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Fluoxetine *versus* sertraline in the treatment of patients with undifferentiated somatoform disorder: A randomized, open-label, 12-week, parallel-group trial☆

Changsu Han [a,b], Chi-Un Pae [a,c,*], Bun Hee Lee [a], Young-Hoon Ko [a], Prakash S. Masand [b], Ashwin A. Patkar [b], In-Kwa Jung [a]

[a] *Department of Psychiatry, Korea University, College of Medicine, Seoul, South Korea*
[b] *Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA*
[c] *Department of Psychiatry, Kangnam St. Mary's Hospital, The Catholic University of Korea College of Medicine, Seoul, South Korea*

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Abstract

The present study was conducted to compare the effectiveness and tolerability of fluoxetine and sertraline in the treatment of undifferentiated somatoform disorder (USD), using the Patient Health Questionnaire (PHQ-15), which was specifically designed for assessing the severity of somatic symptoms. A randomized, 12-week, open-label trial of fluoxetine (10–60 mg/d) and sertraline (25–350 mg/d) in patients with USD was conducted. Six visits, at baseline and weeks 1, 2, 4, 8, and 12, were scheduled. Assessments for effectiveness and tolerability were conducted at each visit. The primary effectiveness measure was the mean change in PHQ-15 total score, from baseline to the end of treatment. Secondary effectiveness measures were the mean changes in total scores on the Beck Depression Inventory (BDI) and the 12-item General Health Questionnaire (GHQ-12), from baseline to the end of treatment. A total of 45 subjects were enrolled; of them, 28 were randomly assigned to receive fluoxetine and 17 to receive sertraline. The total score on the PHQ-15 from baseline to the end of treatment significantly decreased in the fluoxetine (-10.7, $p<0.0001$) and sertraline (-10.3, $p<0.0001$) treatment groups, with no between-group difference ($F=0.0701$, $p=0.7924$). Overall, both treatments were well tolerated and no serious adverse event was reported. This study suggests that both agents may have a potential role in the treatment of USD. A double-blind, placebo-controlled trial and/or head-to-head comparison study with larger samples are required to draw more definite conclusions.

Keywords: Fluoxetine; Open-label; Patient Health Questionnaire; Sertraline; Undifferentiated somatoform disorder

1. Introduction

The prevalence of undifferentiated somatoform disorder (USD) is known to be quite high, although it varies according to the criteria used to identify it. In a recent study, the prevalence of USD was estimated at 16.1%, which increased to 21.9% when the severity of clinical impairment was ignored (de Waal et al., 2004). Other studies across the world support this high prevalence of USD: 27.3% in Denmark (Fink et al., 1999), 13.8% in Italy (Faravelli et al., 1997), 10.2% in Norway (Leiknes et al., 2007), 19.7% in Germany (Grabe et al., 2003), 12.0% in Saudi Arabia (El-Rufaie et al., 1999), and 30.6% in China (Chang et al., 2005).

Comorbidity of USD and other psychiatric disorders is also high, especially depressive and anxiety disorders (de Waal et al., 2004; Maier and Falkai, 1999). The functional impairment

Abbreviations: ANOVA, analysis of variance; BDI, Beck Depression Inventory; DA, dopamine; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition; ECG, electrocardiogram; GHQ-12, 12-item General Health Questionnaire; ITT, intent-to-treat; 5-HTT, serotonin transporter; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; 5-HIAA, 5-hydroxyindoleacetic acid; LOCF, last observation carried forward; NE, norepinephrine; NNT, number needed to treat; NRI, norepinephrine reuptake inhibitor; OD, observed difference; OTC, over-the-counter; PHQ-15, Patient Health Questionnaire; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants; USD, undifferentiated somatoform disorder.

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* Corresponding author. Department of Psychiatry, Kangnam St. Mary's Hospital, The Catholic University of Korea College of Medicine, Seoul 137-701, South Korea. Tel.: +82 2 590 2718; fax: +82 2 594 3870; Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, 2218 Elder Street, DUMC Box 3419, Durham, NC 27705, USA. Tel.: +1 919 668 3633; fax: +1 919 668 5418.

E-mail addresses: pae@catholic.ac.kr, chiun.pae@duke.edu (C.-U. Pae).

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can be severe (Katon et al., 1991; Kroenke et al., 1997) and it appears to show a progressive and chronic course (Arnold et al., 2006; Khan et al., 2003).

