[57] Moreover, in other studies CBT has been associated with decreased use of antianxiety medications.[58]

Applied Relaxation

One trial compared the efficacy of 12 sessions of ND therapy, AR, or CBT for GAD, although not with placebo control.[59] For this study's purposes, ND therapy was described to patients as a means of exploring their life experiences in a relaxed environment with the goal of increasing their self-awareness and understanding of anxiety. Treatment with AR and CBT generated clinically meaningful change on both responder status and end-state functioning more often than did ND therapy ($P<.01$). Follow-up indicated that by 12-months postassessment, significantly more ND therapy patients received subsequent treatment (61% of ND therapy, 17% of AR, and 16% of CBT patients).

COMBINATION THERAPY

A limited number of trials comparing a combination of pharmacotherapy and psychotherapy with single therapy have failed to show additional benefit of combined treatment.[60] One 6-week, randomized, double-blind study examined combined treatment of diazepam or placebo plus weekly psychotherapy.[61] A small effect of diazepam was observed at the first-week assessment but not thereafter. A more detailed breakdown revealed some efficacy in patients with moderate or severe levels of anxiety, but not in those with low levels of anxiety.

Diazepam treatment in combination with psychotherapy was also examined in 101 patients with GAD, each allocated to one of five treatment groups—diazepam, placebo, CBT, diazepam plus CBT, or placebo plus CBT.[62] After 10 weeks of treatment, the CBT-diazepam group showed the greatest improvements in symptom severity and overall change in symptoms. However, a 6-month follow-up revealed that similar proportions of patients from each treatment group received psychotropic medication after the end of the study.

In another study, 60 patients with GAD were randomized to one of four treatment strategies: buspirone and anxiety management training; buspirone and ND therapy, in which patients were allowed to choose the topics they would

Main Efficacy Variables	Efficacy Outcome	Tolerability Outcome
HAM-A CGI	>Placebo	Discontinuation due to adverse event: 14% placebo 24% venlafaxine XR (P=.05)
HAM-A CGI	>Placebo	Most common adverse events with venlafaxine XR leading to discontinuation: nausea, headache, dizziness, sweating, insomnia
HAM-A	No significant difference between treatments	Discontinuation rate: 26% clorazepate 33% buspirone
HAM-A	>Placebo	Most common treatment-related adverse events: single-blind phase: nausea (21.5% of patients); double-blind phase: headache (6.9% paroxetine versus 5.2% placebo)

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discuss; placebo and anxiety management training; and placebo and ND therapy.[60] The psychological treatments comprised seven sessions of 45 minutes each. Buspirone was given in flexible dosage up to 30 mg/day. Patients exhibited significant improvement on HAM-A and HADS at 4 and 8 weeks. However, there were no differences among treatment groups. It is possible that the small sample size (distributed among four treatment groups) and high dropout rate for patients receiving buspirone treatment (12 of 16 dropouts) limited the ability of this study to detect statistical differences.[60]

OVERVIEW OF AVAILABLE TREATMENT GUIDELINES

Currently, there are no published guidelines for the long-term treatment of GAD. Schweizer and Rickels[63] have outlined strategies for the treatment of GAD in the primary care setting. In this report, the authors suggest that use of a benzodiazepine is favored for short-term treatment when there is evidence of episodes of panic or when GAD presents with prominent adrenergic symptoms, even in the absence of panic attacks.[63] Buspirone should be favored over benzodiazepines in clinical situations where the following concerns arise[63]:

- Impairment in psychomotor function, attention, vigilance, or cognition and memory
- Potentiation of alcohol or sedative effects of other medications
- Prominent aggression and/or irritability
- Abuse potential (eg, diagnosis or history of alcoholism)
- Risk of acute discontinuation

With the advent of the newly approved antidepressants venlafaxine XR and paroxetine for GAD, the SSRIs and SNRIs may be preferred for both acute and long-term therapy for GAD. Because psychiatric comorbidity in patients with GAD is common, pharmacotherapies for GAD should have demonstrated efficacy in comorbidity.[46] CBT has also shown efficacy in several studies, with sustained results up to 1 year after treatment.[57]

CONCLUSION

GAD is known to be a chronic, recurring, and distressing disorder that responds to both pharmacological and some psychotherapeutic interventions. Both pharmacotherapy and, to a lesser extent, some types of psychotherapy have shown benefit in the acute treatment of GAD. Medication treatments which are Food and Drug Administration-approved for the treatment of GAD include buspirone, venlafaxine, and paroxetine. Although benzodiazepines are commonly used for the acute treatment of GAD, their use may be limited due to adverse effects, withdrawal symptoms, development of tolerance, and high relapse rates upon discontinuation. Few randomized controlled trials of either pharmacotherapy or psychotherapy have studies the long-term treatment of GAD and no guidelines currently exist. Further long-term studies, which will allow researchers to observe remission rates and thereby give a clearer profile of the possible outcomes of treatment, are required. CNS

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