Research paper

Do social functioning and symptoms improve with continuation antidepressant treatment of persistent depressive disorder? An observational study

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\textbf{ARTICLE INFO}

\textbf{Keywords:}
Dysthymic disorder
Persistent depressive disorder
Maintenance treatment
Psychosocial functioning
Psychopharmacology
Serotonin norepinephrine reuptake inhibitor
Duloxetine

\textbf{ABSTRACT}

\textbf{Objective:} To determine efficacy of continued treatment with the serotonin norepinephrine reuptake inhibitor duloxetine on symptom reduction and functional improvement in outpatients with dysthymia.

\textbf{Method:} Fifty outpatients with DSM-IV-TR diagnosed dysthymia who had participated in a 10 week double-blind, placebo-controlled study of duloxetine received open treatment for three months. Nineteen duloxetine responders continued duloxetine, 24 patients initially treated with placebo started open duloxetine treatment, and 7 duloxetine non-responders were treated with desvenlafaxine or bupropion, selected by clinician choice.

\textbf{Results:} Patients continuing duloxetine maintained symptom improvement, 84\% meeting response and 63\% remission criteria at week 22. Patients initially treated with placebo showed similarly high levels of response (83\%) and remission (62\%) at week 22, and most duloxetine non-responders subsequently responded to other antidepressants. Duloxetine-continuation patients improved modestly between weeks 10 and 22 on measures of social and cognitive functioning and temperament. Despite this improvement concurrently across several functional domains, 66.7\% of patients continuing duloxetine remained in the impaired range of functioning according to the Social Adjustment Scale (SAS).

\textbf{Conclusions:} Continued duloxetine treatment appears to be effective in maintaining symptom response in dysthymic disorder, and has positive effects on social functioning. However, the majority of patients do not show normalization of functioning, even when controlling for remission status. Additional treatments should be considered to target residual impairments in social functioning in mood remitted patients with persistent depressive disorder.

1. Introduction

Non-major chronic depression, known in DSM-III through DSM-IV-TR as Dysthymic Disorder (DD) and in DSM-5 as persistent depressive disorder (PDD), is associated with significant functional impairment, including poor social functioning, high rates of health care utilization, and increased unemployment and use of public entitlements (Berndt et al., 2000; Friedman, 1993; Keller, 1994; Klein, Shankman, and Rose, 2006; Rappaport et al., 2005). Few studies have focused on the effects of treatment on social functioning. Of numerous acute randomized placebo-controlled trials of antidepressants for dysthymia (e.g., Bakish et al., 1993; Barrett et al., 2001; Bersani et al., 1991; Boyer et al., 1999; Hellerstein et al., 1993; Reyntjens et al., 1986; Versiani et al., 1997), few included social functioning measures (Hellerstein et al., 2010; Koelsis et al., 1997; Ravindran et al., 2000).

Although acute treatment studies demonstrated improvements in psychosocial functioning, end of treatment level of functioning generally remains lower than controls (e.g., Friedman et al., 1995), or improves to the level of controls only in those satisfying criteria for response (Ravindran et al., 2000) or remission (Koelsis et al., 1997). Residual deficits in functioning can persist long-term, even after clinical symptoms have remitted, as has been shown in mood disorders...
in general (e.g., Bijl and Ravelli, 2000; Kennedy et al., 2007; Ormel et al., 2004), and specifically in dysthymia, as Rhebergen et al. showed over a 3 year follow-up study (Rhebergen et al., 2010).

Social functioning deficits have been associated with abnormalities in temperament, particularly high levels of Harm Avoidance (HA) (Cloninger et al., 1993; Hellerstein et al., 2000), a personality trait characterized by excessive worrying, pessimism, and shyness, and by being fearful and easily fatigued (Cloninger et al., 1991); HA has been shown to decrease significantly with acute antidepressant treatment, and to be associated with improved social functioning (Hellerstein et al., 2000), though it remains elevated compared to community norms. The focus on acute phase symptom response in the majority of dysthymia clinical trials therefore limits understanding of the course of social functioning throughout the disease process: in particular, whether longer duration of treatment leads to further improvement in social functioning.

Previous studies of continuation treatment of DD include tricyclics (TCAs; Friedman et al., 1999; J.H. Kocsis et al., 1996) and selective serotonin reuptake inhibitors (SSRIs; J. Kocsis et al., 2002), although the majority of dysthymic subjects in these studies had coexisting major depressive disorder. Of the studies that assessed effects on global levels of functioning (Friedman et al., 1999; J. Kocsis et al., 2002), results suggest that although patients generally maintain gains in symptom improvement, social functioning shows only modest additional improvement during continuation treatment. Since serotonin norepinephrine reuptake inhibitors (SNRIs) are thought to be more potent than single mechanism medications (Thase et al., 2001), continuation treatment with SNRIs might lead to greater functional improvement.