The etiology and pathogenesis of USD are not fully understood. Despite limited evidence, serotonin has been consistently suggested to be implicated in the pathogenesis and treatment of somatofrom disorders based on several preclinical (Hains et al., 2003; Svensson et al., 2006; Zhao et al., 2007) and clinical studies (Aragona et al., 2005; Arnold et al., 2002; d'Amato et al., 1999; Lee et al., 2005; Patkar et al., 2007; Rani et al., 1996; Saper et al., 1994; Turkington et al., 2002; Vahedi et al., 2005; Varia et al., 2000). The involvement of serotonin may also explain the comorbid mood and anxiety symptoms in patients with USD (Kroenke, 2003). In addition, emerging evidence also points to alterations in the serotonin transporter (5-HTT) in patients with USD, although the functional significance is unclear (Belous et al., 2001).

Increasing evidence suggests that antidepressants affecting the serotonin neurotransmission system, such as tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), may potentially be effective in treating somatoform disorders. A large metaanalysis of 94 RCTs, primarily consisting of studies on TCAs and SSRIs for unexplained somatic symptoms, found absolute differences in improvement of somatic symptoms between the antidepressant and placebo groups (O'Malley et al., 1999). Moreover, subsequent studies have also demonstrated that antidepressants have an important role in treating various somatic symptoms (O'Malley et al., 2000; O'Malley et al., 1999; Saarto and Wiffen, 2005; Tomkins et al., 2001), and the efficacy and safety of other pharmacological agents have been also reported in the treatment of somatoform disorders (Maurer et al., 1999; Muller et al., 2004; Volz et al., 2000; Volz et al., 2002).

However, the previous data were largely from TCAs; findings with SSRIs are relatively limited. In addition, very few clinical trials have directly compared the effectiveness and tolerability of SSRIs in patients with USD, and even fewer have used objectively validated scales for measuring somatic complaints. Thus, the present study was conducted to evaluate the comparative effectiveness and tolerability of fluoxetine and sertraline in the treatment of USD.

2. Methods

2.1. Design

We conducted a randomized, 12-week, open-label, parallel-group trial to compare the effectiveness and tolerability of fluoxetine and sertraline in patients with USD.

2.2. Subjects

The study was reviewed and approved by the institutional review board. All subjects provided written informed consent prior to participating in the study.

Eligible subjects with USD, based on the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) criteria (Association, 1994), were those aged 18 or older (male or female) who had somatic symptoms almost every day for at least 6 months and were not taking an active prescription medications to control their somatic complaint [over-the-counter (OTC) medications, such as acetaminophen, up to 2 g/d, and ibuprofen, up to 1.2 g/d, were allowed]. In addition, if the patient was a woman of reproductive age, she had to agree to use approved methods of contraception.

Excluded subjects were those who had a history of (and/or current) psychotic disorders (such as schizophrenia, schizoaffective disorder, and bipolar disorder) or had current AXIS I disorders that could possibly account for the somatic symptoms (*e.g.*, major depressive disorder, anxiety disorders, factitious disorder, malingering, or other somatoform disorder such as somatization disorder). In addition, those suffering from substance abuse or dependence in the previous 12 months, those with a history of hypersensitivity to fluoxetine or sertraline, and those currently being treated with any psychotropic medication were excluded. Moreover, those who had participated in any clinical trial in the previous 30 days or were involved in workers compensation, disability, or related litigation, were also ineligible. Women who were breast-feeding or who were pregnant were excluded.

2.3. Psychiatric diagnosis

The AXIS I diagnosis was evaluated by the consensus between two board-certified psychiatrists (CH, BHL) upon study entry, according to DSM-IV criteria.

2.4. Medication

The allocation of each medication was based on a computer-generated randomization code. Fluoxetine and sertraline were dosed using a forced flexible titration strategy, starting respectively at 10 mg/d and 25 mg/d and increasing weekly in 10 mg/d and 50 mg/d increments; the maximum dose was 60 mg/d and 350 mg/d, respectively, based on clinical responses and tolerability. No other psychotropic medications were permitted during the study, except hypnotics for insomnia and benzodiazepines for anxiety that were only allowed for temporary control of those symptoms.

Prescription analgesics, muscle relaxants, and steroids were not allowed during the study. Concomitant medications, such as OTC acetaminophen, were only allowed on an as-needed basis.

2.5. Assessment

The study lasted for 12 weeks with six visits: at baseline and weeks 1, 2, 4, 8, and 12. Assessments for effectiveness and tolerability were made at each visit.

2.5.1. Effectiveness measures

2.5.1.1. Primary endpoint. The primary effectiveness measure was the mean change in Patient Health Questionnaire (PHQ-15)