# Duloxetine as an SNRI treatment for generalized anxiety Disorder (GAD): results from a placebo and active-controlled trial

Characterized by persistent, difficult-to-control, chronic worry, GAD is a prominent anxiety disorder owing to its pervasiveness, chronicity, and functional impairment. The underlying neurobiology of GAD suggests involvement of several neurotransmitter systems, including serotonin, norepinephrine, and g-aminobutyric acid (GABA) transmission. In this context, the development of dual-reuptake inhibitors of serotonin and norepinephrine (SNRIs) has been particularly useful and promising for the treatment of GAD.

This was a multicenter, randomized, double-blind, flexible-dose, placebo and active-controlled (venlafaxine extended-release 75–225 mg/day) acute therapy trial designed to assess the efficacy and tolerability of duloxetine 60–120 mg/day during 10 weeks of treatment in adults with DSM IV-defined GAD. The primary efficacy outcome measure was mean change from baseline to endpoint in the Hamilton Anxiety Rating Scale total score assessed using analysis of covariance. Secondary efficacy measures included the following: HAMA Psychic Anxiety Factor Score, Somatic Anxiety Factor Score, mood item, and tension item; the HADS Anxiety and Depression subscales scores (HADS); the CGI-I and PGI-I rating scales; and the Sheehan Disability Scale Impairment scores. Response, remission, and sustained improvement rates also were determined. Although venlafaxine XR was used as an active comparator, the study was not powered to compare efficacy between venlafaxine XR and duloxetine.

A total of 487 patients were randomly assigned to duloxetine (n= 162), venlafaxine XR (n= 164), or placebo (n= 161). No statistically significant differences were seen in demographics, baseline symptoms, or illness severity measures. The majority of the sample was women (62.6%), with a mean age of 40.8 years. The mean baseline HAMA scores of approximately 25 indicated moderately severe GAD. Significantly greater improvement on the HAMA total score occurred in the duloxetine ($P = 0.007$) and venlafaxine XR ($P \leq 0.001$) groups compared with the placebo group. The mean decrease in the HAMA total scores was 11.8 for duloxetine (46% improvement from baseline) and 12.4 for venlafaxine XR (50% improvement from baseline) compared with 9.2 (37% improvement from baseline) in the placebo group. Differences between duloxetine and placebo were significant as early as week 1 and remained significant at each subsequent visit (Fig.1). The overall effect sizes for the HAMA was 0.33 (95% CI: 0.10, 0.55) for duloxetine and 0.34 (95% CI: 0.12, 0.56) for venlafaxine XR.

Both duloxetine and venlafaxine XR-treated patients demonstrated significantly greater improvements compared with placebo-treated patients on most of the secondary efficacy measures: HAMA psychic anxiety factor score, HAMA anxious mood (item 1), HAMA tension (item 2), and the HADS anxiety and depression subscales (both groups vs. placebo, all comparisons, $P \leq 0.01$). Additionally, duloxetine and venlafaxine XR-treated patients had significantly greater improvement ratings at endpoint compared with placebo-treated patients on the CGI-I and PGI-I (both groups vs. placebo, all comparisons, $P \leq 0.01$).

Using the CGI-I endpoint score, the percentage of responders was significantly greater for both duloxetine (55.7%, $P=0.007$) and venlafaxine XR (60.4%, $P \leq 0.001$) compared with placebo (41.8%). Venlafaxine XR-treated patients (30%), but not duloxetine-treated patients (23%), met remission criteria at a rate significantly greater than placebo-treated patients (19%; venlafaxine XR vs. placebo, $P \leq 0.05$). Sustained improvement rates were significantly greater in both active treatment groups (duloxetine 55%; venlafaxine XR 54%) compared with the placebo group (39%, both groups, $P \leq 0.01$).

Duloxetine and venlafaxine XR-treated patients also experienced significantly greater improvements in their functioning, as shown by changes from baseline to endpoint in the Sheehan Disability Scale global improvement score compared to placebo-treated patients (Fig.2).

Overall discontinuation rates did not differ among the three groups, but adverse event-related discontinuation was significantly higher in the duloxetine (14.2%, $P < 0.001$) and venlafaxine XR (11.0%, $P =0.001$) groups than in the placebo group (1.9%). During the 2-week drug-tapering phase, discontinuation emergent adverse events were significantly greater in the venlafaxine XR group (26.9%, $P = 0.04$), but not in the duloxetine group (19.4%, $P= 0.448$) compared with placebo (15.8%).

In summary, both duloxetine and venlafaxine XR were efficacious and well tolerated for the short-term treatment of GAD. The clinical improvements observed with both active treatments indicate that SNRIs can reliably serve as first-choice pharmacological interventions for GAD.

*Excerpted from: James Hartford, Susan Kornstein, Michael Liebowitz, Teresa Pigott, James Russell, Michael Detke, Daniel Walker, Susan Ball, Eduardo Dunayevich, Jeff Dinkel and Janelle Erickson. Duloxetine as an SNRI treatment for generalized anxietydisorder: results from a placebo and active-controlled trial. International Clinical Psychopharmacology 2007, 22:167–174 A2164 Feb 2010*