Psychopharmacology of anxiety disorders

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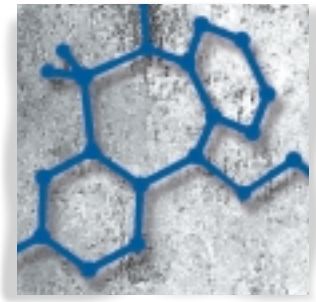

Exposure of the general population to a 1:4 lifetime risk of disabling anxiety has inspired generations of fundamental and clinical psychopharmacologists, from the era of the earliest benzodiazepines (BZ) to that of the selective serotonin reuptake inhibitors (SSRIs) and related compounds, eg, the serotonin and norepinephrine reuptake inhibitors (SNRIs). This comprehensive practical review summarizes current therapeutic research across the spectrum of individual disorders: generalized anxiety disorder (GAD), panic disorder (PD) and agoraphobia (social anxiety disorder), compulsive disorder (OCD), phobic disorder (including social phobia), and posttraumatic stress disorder (PTSD). Specific diagnosis is a precondition to successful therapy: despite substantial overlap, each disorder responds preferentially to specific pharmacotherapy. Comorbidity with depression is common; hence the success of the SSRIs, which were originally designed to treat depression. Assessment (multidomain measures versus individual end points) remains problematic, as—frequently—do efficacy and tolerability. The ideal anxiolytic remains the Holy Grail of worldwide psychopharmacologic research.

Dialogues Clin Neurosci. 2002;4:271-285.

Keywords: *generalized anxiety disorder; panic disorder; social anxiety disorder; posttraumatic stress disorder; obsessive compulsive disorder; benzodiazepine; antidepressant*

Anxiety disorders are the most common and among the most disabling of mental disorders in adults and adolescents.[1] Although many are highly circumscribed fears of mild-to-moderate severity, it has been estimated by the Epidemiological Catchment Area (ECA) study[2] that approximately one quarter of people will experience severe symptoms, disability, and handicap as a consequence of anxiety disorders at some time during their lifetime. These disorders are associated with significant morbidity[3] and increased mortality, probably as a consequence of increased suicide rates among sufferers. The direct and indirect costs to the health service and economy are considerable. Although persons who suffer from anxiety disorders are high consumers of all types of health services, only a minority receive specific help.[4]

The spectrum of anxiety disorders includes generalized anxiety disorder (GAD), panic disorder (PD) and agoraphobia, obsessive-compulsive disorder (OCD), phobic disorder (including social phobia), and posttraumatic stress disorder (PTSD). With the discovery of new psychotropic medications, specific diagnosis within this spectrum is essential because each of these disorders responds to specific pharmacotherapy. The approach to anxiety should also recognize that anxiety and depression are often comorbid conditions.

Selective serotonin reuptake inhibitors (SSRIs), which were designed to treat depression, are also effective for many anxiety disorders. They have revolutionized the treatment of anxiety, replacing chronic use of benzodiazepines (BZs). SSRIs are effective for OCD, PDs,

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Pharmacological aspects

Selected abbreviations and acronyms

BZ	*benzodiazepine*
GABA	*γ-aminobutyric acid*
GAD	*generalized anxiety disorder*
MAOI	*monoamine oxidase inhibitors*
OCD	*obsessive-compulsive disorder*
PD	*panic disorder*
PTSD	*posttraumatic stress disorder*
RIMA	*reversible inhibitor of monoamine oxidase A*
SNRI	*serotonin and norepinephrine reuptake inhibitor*
SRI	*serotonin reuptake inhibitor*
SSRI	*selective serotonin reuptake inhibitor*
TCA	*tricyclic antidepressant*

phobias, PTSD, and GAD *(see Table I)*. Other antidepressants, including tianeptine, have proven effective in adjustment disorders in which both anxiety and depression are involved. Doses of SSRIs for anxiety disorders could be higher than those used for depression, but must be started at lower doses to minimize the short-term agitation sometimes experienced with these medications. The patient should be counseled that side effects often diminish with time and also that empirical switching to another SSRI may be necessary.

Although tricyclic antidepressants (TCAs) have been used with success in anxiety disorders *(Table I)*, drowsiness, anticholinergic side effects, and toxicity have made these medications less popular. Also, monoamine oxidase inhibitors (MAOIs) are effective for anxiety, but their dietary restrictions and side-effect profile have limited their use.

BZs are the oldest class of medications used to treat anxiety. Although they have the advantage of rapid onset of action, they carry the risk of dependence, sedation, and tolerance. Withdrawal syndromes resulting in rebound anxiety, even reactions as severe as delirium tremens, are possible. BZs should be avoided in patients with a past history of substance abuse, personality disorder, or dosage escalation. These medications are ideal for patients who experience infrequent bouts of anxiety or episodes of anxiety-related insomnia.

Buspirone is a nonbenzodiazepine indicated for GAD. In head-to-head trials, it works as well as BZs for GAD, but has a slower onset of action and lacks sedative properties. It is therefore less useful for the anxious patient who needs a sedative. It does not impair alertness and lacks abuse potential.

A number of well-controlled clinical trials support the empirical evidence of effective pharmacotherapy of anx-

Medication	Starting dose (mg)	Therapeutic range (mg/day)	Common side effects	Indications (underscore indicates FDA approval)
• *Tricyclic antidepressants*				
Clomipramine	25	25-250	Weight gain, sedation, dry mouth	OCD, PD/AG, PTSD, GAD
Imipramine	10-25	150-300	Sedation, dry mouth	PD/AG, GAD, PTSD
• *Selective serotonin reuptake inhibitors*				
Citalopram	10	10-60	Nausea, somnolence, dry mouth	PD/AG, OCD, PTSD, SAD, GAD
Fluoxetine	5-10	10-80	Nausea, anorexia, insomnia, somnolence	OCD, PD/AG, PTSD, SAD, GAD
Fluvoxamine	50	50-300	Nausea, insomnia, somnolence, headache	OCD, PD/AG, PTSD, SAD, GAD
Paroxetine	10	10-50	Nausea, somnolence, ejaculation failure	OCD, PD/AG, SAD, PTSD, GAD
Sertraline	25	50-200	Nausea, insomnia, ejaculation failure	OCD, PD/AG, PTSD, SAD, GAD
• *Novel antidepressants*				
Venlafaxine	37.5	37.5-300	Nausea, dry mouth, insomnia, dizziness	GAD, PD/AG
• *Other medications*				
Buspirone	5 (bid)	15-60	Dizziness, nausea	GAD
Propranolol	20	20-160	Depression, sedation	Performance anxiety
• *Benzodiazepines*				
Alprazolam	0.25 (tid)	0.25-4	Drowsiness, withdrawal	GAD, PD/AG, PTSD
Clonazepam	0.25 (bid)	0.25-4	Somnolence, fatigue, depression	PD/AG, GAD, PTSD
Lorazepam	0.5 (tid)	1-6	Sedation, dizziness	GAD, PD/AG, SAD

Table I. Common medications used in the treatment of anxiety. FDA, Food and Drug Administration; GAD, generalized anxiety disorder; OCD, obsessive-compulsive disorder; PD/AG, panic disorder/agoraphobia; PTSD, posttraumatic stress disorder; SAD, social anxiety disorder.

iety disorders. However, the ideal anxiolytic does not exist, and current research into some new compounds is very active and promising. Pharmacological treatment evidence for each anxiety disorder will be briefly reviewed.

Generalized anxiety disorder

Benzodiazepines

Several studies have documented that BZs are more effective than placebo in GAD.[5-9] There is also evidence that BZs may be more effective on specific GAD symptoms, particularly the somatic/autonomic symptoms in contrast to the psychic symptom cluster, which includes apprehensive worry and irritability.[10] For example, several studies have shown that irritability may worsen in conjunction with high-potency BZs,[11] and that low levels of depressive symptoms may predict a less favorable response to BZs.[9] Other data suggest that, although they respond less well to BZs, psychic symptoms may be more responsive to other drugs altogether, such as buspirone or imipramine.[9-10,12] Overall, BZs still remain a widely used treatment option for GAD, partly no doubt because of their rapid onset of action, with maximum effect achieved within 2 weeks, and their generally good tolerance[9,13]; however, there are few controlled data to support continued benefits of BZs in the long term in GAD. Information from some 6 to 8 months' maintenance therapy trials have found continued efficacy over time,[14-17] but since GAD is often a long-term and unremitting disorder,[18] it needs to be stated that pharmacotherapy, whether with BZs or other drugs, may need to continue for many years in a significant number of patients.

Results generally show that approximately 70% of patients will respond to adequate BZ treatment (up to 40 mg/day of diazepam or equivalent for at least 3-4 weeks), but less than two thirds will achieve remission of symptoms. In long-term use, tolerance to side effects does occur, but tolerance to the anxiolytic effect of the BZs does not appear.[19] With regard to dependence and withdrawal, compounds with a slower onset of action, for example, oxazepam, have little reinforcing potential, while those with a long half-life, for example, diazepam and chlordiazepoxide, have a lower propensity to produce withdrawal symptoms, even if stopped abruptly. Anyway, discontinuation of acute treatment should be slow because of the potential for rebound anxiety and/or clinical relapse, and an adequate pretreatment assessment should be an important step to evaluate whether a subject would be suitable for BZ therapy, including previous history of withdrawal, liability of abuse, or likelihood of poor compliance. For this reason, and because of the high prevalence of comorbid depression, attention has focused also on different medications and antidepressants as potential treatment for GAD *(Table II)*.

Azapirones

The first pharmacological treatment for GAD beyond BZs was the azapirone buspirone, a partial 5-hydroxytryptamine (serotonin, 5-HT)–1A (5-HT_{1A}) agonist, which decreases the function of postsynaptic 5-HT_2 receptors. It has been demonstrated to show efficacy in GAD[10,20-22] and has been associated with maintenance of efficacy over a period of several months.[15,16]

Buspirone is given in two or three divided doses up to 60 mg/day, and its effect is usually not apparent until 2 to 3 weeks into treatment, in contrast to the almost immediate effects of BZs. It is not sedating like the BZs; it is not associated with psychomotor impairment, tolerance, dependence, or withdrawal; and it does not interact with alcohol.

