Pharmacotherapy of anxiety disorders: a critical review

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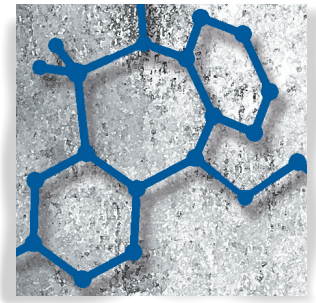

Given the enormous contribution of anxiety disorders to the burden of disease, it is key to optimize their prevention and treatment. In this critical review we assess advances in the pharmacotherapy of anxiety disorders, as well as remaining challenges. In recent decades, the field has seen rigorous clinical trial methods to quantify the efficacy and safety of serendipitously discovered agents, more focused development of medications with selective mechanisms of action, and the gradual translation of insights from laboratory research into proof-of-principle clinical trials. On the positive side, a considerable database of studies shows efficacy and relative tolerability of the selective serotonin reuptake inhibitors in the major anxiety disorders, and secondary analyses of such datasets have informed questions such as optimal definition of response and remission, optimal dose and duration, and comparative efficacy of different agents. Significant challenges in the field include barriers to appropriate diagnosis and treatment of anxiety disorders, failure of a significant proportion of patients to respond to first-line pharmacotherapy agents, and a limited database of efficacy or effectiveness studies to guide treatment in such cases.

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Introduction

Optimizing the prevention and treatment of anxiety disorders is a key goal for contemporary psychiatry, given that these are the most common of the mental disorders, that they increase the risk for comorbid mood and substance use disorders, and that they contribute significantly to the global burden of disease.[1,2] Pharmacotherapy likely has the potential to make an important contribution to such interventions.

Indeed, there have been a number of advances in the pharmacotherapy of anxiety disorders in recent decades. An important early step was the development of rigorous clinical trial methods to quantify the efficacy and safety of serendipitously discovered agents. A subsequent significant advance was the transition to more focused pharmaceutical development of agents with selective mechanisms of action. More recently, animal laboratory studies and psychobiological clinical research have further advanced our understanding of the neural circuitry and molecular systems that underpin the anxiety disorders, and so provided novel treatment targets.

Nevertheless, there remain significant challenges in the field. These include various barriers to appropriate diag-

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nosis and treatment of anxiety disorders, failure of a significant proportion of patients to respond to first-line pharmacotherapy agents, and an ongoing lack of data on a number of key questions. In this paper we provide a critical review of the pharmacotherapy of anxiety disorders, summarizing advances in the field, as well as pointing out some of the areas that need to be addressed in future work.

Generalized anxiety disorder

In many ways, developments in the pharmacotherapy of generalized anxiety disorder (GAD) reflect the history of the field of anxiety disorders as a whole. Anxiety is a symptom that has been present since the beginning of time, and anxiolytic agents have long been part of the armamentarium of traditional healers and early physicians. The effects of early medications were discovered serendipitously, they sometimes had a poor risk:benefit ratio (eg, the barbiturates), and trials were either nonexistent or limited by methodological problems including a lack of reliable diagnostic criteria and valid measures of symptom severity.

The introduction of benzodiazepines and tricyclic antidepressants (TCAs) was an important advance in the pharmacotherapy of GAD; these agents were studied in rigorous randomized controlled trials, and were shown to have an acceptable risk:benefit ratio.[3] Subsequent work with agents that targeted particular molecular systems, such as the selective serotonin reuptake inhibitors (SSRIs) and the serotonin and noradrenaline reuptake inhibitors (SNRIs), constituted another important step, insofar as the quality of trials and risk:benefit ratio further improved.[4-7] *(Table I)*. Indeed, most current treatment guidelines emphasize that SSRIs and SNRIs are the first-line pharmacotherapy agents of choice in GAD.[8-11] Finally, more recent ongoing basic and clinical psychobiology research has led to novel molecular targets for future development.[12-14]

As their name suggests, SSRIs inhibit the reuptake of serotonin at the presynaptic membrane by the serotonin (5-HT) transport pump, thus increasing synaptic concentration of the neurotransmitter. SSRIs currently available for clinical use are citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline. There is evidence to support the efficacy and tolerability of escitalopram, fluoxetine, paroxetine, and sertraline in the short and longer-term management of GAD,[7,8] and both escitalopram and paroxetine have FDA approval for this indication.[15] Clinical trials have studied paroxetine 20 to 50 mg/day and escitalopram 10 to 20 mg/day,[5] but in practice patients can be started on even low doses and titrated up (for example an initial paroxetine dosage of 10 mg/day, titrated upwards every 7 days, may be used, *Table I*).[16]

TCAs inhibit reuptake of both noradrenaline and serotonin, but also act on a range of other neurotransmitter systems, accounting for their relatively poor safety and tolerability profile. Venlafaxine and duloxetine are SNRIs which act selectively to inhibit reuptake of noradrenaline and serotonin. The use of both agents in the short-term management of GAD is supported by a number of RCTs,[6,7] and venlafaxine was the first antidepressant to receive FDA approval for the treatment of GAD.[16] Venlafaxine studies used an initial dosage of 37.5 mg or 75 mg, which was then titrated up to a maximum of 225 mg; duloxetine studies ranged from 60 to 120 mg.[17-19]