To our knowledge there are no published studies of double-blind placebo-controlled SNRI treatment for DD, followed by open continuation SNRI treatment with continued tracking of symptoms and psychosocial functioning. In a double-blind placebo-controlled study of 57 adults diagnosed with DD (Hellerstein et al., 2012), we reported the efficacy of duloxetine vs. placebo in acute (10 week) treatment, with the duloxetine group exhibiting higher rates of treatment response (66% vs. 25%) and remission (55% vs. 14%). At baseline, social functioning, measured by the Social Adjustment Scale (SAS), (Weissman and Bothwell, 1976; Weissman et al., 1978) averaged 2.47±0.49, approximately 2 SD above community norms (1.59±0.33) (Weissman et al., 1978), with higher scores indicating worse functioning. After 10 weeks of duloxetine treatment SAS scores dropped to 2.12±0.43, not a significant difference from placebo-treated patients, who also showed improvement (SAS scores dropping from 2.61±0.48 to 2.42±0.51) (Hellerstein et al., 2012). For the continuation phase of our study, participants were provided open antidepressant treatment for an additional 12 weeks, with those initially assigned to placebo receiving active duloxetine treatment.

We hypothesized that, during continuation treatment,

1) Patients receiving duloxetine in phase 1 would exhibit continued symptom improvement at week 22, as defined by clinician and self-rated depression and treatment response.
2) Patients continuing duloxetine would demonstrate additional functional improvements.
3) Patients treated with placebo in phase 1 would improve with open-label duloxetine in the continuation phase, on symptom and psychosocial functioning measures.

2. Methods

2.1. Subjects

2.1.1. Inclusion criteria

The double-blind placebo-controlled study enrolled adults aged 18–75 years, who presented at pre-treatment with HRSD-24 > 12. They had current DSM-IV-TR diagnoses of dysthymic disorder (DD) or depression NOS (with duration > 2 years), and were deemed likely to be compliant with study procedures.

2.1.2. Exclusion criteria

DSM-IV-TR diagnosis of major depression in the prior 3 months; bipolar disorder, schizophrenia or other psychotic disorders; dementia or other cognitive impairment; and drug or alcohol abuse or dependence within the prior 6 months. Other exclusions included current psychoactive medication use; serious risk for suicide; unstable medical conditions; current or planned pregnancy; current eating disorder; and lack of capacity to consent to study participation.

2.2. Procedure

For a full description of study procedures see Hellerstein et al. (2012). The 10-week double-blind placebo-controlled trial of duloxetine was followed by a 12-week open label phase of treatment with duloxetine (or for duloxetine non-responders, other antidepressants).

The study took place at the Depression Evaluation Service (DES) of the New York State Psychiatric Institute (NYSPI) between August 2006 and December 2011; all study procedures were approved by the NYSPI/Columbia University Department of Psychiatry Institutional Review Board (IRB). DES clinicians obtained psychiatric and medical history and administered standardized assessments including the Structured Clinical Interview for DSM-IV-TR SCID-P (First et al., 1996) and HRSD-24 (Hamilton, 1960). A physical examination was performed and blood and urine samples were collected, including urine toxicology. Those meeting all inclusion criteria and no exclusion criteria were offered study participation.

At week 10 of the double-blind phase, subjects were provided open-label medication treatment. Assessments during the continuation phase occurred at weeks 14, 16, 18 and 22 at which time physicians administered clinical rating scales, and patients completed self-rated forms.

2.3. Drug administration

Patients continuing duloxetine after week 10 generally remained on their current dose, which could be adjusted clinically based on efficacy or side effects. Patients beginning duloxetine at week 10 were treated with 30 mg in the morning, which could be raised by one capsule after one week. The dose could then be increased by 30 mg/day every two weeks to a maximum of 4 capsules (120 mg/day), in the absence of sufficient response and significant adverse events. Duloxetine non-responders were switched to desvenlafaxine or bupropion, at the clinician’s discretion.

2.4. Measures

Depression severity was assessed by clinician (Hamilton Rating Scale for Depression, 24-item, HRSD-24; Hamilton, 1960) and self-report (Beck Depression Inventory, BDI-2; Beck et al., 1961) using standard depression symptom measures used in the United States. We also used the clinician-rated Cornell Dysthymia Rating Scale (CDRS; Cohen, 1997; Hellerstein et al., 2002) to assess symptoms of chronic depression. Social adjustment was measured using the Social Adjustment Scale (SAS; M. M. Weissman and Bothwell, 1976), a self-report that assesses functioning in nine social and work-related domains. Temperament was measured using the Temperament and Character Inventory (TCI; Cloninger et al., 1998, 1991, 1993), a self-report with subscales corresponding to Harm Avoidance (HA), Reward Dependence, Novelty Seeking, and Persistence. As noted in the Introduction, elevated HA levels have been found in chronically depressed patients, to be associated with psychosocial impairment, and to improve but not normalize after acute antidepressant treatment.
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