Predominant clinical features	First-line treatment	Partial or no response
• Somatic and autonomically driven symptoms • History of abuse absent • Sedation is needed	***BZ***	Add or switch to a medication from a different class from the starting medication: ***SSRI*** or ***TCA*** or ***buspirone*** or ***BZ***
• Psychic symptoms (apprehensive worry, tension, irritability) • Presence of history of abuse • Sedation is not needed or is contraindicated	***Buspirone***	
• Depressive symptoms are intermixed with anxiety • BZs or buspirone are contraindicated	***SSRI*** or ***TCA*** or ***trazodone***	Add ***buspirone*** or ***BZ***

Table II. Generalized anxiety disorder (GAD): therapeutic strategies. BZ, benzodiazepine; SSRI, selective serotonin reuptake inhibitor; TCA, tricylic antidepressant.

The drug works well when there are conspicuous symptoms of worry, apprehensive tension, and irritability,[10] and where depressive symptoms are intermixed with anxiety,[23] while it is less effective than BZs on somatic and autonomically driven symptoms.[24,25] Patients who have had previous good responses to BZs do not appear to respond as well to buspirone,[22] probably due to the lack of sedative effect and inability to alleviate BZ withdrawal symptoms, but starting buspirone 2 to 3 weeks before tapering the BZs has produced better results.[26]
Other azapirone drugs have been assessed in GAD, like gepirone,[27,28] ipsapirone,[29] and more recently flesinoxan and tandospirone, but with more equivocal results.

Antidepressants

Although antidepressants are now well-established treatments of choice in several anxiety disorders (eg, PD, social phobia, OCD, and PTSD), their role in the treatment of GAD remains unclear. Little attention has been given to the fact that several studies have provided encouraging support for their efficacy. Perhaps the obscurity of these findings relates to the general uncertainty about the nature of GAD, its constantly changing criteria, and the apparent belief that it is a highly placebo-responsive disorder.[30] Early retrospective analyses of subjects with anxiety neurosis[21,31] have supported the possible efficacy of tricyclic drugs in GAD-like states. Further controlled trials by Kahn et al,[32] Hoehn-Saric et al,[12] and Rickels et al[9] have provided evidence for the benefit of imipramine and trazodone in GAD. Imipramine was more effective than diazepam on psychic anxiety symptoms, and it would also be expected to have significant antidepressant effects. Its reuptake-inhibiting effects on serotonin and norepinephrine confer a double advantage relative to some of the more selective compounds mentioned above.
Trazodone, a serotonin reuptake inhibitor (SRI) and 5-HT_2 receptor antagonist, has also been found to be effective and remains a little-used, but potentially effective drug for the disorder at doses of up to 400 mg/day, with doses of 200 to 300 mg/day often being sufficient. However, due to its side-effect profile, trazodone is unlikely to be a first choice, but can be a useful backup drug for more difficult to treat or nonresponsive patients. Its hypnotic properties are also useful where insomnia is a major problem.
Nefazodone is a combined SRI, 5-HT_2 antagonist, and weak adrenergic antagonist, which may also be beneficial in GAD. Nefazodone enjoys the advantage of greater patient acceptability and tolerability than trazodone. One open-label study in GAD has suggested benefit for this drug,[33] as is also the case for the SSRI paroxetine.[34]
The most recent development in the pharmacotherapy of GAD, largely out of consideration of the results of the studies with TCAs, has been the controlled comprehensive trials with venlafaxine, a serotonin and norepinephrine reuptake inhibitor (SNRI). In five placebo-controlled 8-week trials, venlafaxine has demonstrated efficacy significantly greater than placebo in the treatment of GAD patients without accompanying depression. Venlafaxine (75, 150, and 225 mg/day) produced greater effects than placebo after 1 week of the study, and these improvements were maintained throughout the remainder of trials.[35,36] These findings were replicated in a large 6-month trial evaluating long-term treatment of GAD. Although most of the improvement on venlafaxine occurred in the first 4 weeks, subjects continued to improve over the 6-month period.[37,38] Current trials have not established an optimal dosage for venlafaxine in the treatment of GAD, with positive results observed at dosages as low as 37.5 mg/day. However, data suggest that 75 to 150 mg/day is probably the most appropriate dosage range. Mild side effects including nausea, insomnia, dry mouth, and dizziness were principally seen at the initiation of treatment and cleared up over time.
Another double-blind, 8-week study compared venlafaxine (up to 150 mg/day), with buspirone (up to 30 mg/day), and placebo in outpatients with GAD. Both drugs were superior to placebo, but venlafaxine showed an earlier effect and advantage over buspirone in secondary outcome measures, notably the Hamilton Depression Scale anxiety subscore.[39]
The results of these studies indicate that antidepressants offer promise in GAD, even if they appear to be better in treating psychic anxiety symptoms, while BZs are probably superior in treating the somatic symptoms.[40]

Other drugs

Several other drugs have been assessed in GAD. The well-established anxiolytic effects of BZs are modified by several drawbacks, primarily of physical dependence, withdrawal symptoms, and sedation. The development of partial agonists at the γ-aminobutyric acid (GABA)/BZ receptor complex offers some potential advantages over the traditional BZs. These BZ-like compounds

should be effective anxiolytics, but less likely to produce sedation, tolerance, withdrawal, abuse liability, memory impairment, and ethanol potentiation. These newly developed compounds are either BZ derivatives or of a different chemical structure, that is, imidazopyridine and β-carbolines. The most comprehensively studied has been the β-carboline abecarnil. In an initial double-blind trial, Ballenger et al[41] demonstrated clinical efficacy at doses in the range of 3 to 9 mg/day, without withdrawal symptoms after short-term treatment. Further placebo-controlled studies[42,43] have shown modest treatment effects; however, at higher doses, there is some evidence of withdrawal symptoms.

Hydroxyzine, an antihistaminergic compound, has been reported to produce improvement in 60% to 90% of patients with GAD.[44] It can be very sedating when high doses are used (50 and 100 mg qid), but a more recent study[45] showed that it can be effective at low doses (50 mg/day) as well. After 5 weeks of treatment, 86% of the patients improved compared with 47% with placebo, and the drug was well tolerated.

β-Blockers have been used for the treatment of some anxiety disorders, but the evidence so far does not support their use in GAD.[46]

Finally, anecdotal experiences report potential value of kava and passionflower extract in the treatment of GAD.[47-49]

Panic disorder

Benzodiazepines

Alprazolam, the first licensed BZ for the treatment of panic, was studied in a large multinational placebo-controlled trial (Cross National Collaborative Panic Study) conducted in two 8-week phases: during the first it was compared with placebo, and then it was compared with both placebo and imipramine. Patients showed significant improvements in all major symptom areas, like number of panic attacks, avoidance behavior, and residual anxiety between attacks,[50,51] with improvements also maintained in longer-term studies.[52] Other high-potency BZs, such as clonazepam[53] and lorazepam,[19] showed similar efficacy. BZs are usually well tolerated and they have a rapid onset of action (1-2 weeks). Potential problems with long-term use of BZs in PD are tolerance, dependence, and withdrawal symptoms on discontinuation, but a 2.5-year naturalistic follow-up study found little evidence of tolerance to the antipanic effect of alprazolam, and efficacy was maintained without dose escalation.[54]

Although some studies have failed to observe a difference between alprazolam and imipramine in treatment of the common comorbid depressive symptoms,[55] several large meta-analyses have suggested a reduced efficacy for the BZs compared with TCAs[56] and antidepressants in general *(Table III)*.[57,58]

Antidepressants

Early in the 1960s, investigators documented that imipramine[59] and the MAOIs, particularly phenelzine,[60] were both effective treatments of PD.[61] Other TCAs also proved effective, especially clomipramine, and the improvement was not dependent on the treatment of concurrent affective symptoms. Following the demonstration of efficacy of the non-SSRI clomipramine, a number of large randomized trials have now demon-

Predominant clinical features	First-line treatment	Partial or no response
• Mild symptoms • No cardiovascular system pathology or seizure history • SSRI intolerability	***TCA*** (clomipramine, imipramine)	Add a ***mood stabilizer*** (valproate, lithium, gabapentin) or switch to an ***SSRI*** (eventually try ***venlafaxine*** or ***reboxetine***)
• Severe symptoms • High frequency of attacks • Invalidating symptoms • History of abuse absent	***High-potency BZ*** (alprazolam, clonazepam)	Add an ***SSRI***, a ***TCA***, or a ***mood stabilizer*** (valproate, lithium, gabapentin)
• SSRIs are not contraindicated	***SSRI***	Add a ***mood stabilizer*** (valproate, lithium, gabapentin) or switch to a ***TCA*** or a different ***SSRI*** (eventually try ***venlafaxine*** or ***reboxetine***)

Table III. Panic disorder (PD): therapeutic strategies. BZ, benzodiazepine; SSRI, selective serotonin reuptake inhibitor; TCA, tricylic antidepressant.

strated the efficacy of SSRIs in PD, both in comparison with placebo and clomipramine. Well-controlled trials provided evidence[62] that fluvoxamine, paroxetine, citalopram, sertraline, and fluoxetine have similar efficacies, although comparison trials between different SSRIs are generally lacking. A recent effect-size analysis of controlled studies of treatment for PD also revealed no significant differences between SSRIs and older antidepressants in terms of efficacy or tolerability in short-term trials.[63] As has been observed in all the trials, effective treatments reduce all the symptoms of PD, the frequency and severity of panic attacks, agoraphobic avoidance, anxiety, and comorbid depression. Although there are different responses of each of these symptoms to these treatments (eg, agoraphobic avoidance is the most difficult to treat), successful treatments effectively reduce all these aspects of the PD syndrome, but appropriate outcome measures for PD still remain a problem.[64] Reduction of panic-attack frequency has been widely utilized, but has been unreliable as a single measure, and most investigators now use multidomain measures.[64]

The percentage of patients who become free of panic attacks is generally 50% to 80% in acute trials lasting 6 to 8 weeks with various medications.[65] In patients who are treated for longer periods, this percentage most often rises. It is generally true that the longer PD patients are treated, the more complete and comprehensive is their response. In the large Cross-National Collaborative Panic Study,[66] after 8 to 12 months of treatment, three fourths of patients were free of panic attacks. In a large 12-month comparison of paroxetine and clomipramine, the panic-free rates were 85% and 72%, respectively, rising from about 55% at 3 months.[67]

The anxiety that PD patients experience between panic attacks can be considerable. This anxiety is reduced by all effective therapies with little difference between treatments.[56,58] In a similar fashion, most effective treatments decrease the common comorbid depressive symptoms, again generally with little difference between treatments.[65]

Agoraphobia is probably the most treatment-resistant symptom in PD. Although effective pharmacotherapy does significantly reduce agoraphobia avoidance, in vivo exposure is often employed to reduce avoidance behaviors. There is no standard measure employed in the literature of improvement in agoraphobic avoidance, making comparisons across studies and treatments difficult. Nonetheless, in a review of 16 studies,[68] remission of agoraphobia occurred in ranges varying from 18% to 64%, and in a 12-month naturalistic study,[69] 69% of patients became free of avoidance.