There are relatively few maintenance studies of SSRIs and SNRIs in the longer-term treatment of GAD.[7] However, such trials have consistently indicated that early discontinuation of these agents is associated with a high risk of relapse. Thus, most treatment guidelines suggest that after a response to pharmacotherapy is obtained, treatment should be continued for at least a year, and that discontinuation should be done gradually.[3,9-11]

Agomelatine is a melatonergic agonist (MT_1 and MT_2 receptors) and $5HT_{2C}$ antagonist that is registered for treatment of depression by the European Medical Agency. There are also several lines of evidence suggesting that agomelatine may be effective in GAD. First, this agent demonstrates anxiolytic activity in various rodent models.[20] Second, it reduces anxiety symptoms in patients with depression.[21] Finally, agomelatine 25 to 50 mg/day was found efficacious in a recent trial in GAD.[22] Remarkably, agomelatine was as well tolerated as the placebo, and patients suffered no discontinuation emergent symptoms. Initial data from a relapse prevention trial are also promising.[23]

Benzodiazepines exert their anxiolytic effect by binding to a specific site on the γ-aminobutyric acid (GABA)-receptor, thus potentiating the effect of the inhibitory neurotransmitter GABA. A number of randomized controlled trials support the use of these agents in the short-term treatment of GAD,[24] and alprazolam is FDA-

approved for the treatment of GAD.[15] A recent meta-analysis found that the efficacy of benzodiazepines was comparable to that of the SSRIs and venlafaxine in the treatment of GAD.[25]

However, although the benzodiazepines have the advantage of a particularly early onset of action (sometimes within 15 to 60 minutes), higher dosages of these agents may be associated with a number of adverse effects, including sedation, physical dependence, and impaired concentration.[16] Furthermore, they are ineffective for treating comorbid depression, and may be less effective for treating the psychic than the somatic symptoms of GAD.[26] Long-term use of these agents may be associated with problematic withdrawal symptoms and rebound anxiety.[16] Thus most treatment guidelines do not recommend benzodiazepines as a first-line pharmacotherapy in GAD.[8-11]

Buspirone is a partial agonist of the 5-HT_{1A} receptor. Although there is evidence of good efficacy and tolerability in GAD,[27] clinicians remain somewhat sceptical of its utility, perhaps because of relatively unfavorable reports of its value from patients previously exposed to benzodiazepines. Given the evidence base, buspirone may certainly be considered in the treatment of patients with GAD, and on theoretical grounds this agent may have a particularly useful role in those with comorbid alcohol dependence (where benzodiazepines are partially contraindicated)[28] and in the augmentation of SSRIs in treatment-refractory GAD.[29]

Gabapentin and pregabalin are structurally analogous

	Study	Year	Population	Intervention	Effect of intervention
Paroxetine	Rickels et al[158]	2003	Adults (≥18 years)	8 weeks of paroxetine 20 or 40 mg/day, or placebo.	Response was achieved by 62% and 68% of the patients receiving 20 and 40 mg of paroxetine, respectively, compared with a 46% response rate in the placebo group. Remission was achieved by 30% and 36% of patients in the 20- and 40-mg paroxetine groups,respectively, compared with 20% given placebo. Both doses of paroxetine were well tolerated.
	Stocchi et al[159]	2003	Adults	Paroxetine (20-50 mg/day) for 8 weeks; followed by 24 weeks of paroxetine (n=278) or placebo (n=288)	Significantly fewer paroxetine than placebo patients relapsed during the 24-week double-blind phase (10.9% vs 39.9%; *P*<.001). Placebo patients were almost 5 times more likely to relapse than paroxetine patients (estimated hazard ratio=0.213 [95% CI=0.1 to 0.3]; *P*<.001). Twice as many paroxetine patients as placebo patients (73%) achieved remission. Paroxetine was well tolerated, with no unexpected adverse events reported.
	Pollack et al[160]	2001	Adults (≥18 years)	Treatment with paroxetine (20-50 mg/day) or placebo for 8 weeks.	A significantly greater proportions of paroxetine-treated patients achieved response or remission by week 8, compared with the placebo group. Treatment with paroxetine was well tolerated.
Escitalopram	Lenze et al[154]	2009	Older adults (≥60 years)	Twelve weeks of 10-20 mg/day of escitalopram (n=85) or matching placebo	Higher cumulative response rate for escitalopram (69%; 95% CI 58%-80%) versus placebo (51%; 95% CI 46%-67%)
	Davidson et al[161]	2004	Adults (≥18 years)	Escitalopram 10 mg/day for the first 4 weeks and then flexibly dosed from 10-20 mg/day (n=158), versus placebo for 8 weeks	Response rates at week 8 were 68% for escitalopram and 41% for placebo (P<.01) for completers, and 58% for escitalopram and 38% for placebo LOCF values (*P*<.01).

