Efficacy and Safety of Duloxetine in the Treatment of Generalized Anxiety Disorder: A Flexible-dose, Progressive-titration, Placebo-controlled Trial

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Objective: Generalized anxiety disorder (GAD), a highly prevalent and chronic illness, is associated with dysregulation in both serotonergic and noradrenergic neurotransmission. The present study examined the efficacy and safety of duloxetine hydrochloride, a balanced and potent dual reuptake inhibitor of serotonin and norepinephrine, for the treatment of GAD.

Methods: In a 10-week, double-blind, progressive-titration, flexible-dose trial, 327 patients [Mean age = 41.6 yrs; 61.8% female] with a DSM-IV defined GAD diagnosis were randomized to receive either duloxetine 60 mg/day to 120 mg/day (N=168) or placebo (N=159) treatment. The primary efficacy outcome measure was mean change from baseline in the Hamilton Anxiety Scale (HAMA) total score; secondary outcome measures included changes in HAMA items anxious mood and tension; Clinical Global Impressions Improvement (CGI-I) scores, and response rates defined as ≥50% reduction in HAMA total from baseline to treatment endpoint.

Results: Compared with placebo, patients who received duloxetine treatment demonstrated significantly greater reduction in HAMA total scores (Mean decrease duloxetine=8.27, SD=9.56 vs placebo=6.49, SD=9.13, P = .02); greater improvement ratings at endpoint (CGI-I end-point duloxetine Mean=2.65, SD=1.33 vs placebo Mean=2.94, SD=1.27, P = .04), and a higher response rate (duloxetine=42% vs placebo=30%, P = .03). Groups did not differ in incidence of serious adverse events (SAEs). The AEs most frequently associated with duloxetine were nausea, dizziness, and somnolence, and the rate of discontinuation due to AEs was 20.2% for duloxetine and 8.2% for placebo (P = .02).

Conclusions: In this trial, duloxetine was an effective, safe pharmacological intervention for GAD. Duloxetine resulted in clinically significant improvement in anxiety symptom severity and overall impairment compared with placebo.
BACKGROUND

- Generalized anxiety disorder (GAD) is characterized by pervasive, difficult to control worry that results in hypervigilance, multiple somatic symptoms, and impaired functioning.1
- Pre-clinical and clinical studies have suggested duloxetine is efficacious for reducing anxiety symptoms.2,3

Hypothesis: Duloxetine 60-120 mg/day will be superior to placebo for the treatment of DSM-IV defined GAD during a 10-week, double-blind, acute therapy trial.

METHODS

- Patients were ≥18 years of age and recruited from 27 outpatient treatment centers

Inclusion criteria:
- DSM-IV GAD determined by the Mini International Neuropsychiatric Interview and confirmed by study psychiatrist
- Clinical Global Impression Severity Score of ≥4 (moderate)
- Hospital Anxiety and Depression Scale (HADS) anxiety subscale score ≥10
- Covit Anxiety Scale (CAS) total score ≥9; Raskin Depression Scale (RDS) with no item ≥3; CAS total > RDS total
- Medically healthy as determined by physical exam, electrocardiogram, and laboratory blood and urine analyses

Main exclusion criteria:
- Recent (6 mo) diagnosis of major depression or substance abuse/dependence
- Past year history of panic, post-traumatic stress, or eating disorders
- Lifetime history of obsessive-compulsive disorder, bipolar or psychotic illness
- Concomitant psychotropic or excluded medication use

Primary Outcome Measure
- Hamilton Anxiety Scale (HAMA) total score using the Structured Interview Guide for HAMA (SIGH-A).4

Secondary Outcome Measures
- HAMA items anxious mood and tension (items 1 and 2)
- HAMA Psychic Anxiety and Somatic Anxiety Factors
- Hospital Anxiety and Depression Scale (HADS) subscale scores
- Clinical and Patient Global Impressions Improvement ratings (CGI-I, PGI-I)
- Treatment outcome status based on HAMA total score changes at end of treatment
  - Response ≥50% reduction from baseline to endpoint
  - Sustained improvement: 30% reduction at any visit after baseline that is then sustained at all subsequent visits
  - Remission rate: HAMA total score ≤7 at endpoint

Safety Measures
- Vital signs, weight, and spontaneously reported adverse events were recorded at each visit
- ECG, blood chemistry and urinalysis (includes drug screen) at pre- and post-treatment

Study Design
- 10-week, acute, double-blind, randomized, placebo-controlled, study
- Patients were assigned 1:1 to either duloxetine or placebo
- Starting dose was 60 mg/day; a dose decrease was allowed for first 2 weeks, but patients had to be taking minimum of 60 mg/day after 2 weeks of treatment
- Study visits were conducted at 1, 2, 4, 7, and 10 weeks
- Dose was required to be increased at visit 4 and subsequent visits if the CGI-I score was >3 (minimal improvement, no change, or worse) and patients could tolerate dose increase; maximum dose was 120 mg/day

Statistical Methods
- All analysis were conducted on the intent-to-treat sample, which included patients who had a baseline observation and ≥1 post-randomization observation
- Analysis model was an ANCOVA based on LOCF with baseline severity as the covariate and investigator site and treatment group as fixed effects
- The mixed effects repeated measures model (MMRM) was also conducted secondarily

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