Improvement in agoraphobic avoidance occurs with all the effective treatments, probably more or less equally, although this has not been rigorously studied. The BZs are as effective as antidepressants in reducing avoidance, although effects begin earlier with the BZs.[58] Improvement is seen as early as the first or second week with BZs and as early as the fourth week with the antidepressants,[70,71] although improvement in agoraphobia is often the last portion of the syndrome to respond, and patients continue to improve for at least 3 to 6 months. Recent trials suggest that a significant response to antidepressants may occur in the first 2 to 4 weeks, which is earlier than previously thought.[71,72] An important phenomenon in the early stages of treatment (both with TCAs and SSRIs) could be the paradoxical and transient increase in anxiety and number of panic attacks, the so-called "jittering syndrome." To initiate treatment at a very low dose, or to cover this first period with a high-potency BZ, such as clonazepam or alprazolam, could be useful approaches.

Dietary restrictions and side effects have limited the use of MAOIs, but the introduction of the reversible inhibitors of monoamine oxidase A (RIMAs), such as moclobemide, renewed the interest in this class of agents. The results, though, so far are conflicting, with an 8-week study showing efficacy for moclobemide in PD,[73] and another one failing to do so.[74]

A small case series suggested that venlafaxine may be effective in the treatment of PD,[75] and mirtazapine provided good evidence both in an open-label study with a single-blind placebo run-in period,[76] and in a 8-week double-blind comparison with fluoxetine.[77] Reboxetine, a selective norepinephrine reuptake inhibitor was effective and well tolerated in an 8-week, placebo-controlled, double-blind trial,[78] with a significant reduction in the mean number of panic attacks and phobic symptoms at doses of 6 to 8 mg/day.

Other drugs

Buspirone in PD failed to show any efficacy even at high doses (60 mg/day).[79] Pagoclone, a cyclopyrrolone that is believed to act as a partial agonist at the $GABA_A$/BZ receptor provided some preliminary evidence in a crossover trial with placebo.[80] β-Blockers provided con-

flicting results, with some positive small crossover trials, but a negative double-blind trial of propranolol with alprazolam and placebo.[81] Initial evidence suggested that gabapentin[82] and sodium valproate may be effective in PD, while carbamazepine is not.[83] Also Ca-channel blockers have shown mixed results.[84]

Social anxiety disorder

Benzodiazepines

There is a limited number of controlled studies testing BZs in the treatment of social anxiety disorder. Clonazepam was shown to be effective in one 10-week, double-blind trial versus placebo, with 78% of patients responding to an average dosage of 2.4 mg/day.[85] Almost 85% of patients had some response, with 50% having a marked response and 50% having a moderate one. There has been only one double-blind study of alprazolam, in which Gelernter et al[86] compared alprazolam (mean dose 4.2 mg/day) with phenelzine, cognitive behavioral group therapy, and placebo over a 12-week period. Only 38% of patients on alprazolam were considered responders at end point compared with 69% on phenelzine, 24% on cognitive behavioral group therapy, and 20% on placebo.

Versiani et al[87] conducted a 12-week, double-blind study to compare bromazepam (mean dose 21 mg/day) to placebo, with a response rate of 83% of patients on active drug versus 20% of patients on placebo.

Antidepressants

Only anecdotal evidence supports the efficacy of TCAs for the treatment of social anxiety disorder,[88] mainly due to early observations that patients with atypical depression with marked interpersonal sensitivity and sociophobic features show a better response with MAOIs than TCAs.[89]

There were three early controlled trials[86,90,91] in which phenelzine (up to 90 mg/day) was found to be quite effective, with 64% of patients obtaining clinically significant responses, which increased when treatment was extended to 4 months. These results were replicated by Heimberg et al[92] in 1998.

In a comparison between phenelzine and moclobemide, phenelzine appeared roughly equivalent, but appeared to work faster.[91] By week 16, 91% of the phenelzine patients versus 82% of moclobemide patients were nearly asymptomatic, although moclobemide was better tolerated. In the Gelernter et al[86] trial, phenelzine was also better than alprazolam in terms of efficacy.

As mentioned above, RIMAs have also been studied. Brofaromine (up to 150 mg/day) was promising and roughly comparable to moclobemide, with response rates of 80%,[93] 78%,[94] and 50%.[95] Moclobemide, after the promising results of Versiani et al,[91] produced a less robust result in the large multicenter controlled study that followed,[96] in which 600 mg/day was superior to placebo (47% of responders compared with 34% receiving placebo). Another large multicenter trial,[97] as well a single study,[98] failed to confirm the efficacy of this drug in social anxiety.

Certainly the greatest amount of carefully controlled data are from the recent paroxetine studies.[99-101] In multicenter, double-blind, placebo-controlled, 12-week trials in severely symptomatic patients with social phobia, 55% of patients had a marked or moderate response at a mean dosage of 36.6 mg/day. Scores on the Liebowitz Social Anxiety Scale fell about 40% on paroxetine (30.5 points). Differences were observed in the second week and throughout the remainder of the trial. These positive findings were confirmed by Baldwin et al[102] and Allgulander.[103]

Other controlled trials with SSRIs include fluvoxamine,[88,104] sertraline,[105,106] fluoxetine,[107] venlafaxine,[108] and nefazodone.[109] In these trials, the clinically significant response rates of patients were in the 42% to 77% range.

Finally, open trials of citalopram[110-112] and buproprion[113] have suggested that these drugs may be effective in the treatment of social anxiety disorder, but controlled studies are needed to confirm preliminary results.

Other drugs

Buspirone has been shown to be effective as a primary treatment in two thirds of patients in early trials,[114,115] as well as an augmenting agent with SSRIs.[116] One controlled trial failed to find significant differences between buspirone and placebo.[117] Also the β-blocker atenolol, despite early promise, proved ineffective when tested in patient populations with generalized symptoms of social phobia.[90,118] Pindolol was no more effective than placebo in augmenting the effects of paroxetine treatment for generalized social phobia.[119]

High doses of gabapentin (3600 mg/day) provided encouraging preliminary results in a 14-week, placebo-controlled study.[120] Pregabalin, a follow-up compound of the GABA agonist gabapentin, is being developed for the potential treatment of several central nervous system disorders and anxiety, including social anxiety disorder.[121]

Posttraumatic stress disorder

Benzodiazepines

PTSD is a complex syndrome occurring after one or more traumatic events and involves multiple anxiety symptoms, including flashbacks, emotional numbing, avoidance of the reminders of the event, and so forth. This disorder was first recognized after military combat, but is now seen frequently after rape, assault, and accidents. Although there is no established pharmacotherapy for PTSD, there are multiple medications that seem to be effective in reducing these symptoms, particularly flashbacks, phobic avoidance, depression, anxiety, startle reaction, impulsivity, and hypervigilance *(Table IV)*. BZs seem to be helpful in suppressing hyperarousal symptoms. The first placebo-controlled trial was conducted by Braun et al[122] using alprazolam up to 6 mg/day. Although the core symptoms of the syndrome (intrusion and avoidant/numbing symptoms) did not improve significantly compared with placebo, they reported a positive effect in subjective well-being and a reduction in anxiety, irritability, and insomnia. Open trials with alprazolam and clonazepam came to similar results,[123] but withdrawal symptoms were particularly severe, especially considering the substantial comorbidity of PTSD with alcohol and drug abuse.
O'Brien and Nutt[124] hypothesized that early BZ treatment of trauma survivors may protect toward future development of PTSD, but the data are still controversial, especially concerning how soon after the event treatment has to be started to offer this protection.[125]

Antidepressants

TCAs have been shown to be helpful in three controlled trials. Imipramine (up to 300 mg/day) decreased intrusive thoughts, nightmares, and flashbacks with no effect on numbing or avoidance in an 8-week study.[126,127] Amitriptyline (up to 300 mg/day) has also been shown to reduce avoidance and anxiety in an 8-week trial, but it had no effect in the re-experiencing of intrusive thoughts and images.[128] Desipramine failed to show any advantage over placebo in a 4-week study,[129] but at relatively low doses compared with the two previous trials. Moreover, as highlighted by Friedman,[123] TCAs have been tested mainly on samples of veterans with severe chronic PTSD, while SSRIs and MAOIs have been tested in nonveteran samples. An important finding arising from these studies is the lack of placebo response in PTSD compared with other anxiety disorders.
MAOIs have also been shown to be effective (phenelzine up to 75 mg/day) in reducing intrusive thoughts and flashbacks after 8 weeks of treatment,[126] but other trials have failed to observe positive effects.[130] MAOIs appear to produce moderate to good clinical improvement, primarily affecting PTSD intrusive recollections, flashbacks, and nightmares, while hyperarousal, numbing, and avoidance behavior are scarcely affected. In addition, the usual dietary and medication restrictions of the MAOIs are more problematic in this patient group, given the high incidence of substance abuse.[123] Early trials with combat veterans suggest that the reversible MAOI moclobemide is promising.[131]

Predominant clinical features	First-line treatment	Partial or no response
• Intusive thoughts and flashbacks, hyperarousal, impulsivity	***SSRI*** (fluoxetine, paroxetine, sertraline) or ***mood stabilizer*** (carbamazepine, lithium, valproate)	***SSRI*** and/or ***mood stabilizer*** (also topiramate and gabapentin) ***combination***
• Anxiety without severe depression, irritability, insomnia	***Alprazolam***, ***clonazepam***, or ***buspirone***	
• Depressive symptoms	***SSRI*** (fluoxetine, paroxetine, sertraline), or ***TCA*** (imipramine, amitriptyline), or phenelzine	Add ***nefazodone*** or ***trazodone*** for concurrent sleep disorders
• Psychotic symptoms, aggressivity, or agitation	***Olanzapine***	

Table IV. Posttraumatic stress disorder (PTSD): therapeutic strategies. SSRI, selective serotonin reuptake inhibitor; TCA, tricylic antidepressant.

