Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Psychiatric Research 39 (2005) 161–172
JOURNAL OF PSYCHIATRIC RESEARCH
www.elsevier.com/locate/jpsychires

Onset of action for duloxetine 60 mg once daily: double-blind, placebo-controlled studies

Stephen K. Brannan[a], Craig H. Mallinckrodt[b], Michael J. Detke[b,c,d,e,*], John G. Watkin[b], Gary D. Tollefson[b]

[a] *Cyberonics, Houston, TX, USA*
[b] *Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, USA*
[c] *Department of Psychiatry, Indiana University School of Medicine, Indianapolis, IN, USA*
[d] *Department of Psychiatry, McLean Hospital, Belmont, MA, USA*
[e] *Department of Psychiatry, Harvard Medical School, Boston, MA, USA*

Received 26 September 2003; received in revised form 14 May 2004; accepted 17 May 2004

Abstract

Background. It is widely believed that most antidepressant medications exhibit a delay of 2–4 weeks before clinically relevant improvement can be observed among patients. During this latency period, patients continue to be symptomatic and functionally impaired. Thus, time to onset of effect is an important attribute of a new pharmacotherapy. We assessed the onset of effect for duloxetine, utilizing analytical methods previously recommended in the literature.

Method. Efficacy data were pooled from two identical, but independent, randomized, double-blind, placebo-controlled, 9-week clinical trials of duloxetine (60 mg QD). Efficacy measures included the 17-item Hamilton Rating Scale for Depression ($HAMD_{17}$), $HAMD_{17}$ subscales (Maier, core, and anxiety), and the Clinical Global Impression of Severity (CGI-S) and Patient Global Impression of Improvement (PGI-I) scales. In each individual study, duloxetine demonstrated statistically significant advantages over placebo on multiple outcomes. The present analysis utilized pooled data to more accurately and fully characterize the onset of effect for duloxetine.

Results. Median times to sustained improvements of 10% and 20% in the $HAMD_{17}$ total score among duloxetine-treated patients were 14 days and 21 days, respectively, compared with 34 days and 49 days, respectively, for placebo-treated patients ($p < 0.001$ for both results). The median time to sustained 30% improvement in $HAMD_{17}$ total score was 35 days for duloxetine-treated patients, while the median time for placebo-treated patients was not estimable since less than half of the patients met this criterion by the end of the trial. For duloxetine-treated patients, median times to sustained 10%, 20%, and 30% improvements on the Maier subscale of the $HAMD_{17}$ were the same as those for the $HAMD_{17}$ total score: 14, 21, and 35 days, respectively. However, in other analyses, changes in core emotional symptoms as measured by subscales of the $HAMD_{17}$ were somewhat faster than changes in overall symptomatology. The probabilities of achieving a sustained 30% improvement (Maier subscale) at Week 1 for duloxetine- and placebo-treated patients were 16.2% vs. 4.8%, respectively ($p < 0.001$). The corresponding probabilities of sustained improvement at Weeks 2 and 3 for duloxetine were 32.5% and 45.4%, respectively, compared to 12.8% and 21.4% for placebo ($p < 0.001$ for both comparisons).

Conclusion. The absence of an active comparator limits the conclusions which can be drawn regarding the rapidity of onset of clinically meaningful improvement. However, results from the present investigation may be useful to clinicians in consideration of treatment options for individual patients.

Keywords: Onset of action; Antidepressant; Serotonin reuptake inhibitor; Norepinephrine reuptake inhibitor; Duloxetine

1. Introduction

It is widely believed that most antidepressant medications exhibit a delay of 2–4 weeks following the

* Corresponding author. Tel.: +1-3172776420; fax: +1-3172766026.
E-mail address: mdetke@lilly.com (M.J. Detke).

0022-3956/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jpsychires.2004.05.005

initiation of therapy before clinically relevant improvement can be observed among patients (Nierenberg et al., 2000; Blier, 2001a; Stahl et al., 2001). During this interval, the patient continues to be symptomatic and functionally impaired. Unfortunately, such a latency period prior to the onset of antidepressant action may contribute to a perception that the medication and/or dose is not effective. This may in turn lead to an unnecessary dose titration by the clinician, or to reduced patient compliance with the dosing regimen. Thus, both continued morbidity and prolonged reduction in quality of life are potential byproducts of a delay in onset of antidepressant activity.

