Available online at www.sciencedirect.com
ScienceDirect
European Psychiatry 21 (2006) 367–378
EUROPEAN PSYCHIATRY
http://france.elsevier.com/direct/EURPSY/

Original article

Duloxetine in the treatment of major depressive disorder: a placebo- and paroxetine-controlled trial

D.G.S. Perahia [a,b,*], F. Wang [c], C.H. Mallinckrodt [c], D.J. Walker [c], M.J. Detke [c,d,e]

[a] *Lilly Research Center, Erl Wood, Sunninghill Road, Windlesham, Surrey GU20 6PH, UK*
[b] *The Gordon Hospital, London, UK*
[c] *Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN, USA*
[d] *Indiana University School of Medicine, Indianapolis, IN, USA*
[e] *Harvard Medical School, Boston, MA, USA*

Received 8 December 2005; received in revised form 17 March 2006; accepted 19 March 2006
Available online 11 May 2006

Abstract

Objective: Duloxetine doses of 80 and 120 mg/day were assessed for efficacy and safety in the treatment of major depressive disorder (MDD).

Methods: In this randomized, double-blind trial, patients age ≥ 18 meeting DSM-IV criteria for MDD were randomized to placebo ($N = 99$), duloxetine 80 mg/day ($N = 93$), duloxetine 120 mg/day ($N = 103$), or paroxetine 20 mg/day ($N = 97$). The primary outcome measure was mean change from baseline in the 17-item Hamilton rating scale for depression ($HAMD_{17}$) total score after 8 weeks of treatment; a number of secondary efficacy measures also were assessed. Safety and tolerability were assessed via collection and analysis of treatment–emergent adverse events (TEAEs), vital signs, and weight. The Arizona sexual experiences scale was used to assess sexual functioning. Patients who had a ≥ 30% reduction from baseline in the $HAMD_{17}$ total score at the end of the acute phase entered a 6-month continuation phase where they remained on the same treatment as they had taken during the acute phase; efficacy and safety/tolerability outcomes were assessed during continuation treatment.

Results: More than 87% of patients completed the acute phase in each treatment group. Duloxetine-treated patients (both doses) showed significantly greater improvement ($P < 0.05$) in the $HAMD_{17}$ total score at week 8 compared with placebo. Paroxetine was not significantly different from placebo ($P = 0.089$) on mean change on the $HAMD_{17}$. Duloxetine 120 mg/day also showed significant improvement on most secondary efficacy measures (six of nine) compared with placebo while duloxetine 80 mg/day (three of nine) and paroxetine (three of nine) were significantly superior to placebo on fewer secondary measures. $HAMD_{17}$ mean change data from this study and an identical sister study were pooled as defined a priori for the purposes of performing a non-inferiority test versus paroxetine. Both duloxetine doses met statistical criteria for non-inferiority to paroxetine. TEAE reporting rates were low in all treatment groups and no deaths occurred in the acute or continuation phases.

Conclusions: The efficacy of duloxetine at doses of 80 and 120 mg/day in the treatment of MDD was demonstrated. Tolerability, as measured by TEAEs, and safety were similar to paroxetine 20 mg/day and consistent with previous published data on duloxetine in the treatment of MDD.

Keywords: Duloxetine; Major depressive disorder; Placebo; Paroxetine

1. Introduction

Duloxetine, a serotonin and norepinephrine reuptake inhibitor (SNRI), has been shown to be an effective treatment for patients with major depressive disorder (MDD) [1–6]. Eight acute (8–9 weeks duration), double-blind, placebo-controlled clinical trials, of which two had a 26-week continuation phase, and one relapse prevention study [7], were used for the registration of duloxetine in the treatment of MDD in the United States, Europe, and elsewhere. Seven of these trials (five with an active comparator) have been published individually or as part of a review ([1–7], the present study will be the eighth). Despite the failure of antidepressants in general to separate statistically from placebo in more than 50% of recent trials [8], duloxetine was significantly superior to placebo on the primary outcome measure of the 17-item Hamilton rating scale for depression ($HAMD_{17}$) [9] in five of the seven published acute trials.

* Corresponding author.
E-mail address: d.perahia@lilly.com (D.G.S. Perahia).

0924-9338/$ - see front matter © 2006 Elsevier SAS. All rights reserved.
doi:10.1016/j.eurpsy.2006.03.004

A previously published duloxetine trial with a study design identical to the one presented in this paper found that duloxetine doses of 80 and 120 mg/day, as well as the active comparator paroxetine 20 mg/day, were significantly superior compared to placebo on nearly all primary and secondary efficacy measures [4]. Both that study and the present study were part of the registration package described above and were intended to be separate publications as well. The protocols, which were filed with regulatory agencies prior to conduct of the studies, specified this a priori. The results from the current study are presented, discussed, and compared with the results from the previous study.