SSRIs have been observed to be helpful in open studies, especially with fluoxetine up to 80 mg/day.[132,133] This has been confirmed in a placebo-controlled trial of veteran and civilian trauma victims.[134] Approximately two thirds of patients experienced decreases in the core symptoms of PTSD including hyperarousal, numbing, avoidance, and intrusive images. Penava et al[135] conducted an effect-size analysis of controlled studies where fluoxetine showed the biggest effect compared with the other antidepressant and BZs studied so far.
Sertraline has also been reported effective[136] in long-term treatment[137,138] and paroxetine (20-40 mg/day) was superior than placebo in two recent 12-week, double-blind studies.[139,140]
Nefazodone (350-450 mg/day) has been shown to significantly improve most symptoms, including intrusive thoughts, avoidant behaviors, emotional numbing, nightmares, sleep, depression, and anger,[141,142] and there is only anecdotal evidence for improvement with trazodone.[123]

Other drugs

The anticonvulsant carbamazepine has been shown to decrease flashbacks, hyperarousal, and impulsivity.[143,144] Lithium and valproic acid may be helpful as well,[145-147] particularly in patients with poor impulse control.[148] Open-label topiramate[149] and gabapentin[150] appeared effective as add-on therapy for chronic PTSD.
Buspirone (15-35 mg/day) was reported to be effective in reducing anxiety, insomnia, flashbacks, and depressed mood in three PTSD war veterans after 2 weeks of treatment.[151]
Some case reports with atypical neuroleptics and an open-label study with olanzapine have been positive for the treatment of the core symptoms and the psychotic symptoms that PTSD patients may exhibit.[123,152]
Open-label propranolol (120-160 mg/day) improved hyperarousal, sleep, nightmares, explosiveness, and psychosocial functioning in 11 out of 12 Vietnam veterans,[153] and acute, posttrauma propranolol may have a preventive effect on subsequent PTSD.[154]
The α_1-adrenergic antagonist prazosin[155] and α_2-adrenergic agonists clonidine and guanfacine also provided some preliminary promising results.[123,153]

Obsessive-compulsive disorder

Benzodiazepines

BZs are not a first-choice treatment for OCD *(Table V)*, and few data exist to date. Clonazepam, a BZ that also affects serotonergic transmission, was compared with clomipramine and clonidine in a crossover, double-blind study with each treatment lasting for 6 weeks.[156] The first two drugs were equally effective, while clonidine was largely ineffective. Clonazepam provided an early improvement (2-3 weeks), unrelated to changes in anxiety, and there was a significant cross-response between clomipramine and clonazepam, with patients who failed on clomipramine showing a clinically significant response to clonazepam.

Predominant clinical features	First-line treatment	Partial or no response
• Depressive symptoms, recurrent course with bipolar spectrum comorbidity	***SSRI*** Eventually ***switch to a different SSRI or SRI*** (clomipramine or intravenous clomipramine) (Potentiation ***with buspirone, clonazepam, tryptophan, pindolol***)	Add ***mood stabilizer*** (lithium, gabapentin)
• Highly anxious obsessional subjects		Add ***BZ*** (clonazepam)
• Prevalent symmetry and atypical obsession or high level of anxiety to treatment		Add ***MAOI*** or ***SNRI*** and eventually ***neuroleptic***
• Severe hoarding symptoms		Add different ***typical/atypical neuroleptic*** (pimozide, haloperidol, risperidone, olanzapine)
• Tics, psychotic symptoms		Add different ***typical/atypical neuroleptic*** (pimozide, haloperidol, risperidone, olanzapine)

Table V. Obsessive-compulsive disorder (OCD): therapeutic strategies. BZ, benzodiazepine; MAOI, monoamine oxidase inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricylic antidepressant.

Pharmacological aspects

Antidepressants

Pharmacological investigations have demonstrated that OCD responds selectively to drugs that act as potent inhibitors of the synaptic reuptake of serotonin. The first medication demonstrated to be effective in OCD was clomipramine (150-250 mg/day) with 40% of patients (versus 4% for placebo) having a clinically significant decrease in symptoms independently of its antidepressant effect.[157-159] Subsequently, all of the SSRIs have been shown to be effective, including fluvoxamine (100-300 mg/day), fluoxetine (20-80 mg/day), paroxetine (40-60 mg/day), sertraline (50-200 mg/day), and citalopram (20-60 mg/day).[159] Most recent controlled trials find that about 50% of patients experience a 25% to 35% drop in scale scores of OCD, primarily utilizing the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). This magnitude of change typically results in significant improvement in function; however, interfering symptoms usually persist.
Relative efficacy between the SRIs has been difficult to determine. Two meta-analysis suggested greater efficacy for chlorimipramine[160,161]; however, these trials were performed over a 7- to 10-year time period, during which placebo rates rose significantly, making any conclusion suspect. In fact, in several head-to-head trials, clomipramine was found to have equal efficacy to fluoxetine,[162] paroxetine,[163] and sertraline,[164] with SSRIs being better tolerated than clomipramine. A more recent meta-analysis generally failed to find any significant difference between the SRIs, although it again suggested some advantage for clomipramine. However, this meta-analysis involved many of the trials mentioned above and has the same problem in interpretation.[165] There was no observed difference in a trial comparing fluvoxamine, paroxetine, and citalopram.[166]
Due to their similar effects, it is difficult to choose between SSRIs, and the selection of a drug largely depends upon personal preference, even if the possibility of a drug interaction or the various pharmacokinetic profiles could influence the choice. Dosages of these medications have often been described as being significantly higher than antidepressant dosages (eg, 60-80 mg/day fluoxetine); however, in large carefully controlled trials, there has been no observed significant difference between response to higher and lower dosages for the SSRIs (eg, 50 and 200 mg/day sertraline).[167] This clinical impression may well relate to the slow onset of effectiveness with many patients taking 10 to 12 weeks to improve (longer than 4-8 weeks for depression), during which physicians continue to raise the patients' doses, mistakenly thinking it was the increased dose, not time, that was responsible for improvement. For this reason, it is helpful to warn patients about this from the outset, and slowly titrate doses upwards to avoid side effects.
Many patients will not respond or will partially respond to the first SSRI, but will respond to another antiobsessional agent. Therefore, sequential trials are frequently required, which easily can take up to a year to accomplish.
Limited available evidence suggests that when effective pharmacotherapy is discontinued, most patients (90%) do relapse.[168] Therefore, current practice is to continue effective pharmacotherapy for at least 1 to 2 years or indefinitely. In a large extension study by Greist et al,[167] 118 patients who had responded to 12 weeks' treatment with either sertraline or placebo continued their treatment, in a double-blind way, for 40 weeks. Therapy gains with sertraline were maintained with continued medication as long as they remained on active medication, without tolerance developing. The 59 patients who completed this study were followed up for a second year on open-label sertraline, whereupon they showed additional clinical improvements.[169] Another trial with paroxetine demonstrated continued efficacy for 12 months in the majority of patients.[170]
The effectiveness of potent SRIs is now well established in the treatment of OCD, but despite these advances, nearly 40% to 60% of patients experience minimal to no improvement in symptoms with these treatments. Furthermore, in patients who do respond to SRIs, the degree of improvement is often incomplete, with few patients experiencing full symptom remission.[171] For these reasons, attempts to augment or improve the average response with pharmacological strategies targeting serotonergic or other neurotransmitter systems are routine. There is no agent that is routinely effective as an augmenting agent, although there is some support for clonazepam, clonidine, trazodone, nefazodone, tryptophan, and pindolol.[172] There is clear evidence of benefit for traditional neuroleptics[173] and more recently the atypical neuroleptics (eg, risperidone, olanzapine, and quetiapine), principally in the patients with OCD who have comorbid tic disorders.[174-177]
Intravenous clomipramine has also been shown to be more effective than oral administration.[178,179]
Two controlled studies were performed to test the

MAOI phenelzine efficacy in OCD. The first one[180] found phenelzine (up to 75 mg/day) and clomipramine (up to 225 mg/day) both effective with no significant difference between the two drugs, while another one comparing phenelzine (60 mg/day) with fluoxetine (80 mg/day) and placebo found that phenelzine was no better than placebo.[181]

Other drugs

Buspirone produced an effect similar to clomipramine in a small double-blind study with 18 patients,[182] but the results from controlled trials of buspirone augmentation to SRIs were less encouraging.[183,184]

Inositol (18 mg/day) was superior to placebo and well tolerated in a short-term, double-blind, controlled trial with crossover design performed in OCD.[185]

Lithium has been suggested to further reduce obsessive-compulsive symptoms when added to therapy with antidepressants,[186-188] although controlled studies have not substantiated these observations,[189] and gabapentin was reported to further reduce OC symptoms when added in an open-label manner to ongoing fluoxetine (30-100 mg/day) treatment in five OCD patients.[190] ❑

