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# Therapeutic options: Addressing the current dilemma

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**Abstract** The main therapy for the symptomatic management of generalized anxiety disorder (GAD) is pharmacotherapy, although comprehensive management methods also include psychotherapeutic interventions. Traditionally, treatments including anxiolytics and antidepressants have been used in GAD management, but prescribing physicians have more recently moved towards using selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs). Indeed, newer medicines have been shown to be as effective as older treatments, but with improved safety and tolerability. Although the best way to treat GAD has yet to be established, these patients clearly need long-term supervision. Ideally, physicians should prescribe treatment with the purpose of ultimately eliminating symptoms and re-establishing normal function. To achieve this goal, physicians need a more effective, faster acting, safer, and better tolerated drug than the many existing GAD treatments.


## 1. Introduction

The diagnosis of generalized anxiety disorder (GAD) did not become official until 1980 when the American Psychiatric Association published the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition (DSM-III) (American Psychiatric Association, 1980). Despite evidence from major epidemiologic studies of substantial prevalence, GAD often goes undiagnosed (Weiller et al., 1998). Patients with GAD show substantial functional impairment, seek more assistance from their primary care physician or healthcare services, have high use of medications, and develop comorbid psychiatric disorders (Wittchen et al., 1994). Furthermore, these patients often experience some cognitive dysfunction that interferes with their ability to cope with the symptoms of this disorder (Aikins and Craske, 2001). As a result, the probability of GAD sufferers perceiving normal environmental stimuli as threatening is greatly increased (Aikins and Craske, 2001).

Physicians should prescribe treatment with the intention of eventually eliminating the symptoms of anxiety and fully restoring normal function. While the management of treatment may be complicated by the presence of comorbid conditions (for a review, please see Nutt et al., 2005), realizing these treatment goals will reduce the rate of overutilization of healthcare services. Pharmacotherapy is the primary treatment for GAD, although more wide-ranging treatment methods also include behavioral and psychotherapeutic interventions (Lader and Bond, 1998). Historically, a range of treatments, including anxiolytics and antidepressants, has been used in the management of GAD. However, different medications have differing modes of action, uses, and adverse events (AEs). More recently, prescribing physicians have moved towards the use of selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) as first-line therapy due to their safety and tolerability profile. Regardless of the chosen therapy, the core aim of pharmacologic intervention is to improve symptomatology. Although the best treatment approach for managing GAD throughout a patient's life has not yet been determined, this article will review the current pharmacologic options, the primary evidence supporting the

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use of each group of agents, and the utility of psychotherapy in treating GAD. The discussion will also evaluate the relative merits and risks of each of the drug classes, and the therapeutic deficits encountered with the available agents.

## 2. Pharmacotherapy

Following diagnosis, including those patients with subthreshold level GAD, the physician must rapidly set up treatment targets for both symptom improvement and duration of the treatment. Physicians should also endeavor to establish a sympathetic and two-way relationship with their patient; they should discuss the benefits and risks of each potential medication with the patient and acknowledge any concerns that he or she may have regarding their therapeutic regimen. In addition, physicians must recognize that these patients are often long-standing sufferers with newly diagnosed symptoms. This means that treatment targets should usually be viewed from the position of long-term management of the GAD patient.

Physicians have at their disposal many efficacious pharmacologic agents. Medications should be prescribed at the lowest efficacious dose to minimize side effects, while ensuring not only improvement but also remission. Recently developed drugs have been shown to be not only as effective as older medications, but also safer and better tolerated. In addition, current research into the neurobiology and neuropathology of GAD is beginning to be converted into potential future therapies.

### 2.1. Selective serotonin reuptake inhibitors

The relative safety and tolerability of SSRIs is considered to be due to their selective action. While other antidepressants influence several factors involved in the communication between neurons, the action of SSRIs is focused primarily on the reuptake of serotonin by the presynaptic neuron, also providing less potential for side-effects. The inhibition of the serotonin reuptake transporter of the presynaptic cell allows the SSRIs to increase the level of serotonin in the synaptic cleft. This in turn both increases the time in which serotonin can bind to the receptors of post-synaptic cells and increases the quantity of serotonin molecules present in the synaptic cleft. Some of the SSRIs also exhibit other neuropharmacologic effects, including the inhibition of dopamine reuptake by sertraline and the relatively high affinity of paroxetine versus other SSRIs in blocking norepinephrine reuptake (Nemeroff and Owens, 2004).