Table I. Selected placebo-controlled randomized controlled trials in generalized anxiety disorder.

to GABA and bind to the $\alpha_2\delta$ subunit of the voltage-gated calcium channels in the CNS. They exert their effects by increasing glutamic acid decarboxylase activity, thus also increasing levels of neuronal GABA and inhibiting the release of excitatory neurotransmitters such as glutamate, noradrenaline, and substance P.[30] A number of randomized, placebo-controlled trials have demonstrated efficacy and tolerability of pregabalin over the short term, and pregabalin was effective in preventing symptom relapse.[30] Pregabalin was also found to be efficacious and well-tolerated in elderly patients with GAD.[31] The relatively favorable side-effect profile of pregabalin makes it another useful treatment option in GAD.[7] Current treatment guidelines recommend a dose range of 150 to 600 mg/day for adult patients.[9]

Antipsychotic agents have also been studied as monotherapy in GAD. There is evidence that the atypical antipsychotic quetiapine is more effective than placebo in improving clinical response and remission rates in patients with GAD.[32,33] However, risk:benefit ratio remains a concern given the possibility of adverse events such as metabolic syndrome. On the other hand, these agents may have a role to play in treatment-refractory patients, with evidence suggesting that various antipsychotic agents may be beneficial as augmentation strategies in those with treatment-refractory GAD.[34,35]

Indeed, in clinical practice a significant proportion of patients with GAD fail either to receive appropriate therapy or to respond to first-line pharmacotherapy. An immediate step in the management of the latter group of patients is to ensure that diagnosis is correct, that psychiatric and medical comorbidity has not been overlooked, and that the trial is of sufficient duration and dosage.[36] Next steps include switching to a different agent, or augmentation.[8,9,16,37] There are few switch studies in GAD, but the literature on depression suggests that a different SSRI or an agent from a different class might be useful in refractory cases. Pharmacotherapy augmentation strategies include the addition to SSRI/SNRI treatment of buspirone,[29] pregabalin,[38] or low doses of atypical antipsychotics.[35,34] Although data on the value of combined pharmacotherapy and psychotherapy in GAD is surprisingly limited,[39] psychotherapy augmentation strategies may also be considered.

In addition to the glaring absence of data on how best to approach the treatment-refractory GAD patient, a number of other gaps in the literature deserve to be highlighted. First, most treatment data on GAD derive from trials of GAD patients without comorbidity recruited by academic centers; there are few data on effectiveness in real-world settings, where the vast majority of patients with GAD present, often with a range of comorbid psychiatric and medical disorders and symptoms. Second, there are relatively few data on "special" populations, including children and adolescents and geriatric patients with GAD,[40,41] or on whether early pharmacotherapy of GAD is able to prevent subsequent onset of mood and substance-use disorders.[42]

Several promising future lines of investigation of GAD have, however, been opened up by ongoing work on the psychobiology of GAD. Work on the role of the glutamate system in fear extinction,[43] on the role of neuropeptides in stress responses,[44] and on a range of second messenger or other downstream systems,[45,46] for example, may ultimately lead to new treatments for GAD. The development of a personalized approach to the pharmacotherapy of GAD will depend ultimately on the incorporation of genetic and/or imaging methodologies into research on the pharmacotherapy of GAD; surprisingly little such work has been done to date, and much more is therefore needed.

Obsessive-compulsive disorder

The serendipitous discovery that clomipramine (CMI), a more serotonergic tricyclic, is effective for obsessive-compulsive disorder (OCD) was important in giving impetus to a serotonin hypothesis of OCD.[47] Subsequent work found that the more selective SSRIs were not only efficacious but also well-tolerated.[48] More recent psychobiological research has focused on delineating the role of neurotransmitters other than serotonin; dopaminergic augmentation strategies have been used clinically for some time now,[49] and a range of other molecular treatment targets are being pursued.[50,51]

Anecdotal reports of the efficacy of CMI in OCD were followed by rigorous randomized controlled trials. Such work demonstrated that clomipramine was more efficacious than both placebo and noradrenergic tricyclic agents such as desipramine, and that it was efficacious in both adults as well as in children and adolescents with OCD.[52] Such work led to the first FDA approval for OCD pharmacotherapy.[15] The use of intravenous (IV) CMI for refractory OCD has also been investigated,[53,54] as this route of administration avoids first-pass hepatic

metabolism which breaks CMI down to its less potent form, desmethyl-clomipramine.