REFERENCES

1. Oakley-Browne MA. The epidemiology of anxiety disorders. *Int Rev Psychiatry*. 1991;3:243-252.
2. Robbins N, Regier DA. *Psychiatric Disorder in America: the Epidemiologic Catchment Area study*. New York, NY: Library of Congress Cataloging-in-Publication Data; 1991.
3. Markowitz JS, Weissman MM, Ouellette R, Lish JD, Klermanm GL. Quality of life in panic disorder. *Arch Gen Psychiatry*. 1989;46:984-992.
4. Klerman GL, Weissman MM, Ouellette R, Johnson J, Greenwald S. Panic attacks in the community. Social morbidity and health care utilization. *JAMA*. 1991;265:742-746.
5. Greenblatt DJ, Shader RI. Drug therapy. Benzodiazepines. *N Engl J Med*. 1974;291:1011-1015.
6. Greenblatt DJ, Shader RI. Drug therapy. Benzodiazepines. *N Engl J Med*. 1974;291:1239-1243.
7. Greenblatt DJ, Shader RI, Abernethy DR. Drug therapy: current status of benzodiazepines. Part One. *N Engl J Med*. 1983;309:354-358.
8. Greenblatt DJ, Shader RI, Abernethy DR. Drug therapy: current status of benzodiazepines. Part Two. *N Engl J Med*. 1983;309:410-416.
9. Rickels K, Downing R, Schweitzer E, et al. Antidepressants for the treatment of generalized anxiety disorder: a placebo-controlled comparison of imipramine, trazodone, and diazepam. *Arch Gen Psychiatry*. 1993;50:884-895.
10. Rickels K, Weisman K, Norstad N, et al. Buspirone and diazepam in anxiety: a controlled study. *J Clin Psychiatry*. 1982;43:81-86.
11. Rosenbaum JE, Woods SW, Groves JE, et al. Emergence of hostility during alprazolam treatment. *Am J Psychiatry*. 1984;141:792-793.
12. Hoehn-Saric R, McLeod DR, Zimmerli WD. Differential effects of alprazolam and imipramine in generalized anxiety disorder: somatic versus psychic symptoms. *J Clin Psychiatry*. 1988;49:293-301.
13. Davidson JR. Pharmacology of generalized anxiety disorder. *J Clin Psychiatry*. 2001;62(suppl 11):46-50.
14. Rickels K, Case WG, Downing RW, et al. Long-term diazepam therapy and clinical outcome. *JAMA*. 1983;250:767-771.
15. Rickels K, Fox IL, Greenblatt DJ, et al. Clorazepate and lorazepam: clinical improvement and rebound anxiety. *Am J Psychiatry*. 1988;145:312-317.
16. Rickels K, Schweitzer E, Csanalosi I, et al. Long-term treatment of anxiety and risk of withdrawal: prospective comparison of clorazepate and buspirone. *Arch Gen Psychiatry*. 1988;45:444-450.
17. Schweitzer E, Rickels K. Pharmacological treatment for generalized anxiety disorder. In: Mavissakalian MR, Prien RF, eds. *Long-Term Treatments of Anxiety Disorders*. Washington, DC: American Psychiatric Press; 1996:201-220.
18. Blazer DG, Hughes DC, George LK, Swartz M, Boyar J. Generalized anxiety disorder. In: Bobus LN, Regier DA, eds. *Psychiatric Disorders in America: The Epidemiological Catchment Area Study*. New York, NY: Fress Press; 1991:180-203.
19. Rickels K, Schweizer E. Benzodiazepines for the treatment of panic attacks: a new look. *Psychopharmacol Bull*. 1986;22:93-99.
20. Kastenholz KV. Buspirone, a novel nonbenzodiazepine anxiolytic. *Clin Pharmacol*. 1984;3:600-607.
21. Cohn JB, Bowden CL, Fisher JG, et al. Double-blind comparison of buspirone and clorazepate in anxious outpatients. *Am J Med*. 1986;80(suppl 3b):10-16.
22. Sussman N. Treatment of anxiety with buspirone. *Psychiatr Ann*. 1987;17:114-120.
23. Rickels K, Amsterdam J, Clary C, et al. Buspirone in major depression: a controlled study. *J Clin Psychiatry*. 1991;52:34-38.
24. Schweitzer E, Rickels K. Buspirone in the treatment of panic disorder: a controlled pilot comparison with clorazepate. *J Clin Psychopharmacol*. 1988;8:803.
25. Sheehan D, Raj AB, Sheehan KH, et al. Is buspirone effective for panic disorder? *J Clin Psychopharmacol*. 1990;10:3-11.
26. Delle Chiaie R, Pancheri P, Casacchia M, Stratta P, Kotzalidis GD, Zibellini M. Assessment of the efficacy of buspirone in patients affected by generalised anxiety disorder, shifting to buspirone from prior treatment with lorazepam: a placebo-controlled, double-blind study. *J Clin Psychopharmacol*. 1995;15:12-19.
27. Csanalosi I, Schweizer E, Case WG, et al. Gepirone in anxiety: a pilot study. *J Clin Psychopharmacol*. 1987;7:31-33.
28. Rickels K, Schweizer E, De Martinis M, Mandos L, Mercer C. Gepirone and diazepam in generalised anxiety disorders: a placebo-controlled trial. *J Clin Psychopharmacol*. 1997;17:272-277.
29. Borison RL, Albrecht JW, Diamond L. Efficacy and safety of a putative anxiolytic agent: ipsapirone. *Psychopharmacol Bull*. 1990;26:207-210.
30. Schweizer E, Rickels K. Placebo response in generalized anxiety: its effects on the outcome of clinical trials. *J Clin Psychiatry*. 1997;58(suppl 11):30-38.
31. Johnstone EC, Cunningham Owens DG, Frith CD, et al. Neurotic illness and its response to anxiolytic and antidepressant treatment. *Psychol Med*. 1980;10:321-328.
32. Kahn RJ, McNair DM, Lipman RS, et al. Imipramine and chlordiazepoxide in depressive and anxiety disorders. *Arch Gen Psychiatry*. 1986;43:79-85.
33. Hedges DW, Reimherr FW, Strong RE, et al. An open trial of nefazodone in adult patients with generalized anxiety disorder. *Psychopharmacol Bull*. 1996;32:671-676.
34. Rocca P, Fonzo V, Scotta M, et al. Paroxetine efficacy in the treatment of generalized anxiety disorder. *Acta Psychiatr Scand*. 1997;95:444-450.
35. Haskins JT, Aguiar L, Pallay A, Rudolph R. Double-blind, placebo-controlled study of once daily venlafaxine XR (V-XR) in outpatients with generalized anxiety disorder. Presented at the Annual Meeting, Anxiety Disorders Association of America, San Diego, Calif, March 1999.

Psicofarmacología de los trastornos de ansiedad

La población general se expone a un riesgo de vida de 1:4 para la ansiedad incapacitante, lo que ha inspirado a generaciones de psicofarmacólogos básicos y clínicos, desde la época de las primeras benzodiazepinas (BZ) hasta la de los inhibidores selectivos de la recaptación de serotonina (ISRS) y compuestos relacionados, por ejemplo, los inhibidores de la recaptación de serotonina y de noradrenalina (IRSN). Este extenso y práctico artículo de revisión resume la investigación terapéutica actual a través del espectro de los trastornos individuales: trastorno de ansiedad generalizada (TAG), trastorno de pánico (TP) y agorafobia (trastorno de ansiedad social), trastorno compulsivo (TOC), trastorno fóbico (incluyendo la fobia social) y el trastorno por estrés postraumático (TEPT). El diagnóstico específico es una condición previa para una terapia exitosa: a pesar de una considerable sobreposición, cada trastorno responde de preferencia a una terapia farmacológica específica. La comorbilidad con la depresión es frecuente; de ahí el éxito de los ISRS, los cuales fueron originalmente diseñados para tratar la depresión. La evaluación sigue siendo un problema (mediciones multivariadas versus puntuación final individual), al igual que – con frecuencia – evaluar la eficacia y la tolerancia. El ansiolítico ideal sigue siendo el "Santo Grial" de la investigación psicofarmacológica mundial.

Psychopharmacologie des troubles anxieux

Dans la population générale, l'exposition au risque d'anxiété invalidante est de 1/4 au cours de la vie; ceci a inspiré des générations de psychopharmacologues fondamentalistes et cliniques, de l'ère des premières benzodiazépines (BZ) à celle des inhibiteurs sélectifs de la recapture de la sérotonine (ISRS) et autres composés apparentés, par ex. la sérotonine et les inhibiteurs de la recapture de la noradrénaline (IRN). La présente analyse pratique résume de façon exhaustive la recherche thérapeutique actuelle à travers un éventail de troubles tels que : anxiété généralisée (TAG), trouble panique (TP) et agoraphobie (trouble anxieux social), trouble compulsif (TOC), névrose phobique (y compris la phobie sociale), et névrose de stress posttraumatique (TSPT). Un diagnostic spécifique est le prérequis d'un traitement efficace : en dépit des intrications importantes, chaque trouble répond de façon préférentielle à une pharmacothérapie spécifique. La comorbidité avec la dépression est fréquente ; d'où le succès des ISRS, qui étaient au départ conçus pour le traitement de la dépression. L'évaluation (mesures dans plusieurs domaines versus *critères individuels) reste problématique, comme le sont - souvent - l'efficacité et la tolérance. L'anxiolytique idéal demeure la quête du Graal de la recherche psychopharmacologique mondiale.*

36. Rickels K, Pollack MH, Sheehan DV, Haskins JT. Efficacy of extended-release venlafaxine in nondepressed outpatients with generalised anxiety disorder. *Am J Psychiatry*. 2000;157:968-974.

37. Haskins JT, Rudolph R, Aguiar L, Entsuah R. Double-blind, placebo-comparator–controlled study of once-daily venlafaxine XR (V-XR) and buspirone (Bsp) in outpatients with generalized anxiety disorder (GAD). Presented at the Meeting of the European College of Neuropsychopharmacology, Paris, France, October-November 1998.

38. Haskins JT, Rudolph R, Aguiar L, Entsuah R. Double-blind, placebo-/comparator-controlled study of once daily venlafaxine XR (V-XR) and buspirone (Bsp) in outpatients with generalized anxiety disorder (GAD). Presented at the Annual Meeting of the Anxiety Disorders Association of America, San Diego, Calif, March 1999.

39. Davidson JRT, DuPont RL, Hedges D, Haskins JT. Efficacy, safety, and tolerability of venlafaxine extended release and buspirone in outpatients with generalised anxiety disorder. *J Clin Psychiatry*. 1999;60:528-535.

40. Nutt DJ, Argyropoulos SV, Forshall S. In: *Generalized Anxiety Disorder: Diagnosis, Treatment and its Relationship to Other Anxiety Disorders*. London, UK: Martin Dunitz; 1998:63-77.

41. Ballenger JC, McDonald S, Noyes R, et al. The first double-blind, placebo-controlled trial of a partial benzodiazepine agonist abecarnil in generalized anxiety disorder. *Psychopharmacol Bull*. 1991;27:171-179.

42. Lydiard RB, Ballenger JC, Rickels K for the Abecarnil Work Group. A double-blind evaluation of the safety and efficacy of abecarnil, alprazolam, and placebo in outpatients with generalized anxiety disorder. *J Clin Psychiatry*. 1997;58(suppl 11):11-18.

43. Pollack MH, Worthington JJ, Manfro, GG, et al. Abecarnil for the treatment of generalized anxiety disorder: a placebo-controlled comparison of two dosage ranges of abecarnil and buspirone. *J Clin Psychiatry*. 1997;58(suppl 11):19-23.