SSRIs have been shown to be efficacious in the treatment of both depression and anxiety disorders, such as obsessive-compulsive disorder, panic disorder, and social anxiety disorder (Zohar and Westenberg, 2000). Three, 8-week, randomized controlled trials found paroxetine (20–50 mg per day), which is approved for the treatment of GAD, to be significantly more effective than 2′-chlorodesmethyldiazepam (lorazepam) (Rocca et al., 1997) and placebo (Rocca et al., 1997; Pollack et al., 2001; Rickels et al., 2003) in reducing Hamilton Anxiety Rating scale (HAM-A) (Fig. 1A) and Sheehan Disability Scale scores in GAD patients. Furthermore, in a longer term GAD study (Stocchi et al., 2003), following an 8-week lead-in phase in which all patients

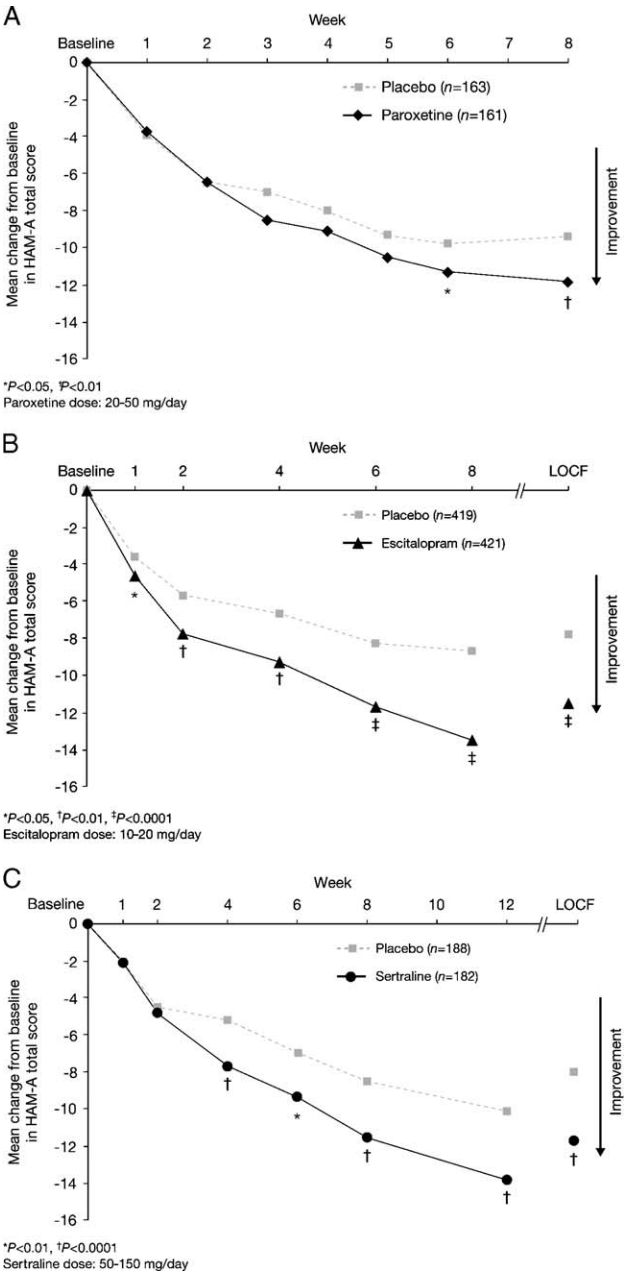


**Figure 1** Mean change from baseline in HAM-A scores for paroxetine (Pollack et al., 2001, adapted/reprinted by permission, Physicians Postgraduate Press, Copyright 2001), escitalopram (reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley and Sons, Inc.), and sertraline (reprinted with permission from the American Journal of Psychiatry, Copyright 2004. American Psychiatric Association) versus placebo. (A) Paroxetine (Pollack et al., 2001). (B) Escitalopram (Allgulander et al., 2004). (C) Sertraline (Davidson et al., 2004). HAM-A = Hamilton Rating Scale for Anxiety. LOCF = last observation carried forward analysis.

received paroxetine, significantly fewer paroxetine than placebo patients relapsed during the subsequent 24-week, double-blind phase of a long-term study. Placebo patients were almost five times more likely to relapse than those given paroxetine (Stocchi et al., 2003). Moreover, a 4–6-month course of paroxetine in previously untreated