Available online at www.sciencedirect.com
ScienceDirect
Journal of Psychiatric Research 42 (2008) 1042–1049
JOURNAL OF PSYCHIATRIC RESEARCH
www.elsevier.com/locate/jpsychires

Examining quality of life in patients with generalized anxiety disorder: Clinical relevance and response to duloxetine treatment

Mark H. Pollack [a,*], Jean Endicott [b], Michael Liebowitz [b], James Russell [c], Michael Detke [c,d,e], Melissa Spann [c], Susan Ball [c,e], Ralph Swindle [c]

[a] Center for Anxiety and Traumatic Stress Disorders, Massachusetts General Hospital/Harvard Medical School, Simches Research Building, 185 Cambridge Street, Suite 2200, 2nd Floor, Boston, MA 02114, United States
[b] New York State Psychiatric Institute/College of Physicians and Surgeons, Columbia University, New York, NY, United States
[c] Lilly Research Laboratories, Indianapolis, IN, United States
[d] McLean Hospital/Harvard Medical School, Boston, MA, United States
[e] Indiana University School of Medicine, Indianapolis, IN, United States

Received 14 February 2007; received in revised form 19 November 2007; accepted 21 November 2007

Abstract

Background: Duloxetine, a serotonergic noradrenergic reuptake inhibitor, improved functional outcomes in each of three clinical studies for the treatment of adults with generalized anxiety disorder (GAD). Using comparison norms, the current work describes the clinical relevance of these functional improvements in terms of return to normative functioning and symptom remission.
Methods: Data were pooled at the individual patient level from three double-blind, placebo-controlled trials of duloxetine treatment (9–10 weeks acute therapy, dose ranges 60–120 mg). Inclusion/exclusion criteria were consistent across studies, and outcome measures included the Sheehan Disability Scale (SDS), Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF), and European Quality of Life 5 Dimensions (EQ-5D).
Results: Adult patients (mean age = 42.4 years; 65% women) were randomly assigned to duloxetine ($N = 668$) or placebo ($N = 495$). At baseline, the majority of patients were impaired on the SDS global functioning (89%), Q-LES-Q-SF maximum percent (95%), and EQ-5D (76%) scores. On each measure, a greater percentage of duloxetine-treated patients converted from an impaired baseline to a normative endpoint score than did placebo-treated patients ($p \leqslant 0.001$, all comparisons). Remission defined as a HAMA total score at endpoint of $\leqslant 10$, compared with $\leqslant 7$, captured a greater proportion of patients who were functionally in remission.
Conclusions: GAD is associated with substantial impairment in functioning and subjective well-being, and patients treated with duloxetine 60–120 mg/day, compared with placebo, experienced a greater return to normative functioning. Attention to role functioning and quality of life may refine our definition of remission when using standard symptom measures of anxiety.

Keywords: Quality of life; Generalized anxiety disorder; Duloxetine; Clinical relevance

1. Introduction

As part of evaluating the effectiveness of treatment interventions, clinicians and researchers concur that impact on an individual's quality of life is a crucial outcome. Despite this importance, quality of life remains a complicated construct for measurement (Holmes, 2005). Different conceptualizations have been proposed, but most definitions of "quality of life" incorporate three key areas: role functioning, subjective well-being, and overall health status (Patrick and Chiang, 2000). Role functioning signifies the ability to perform one's duties, engage in social relationships, and manage self-care. Subjective well-being is more broadly

* Corresponding author. Tel.: +1 617 724 0844; fax: +1 617 643 3080.
E-mail address: mpollack@partners.org (M.H. Pollack).

0022-3956/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jpsychires.2007.11.006

characterized, but usually involves happiness and satisfaction with life activities. Overall health status may refer to variables related to the specific disease process, but more often reflects a holistic assessment as well (Holmes, 2005).

Clinical trials have increasingly included measures of these aspects of quality of life in evaluation of pharmacological treatments, but the dilemma then advances from the detection of to the interpretation of change. Given the subjective nature of quality of life indices, the mean changes associated with treatment interventions can be difficult to translate into personal or clinical relevance for the individual patient. Several methods for assigning meaningfulness to change have been advocated, including the use of effect sizes (mean changes in terms of standard deviations), comparison of the self-report with an external criterion (e.g., a global measure of change), or statistical methods (e.g., standard error of measurement) (Patrick and Chiang, 2000; Wyrwich et al., 1999). For most patients, an intuitive meaningful change would be a return to a premorbid state of well-being; however, chronic illnesses may result in a diminished baseline that can obscure this reference point. Under these conditions, the use of an absolute reference, such as normative values from healthy controls, can provide a more meaningful context for the interpretation of within-subject change.