44. Barranco SF, Bridger W. Treatment of anxiety with oral hydroxyzine: an overview. *Curr Ther Res*. 1977;22:217-227.

45. Ferreri M, Hantouche EG. Recent clinical trials of hydroxyzine in generalised anxiety disorder. *Acta Psychiatr Scand Suppl*. 1998;393:102-108.

46. Hayes PE, Schulz SC. Beta-blockers in anxiety disorders. *J Affect Disord*. 1987;13:119-130.

47. Boerner RJ. Kava kava in the treatment of generalized anxiety disorder, simple phobia and specific social phobia. *Phytother Res*. 2001;15:646-647.

48. Abadi S, Papoushek C, Evans MF. Is kava extract effective for treating anxiety? *Can Fam Physician*. 2001;47:1745-1747.

49. Akhondzadeh S, Naghavi HR, Vazirian M, Shayeganpour A, Rashidi H, Khani M. Passionflower in the treatment of generalized anxiety: a pilot double-blind randomized controlled trial with oxazepam. *J Clin Pharm Ther*. 2001;26:363-367.

50. Ballenger JC, Burrows GD, DuPont RL Jr, et al. Alprazolam in panic disorder and agoraphobia: results from a multicenter trial. I. Efficacy in short-term treatment. *Arch Gen Psychiatry*. 1988;45:413-422.
51. Andersch JC, Rosenberg NK, Kullingsjo H. Efficacy and safety of alprazolam, imipramine and placebo in the treatment of panic disorder. A Scandinavian multicentre study. *Acta Psychiatr Scand*. 1991;365(suppl):18-27.
52. Schweizer E, Rickels K, Weiss S, Zavodnick S. Maintenance drug treatment for panic disorder: II. Short- and long-term outcome after drug taper. *Arch Gen Psychiatry*. 1993;50:61-68.
53. Chouinard G, Labonte A, Fontaine R. New concepts in benzodiazepine therapy: rebound anxiety and new indications for the more potent benzodiazepines. *Prog Neuropsychopharmacol Biol Psychiatry*. 1983;7:669-673.
54. Nagy LM, Krystal JH, Woods SW, Charney DS. Clinical and medication outcome after short-term alprazolam and behavioral group. *Arch Gen Psychiatry*. 1989;46:993-999.
55. Lesser IM, Rubin RT, Rifkin A, et al. Secondary depression in panic disorder and agoraphobia. Dimensions of depressive symptomatology and their response to treatment. *J Affect Disord*. 1989;16:49-58.
56. Cox B, Endler NS, Lee PS, Swinson RP. A meta-analysis of treatments of panic disorder with agoraphobia: imipramine, alprazolam, and in vivo exposure. *J Behav Ther Exp Psychiatry*. 1992;23:175-182.
57. Clum GA, Clum GA, Surls R. A meta-analysis of treatments for panic disorder. *J Consult Clin Psychol*. 1993;61:317-326.
58. Van Balkom AJ, Bakker A, Spinhoven P, Blaauw BM, Smeenk S, Ruesink B. A meta-analysis of the treatment of panic disorder with or without agoraphobia: a comparison of psychopharmacological, cognitive-behavioral, and combination treatments. *J Nerv Ment Disord*. 1997;185:510-516.
59. Klein DF, Fink M. Psychiatric reaction patterns to imipramine. *Am J Psychiatry*. 1962;119:432-438.
60. Sargant W, Dally P. Treatment of anxiety states by antidepressant drugs. *BMJ*. 1962;1:6-9.
61. Ballenger JC, Lydiard RB, Turner SM. Panic disorder and agoraphobia. In: Gabbard GO, ed. *Treatments of Psychiatric Disorders Vol 2*. 2nd ed. Washington, DC: American Psychiatric Press; 1997:1421-1452.
62. Ballenger JC. Selective serotonin reuptake inhibitors (SSRIs) in panic disorder. In: Nutt DJ, Ballenger JC, Lepine J-P, eds. *Panic Disorder. Clinical Diagnosis, Management and Mechanisms*. London, UK: Martin Dunitz; 1999:159-178.
63. Otto MW, Tuby KS, Gould RA, McLean RY, Pollack MH. An effect-size analysis of the relative efficacy and tolerability of serotonin selective reuptake inhibitors for panic disorder. *Am J Psychiatry*. 2001;158:1989-1992.
64. Shear MK, Brown TA, Barlow DH, et al. Multicenter collaborative panic disorder severity scale. *Am J Psychiatry*. 1997;154:1571-1575.
65. Den Boer JA. Pharmacotherapy of panic disorder: differential efficacy from a clinical viewpoint. *J Clin Psychiatry*. 1998;59(suppl 8):30-36.
66. Cross National Collaborative Panic Study, Second Phase Investigators. Drug treatment of panic disorder: comparative efficacy of alprazolam, imipramine and placebo. *Br J Psychiatry*. 1993;160:191-202.
67. Lecrubier Y, Judge R. Long-term evaluation of paroxetine, clomipramine and placebo in panic disorder. Collaborative Paroxetine Panic Study Investigators. *Acta Psychiatr Scand*. 1997;95:153-160.
68. Roy-Byrne PP, Cowley DS. Course and outcome in panic disorder: a review of recent follow-up studies. *Anxiety*. 1995;1:151-160.
69. Marchesi C, Ampollini P, Signifredi R, Maggini C. The treatment of panic disorder in a clinical setting: a 12-month naturalistic study. *Neuropsychobiology*. 1997;36:25-31.
70. Ballenger JC. Medication discontinuation in panic disorder. *J Clin Psychiatry*. 1992;53S:26-31.
71. Ballenger JC, Davidson JR, Lecrubier Y, Nutt DJ, Baldwin DS, den Boer JA. Consensus statement on panic disorder from the International Consensus Group on Depression and Anxiety. *J Clin Psychiatry*. 1998;59(suppl 8):47-54.
72. Pohl RB, Wolkow RM, Clary CM. Sertraline in the treatment of panic disorder. A double-blind multicenter trial. *Am J Psychiatry.* 1998;155:1189-1195.
73. Tiller JW, Bouwer C, Behnke K. Moclobemide for anxiety disorders: a focus on moclobemide for panic disorder. *Int Clin Psychopharmacol*. 1997;12(suppl 6):s27-s30.
74. Loerch B, Graf-Morgenstern M, Hautzinger M, et al. Randomised placebo-controlled trial of moclobemide, cognitive-behavioral therapy and their combination in panic disorder with agoraphobia. *Br J Psychiatry*. 1999;174:205-212.
75. Geracioti TD. Venlafaxine treatment of panic disorder: a case series. *J Clin Psychiatry*. 1995;56:408-410.
76. Boshuisen ML, Slaap BR, Vester-Blokland ED, den Boer JA. The effect of mirtazapine in panic disorder: an open-label pilot study with a single-blind placebo run-in period. *Int Clin Psychopharmacol*. 2001;16:363-368.
77. Ribeiro L, Busnello JV, Kauer-Sant'Anna M, et al. Mirtazapine versus fluoxetine in the treatment of panic disorder. *Braz J Med Biol Res*. 2001;34:1303-1307.
78. Versiani M, Cassano GB, Perugi G, et al. Reboxetine, a selective norepinephrine reuptake inhibitor, is an effective and well-tolerated treatment for panic disorder. *J Clin Psychiatry*. 2002;63:31-37.
79. Sheehan DV, Raj AB, Harnett-Sheehan K, Soto S, Knapp E. The relative efficacy of high-dose buspirone and alprazolam in the treatment of panic disorder: a double-blind placebo-controlled study. *Acta Psychiatr Scand*. 1993;88:1-11.
80. Sandford JJ, Forshall S, Bell C, et al. Crossover trial of pagoclone and placebo in patients with *DSM-IV* panic disorder. *J Psychopharmacol*. 2001;15:205-208.
81. Munjack DJ, Crocker B, Cabe D, et al. Alprazolam, propranolol, and placebo in the treatment of panic disorder and agoraphobia with panic attacks. *J Clin Psychopharmacol*. 1989;9:22-27.
82. Layton ME, Friedman SD, Dager SR. Brain metabolic changes during lactate-induced panic: effects of gabapentin treatment. *Depress Anxiety*. 2001;14:251-254.
83. Laufer N, Weizman A. Other drug treatments and augmentation therapies for panic disorder. In: Nutt, DJ, Ballenger, JC, Lepine, J-P, eds. *Panic Disorder. Clinical Diagnosis, Management and Mechanisms*. London, UK: Martin Dunitz; 1999:179-202.
84. Balon R, Ramesh C. Calcium channel blockers for anxiety disorders? *Ann Clin Psychiatry*. 1996;8:215-220.
85. Davidson JRT, Potts N, Richichi E, Krishnan R, Ford SM, Smith R. Treatment of social phobia with clonazepam and placebo. *J Clin Psychopharmacol*. 1993;13:423-428.
86. Gelernter CS, Uhde TW, Cimbolic P, et al. Cognitive-behavioral and pharmacological treatments for social phobia. A controlled study. *Arch Gen Psychiatry*. 1991;48:938-945.
87. Versiani M, Nardi AE, Figueira I, Mendlowicz M, Marques C. Double-blind placebo-controlled trial with bromazepam in social phobia. *J Brasil Psiquiatria*. 1997;46:167-171.
88. Van Vliet M, Den Boer JA, Westenberg HG. Psychopharmacological treatment of social phobia: a double-blind, placebo-controlled study with fluvoxamine. *Psychopharmacol (Berl)*. 1994;115:128-134.
89. Pollack MH, Gould RA. The pharmacotherapy of social phobia. *Int Clin Psychopharmacol*. 1996;11(suppl 3):71-75.
90. Liebowitz MR, Schneier F, Campeas R, Hollander E. Phenelzine vs atenolol in social phobia: a placebo-controlled comparison. *Arch Gen Psychiatry*. 1992;49:290-300.
91. Versiani M, Nardi AE, Mundim FD, Alves AB, Leibowitz MR, Amrein R. Pharmacotherapy of social phobia: a controlled study with moclobemide and phenelzine. *Br J Psychiatry*. 1992;161:353-360.
92. Heimberg RG, Liebowitz MR, Hope DA, et al. Cognitive-behavioral group therapy versus phenelzine in social phobia: 12-week outcome. *Arch Gen Psychiatry*. 1998;55:1133-1141.
93. Van Vliet M, Den Boer JA, Westenberg HGM. Psychopharmacological treatment of social phobia: clinical and biochemical effects of brofaromine, a selective MAO-A inhibitor. *Eur Psychopharmacol*. 1992;2:21-29.
94. Fahlen T, Nilsson HL, Borg K, Humble M, Pauli U. Social phobia: the clinical efficacy and tolerability of the monoamine oxidase-A and serotonin uptake inhibitor brofaromine. A double-blind, placebo-controlled study. *Acta Psychiatr Scand*. 1995;92:351-358.
95. Lott M, Greist JH, Jefferson JW, et al. Brofaromine for social phobia: a multicenter, placebo-controlled, double-blind study. *J Clin Psychopharmacol*. 1997;17:255-260.