With the introduction of the SSRIs, several studies of these agents were undertaken in OCD, and these generally showed efficacy and safety.[55] Fluoxetine, fluvoxamine, paroxetine, and sertraline have all been FDA-approved for OCD.[56] While several meta-analyses have suggested that CMI may be more effective than SSRIs *(Table II)*,[57] this finding may reflect the fact that early studies were characterized by a lower placebo response rate. Head-to-head comparisons of CMI and SSRIs have shown equal efficacy and superior tolerability for the SSRIs.[58] Thus, the SSRIs are now typically viewed as the first-line choice for OCD.[8,9,11,56,59]

A meta-analysis of medication dosage findings in OCD suggests that patients who fail to respond to low-dose therapy should be increased to a higher dose.[60] An adequate trial in OCD should be at least 12 weeks in length.[61] Although there is less published work on the longer-term treatment of OCD, a number of studies have demonstrated that early discontinuation often leads to relapse.[58] Guidelines therefore suggest that patients who respond to initial acute treatment should then be continued for at least 1 year, and withdrawn gradually.[8,9,56,59] It has been suggested that efficacy can be maintained even after a reduction in dosage of long-term treatment, with the benefits of improved tolerability and adherence.[62]

Unfortunately, up to 50% of patients with OCD treated with an adequate trial of SSRI fail to respond fully.[63] Basic work on the psychobiology of OCD has suggested that neurotransmitters other than serotonin may be important in its pathogenesis. Indeed, the best studied SSRI-augmenting agents in OCD are low-dose atypical antipsychotics. Early work suggested that these were particularly useful in patients with comorbid tics,[64] but subsequent work has indicated that they may be useful in both patients with and without tic disorders.[65,66]

More recently, evidence for the role of the glutamatergic system in mediating OCD has emerged, and there has been interest in using glutamate-modulating drugs in the augmentation of treatment-resistant OCD. The anticonvulsant agent topiramate, which inhibits glutamatergic neurotransmission, may be useful in treatment-refractory OCD.[67] Riluzole, which inhibits the release of glutamic acid, thus also blocking glutamatergic neurotransmission, has been found effective in proof of principle trials.[68,69] Memantine, another glutamatergic agent, may also be useful in treatment-refractory OCD.[70] There has also been interest in using the NMDA partial agonist, cycloserine, in combination with CBT in OCD.[71]

Several other somatic treatment options in OCD are also being explored. First, a range of other mechanisms have been targeted by SSRI-augmentation strategies, including use of the 5-HT_3 receptor antagonist, ondansetron.[72] Second, given the abundance of literature on autoimmu-

Study	Year	Population	Intervention	Effect of intervention
Eddy et al[162]	2004	Adult	Psychotherapy and pharmacotherapy	A range of pharmacological and psychological interventions led to substantial improvement for the average patient, with individual psychotherapies, clomipramine, and other serotonin reuptake inhibitors faring best.
Ackerman and Greenland[163]	2002	Adult	CMI/SSRI (fluvoxamine, sertraline, paroxetine) vs placebo	CMI/SSRIs are superior to placebo in treating patients with OCD.
Picinelli et al[164]	1995	Adult	Antidepressant drug treatment	The response rate for CMI is superior to placebo and to SSRIs (fluoxetine, fluvoxamine, and sertraline).
Greist et al[165]	1995	Adolescent-Adult (aged 14+ yrs)	Serotonin transport inhibitors (STIs)	Four STIs (clomipramine hydrochloride, fluoxetine hydrochloride, fluvoxamine maleate, and sertraline hydrochloride) are of substantial benefit for the treatment of OCD. An apparent efficacy advantage and low dropout rate was found for clomipramine.
Stein et al[166]	1995	Adult	Serotonin reuptake inhibitors (SRIs)	SRIs have a significant benefit, with clomipramine more effective than fluoxetine.

Table II. Selected meta-analyses of obsessive-compulsive disorder treatment. CMI, clomipramine; SSRI, selective serotonin reuptake inhibitor; OCD, obsessive-compulsive disorder

nity in OCD, one strand of work has focused on the use of immunoglobulins and plasmapheresis in patients with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS).[73-75] Third, given the work on the neural circuitry of OCD, neurosurgery to remove specific lesions[76] or deep brain stimulation after implantation of electrodes has been investigated.[77,78] Such approaches provide promise for the future management of refractory OCD.

Panic disorder

Research on the pharmacotherapy of panic disorder (PD) was given significant impetus by the early serendipitous finding that tricyclic antidepressants are effective, and the hypothesis that different pharmacological agents are effective for different anxiety disorders.[79] Subsequent research done in order to register alprazolam and other benzodiazepines for the treatment of panic disorder did not provide a great deal of support for this hypothesis, but was important in contributing to the development of clinical trial methods in this condition. Subsequent rigorous randomized controlled trials of the SSRIs in PD were again an important advance insofar as they provided an effective and relatively well-tolerated treatment option.[80-82] As in the case of GAD and OCD, however, much further work is required to optimize the treatment of refractory cases. Fortunately, ongoing studies of the psychobiology of PD have provided several leads which may be helpful in developing more targeted therapies in the future.[80]

Early work on tricyclic agents such as imipramine and clomipramine demonstrated that these agents were efficacious in PD, reducing the frequency of panic attacks and the severity of anticipatory anxiety.[80] These older agents appear as effective as more recent antidepressant agents.[83] However, the widespread use of these agents is limited by their relatively unfavorable side-effect profile, including problematic anticholinergic and antiadrenergic effects,[84] and they are not recommended as first-line agents.[8-11]

Similarly, while classic monoamine oxidase inhibitors (MAOIs) may be effective for panic disorder, they are not commonly prescribed for this indication. These agents exert their antidepressant effect by inhibiting the MAO enzyme, so decreasing the breakdown of serotonin and noradrenaline and increasing the net level of these neurotransmitters in the CNS.[15] However, as is the case with TCAs, the widespread use of MAOIs is generally limited by their associated adverse effects (including the risk of hypertensive crisis when taken with tyramine-containing foods) and their numerous potential drug interactions.