2. Subjects and methods

2.1. Study design

This was a multi-site, randomized, double-blind, placebo- and paroxetine-controlled study comprising an initial 8-week acute treatment phase followed by a 6-month continuation phase (Study HMAYb). Patients who had a $\geq 30\%$ reduction from baseline in $HAMD_{17}$ total score at the end of the acute phase continued on the same (blinded) treatment during the continuation phase. This 30% cut-off was chosen because it was felt to be unethical for patients who were not showing clinically meaningful improvement on treatment to continue in the study. The study utilized a double-blind, variable-duration placebo lead-in at the beginning of the acute phase and a placebo lead-out at the end of the continuation phase to minimize possible bias in the ratings of efficacy and tolerability associated with patient and investigator knowledge of the onset and conclusion of active drug therapy. The primary outcome measure was mean change from baseline as measured by the $HAMD_{17}$ total score during 8 weeks of acute treatment. The protocol was approved by each site's ethics committee, in accordance with the principles of the Declaration of Helsinki, and patients provided written informed consent prior to participation in any study-related procedures.

2.2. Patients

Male and female outpatients of at least 18 years of age who met criteria for MDD as defined by the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) were recruited from 22 sites in Bulgaria, Croatia, Hungary, Poland, Romania, Russia, and Slovakia. The MDD diagnosis was confirmed via the use of the Mini International Neuropsychiatric Interview (MINI) [10]. In addition, patients were required to have both a clinical global impression of severity (CGI-S) rating ≥ 4 (moderate) and $HAMD_{17}$ total score ≥ 15 at the screening and baseline study visits. Exclusion criteria included having any current primary DSM-IV Axis I diagnosis other than MDD or any anxiety disorder as a primary diagnosis within the year preceding enrollment; any previous diagnosis of bipolar disorder, psychosis, or schizoaffective disorder, lack of response to at least two adequate courses of antidepressant therapy (at least 4 weeks' duration) within the therapeutic dose range during their current MDD episode, and serious suicide risk. A history of substance abuse or dependence within the past year or a positive urine drug screen; or a serious medical illness (cardiovascular, hepatic, renal, respiratory, hematological, endocrine, or neurological disease, or clinically significant laboratory abnormality) were other reasons for being excluded from the study. Patients were permitted to take non-prescription, but not prescription, analgesic medications. Patients were not selected for the presence, type, or severity of pain.

2.3. Treatments

Patients were randomly assigned in a 1:1:1:1 ratio to placebo, duloxetine 80 mg/day (administered as 40 mg twice daily [BID]), duloxetine 120 mg/day (administered as 60 mg BID), or paroxetine 20 mg/day (administered once daily). Treatments were administered in a double-blind fashion via the use of a double-dummy study drug design. A forced-fixed titration schedule was designed into the protocol. Patients randomly assigned to duloxetine 80 mg/day had their dose titrated in the following manner: 3 days at 20 mg BID, then to 40 mg BID. Patients randomly assigned to duloxetine 120 mg/day had their dose titrated in the following manner: 3 days at 20 mg BID, 3 days at 40 mg BID, and then to 60 mg BID. No dose titration was used for patients assigned to paroxetine 20 mg.

2.4. Efficacy measures

Efficacy was assessed using the $HAMD_{17}$ total score as the primary efficacy measure. Secondary measures included the following: $HAMD_{17}$ subscales (anxiety/somatization, core factor, Maier, sleep, and retardation) [11–13]; the Montgomery–Asberg depression rating scale (MADRS) [14]; the Hamilton anxiety rating scale (HAMA) [15]; the CGI-S and patient global impression of improvement (PGI-I) scales [16]; the Sheehan disability scale (SDS) [17]; visual analog scales (VAS) for pain [18]; and the somatic symptom inventory (SSI) [19].

2.5. Safety and tolerability assessments

Spontaneously reported adverse events, vital signs, and weight were recorded at each visit. An adverse event was considered treatment–emergent if it was new or a worsening of a pre-existing symptom compared with the event reported at baseline. The Arizona sexual experiences scale (ASEX) [20] was administered prior to randomization, at the end of acute therapy, and once during the continuation phase. At baseline and at endpoint, patients answering at least the first two ASEX questions (patients that did not were not evaluated) were considered to have sexual dysfunction if the sum of the ASEX items was ≥ 19, the score on any single item was 5, or at least three items had a score ≥ 4; patients who did not meet any of these criteria were classified as having normal sexual function [20].

Laboratory tests (hematology, clinical chemistry, and urinalysis) were conducted at baseline, endpoint, and selected visits in between. Supine blood pressure and heart rate were recorded at each visit. A patient was considered to have sustained elevation in blood pressure if either: (1) systolic blood pressure