96. Katschnig H, Stein M, Buller R (on behalf of the International Multicenter Clinical Trial Group on Moclobemide in Social Phobia). Moclobemide in social phobia: a double-blind, placebo-controlled clinical study. *Eur Arch Psychiatry Clin Neurosci*. 1997;247:71-80.
97. Noyes R Jr, Moroz G, Davidson JRT, et al. Moclobemide in social phobia: a controlled-dose response trial. *J Clin Psychopharmacol*. 1997;17:247-254.
98. Schneier FR, Goetz D, Campeas R, Fallon B, Marshall R, Liebowitz MR. Placebo-controlled trial of moclobemide in social phobia. *Br J Psychiatry*. 1998;172:70-77.
99. Stein MB, Liebowitz MR, Lydiard RB, Pitts CD, Bushnell W, Gergel I. Paroxetine treatment of generalized social phobia (social anxiety disorder): A randomized controlled trial. *JAMA*. 1998;280:708-713.
100. Stein DJ, Stein MB, Goodwin W, Kumar R, Hunter B. The selective serotonin reuptake inhibitor paroxetine is effective in more generalized and in less generalized social anxiety disorder. *Psychopharmacology (Berl)*. 2001;158:267-272.
101. Stein DJ, Stein MB, Pitts CD, Kumar R, Hunter B. Predictors of response to pharmacotherapy in social anxiety disorder: an analysis of 3 placebo-controlled paroxetine trials. *J Clin Psychiatry*. 2002;63:152-155.
102. Baldwin D, Bobes J, Stein DJ, Scharwachter I, Faure M. Paroxetine in social phobia/social anxiety disorder. Randomised, double-blind, placebo-controlled study. Paroxetine Study Group. *Br J Psychiatry*. 1999;175:120-126.
103. Allgulander C. Paroxetine in social anxiety disorder: a randomized placebo-controlled study. *Acta Psychiatr Scand*. 1999;100:193-198.
104. Stein MB, Fyer AJ, Davidson JRT, Pollack MH, Wiita B. Fluvoxamine treatment so social phobia (social anxiety disorder): a double-blind, placebo-controlled study. *Am J Psychiatry*. 1999;156:756-760.
105. Katzelnick DJ, Kobak KA, Greist JH, Jefferson JW, Mantle JM, Serlin RC. Sertraline for social phobia: a double-blind, placebo-controlled, crossover study. *Am J Psychiatry*. 1995;152:1368-1371.
106. Van Ameringen MA, Lane RM, Walker JR, et al. Sertraline treatment of generalized social phobia: a 20-week, double-blind, placebo-controlled study. *Am J Psychiatry*. 2001;158:275-281.
107. Van Ameringen M, Mancini C, Streiner DL. Fluoxetine efficacy in social phobia. *J Clin Psychiatry*. 1993;54:27-32.
108. Kelsey JE. Venlafaxine in social phobia. *Psychopharmacol Bull*. 1995;31:767-771.
109. Van Ameringen MV, Mancini C, Oakman JM. Nefazodone in social phobia. *J Clin Psychiatry*. 1999;60:96-100.
110. Bouwer C, Stein CJ. Use of the selective serotonin reuptake inhibitor citalopram in the treatment of generalized social phobia. *J Affect Disord*. 1998;49:79-82.
111. Simon NM, Sharma SG, Worthington JJ, Marzol PC, Pollack MH. Citalopram for social phobia: a clinical case series. *Prog Neuropsychopharmacol Biol Psychiatry*. 2001;25:1469-1474.
112. Varia IM, Cloutier CA, Doraiswamy PM. Treatment of social anxiety disorder with citalopram. *Prog Neuropsychopharmacol Biol Psychiatry*. 2002;26:205-208.
113. Emmanuel NP, Lydiard RB, Ballenger JC. Treatment of social phobia with bupropion. *J Clin Psychopharmacol*. 1991;11:276-277.
114. Schneier FR, Franklin R, Saoud JB, et al. Buspirone in social phobia. *J Clin Psychopharmacol*. 1993;13:251-256.
115. Munjack DJ, Bruns J, Baltazar PL, et al. A pilot study of buspirone in the treatment of social phobia. *J Anxiety Disord*. 1991;5:87-98.
116. Van Ameringen, M, Mancini, C, Wilson, C. Buspirone augmentation of selective serotonin reuptake inhibitors (SSRIs) in social phobia. *J Affect Disord*. 1996;39:115-121.
117. Van Vliet IM, Den Boer JA, Westenberg HGM, Pian KLH. Clinical effects of buspirone in social phobia: a double-blind, placebo-controlled study. *J Clin Psychiatry*. 1997;58:164-168.
118. Turner SM, Beidel DC, Jacob RG. Social phobia: a comparison of behavior therapy and atenolol. *J Consult Clin Psychol*. 1994;62:350-358.
119. Stein MB, Sareen J, Hami S, Chao J. Pindolol potentiation of paroxetine for generalized social phobia: a double-blind, placebo-controlled, crossover study. *Am J Psychiatry*. 2001;158:1725-1727.
120. Pande AC, Davidson JR, Jefferson JW, et al. Treatment of social phobia with gabapentin: a placebo-controlled study. *J Clin Psychopharmacol*. 1999;19:341-348.
121. Selak I. Pregabalin (Pfizer). *Curr Opin Invest Drugs*. 2001;2:828-834.
122. Braun P, Greenberg D, Dasberg H. Core symptoms of post-traumatic stress disorder un-improved by alprazolam treatment. *J Clin Psychiatry*. 1990;51:236-238.
123. Friedman MJ. Current and future drug treatment for posttraumatic stress disorder patients. *Psychiatry Ann*. 1998;28:461-468.
124. O'Brien M, Nutt DJ. Loss of consciousness and post-traumatic stress disorder. *Br J Psychiatry*. 1998;173:102-104.
125. Gelpin E, Bonne O, Peri T, Brandes D, Shalev AY. Treatment of recent trauma survivors with benzodiazepines: a prospective study. *J Clin Psychiatry*. 1996;57:390-394.
126. Frank JB, Kosten TR, Giller EL, Dan E. A randomized clinical trial of phenelzine and imipramine for post-traumatic stress disorder. *Am J Psychiatry*. 1988;145:1289-1291.
127. Kosten TR, Frank JB, Dan E, McDougle CJ, Giller Jr EL. Pharmacotherapy for post-traumatic stress disorder using phenelzine or imipramine. *J Nerv Ment Dis*. 1991;179:366-370.
128. Davidson JRT, Kudler HS, Saunders WB, et al. Predicting response to amitriptyline in post-traumatic stress disorder. *Am J Psychiatry*. 1993;150:1024-1029.
129. Reist C, Kauffmann CD, Haier RJ, et al. A controlled trial of desipramine in 18 men with post-traumatic stress disorder. *Am J Psychiatry*. 1989;146:513-516.
130. Shestatzky M, Greenberg D, Lerer B. A controlled trial of phenelzine in posttraumatic stress disorder. *Psychiatry Res*. 1988;24:149-155.
131. Neal LA, Shapland W, Fox C. An open trial of moclobemide in the treatment of post-traumatic stress disorder. *Int Clin Psychopharmacol*. 1997;12:231-237.
132. McDougle CJ, Southwick SM, Charney DS, St James RL. An open trial of fluoxetine in the treatment of post-traumatic stress disorder. *J Clin Psychopharmacol*. 1991;11:325-327.
133. Nagy LN, Morgan CA, Southwick SM, Charney DS. Open prospective trial of fluoxetine for post-traumatic stress disorder. *J Clin Psychopharmacol*. 1993;13:107-113.
134. Van der Kolk BA, Dreyfuss D, Michaels M, et al. Fluoxetine in post traumatic stress disorder. *J Clin Psychiatry*. 1994;55:517-522.
135. Penava SJ, Otto MW, Pollack MH, Rosenbaum JF. Current status of pharmacotherapy for PTSD: an effect size analysis of controlled studies. *Depress Anxiety*. 1997;4:240-242.
136. Kline NA, Dow BM, Brown SA, Matloff JL. Sertraline efficacy in depressed combat veterans with post-traumatic stress disorder. *Am J Psychiatry*. 1994;151:621.
137. Rapaport MH, Endicott J, Clary CM. Posttraumatic stress disorder and quality of life: results across 64 weeks of sertraline treatment. *J Clin Psychiatry*. 2002;63:59-65.
138. Davidson J, Pearlstein T, Londborg P, et al. Efficacy of sertraline in preventing relapse of posttraumatic stress disorder: results of a 28-week double-blind, placebo-controlled study. *Am J Psychiatry*. 2001;158:1974-1981.
139. Marshall RD, Beebe KL, Oldham M, Zaninelli R. Efficacy and safety of paroxetine treatment for chronic PTSD: a fixed-dose, placebo-controlled study. *Am J Psychiatry*. 2001;158:1982-1988.
140. Tucker P, Zaninelli R, Yehuda R, Ruggiero L, Dillingham K, Pitts CD. Paroxetine in the treatment of chronic posttraumatic stress disorder: results of a placebo-controlled, flexible-dosage trial. *J Clin Psychiatry*. 2001;62:860-868.
141. Davidson JRT, Weisler RH, Malik ML, Connor KM. Treatment of posttraumatic stress disorder with nefazodone. *Int Clin Psychopharmacol*. 1998;13:111-113.
142. Hertzberg MA, Feldman ME, Beckham JC, Moore SD, Davidson JRT. Open trial of nefazodone for combat-related posttraumatic stress disorder. *J Clin Psychiatry*. 1998;59:460-464.
143. Lipper S, Davidson JR, Grady TA, et al. Preliminary study of carbamazepine in post-traumatic stress disorder. *Psychosomatics*. 1986;27:849-854.
144. Davidson JRT. Drug therapy of post-traumatic stress disorder. *Br J Psychiatry*. 1992;160:309-314.
145. Kitchner I, Greenstein R. Low dose lithium carbonate in the treatment of posttraumatic stress disorder. *Mil Med*. 1985;150:378-381.
146. Keck Jr PE, McLeroy SL, Friedman LM. Valoprate and carbamazepine in the treatment of panic and posttraumatic stress disorders, withdrawal states, and behavioral dyscontrol syndromes. Review. *J Clin Psychopharmacol*. 1992;12(suppl 1):36S-41S.