Alprazolam, a short-acting agent, is the best studied benzodiazepine in panic disorder.[80] It has shown efficacy compared with placebo in short and longer-term studies, and it has been found comparable in effect to the tricyclics and to the SSRIs.[85] Alprazolam as well as a number of other benzodiazepines (clonazepam, diazepam, and lorazepam) are FDA-approved for PD.[15] Nevertheless, once again, given their relatively unfavorable side-effect profile, most treatment guidelines do not list these agents as a first-line option.[8-11]

Fluoxetine, paroxetine, and sertraline have all been rigorously investigated in clinical trials and have received FDA approval for use in PD.[15] They are as effective, but better tolerated, than the older TCAs.[83] There seems to be little difference in efficacy within this group of agents.[80] Current guidelines recommend that active medication be continued for at least a year, in order to prevent relapse and optimize outcome.[8-11]

There is partial evidence that SNRIs and other newer antidepressants are effective in PD.[80] On the one hand, relatively few of these agents have been well studied in PD, not all findings have been consistently positive, and concerns have also been raised about the safety profile of certain agents (eg, venlafaxine) in comparison with the SSRIs.[85] On the other hand, there is some evidence that more noradrenergic antidepressants may be of benefit in PD patients who have failed to respond to serotonergic antidepressants.[86] Thus SNRIs and some other newer antidepressants (for example, mirtazapine and reboxetine) can be considered as a treatment option in the pharmacotherapy of PD.[87]

There is also some evidence of the efficacy of other classes of agent in panic disorder. In particular, anticonvulsant agents have been investigated for use. While early RCTs found gabapentin and carbamazepine to be of limited benefit compared with placebo,[88,89] valproate may be effective in some patients.[90,91] These medications can perhaps be considered as augmenting agents in treatment-refractory PD cases. However, more rigorous clinical investigation is required before they can be recommended for widespread use.[80]

Underdiagnosis and undertreatment of PD remains a particular problem. Further, as above, a proportion of

patients with PD do not respond to first-line pharmacotherapy. As always in such cases, diagnosis should be reaffirmed, and duration and dose optimized.[8] Again, while there has been relatively little rigorous work on switching to agents of a different class, this is a reasonable strategy.[37] Augmentation strategies that have been researched include the addition of pindolol.[92,-94] The addition of psychotherapy (CBT) to pharmacological treatment may also be useful in PD.[95-100]

As in the case of GAD and OCD, then, there has on the one hand been significant progress in the pharmacotherapy of PD (including the introduction of the SSRIs), while on the other hand several challenges remain (including the treatment of patients refractory to the SSRIs). Once again, psychobiological research has provided tantalizing hints of novel treatment targets for future work. Adenosine receptors may, for example, play a unique role in the pathogenesis of PD, and may provide a novel target for future treatments of PD.[101] Alternatively, work on molecular systems that appear to be involved in a number of different anxiety disorders (eg, glutamate, the HPA axis), may also lead to new treatments of PD.[12-14]

Post-traumatic stress disorder

As has been the case in several anxiety disorders, early trials for post-traumatic stress disorder (PTSD) focused on agents that had been proven effective for depression,[102] namely TCAs and MAOIs. And once more, the introduction of the SSRIs led to a series of multisite trials showing comparable efficacy but better tolerability. More recently, there has been ongoing work on the treatment of refractory cases, using other classes of agents such as atypical antipsychotics. Of particular importance has been the emergence of proof-of-principle trials, often grounded in animal literature. These have focused on the pharmacotherapy of PTSD prophylaxis and on the enhancement of psychotherapy for this disorder.

Several TCAs have been investigated in the treatment of PTSD.[103-105] Although some trials have shown efficacy, the relatively unfavorable side effect profile of these agents means that they are not considered a first-line option in most treatment guidelines.[8,9,11,106-109] Similarly, although MAOIs such as phenelzine may be effective in PTSD,[110] their use remains limited by their safety and tolerability profile.