In contrast, a rapid and sustained improvement in depressive symptoms would be expected to lead to an earlier restoration of functional well-being and a potentially more cost-effective outcome. An improved onset of action, especially if evident to the patient, may also diminish non-compliance (Culpepper, 2001). In the context of a risk-benefit assessment, achievement of an accelerated response may offset the potential burden of early treatment-emergent side-effects in some patients, thereby providing an additional incentive for treatment continuation.

A complete understanding of the factors underlying the latency in onset of antidepressant action has yet to be achieved. With older thymoleptics, such as the tricyclic antidepressants (TCAs) or monoamine oxidase inhibitors (MAOIs), their narrow therapeutic indices required a gradual dose titration. Moreover, the side effect profiles of these medications were often evident at less than fully therapeutic dosages (Peretti et al., 2000). These factors not only delayed the onset of response, but also reduced patient adherence to dosing regimens. A newer generation of compounds, the selective serotonin reuptake inhibitors (SSRIs), were far less encumbered by either of these limitations (Anderson and Tomenson, 1995; Montgomery and Kasper, 1995) However, the literature has generally suggested that they too required several weeks of patient exposure before a significant clinical effect, relative to placebo, was evident (Blier et al., 1987; Thompson, 1999). A pharmacologic explanation of this phenomenon has been that the delay may reflect the time required to desensitize 5-HT_{1A} autoreceptors and, in turn, facilitate a resumption of normal 5-HT neuronal firing rates (Blier, 2001b).

Another possible reason underlying the apparent delay in the onset of action may be clinical. A differential rate and/or breadth of individual symptom response to antidepressant medication may characterize the time course in a true drug response. Reviews dealing with the onset of action of antidepressants have emphasized the importance of treating depression as a multifaceted disease, and assessing independently the speed of antidepressant response in several key areas (Katz et al., 1996). Thus, an accelerated response may be the result of a larger number of the syndromal aspects responding more rapidly. Antidepressants that achieve dual reuptake inhibition have been proposed to have a broader spectrum of action (Nelson, 1998). Therefore, this class of medications may demonstrate relatively early effects across multiple symptom domains.

Questions have been raised as to whether or not an acceleration of antidepressant response is even feasible. Quitkin et al. have suggested that a true antidepressant drug response (that is, a delayed, persistent response) is only observable after a two-week period of treatment (Quitkin et al., 1984; Quitkin et al., 1987). However, a number of clinical studies of antidepressant augmentation have reportedly resulted in a more rapid onset of response (Artigas et al., 1996; Cappiello et al., 1998; Berlanga et al., 1992; Bump et al., 1997), and some clinical studies have suggested clear evidence of the onset of action during the first week of antidepressant therapy (Katz et al., 1987; Stassen et al., 1996; Stassen et al., 1999; Katz et al., 2004).

The suggestion of a rapid onset of antidepressant efficacy associated with dual-action antidepressants was initially provided by Nelson et al., who reported that the combination of desipramine (the most noradrenergic of the TCAs) and fluoxetine (an SSRI) produced antidepressant effects more rapidly than did desipramine alone (Nelson et al., 1991). This suggests that a dual-action approach may accelerate time to response. The purported faster onset of action of mirtazapine compared to SSRIs may represent further confirmation of this theory (Blier, 2001a).

Accordingly, we used a variety of outcome measures and analytic approaches to characterize the time to clinically meaningful improvement for duloxetine in overall symptomatology and global measures of wellness, and in specific aspects of depression such as core emotional symptoms. Since the early onset of treatment effects has little value if these improvements are not maintained (Leon et al., 2001), we also investigated sustained as well as initial early treatment responses, and assessed whether this approach would provide greater discrimination between drug and placebo responses when compared with conventional methods.

2. Methods

The present investigation utilized data from two identical, but independent, placebo-controlled trials of duloxetine 60 mg once-daily. Results from these individual studies have been reported previously (Detke et al., 2002a; Detke et al., 2002b), and represent all data currently available for duloxetine at this dose in this patient population (major depression). Both of these