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Early improvement during duloxetine treatment of generalized anxiety disorder predicts response and remission at endpoint

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Abstract

Because many patients do not respond to pharmacotherapy for generalized anxiety disorder (GAD), it would be beneficial to know if early response is predictive of final outcome so that timely clinical decisions can be made about augmentation or alternative treatments. This topic has not been examined with the now recommended first-line treatments (selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors) for GAD. Combined data from three 9 to 10 week acute treatment, multi-center, randomized, placebo-controlled studies of duloxetine for GAD were used to explore early improvement on the Hamilton Anxiety Rating Scale (HAMA) in relation to endpoint HAMA response ($\geqslant$50% improvement from baseline), HAMA remission ($\leqslant$7), Clinical Global Impression-Improvement (CGI-I) response ($\leqslant$2), and functional remission as measured by the Sheehan Disability Scale Global Functional Improvement ($\leqslant$5). For duloxetine-treated patients ($n = 668$), the relationships between the proportion of patients who achieved each category of early (week 2 and week 4) HAMA improvement ($\geqslant$20%, $\geqslant$40%, $\geqslant$60%, and $\geqslant$80%) and achievement of endpoint HAMA response, HAMA remission, CGI response, and SDS remission status were all statistically significant (all P's $\leqslant 0.003$). One hundred percent of the duloxetine-treated patients who showed substantial HAMA improvement (>80%) at week 2, and 93% at week 4, were HAMA responders at endpoint. At week 2, 79% of the duloxetine-treated patients who achieved a HAMA improvement of 40–59% were HAMA responders at endpoint. About half of duloxetine-treated patient showing 40–59% early HAMA improvement were remitters on the SDS at endpoint. These data suggest a connection between early improvement and endpoint response and remission status that can be used to guide clinical decision-making.

Keywords: Generalized anxiety disorder; Duloxetine; Early improvement; Remission

1. Introduction

Generalized anxiety disorder (GAD) is both a common and disabling disorder (Grant et al., 2005; Wittchen, 2002). Its lifetime prevalence ranges from 4.1% to 5.7% and its 12-month prevalence from 2.1% to 3.1% (Kessler et al., 2005a,b). Fewer than half of patients with GAD seen in typical treatment settings achieve remission of their symptoms over 8 years (Yonkers et al., 2003), suggesting that GAD is often a chronic condition. GAD is also associated with substantial impairment in functioning and quality of life (Hoffman et al., 2008). In comparison with other affective, anxiety, and alcohol use disorders, GAD was ranked second behind only agoraphobia in terms of total associated

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functional disability in the European Study of the Epidemiology of Mental Disorders, a general population study of more than 21,000 adults (Buist-Bouwman et al., 2006).

In the past 10 years, selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) have become the recommended first-line pharmacotherapy for GAD due to their effectiveness for both GAD and comorbid disorders and their suitability for long-term use (Ballenger et al., 2001). Although these and other medications, as well as cognitive-behavioral therapy, have shown efficacy in treating GAD, response and remission rates have been disappointing. In general, about 50–60% of patients achieve a clinical response, but only about 25–35% achieve remission (Chambless and Peterman, 2004; Mitte et al., 2005; Goodman et al., 2005; Rickels et al., 2006). Remission is even more difficult to achieve if functional remission, and not just symptomatic remission, is the goal of treatment (Ninan, 2001; Pollack, 2001).

Because many patients do not respond to pharmacotherapy, it would be beneficial to know if early response to such treatment is predictive of final outcome. This knowledge would potentially allow clinicians to quickly alter treatment plans if necessary, rather than subjecting patients to an ongoing treatment approach that likely will not attain remission, at least in the short-term, while in many cases still being associated with troublesome adverse events. Such adverse events are the leading reason for discontinuation of treatment with SSRIs (Bull et al., 2002).

Examination of early response in relation to endpoint response has been conducted for different anxiety and affective disorders. In one report, early (week 1) partial response to alprazolam was found to be significantly correlated with response at 8 weeks in the treatment of panic disorder. (Albus et al., 1990) Also in the treatment of panic disorder, early (weeks 1, 2 and 3) response to sertraline was shown to be significantly correlated with endpoint clinical remission (Pollack et al., 2002). Similarly, a study examining the treatment of major depressive disorder found that partial response to fluoxetine at week 2 was associated with a 0.45 likelihood of response at week 8 (Nierenberg et al., 1995).

To date, there has only been limited research examining the predictive value of early response to pharmacotherapy treatment outcome in GAD. In an analysis of two placebo-controlled studies, it was reported that change in anxiety symptoms from baseline to weeks 1 and 2 predicted response at week 8 for both active drug (diazepam, gepirone, or flesinoxan) and placebo (Rynn et al., 2006). An older study also found that early response to diazepam treatment of DSM-III-defined GAD was associated with later improvement (Downing and Rickels, 1985). No studies, however, have examined early response in relation to endpoint response for the currently recommended first-line treatments (SSRIs, SNRIs) for GAD. Because SSRIs and SNRIs have a slower time course for improvement than benzodiazepines (Rickles and Rynn, 2002), the magnitude, and therefore clinical usefulness, of the connection between early response and endpoint response needs to be separately explored for drugs in this class of medications. Moreover, few studies (none with GAD) have examined early response in relation to endpoint remission status. Given that the recommended goal of GAD treatment is symptomatic remission (Ninan, 2001; Pollack, 2001), it would be clinically useful to connect decision-making based on early response to this treatment goal.

The dual acting SNRI duloxetine has recently been shown to be efficacious in the treatment of GAD in three multi-center, randomized, placebo-controlled trials (Koponen et al., 2007; Rynn et al., 2007; Hartford et al., 2007). In these 9–10 week trials, response rates (defined as a 50% or greater change from baseline to endpoint on the Hamilton Anxiety Rating Scale (Hamilton, 1959) [HAMA]), for duloxetine were in the range of 42–58% and remission (HAMA total score $\leqslant 7$ at endpoint) rates were in the range of 23–38% (depending on study and dosage). Like with other SSRIs and SNRIs in the treatment of GAD, these limited response and remission rates raise the question of whether a clinician can get an early "read" on the potential for final response/remission so that treatment can be adjusted early on if necessary.

The purpose of the current report was to determine whether early response to the SNRI duloxetine in the treatment of GAD is predictive of endpoint symptomatic response and functional remission. A pooled study database of all available duloxetine trials for GAD was used. All three studies in the database were placebo-controlled, which allowed for an assessment of whether the relation between early response and endpoint response/remission was specific to active pharmacotherapy.

In evaluating the connection between early improvement and endpoint response/remission status, it is useful to conduct the analyses of the data in a way that closely follows the clinical decision-making process. At an early point in treatment, such as week 2, the clinician will have a patient who has made a certain amount of improvement thus far. Given this amount of improvement, the clinician would be interested in knowing how likely it is, among patients who have improved a comparable amount, that such a patient will prove to be a responder or remitter after continuing on the current course of treatment. This was evaluated in the current report by creating grouping of degrees of early improvement and then evaluating the likelihood of endpoint response/remission for duloxetine-treated patients within these groupings.

2. Materials and methods

2.1. Study population and procedures

The current report used combined data from three multi-center, randomized, placebo-controlled studies of duloxetine treatment for GAD (Koponen et al., 2007; Rynn et al., 2007; Hartford et al., 2007). All three studies