A number of SSRIs and venlafaxine have been found to be effective and safe in PTSD *(Table III)*.[102] Paroxetine and sertraline are FDA-approved for use in this disorder.[15] Most current guidelines therefore advocate the use of one of the SSRIs and/or SNRIs as first-line pharmacotherapy.[8,9,11,106,108,109]

The available literature suggests that a trial period of about 8 to 12 weeks should be undertaken to assess efficacy.[8,111] Long-term studies suggest that maintenance treatment should be continued in responders for at least a year.[102,112]

Limited data exists on a number of other medication classes in PTSD. For example, the anticonvulsants lamotrigine and topiramate have been found to be effective as either monotherapy[113,114] or augmentation strategy.[115] Once again, however, given the relative paucity of data, such agents are not considered a first-line option in the pharmacotherapy of PTSD.

Limited work has been undertaken in patients not responding to initial SSRI/SNRI treatment, or in special populations such as children and adolescents.[41,116] In treatment-refractory patients, switching to a different SSRI/SNRI can be considered, but has not been well studied. Augmentation with an atypical antipsychotic (eg. risperidone or olanzapine) has been found efficacious in some studies.[117-119] Other considerations include the addition of an anticonvulsant agent, for example topiramate.[115] Treatment guidelines emphasize the need for ongoing assessment of the risk:benefit ratio of such strategies, for example, monitoring metabolic effects.[8,106]

Animal studies of stress have given impetus to the question of whether PTSD can be prevented by early pharmacotherapy. Early proof-of-principle studies suggested that the β-blocker, propanolol, may be efficacious in this context.[120,121] The hypothalamic-pituitary-adrenal (HPA) axis has been well-studied in both animal and human work on stress, and the administration of IV hydrocortisone in the hospital setting has been suggested useful in PTSD prophylaxis.[122,123] However, subsequent work with propanolol and other agents has not always been supportive of the early work,[124,125] and further research in this area remains necessary.

Laboratory research also led to the hypothesis that D-cycloserine, a partial agonist at NMDA (N-methyl D-aspartate) glutamate receptors,[126] may be useful in enhancing CBT in PTSD. Early proof-of-principle trials have shown promise.[127,128] This is a particularly exciting development, as it represents that, for perhaps the first

time, a translational approach in anxiety disorders has led to an efficacious new treatment. Various other molecular targets for CBT augmentation have been suggested,[12] but further work is needed to confirm the effectiveness of such approaches in the clinical context.

Social anxiety disorder

The pharmacotherapy of patients with social anxiety disorder (SAD) was given initial impetus by the finding that MAOIs are effective, but TCAs are not. As in the case of PD and OCD, this suggested that particular agents might be efficacious for particular anxiety disorders. And, once again, although the introduction of the SSRIs for SAD did not support such the hope of pharmacotherapeutic dissection, it did provide an effective and well-tolerated pharmacotherapy. Again, despite the availability of a range of medications for SAD, many patients either do not respond or remit.[129] Thus, there is an ongoing need for further work on treatment-refractory cases and novel treatment targets.

Early on the MAOIs showed efficacy for SAD in a number of placebo-controlled trials.[130] In particular, phenelzine, an irreversible MAOI, was efficacious.[131-133]

	Study year	Population	Intervention	Effect of intervention
Paroxetine	Marshall et al 2001[167]	Adult outpatients	Participants were randomly assigned to take placebo, 20 mg/day of paroxetine, or 40 mg/day of paroxetine for 12 weeks.	Paroxetine-treated patients in both dose groups demonstrated statistically significant response to treatment. Both doses of paroxetine (20 and 40 mg/day) were well tolerated.
	Tucker et al 2001[168]	Adult outpatients (≥18 years)	Participants were randomly assigned to treatment with paroxetine (20-50 mg/day) or placebo for 12 weeks.	At week 12, compared with the placebo group, the paroxetine group showed significantly greater response to treatment and remission. Treatment with paroxetine was well tolerated.
Sertraline	Brady et al 2000[169]	Adult outpatients	Patients were randomized to acute treatment with sertraline hydrochloride in flexible daily dosages of 50 to 200 mg/d, following 1 week at 25 mg/d; or placebo.	Sertraline treatment yielded significantly greater response than placebo. Sertraline was well tolerated.
	Davidson et al 2001[170]	Adult outpatients	Participants were randomized to 12 weeks of double-blind treatment with either sertraline in flexible daily doses in the range of 50 to 200 mg or placebo.	A 60% responder rate for sertraline and a 38% responder rate for placebo was found. Sertraline treatment was well tolerated.
Venlafaxine	Davidson, Rothbaum et al 2006[171]	Adult outpatients	Participants were randomly assigned to receive placebo or flexible doses of venlafaxine ER (37.5-300 mg/d) or sertraline (25-200 mg/d) for 12 weeks or less.	Week 12 remission rates were venlafaxine ER 30.2%, sertraline 24.3%, and placebo 19.6%. The venlafaxine ER group had significantly better scores on outcome measures than placebo. Both treatments were well tolerated.
	Davidson, Baldwin et al 2006[172]	Adult outpatients	Participants were randomly assigned to receive flexible doses of venlafaxine ER (37.5-300 mg/d) or placebo for 24 weeks.	Improvement was significantly greater for the venlafaxine ER group, with a remission rate of 50.9%, compared with 37.5% for placebo. Withdrawal rates were similar between groups with no significant difference in dropouts attributable to adverse events.