Generalized anxiety disorder (GAD) is a chronic anxiety illness that has been shown to result in diminished quality of life as conceptualized by role functioning, well-being, and health state (Mogotsi et al., 2000). In the present study, we pooled data from three double-blind, placebo-controlled clinical trials that examined the efficacy of duloxetine, a serotonergic noradrenergic reuptake inhibitor, for the treatment of adults with GAD. In each of these trials, duloxetine treatment significantly improved anxiety symptom severity for patients with GAD (Hartford et al., 2007; Koponen et al., 2007; Rynn et al., 2007). Measures of role functioning, subjective well-being, and health status were also administered within these 9–10 weeks acute treatment trials. Results from each study showed that patients who were treated with duloxetine experienced significant improvements (defined as mean changes in total scores) compared with placebo in these aspects of quality of life (Endicott et al., 2007). For this manuscript, the primary objective was to place these quality of life improvements into an appropriate clinical context by using comparison norms to describe their relevance in patients with GAD. A secondary objective was to describe the association between quality of life and efficacy measures to provide clinical guidance on the magnitude of symptom change associated with a return to normal functioning.

2. Materials and methods

2.1. Study designs

Data were pooled from three randomized, double-blind, placebo-controlled, multicenter trials conducted in adult outpatient centers in seven countries, including the United States. Study 1 was a 9-week acute treatment study that compared fixed-dose duloxetine 60 mg ($N = 168$), duloxetine 120 mg ($N = 170$), or placebo ($N = 175$). Studies 2 and 3 were flexible-dose studies of duloxetine 60–120 mg ($N = 330$) or placebo ($N = 320$) with 10-week acute therapy. Study 3 also included an active comparator arm, venlafaxine XR 75-225 mg daily, which was not included in the duloxetine pooled analyses.

2.2. Study patients

Men and women $\geqslant 18$ years of age were recruited from outpatient centers. Patients were administered the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) and had to meet the Diagnostic and Statistical Manual, 4th edition, Text Revision (DSM-IV-TR, American Psychiatric Association, 2000) criteria for GAD, and their diagnosis was also confirmed by study psychiatrist. The GAD illness was required to be at least moderately severe as indicated by a Hospital Anxiety Depression Scale (HADS; Zigmond and Snaith, 1983) anxiety subscale score $\geqslant 10$ and a score of $\geqslant 4$ on the Clinical Global Impression-Severity scale (CGI-S; Guy, 1976). To ensure predominance of anxiety symptoms, patients' ratings on the Covi anxiety scale (Covi; Lipman and Covi, 1976) had to be higher than their score on the Raskin Depression Scale (RDS; Raskin et al., 1969) with no item on the RDS rated >3.

Reasons for diagnostic exclusion in each study included any primary DSM-IV Axis I diagnosis other than GAD (including major depressive disorder) within the past 6 months; panic disorder, post-traumatic stress disorder, or an eating disorder within the past year; any past or current obsessive-compulsive disorder, bipolar disorder, psychosis, factitious disorder, or somatoform disorders; or a DSM-IV-defined history of alcohol or any psychoactive substance abuse/dependence within the prior 6 months. Other exclusion criteria were benzodiazepine use 2 weeks prior to randomization; serious suicide risk, initiation of psychotherapy, any medical illness that contraindicated treatment with duloxetine, or the use of any excluded concomitant or other psychotropic medications.

2.3. Efficacy measures

The Hamilton Anxiety Rating Scale (HAMA; Hamilton, 1959) was administered at each visit using the Structured Interview Guide for HAMA (SIGH-A; Shear et al., 2001). The HAMA consists of 14 items that are rated by a clinician using a 0 (not at all present) to 4 (severely disabling) scale; higher total scores indicate greater distress and impairment. The HADS is a self-report measure that consists of two, 7-item subscales (anxiety and depression). Patients rated each item for its frequency. For example, "worrying thoughts go through my head" is rated from 0 (very little) to 3 (a great deal of the time). HADS anxiety