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Unmet Needs in the Treatment of Anxiety Disorders

By Mark H. Pollack, MD

ABSTRACT *~ There are a number of unmet needs in the treatment of anxiety disorders including the need for more effective, rapidly acting, and better tolerated medications; early identification of nonresponse; effective treatments for refractory disorders; prevention of relapse; and promotion of resilience and long-lasting response. Rates of response to contemporary antidepressants and other anxiolytics are often less robust than might be hoped, and remission rates, which have until recently been infrequently measured, are even lower. A small number of mostly uncontrolled studies suggest a role for augmentation of initial therapy with a second modality in patients who do not fully remit to treatment. There also is a small but growing literature which suggests the use of novel anticonvulsants and atypical antipsychotics in the treatment of anxiety disorders should be further studied. However, a definitive place for these newer therapeutic strategies in the anxiety disorder treatment armamentarium awaits evidence from large, controlled studies.* Psychopharmacology Bulletin. *2003;37(Suppl 3): 31-37.*

INTRODUCTION

Anxiety disorders are highly prevalent, with lifetime and 12-month prevalence rates in the United States of 24.9% and 17.2%, respectively.[1] Although the past two decades have witnessed remarkable advances in the treatment of anxiety disorders, current therapeutic strategies often fall far short of ideal. **Domains where improvement is needed include more effective, rapidly acting, and better tolerated medications, early identification of nonresponse, effective treatments for patients who fail or partially respond to therapy, strategies that effectively prevent relapse and foster resilience, and treatments that offer an enduring response. [AU: this is exactly what the abstract says]**

IMPROVED TREATMENTS

Since the availability of the selective serotonin reuptake inhibitors (SSRIs) in the late 1980s and the more recent introduction of the serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine, these agents have been widely used as first-line

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treatment of anxiety disorders because of their broad spectrum of efficacy against common comorbidities (eg, depression) and because of concern about the therapeutic liabilities of the benzodiazepines (eg, abuse/dependence potential and lack of efficacy in depression). However, response rates to SSRI and SNRI treatment for panic disorder, generalized anxiety disorder (GAD), social anxiety disorder, and posttraumatic stress disorder (PTSD) are often less than robust, with most controlled clinical studies reporting response rates of 40% to 70%.[2] Remission is far less commonly assessed, but when reported is generally in the range of 20% to 45% at endpoint.[3-6] Rates of response and remission for obsessive-compulsive disorder (OCD) may be even lower.[2,7] Thus, although a substantial proportion of patients with anxiety disorders can be expected to achieve a partial response to treatment, many remain symptomatic or fail to respond at all.

Only recently has the field begun to consider the issue of remission in the treatment of anxiety disorders. Although there are relatively few large-scale studies or pooled analyses on remission rates in the treatment of anxiety disorders, endpoint scores of 7 or less on the Hamilton anxiety scale (HAM-A) have been suggested as a goal for remission of GAD.[5,8] Remission of PTSD has been operationalized as a score of 20 or less on the Clinician Administered PTSD Scale (CAPS).[6] For panic disorder, remission is considered the complete or nearly complete resolution of the major symptom domains (eg, panic attacks, anticipatory anxiety, avoidance, functional impairment), and for social anxiety disorder a score of less than 30 on the Liebowitz Social Anxiety Scale (LSAS). [9,10]

Patients with anxiety disorders, particularly panic disorder, often poorly tolerate adverse effects. Indeed, intolerance of medication therapy is often a key factor in poor therapeutic outcome. In one review of 190 courses of medication therapy for panic disorder in which effective therapeutic agents were used, side effects were the most common cause of treatment failure, resulting in discontinuation of medication in 27% of patients.[11]

Anxiety symptoms can be extremely distressing, and rapid symptom relief is often a critical determinant of patient adherence and therapeutic success. Among currently employed therapeutic agents, benzodiazepines typically provide the most rapid relief of anxiety symptoms, often within the first 1 or 2 days of treatment. This is a distinct advantage over the SSRIs and other antidepressants, which often require two or more weeks to garner an anxiolytic response. However, drawbacks to benzodiazepine treatment of anxiety disorders include their lack of efficacy for the comorbid depression that is commonly present as well as abuse/liability in predisposed individuals, rebound anxiety with missed doses, adverse interactions with alcohol, physiologic dependence and potential difficulties tapering patients from therapy.[2]

EARLY IDENTIFICATION OF NONRESPONSE

Because of the high rates of partial or nonresponse in the treatment of anxiety disorders, the ability to identify nonresponders early in the course of therapy would improve patient care. There is a need to be able to identify patients who will benefit from watchful waiting during the initiation of treatment versus those who will more fully respond to a dosage increase, augmentation with a second drug, or switching initial therapy to an alternate agent. Response rates in anxiety disorders tend to increase as therapy continues beyond the initial acute 6- to 12-week trial, which underscores the need for patients to persist with their medication therapy. In one study, 54% of patients with PTSD who did not respond to sertraline after the initial 12-week trial achieved a clinical response by the end of an additional 6 months of treatment.[12]

Although these findings are encouraging, it is often difficult for patients with anxiety disorders to stay on therapy for 2 to 3 months without significant clinical improvement. As noted, if the eventual clinical response could be predicted early in therapy, such as within the first 2 weeks, patients would greatly benefit. In one pooled analysis of two placebo-controlled studies of sertraline in patients with panic disorder, remission correlated with global measures of response at week 2 (Clinical Global Impression [CGI] improvement score of ≤2) and week 3 (improvement on HAM-A). In contrast, early changes in panic attack frequency and anticipatory anxiety did not correlate with remission.[13]

