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.

Anxiety disorders are the most common and among the most disabling of mental disorders in adults and adolescents. Although many are highly circumscribed fears of mild-to-moderate severity, it has been estimated by the Epidemiological Catchment Area (ECA) study 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 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.

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,
Pharmacological aspects

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.
xiety 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 tolerance9,13; 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,8 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.18 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-HT2 receptors. It has been demonstrated to show efficacy in GAD10,20,21 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.

### 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, and where depressive symptoms are intermixed with anxiety, while it is less effective than BZs on somatic and autonomically driven symptoms. Patients who have had previous good responses to BZs do not appear to respond as well to buspirone, 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. Other azapirone drugs have been assessed in GAD, like gepirone, ipsapirone, 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. Early retrospective analyses of subjects with anxiety neurosis have supported the possible efficacy of tricyclic drugs in GAD-like states. Further controlled trials by Kahn et al, Hoehn-Saric et al, and Rickels et al 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-HT₂ 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-HT₂ 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, as is also the case for the SSRI paroxetine. 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. 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. 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. 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.

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. 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 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. It can be very sedating when high doses are used (50 and 100 mg qid), but a more recent study 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. Finally, anecdotal experiences report potential value of kava and passionflower extract in the treatment of GAD.

### 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, with improvements also maintained in longer-term studies. Other high-potency BZs, such as clonazepam and lorazepam, 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.

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

#### Antidepressants

Early in the 1960s, investigators documented that imipramine and the MAOIs, particularly phenelzine, were both effective treatments of PD. 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-
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.\(^{53}\) 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 (e.g., 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.\(^{86}\) 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.\(^55\) 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,\(^66\) 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,\(^{50,51}\) 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.\(^51\) 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,\(^71\) 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. Initial evidence suggested that gabapentin and sodium valproate may be effective in PD, while carbamazepine is not. Also Ca-channel blockers have shown mixed results.

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. 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 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 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, 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.

There were three early controlled trials 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 in 1998.

In a comparison between phenelzine and moclobemide, phenelzine appeared roughly equivalent, but appeared to work faster. 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 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%, 78%, and 50%. Moclobemide, after the promising results of Versiani et al, produced a less robust result in the large multicenter controlled study that followed, in which 600 mg/day was superior to placebo (47% of responders compared with 34% receiving placebo). Another large multicenter trial, as well a single study, 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. 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 and Allgulander.

Other controlled trials with SSRIs include fluvoxamine, sertraline, fluoxetine, venlafaxine, and nefazodone. In these trials, the clinically significant response rates of patients were in the 42% to 77% range.

Finally, open trials of citalopram and buproprion 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

Buspiron has been shown to be effective as a primary treatment in two thirds of patients in early trials, as well as an augmenting agent with SSRIs. One controlled trial failed to find significant differences between buspiron and placebo. Also the β-blocker atenolol, despite early promise, proved ineffective when tested in patient populations with generalized symptoms of social phobia. Pindolol was no more effective than placebo in augmenting the effects of paroxetine treatment for generalized social phobia.
High doses of gabapentin (3600 mg/day) provided encouraging preliminary results in a 14-week, placebo-controlled study.\textsuperscript{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.\textsuperscript{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\textsuperscript{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,\textsuperscript{123} but withdrawal symptoms were particularly severe, especially considering the substantial comorbidity of PTSD with alcohol and drug abuse. O’Brien and Nutt\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{128} Desipramine failed to show any advantage over placebo in a 4-week study,\textsuperscript{129} but at relatively low doses compared with the two previous trials. Moreover, as highlighted by Friedman,\textsuperscript{130} 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,\textsuperscript{126} but other trials have failed to observe positive effects.\textsuperscript{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.\textsuperscript{123} Early trials with combat veterans suggest that the reversible MAOI moclobemide is promising.\textsuperscript{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 | Add nefazodone or trazadone for concurrent sleep disorders |
| • Depressive symptoms | SSRI (fluoxetine, paroxetine, sertraline), or TCA (imipramine, amitriptyline), or phenelzine | Add nefazodone 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 al135 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 effective136 in long-term treatment137,138 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 topiramate149 and gabapentin150 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 α1-adrenergic antagonist prazosin155 and α1-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 | Add mood stabilizer (lithium, gabapentin) |
| Highly anxious obsessional subjects | Eventually switch to a different SSRI or SRI (clomipramine or intravenous clomipramine) (Potentiation with buspirone, clonazepam, tryptophan, pindolol) | Add BZ (clonazepam) |
| Prevalent symmetry and atypical obsession or high level of anxiety to treatment | Add MAOI or SNRI and eventually neuroleptic | Add different typical/ atypical neuroleptic (pimozide, haloperidol, risperidone, olanzapine) |
| Severe hoarding symptoms | | Add different typical/atypical neuroleptic (pimozide, haloperidol, risperidone, olanzapine) |
| Tics, psychotic symptoms | | |

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.
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 chlorimipramine160,161; 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.166 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.168 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 neuroleptics173 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 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 SSRIs 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

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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 benzodiacepinas (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 posttraumático (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.

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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 psychopharmacologistes fondamentalistes et cliniques, de l’ère des premières benzodiazépines (BZ) à celles 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 (troubles anxieux sociaux), 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.
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