Table III. Selected placebo-controlled randomized controlled trials of post-traumatic stress disorder treatment.

However, as noted earlier, this class of agent requires dietary restrictions and is associated with a range of potential adverse events.

The newer reversible MAOIs (RIMAs), such as moclobemide and brofaromine, do not require such dietary restrictions and are well tolerated. However, they have not proved consistently efficacious in SAD[130,134]; thus although they are part of the current armamentarium, they are not typically considered first-line agents.[8,9,11,135]

The benzodiazepine clonazepam showed promise in the short- and long-term treatment of patients with SAD.[136,137] However, once again, given risk:benefit considerations, benzodiazepines are not usually recommended as first-line agents for SAD.[8,9,11,135]

Several SSRIs have been shown to be efficacious and relatively well-tolerated in the treatment of SAD.[138,130,139] Both paroxetine and sertraline are FDA-approved for treatment of this disorder *(Table IV)*. Given the substantial evidence base indicating the efficacy and safety of SSRIs, they are typically recommended as the first-line pharmacotherapy in treatment guidelines.[8,9,11,135]

Of the SNRIs, venlafaxine is the best studied in SAD, where it has shown efficacy in a number of RCTs.[134] This agent is therefore considered a reasonable alternative to the use of SSRIs in a number of treatment guidelines, and is FDA-approved for such use.[8,9,11,135]

Current guidelines recommend that active treatment with SSRIs/SNRIs should be continued for at least a

Study	Year	Population	Intervention	Effect of intervention
Van der Linden et al[138]	2000	Adult	Pharmacological (SSRI) versus placebo	The odds ratios of responder status for SSRI versus placebo varied between 2.1 and 26.2. The number of patients who responded to drug treatment was approximately twice the number who responded to placebo. Response rates and effect sizes for SSRIs were larger than those seen in trials of the reversible monoamine oxidase inhibitors (RIMAs).
Federoff et al[173]	2001	Adult	Pharmacological (benzodiazepines, SSRIs, MOAIs); Placebo; Psychological (exposure, cognitive restructuring, exposure plus cognitive restructuring, social skills training, and applied relaxation)	The most consistently effective treatments were pharmacotherapies. Benzodiazepines and SSRIs were equally effective and more effective than control interventions.
Blanco et al[174]	2003	Adult	Pharmacological	The medications with largest effect sizes were phenelzine (effect size, 1.02; 95% Confidence Interval [CI], 0.52–1.52), clonazepam (effect size,.97; 95% CI, 0.49–1.45), gabapentin (effect size,.78; 95% CI, 0.29–1.27), brofaromine (effect size,.66; 95% CI, 0.38–0.94), and the SSRIs (effect size,.65; 95% CI, 0.50–0.81). There were no statistically significant differences between medications or medication groups.
Stein et al[130]	2004	Adult	Pharmacological	Response to treatment by SRIs (RR=0.67; 95% CI=0.59, 0.76), MAOIs (RR=0.43; 95% CI=0.24, 0.76) and RIMAs (RR=0.74; 95% CI=0.59, 0.91) supported the value of these agents. However, the SSRIs were significantly more effective than the RIMAs. Medication was also significantly superior to placebo. The value of long-term medication treatment in treatment responders was supported by 3 comparisons from maintenance studies (relative risk of non-response=0.58; 95% CI=0.39, 0.85) and 5 comparisons from relapse prevention studies (relative risk of relapse=0.33; 95% CI=0.22, 0.49).
Hedges et al[175]	2007	Adult	Pharmacological (SSRIs)	SSRIs are more effective than placebo for social anxiety disorder.

Table IV. Select meta-analyses in seasonal affective disorder treatment. SSRI, selective serotonin reuptake inhibitor, MAOI, monoamine oxidase inhibitor

year.[8,9,11] This recommendation is supported by a number of placebo-controlled relapse-prevention studies.[139]

Several anticonvulsant agents have also been studied in SAD.[134,140,141] Both gabapentin[88] and pregabalin, for example, have shown efficacy compared with placebo. However, neither agent is registered for the treatment of SAD, and additional studies are required before their routine use can be recommended.

A limited number of studies have investigated atypical antipsychotics in SAD.[142] A consideration of risk:benefit ratio suggests that these agents should not yet be viewed as a first-line option in SAD.[135] However, their role as an augmenting strategy in treatment-refractory cases perhaps deserves additional consideration.