EFFECTIVE TREATMENTS FOR NONRESPONDERS

Strategies for improving rates of response and remission in patients with anxiety disorders include augmentation of initial therapy with a second modality and the use of novel therapeutic agents. Though a number of different augmentation strategies have suggestive evidence of efficacy in small, open-label series or case reports, there are few controlled studies that systematically address this critical issue. Mood stabilizers, pindolol, anxiolytics, and other agents have been studied in refractory OCD[14,15] and there are reports of successful augmentation for refractory OCD using antipsychotic agents as well.[15] There are fewer reports of augmentation or combination therapy for other anxiety disorders, but positive experience with benzodiazepines (panic disorder),[16] pindolol (panic disorder),[17] cognitive behavioral therapy (panic disorder),[18] triiodothyronine (PTSD),[19] atypical antipsychotics (PTSD),[20] and buspirone (social anxiety disorder)[21] has been reported.

Desirable features of agents used to augment anxiety disorder treatment include short- and long-term efficacy in both nonresponders and partial responders, relapse prevention, efficacy across a broad range of symptom clusters, and rapid onset of action (ie, during first week of treatment).

Useful augmentation agents also would be well tolerated, simple to administer—and free of abuse potential, withdrawal symptoms during discontinuation, and significant drug interactions.

There is accruing clinical experience and a small, but growing literature on the use of novel anticonvulsants in the treatment of anxiety disorders. For instance, a randomized, placebo-controlled study of 69 patients with social anxiety disorder demonstrated that gabapentin monotherapy (300 to 1200 mg 3 times daily) resulted in significantly greater improvement on clinician- and patient-rated assessments compared with placebo.[22] Positive findings were also reported in a study of gabapentin for the treatment of panic disorder.[23] In addition, findings from a small, randomized, double-blind, placebo-controlled study suggest a possible role for lamotrigine (25 to 500 mg/day) in the treatment of civilian and combat-related PTSD.[24]

PROMOTION OF RESILIENCE

The ability of anxiety treatments to confer or enhance resilience to the noxious effects of future stressors is an area of critical clinical import that is receiving increasing attention. The findings of one small, placebo-controlled trial with fluoxetine in PTSD assessed the impact of treatment on patients' perceived vulnerability to future trauma. Compared with pretreatment baseline values, fluoxetine treatment for 3 months resulted in significantly greater reduction in stress vulnerability assessment scores,[3] suggesting that antidepressant treatment and perhaps other effective treatments may foster resilience to future stressors in individuals with PTSD.

The impact of early intervention strategies in preventing PTSD following exposure to trauma in individuals at risk is another important area that is receiving increasing study. For instance, a small, randomized comparison of a one-week course of imipramine or chloral hydrate assessed rates of acute stress disorder among children and adolescents with severe burn injury at baseline and again at 6-week follow-up. The antidepressant resulted in significantly higher rates of acute stress symptom improvement (83%) compared to the sedative-hypnotic (38%; $P<.02$).[25] In another study (n=41), the administration of a 10-day course of propranolol within 6 hours of a traumatic event, resulted in significantly reduced physiologic arousal, as measured by heart rate and skin conductance during script-driven imagery, at 3 month follow-up, suggestive of a potential protective effect for PTSD.[26] Additional data suggests early administration of cognitive-behavioral therapies in recently traumatized individuals may also reduce the development of PTSD.[27] However, small, but provocative, studies examining the early use of benzodiazepines in the post-trauma period[28,29] suggest possibly deleterious effects in terms of increasing the likelihood of developing PTSD. Similar findings were

reported when examining the impact of single session critical incident debriefing paradigms.[30] In a series of randomized, controlled studies, psychological debriefing of motor vehicle accident victims did not prevent PTSD at the 4-month and 3-year follow-ups. In fact, patients with intrusive recollections and avoidance symptoms in the immediate post-trauma period receiving critical incident stress debriefing had worse outcomes than controls.[31,32]

DURABILITY OF RESPONSE

The duration of clinically significant therapeutic response to the treatment of anxiety disorders is another important area receiving increasing attention (though heretofore relatively unstudied). Relapse is a relatively common occurrence when patients stop treatment. For example, rates of relapse are 30% and 40% for patients with panic disorder after discontinuation of paroxetine[33] and imipramine,[34] respectively. Relapse rates following medication discontinuation in GAD and social anxiety disorder may be even higher.[35,36] Cognitive behavioral therapy is an effective psychosocial treatment option for many anxiety disorders and may be associated with a more persistent clinical response in some trials.[37] Further studies are needed to develop optimal strategies to enhance acute and long-term response and prevent relapse, as well as to identify predictors of sustained remission in order to inform decisions regarding treatment discontinuation.

CONCLUSIONS

There are many unmet needs in the treatment of anxiety disorders. As has happened in treatment studies of major depression, research in anxiety disorders needs to move beyond assessing response and focus on the inculcation of remission as the outcome measure of greatest clinical relevance. The high rates of partial response and nonresponse to existing treatment should prompt further studies that identify predictors of favorable short- and long-term outcome early in the course of treatment. There is a growing literature that suggests the viability of alternate treatment strategies, including augmentation and combination therapy, for refractory anxiety disorders. However, rigorously designed controlled trials are necessary in order to move beyond the current level of what is largely small studies, open-label series, retrospective reviews, and case reports, so that evidence-based recommendations can be used to guide practice and optimize treatment for individuals with anxiety disorders. ✤

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