147. Petty F, Davis LL, Nugent AL, et al. Valproate therapy for chronic, combat-induced posttraumatic stress disorder. *J Clin Psychopharmacol*. 2002;22:100-101.
148. Sutherland SM, Davidson JR. Pharmacotherapy for post-traumatic stress disorder. *Psychiatr Clin North Am*. 1994;17:409-423.
149. Berlant J, van K. Open-label topiramate as primary or adjunctive therapy in chronic civilian posttraumatic stress disorder: a preliminary report. *J Clin Psychiatry*. 2002;63:15-20.
150. Hamner MB, Brodrick PS, Labbate LA. Gabapentin in PTSD: a retrospective, clinical series of adjunctive therapy. *Ann Clin Psychiatry*. 2001;13:141-146.
151. Wells BG, Chu CC, Johnson R, et al. Buspirone in the treatment of post-traumatic stress disorder. *Pharmacotherapy*. 1991;11:340-343.
152. Petty F, Brannan S, Casada J, et al. Olanzapine treatment for post-traumatic stress disorder: an open-label study. *Int Clin Psychopharmacol*. 2001;16:331-337.
153. Kolb LC, Burris BC, Griffiths S. Propranolol and clonidine in the treatment of post-traumatic stress disorder of war. In: van der Kolk BA, ed. *Post-traumatic Stress Disorder: Psychological and Biological Sequelae*. Washington, DC: American Psychiatric Press; 1984:98-107.
154. Pitman RK, Sanders KM, Zusman RM, et al. Pilot study of secondary prevention of posttraumatic stress disorder with propranolol. *Biol Psychiatry*. 2002;15:189-192.
155. Taylor F, Raskind MA. The alpha1-adrenergic antagonist prazosin improves sleep and nightmares in civilian trauma posttraumatic stress disorder. *J Clin Psychopharmacol*. 2002;22:82-85.
156. Hewlett WA, Vinogradov S, Agras WS. Clomipramine, clonazepam, and clonidine treatment of obsessive-compulsive disorder. *J Clin Psychopharmacol*. 1992;12:420-430.
157. Clomipramine Collaborative Study Group. Clomipramine in the treatment of obsessive-compulsive disorder. *Arch Gen Psychiatry*. 1991;48:730-737.
158. Lydiard RB, Brawman-Mintzer O, Ballenger JC. Recent developments in the psychopharmacology of anxiety disorders. *J Consult Clin Psychol*. 1996;64:660-668.
159. Zohar J, Chopra M, Sasson Y, et al. Psychopharmacology of obsessive-compulsive disorder? *World J Biol Psychiatry*. 2000;1:92-100.
160. Piccinelli M, Pini S, Bellantuono C, et al. Efficacy of drug treatment in obsessive-compulsive disorder. *Br J Psychiatry*. 1995;166:424-443.
161. Greist JH, Jefferson JW, Kobak KA, Katzelnick DJ, Serlin RC. Efficacy and tolerability of serotonin transport inhibitors in obsessive-compulsive disorder: a meta-analysis. *Arch Gen Psychiatry*. 1995;52:53-60.
162. Piggott TA, Pato MT, Bernstein S, et al. Controlled comparisons of clomipramine and fluoxetine in the treatment of obsessive compulsive disorder. *Arch Gen Psychiatry*. 1990;47:926-932.
163. Zohar J, Judge R. Paroxetine versus clomipramine in the treatment of obsessive-compulsive disorder. OCD Paroxetine Study Investigators. *Br J Psychiatry*. 1996;169:468-474.
164. Bisserbe JC, Lane RM, Flament MF, et al. A double-blind comparison of sertraline and clomipramine in outpatients with obsessive-compulsive disorder. *Eur Psychiatry*. 1997;153:1450-1454.
165. Kobak KA, Greist JH, Jefferson JW, Katzelnick DJ, Henk HJ. Behavioral versus pharmacological treatments of obsessive compulsive disorder: a meta-analysis. *Psychopharmacology*. 1997;136:205-216.
166. Mundo, E, Bianchi, L, Bellodi, L. Efficacy of fluvoxamine, paroxetine, and citalopram in the treatment of obsessive-compulsive disorder: a single-blind study. *J Clin Psychopharmacol*. 1997;17:267-271.
167. Greist JH, Jefferson JW, Kobak KA, et al. A one-year, double-blind, placebo-controlled fixed dose study of sertraline in the treatment of obsessive-compulsive disorder. *Int Clin Psychopharmacol*. 1995;10:57-65.
168. Pato MT, Zohar-Kadouch R, Zohar J, Murphy DL. Return of symptoms after discontinuation of clomipramine in patients with obsessive compulsive disorder. *Am J Psychiatry*. 1988;145:1521-1525.
169. Rasmussen S, Hackett E, DuBoff E, et al. A 2-year study of sertraline in the treatment of obsessive-compulsive disorder. *Int Clin Psychopharmacol*. 1997;12:309-316.
170. Steiner M. Long-term treatment and prevention of relapse in OCD with paroxetine. Presented at the Annual Meeting of the American Psychiatric Association, Miami, Fla, May 1995.
171. McDougle CJ, Goodman WK, Leckman JF, et al. The psychopharmacology of obsessive-compulsive disorder: implications for treatment and pathogenesis. *Psychiatr Clin North Am*. 1993;16:749-766.
172. Jenike MA, Rauch SL. Managing the patient with treatment-resistant obsessive compulsive disorder: current strategies. *J Clin Psychiatry*. 1994;55(suppl 3):11-17.
173. McDougle CJ, Goodman WK, Leckman JF, Lee NC, Heninger GR, Price LH. Haloperidol addition in fluvoxamine-refractory obsessive compulsive disorder. *Arch Gen Psychiatry*. 1994;51:302-308.
174. McDougle CJ, Epperson CN, Pelton GH, Wasylink S, Price LH. A double-blind, placebo-controlled study of risperidone addition in serotonin reuptake inhibitor–refractory obsessive-compulsive disorder. *Arch Gen Psychiatry*. 2000;57:794-801.
175. Pfanner C, Marazziti D, Dell'Osso L, et al. Risperidone augmentation in refractory obsessive-compulsive disorder: an open-label study. *Int Clin Psychopharmacol*. 2000;15:297-301.
176. Koran LM, Ringold AL, Elliott MA. Olanzapine augmentation for treatment-resistant obsessive-compulsive disorder. *J Clin Psychiatry*. 2000;61:514-517.
177. Mohr N, Vythilingum B, Emsley RA, Stein DJ. Quetiapine augmentation of serotonin reuptake inhibitors in obsessive-compulsive disorder. *Int Clin Psychopharmacol*. 2002;17:37-40.
178. Koran LM, Sallee FR, Pallanti S. Rapid benefit of intravenous pulse loading of clomipramine in obsessive-compulsive disorder. *Am J Psychiatry*. 1997;154:396-401.
179. Fallon BA, Liebowitz MR, Campeas R, et al. Intravenous clomipramine for obsessive-compulsive disorder refractory to oral clomipramine: a placebo-controlled study. *Arch Gen Psychiatry*. 1998;55:918-924.
180. Vallejo J, Olivares J, Marcos T, Bulbena A, Menchon JM. Clomipramine versus phenelzine in obsessive-compulsive disorder. A controlled clinical trial. *Br J Psychiatry*. 1992;161:665-670.
181. Jenike MA, Baer L, Minichiello WE, Rauch SL, Buttolph ML. Placebo-controlled trial of fluoxetine and phenelzine for obsessive-compulsive disorder. *Am J Psychiatry*. 1997;154:1261-1264.
182. Pato MT, Pigott TA, Hill JL, Grover GN, Bernstein SE, Murphy DL. Controlled comparison of buspirone and clomipramine in obsessive-compulsive disorder. *Am J Psychiatry*. 1991;148:127-129.
183. Piggott TA, L'Heureux F, Hill JL, Bihari K, Bernstein SE, Murphy DL. A double-blind study of adjuvant buspirone hydrochloride in clomipramine-treated patients with obsessive-compulsive disorder. *J Clin Psychopharmacol*. 1992;12:11-18.
184. Grady TA, Pigott TA, L'Heureux F, Hill JL, Bernstein SE, Murphy DL. Double-blind study of adjuvant buspirone for fluoxetine-treated patients with obsessive-compulsive disorder. *Am J Psychiatry.* 1993;150:819-821.
185. Fux XM, Levine J, Aviv A, Belmaker RH. Inositol treatment of obsessive-compulsive disorder. *Am J Psychiatry*. 1996;153:1219-1221.
186. Stern TA, Jenike MA. Treatment of obsessive-compulsive disorder with lithium carbonate. *Psychosomatics*. 1983;24:671-673.
187. Rasmussen SA. Lithium and tryptophan augmentation in clomipramine-resistant obsessive-compulsive disorder. *Am J Psychiatry*. 1984;141:1283-1285.
188. Golden RN, Morris JE, Sack DA. Combined lithium-tricyclic treatment of obsessive-compulsive disorder. *Biol Psychiatry*. 1988;23:181-185.
189. McDougle CJ, Price LH, Goodman WK, Charney DS, Heninger GR. A controlled trial of lithium augmentation in fluvoxamine-refractory obsessive-compulsive disorder: lack of efficacy. *J Clin Psychopharmacol*. 1991;11:175-184.
190. Cora-Locatelli G, Greenberg BD, Martin J, Murphy DL. Gabapentin augmentation for fluoxetine-treated patients with obsessive-compulsive disorder. *J Clin Psychiatry*. 1998;59:480-481.