Up to 50% of SAD patients do not respond to initial pharmacological treatment.[129] As always, diagnosis, dose, and duration should be optimized.[36,135] Relatively small switch studies have shown the benefit of treatment with a different agent with proven efficacy, for example venlafaxine[143] or phenelzine.[144] Augmentation strategies that may be considered include the use of buspirone,[145] clonazepam,[146] and combined pharmacological and psychological therapy.[133,147]

There has again been interest in the possibility that D-cycloserine may be useful in enhancing CBT. An early proof-of-principle trial indicated that this agent was significantly more effective than placebo in enhancing CBT.[148] Other targets for CBT augmentation have also been suggested,[12] and this seems an exciting area for future investigation.[149] As in the case of other anxiety disorders, there is significant scope for studies that incorporate genetic and imaging methods into pharmacotherapy studies,[150,151] aiming ultimately at individualizing treatment approaches in SAD.

Conclusion

The glass of pharmacotherapy of anxiety disorders studies seems both half-full and half-empty. On the one hand, there is a good number of randomized clinical trials of anxiety disorders; these have been extensively reviewed and meta-analyzed, and they include a particularly large and persuasive set of studies showing efficacy and relatively good tolerability of the SSRIs in the major anxiety disorders. Secondary analyses of such datasets have informed questions such as optimal definition of response and remission, optimal dose and duration, and comparative efficacy of different agents.[736,152] Innovative questions, such as the use of pharmacotherapy for prophylactic purposes, have begun to be studied.[42,108]

On the other hand, a significant proportion of patients with anxiety disorders fail to be diagnosed and treated,[1] or to respond to first-line agents, and there is a limited database of efficacy or effectiveness studies to guide treatment in such cases. Pharmacotherapy of children and adolescents, and of the elderly with anxiety disorders are other areas where some recommendations can be made, but where much further work is needed.[153,154]

There is a significant research gap in that most studies have been undertaken at academic tertiary centers in high-income countries for registration purposes, while worldwide the vast majority of the clinical burden of anxiety disorders manifests in low- and middle-income countries in the community and in primary care.

Fortunately, although much remains to be learned about the pathogenesis of the anxiety disorders, progress has been made, and such work has led to some of the first bedside neuroscience interventions ever to have emerged directly from the bench.[127,155] Further such work should be encouraged; there is significant scope for merging new neuroscience methodologies, for example, imaging and gene expression[156,157] with pharmacotherapy studies in order to help find new treatment targets, and in order to better personalize future treatment strategies. Funding for such work may, however, require both professionals and lay advocates to emphasize both the untreated burden of anxiety disorders, as well as the rich scientific opportunities that exist. ❑

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Farmacoterapia de los trastornos ansiosos: una revisión crítica

Considerando el gran impacto de los trastornos ansiosos en el costo de las enfermedades, es clave optimizar su prevención y tratamiento. En esta revisión crítica se evalúan tanto los avances en la farmacoterapia de los trastornos ansiosos como los desafíos que persisten. En las últimas décadas en este campo se ha contado con ensayos clínicos con rigurosa metodología para cuantificar la eficacia y seguridad de agentes descubiertos casualmente, con el desarrollo más orientado a medicamentos con mecanismos de acción selectiva y con el traspaso de ideas desde la investigación de laboratorio a los ensayos clínicos de prueba de principios. Como aspecto positivo debe considerarse que existe una gran base de datos de estudios que demuestra la eficacia y la aceptable tolerabilidad de los inhibidores selectivos de la recaptura de serotonina en los principales trastornos ansiosos, y del análisis secundario de estas bases de datos han surgido preguntas relacionadas con la definición óptima de respuesta y remisión, la dosis óptima y la duración y la eficacia comparativa de diferentes fármacos. Existen importantes desafíos en este campo que incluyen las barreras para un apropiado diagnóstico y tratamiento de los trastornos ansiosos, las fallas en la respuesta a agentes farmacológicos de primera línea de una proporción significativa de pacientes y una base de datos limitada sobre la eficacia y efectividad de estudios para guiar el tratamiento en estos casos.

Pharmacothérapie des troubles anxieux : une revue critique

Du fait de l'importance de la contribution des troubles anxieux au fardeau des maladies, il est crucial d'optimiser leur prévention et leur traitement Dans cette revue critique, nous évaluons à la fois les avancées de la pharmacothérapie des troubles anxieux et les défis qui persistent. Ces 10 dernières années, des études cliniques rigoureuses ont permis de quantifier l'efficacité et la tolérance de produits découverts de manière empirique, de développer plus précisément des médicaments aux mécanismes d'action sélectifs et d'appliquer progressivement les idées de la recherche en laboratoire à des études cliniques basées sur des preuves. Du côté positif, une importante base de données des études montre une efficacité et une tolérabilité relative des inhibiteurs sélectifs de la recapture de la sérotonine dans les troubles majeurs de l'anxiété. Des analyses secondaires de ces bases de données ont répondu à des questions portant sur la définition optimale de la réponse et de la rémission, de la meilleure posologie, de la durée et de l'efficacité comparative des différents produits. Les problèmes significatifs qui persistent dans ce domaine sont : les obstacles au diagnostic et au traitement adéquats des troubles anxieux, l'absence de réponse d'un pourcentage significatif de patients aux traitements de première intention et une base de données limitée pour les études d'efficacité pour orienter le traitement dans de tels cas.

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