The Pharmacotherapy of Social Anxiety Disorder

a report by

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Though once dubbed a “neglected anxiety disorder,”1 social anxiety disorder (SAD; also known as social phobia) has been the focus of increasing research and clinical attention over the last 10–15 years as its high prevalence and attendant morbidity has been well documented.2 The initial emphasis on the use of monoamine oxidase inhibitors (MAOIs) for this condition—with their attendant daunting list of potential adverse effects—may also have contributed to the relatively low rate of recognition and treatment in clinical practice. With the demonstration of the clear efficacy of better tolerated and safer pharmacotherapies, as well as the availability of specific cognitive–behavioral therapy (CBT) programs, the barriers to treatment of SAD have gradually been reduced, although the disorder remains underdiagnosed and undertreated. Although this brief article will focus on pharmacological approaches to the treatment of SAD, it should be noted that a psychosocial intervention (CBT) has demonstrated comparable efficacy to standard pharmacotherapy for the treatment of SAD3 with greater durability of effects after treatment discontinuation,4 and thus represents another first-line treatment option for affected individuals.

The overall aim of the pharmacotherapy of SAD is to reduce and eventually eliminate the patient’s anticipatory anxiety about and distress during social interaction and performance situations, as well as the attendant avoidance behavior, and to improve the individual’s quality of life and function.

Serotonin Selective Re-uptake Inhibitors and Serotonin Norepinephrine Re-uptake Inhibitors

Serotonin selective re-uptake inhibitors (SSRIs) and serotonin norepinephrine re-uptake inhibitors (SNRIs) have emerged as first-line pharmacotherapy for the treatment of SAD because of their demonstrable efficacy for this disorder, as well as their broad-spectrum therapeutic effects on other anxiety disorders and depression that may present comorbidly. Furthermore, they have greater tolerability and a better safety profile than the MAOIs, which were the former ‘gold standard’ agents for SAD, and lack the abuse potential and ineffectiveness for comorbid depression of the benzodiazepines. The SSRIs paroxetine and sertraline and the SNRI venlafaxine (extended-release) have specific indications for SAD; however, based on the available evidence it is likely that other agents from these classes are effective as well, although differences in side effect profiles may be clinically relevant in some cases.1 Initiation of significant therapeutic effects usually takes at least two to three weeks, with benefits accruing over weeks or months as patients begin to expose themselves to previously feared situations.

Beta-blockers

Though not effective as primary treatments for generalized SAD,4 beta-blockers—including propranolol and atenolol—are useful for the treatment of ‘performance anxiety’ about public speaking or other performance situations.5,6 By blunting symptoms of physiological arousal such as tachycardia and tremor, which are often an individual’s focus in social situations, the beta-blockers appear to interrupt the escalating fear cycle that drives further anxiety during performance. Pindolol, a beta-blocker with SHT-1A autoreceptor antagonist properties, has in some though not all studies accelerated or augmented response to antidepressants for depression7 and panic disorder,8 although it was ineffective in one placebo-controlled randomized augmentation trial in social phobics.9

Monoamine Oxidase Inhibitors

The MAOIs used to be the gold standard pharmacological treatment for social phobia, but they were eventually supplanted by the better tolerated and safer SSRIs and SNRIs. Phenelzine is the most widely studied MAOI, although tranylcypromine appears effective as well.10,11 Initial observations of their efficacy for the atypical subtype of depression characterized in part by marked sensitivity to rejection12 led to the use of MAOIs in social phobia, and they were subsequently demonstrated to be effective in randomized controlled trials.13 However, the use of MAOIs is associated with troubling side effects, including orthostatic hypotension, paresthesias, weight gain, and sexual dysfunction, as well as the need for careful attention to diet and use of concomitant medication because of the risk of potentially fatal hypertensive and serotonergic syndromes if the proscriptions are violated. As a result, these agents are generally reserved for use in patients failing to respond to easier-to-use agents.

Benzodiazepines

Although benzodiazepines have not been as well studied in SAD as in panic disorder, they appear to be effective, with available studies suggesting efficacy for agents such as clonazepam and alprazolam...
Other Agents

Tricyclic antidepressants (TCAs) do not appear to be effective for SAD, whereas small open trials suggest the potential efficacy of bupropion.

The SHT-1A partial agonist buspirone has not demonstrated efficacy as a monotherapy for SAD, although one report suggests its potential utility as an adjunct for patients incompletely responsive to SSRI therapy. Small studies suggest the potential efficacy of atypicals antipsychotics such as olanzapine, risperidone, aripiprazole, and quetiapine in SAD; however, given concerns about associated metabolic syndrome, weight gain, and extrapyramidal effects, their use is generally reserved for patients remaining symptomatic despite standard interventions.

Additionally, some anticonvulsants—including gabapentin, an alpha-2 delta calcium channel antagonist, and the related compound pregabalin—demonstrated efficacy for social phobia in randomized controlled trials. Valproic acid demonstrated suggestive evidence in an open trial in SAD, whereas results in small studies with levetiracetam have been mixed.

Discussion and Future Directions

A burgeoning of interest in the treatment of SAD has followed the growing understanding of the high prevalence, early onset, chronicity, and morbidity impact, and the associated family, social, and vocational function challenges to the field are to discover ways of optimizing use of the currently available pharmacotherapies—as well as CBT—are effective for many with social anxiety, most treated patients, though improved, do not fully remit. Thus, challenges to the field are to discover ways of optimizing use of the currently available agents and interventions and to develop novel therapeutics. An exciting development in translation research deriving from pre-clinical work on the neural circuitry underlying fear extinction led to the examination of D-cycloserine (DCS), a partial agonist of the N-methyl-D-aspartate (NMDA) receptor in the amygdala, as an agent capable of enhancing extinction learning, and was recently demonstrated to augment the response to CBT in individuals with social phobia.

Replication and extension of this novel work holds the promise of improving outcomes for the treatment of SAD, as well as other fear-based disorders.

References

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