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Paroxetine for Patients with Undifferentiated Somatoform Disorder: A Prospective, Open-Label, 8-Week Pilot Study

Changsu Han, MD[1,2]; David M. Marks, MD[2]; Chi-Un Pae, MD[2,3]; Bun Hee Lee, MD[1]; Young-Hoon Ko, MD[1]; Prakash S. Masand, MD[2]; Ashwin A. Patkar, MD[2]; and In-Kwa Jung, MD[1]

[1]Department of Psychiatry, College of Medicine, Korea University, Seoul, South Korea; [2]Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, North Carolina; and [3]Department of Psychiatry, Kangnam St. Mary's Hospital, The Catholic University of Korea College of Medicine, Seoul, South Korea

ABSTRACT

BACKGROUND: Forty-eight percent of somatic symptoms encountered in the primary care setting are medically unexplained. Such symptoms have been associated with negative impact on quality of life and with functional impairment.

OBJECTIVE: The aim of this study was to assess the potential utility and tolerability of paroxetine for the treatment of undifferentiated somatoform disorder (USD), using the 15-item Patient Health Questionnaire (PHQ-15) to assess the severity of somatic symptoms.

METHODS: A prospective, open-label, 8-week pilot study of paroxetine was conducted in outpatients with USD. Data were collected at baseline and at weeks 1, 2, 4, and 8. The primary measure was the mean change in PHQ-15 total score from baseline to the end of treatment. Secondary effectiveness measures included mean changes in total scores on the Beck Depression Inventory (BDI) and the 12-item General Health Questionnaire from baseline to end of treatment. A physical examination, electrocardiography, complete blood count, blood chemistry, urinalysis, and pregnancy test (for women of childbearing potential) were performed at baseline and the end of treatment. Vital signs were measured during each visit. Adverse events (AEs) were recorded during the study and included those determined using the Systematic Assessment for Treatment Emergent Events-General Inquiry.

RESULTS: Forty-three Korean patients were screened for the study. Twenty-two patients (13 women, 9 men; mean [SD] age, 37.4 [12.4] years) were enrolled and 20 completed the study; 2 patients were lost to follow-up. The mean total score on the PHQ-15 from baseline to the end of treatment was significantly decreased (17.2 vs 4.3; $P = 0.001$), as was the mean total BDI score (12.8 vs. 6.3; $P < 0.001$). Overall, paroxetine was well-tolerated. Nausea and dry mouth were the most commonly reported treatment-emergent AEs (both, 5 [22.7%]); no serious AEs were reported. No abnormal laboratory results were observed.

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CONCLUSION: This open-label pilot study found that paroxetine had potential utility in the treatment of USD and was generally well-tolerated. These results suggest that adequately-powered, double-blind, placebo-controlled trials are warranted to more fully assess the efficacy and safety of paroxetine in the treatment of USD. (*Curr Ther Res Clin Exp.* 2008;69:221–231) © 2008 Excerpta Medica Inc.

KEY WORDS: undifferentiated somatoform disorder, paroxetine, Patient Health Questionnaire, pilot study.

INTRODUCTION

It has been reported that 48% of the somatic symptoms encountered in the primary care setting are medically unexplained, and ≥25% of such symptoms persist beyond 1 year in duration.[1] In addition, unexplained somatic symptoms have been associated with negative impact on quality of life and with functional impairment.[2,3]

The neurobiologic etiology of unexplained somatic symptoms remains poorly understood, although dysfunctions in serotonergic and noradrenergic pathways have been implicated.[4] Pharmacologic treatment paradigms have yet to be developed for unexplained somatic symptoms; however, multiple meta-analyses[5–8] have suggested a role for contemporary antidepressants, including tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) in the treatment of unexplained somatic symptoms. One review[5] found that, out of 94 studies covering 6595 patients, the absolute difference in improvement between antidepressant and placebo groups was 32% for certain somatic symptoms, and this has been replicated in subsequent studies.[6–8] Antidepressants may have a role in the treatment of somatic syndromes, and this role deserves to be clarified.

To date few clinical trials have investigated the effectiveness and tolerability of paroxetine for patients with undifferentiated somatoform disorder (USD); particularly lacking are studies using objectively validated scales measuring somatic complaints.

The present study was conducted to assess the effect and tolerability of paroxetine* for the treatment of USD using the 15-item Patient Health Questionnaire (PHQ-15),[9] which was specifically designed to assess the severity of somatic symptoms. This was intended as a preliminary study to justify a sufficiently powered, randomized, double-blind, placebo-controlled clinical trial.

PATIENTS AND METHODS

DESIGN

This was a prospective, open-label, 8-week study in patients with USD. All clinical outcomes at the end of the study were compared to those at baseline in the same patients. This study was conducted at an outpatient clinic in a university-based training hospital (Korea University Ansan Hospital, Ansan, South Korea). The study was reviewed and approved by the institutional review board. All participants provided written informed consent prior to entering the study.

*Trademark: Paxil® (GlaxoSmithKline, London, United Kingdom).

PATIENTS

All patients were recruited from advertisements in the university and local newspapers. Patient eligibility was determined by 2 board-certified psychiatrists (C.H. and B.H.L.) in accordance with protocol-specific inclusion and exclusion criteria via face-to-face interview. No monetary compensation was provided to patients for their participation.

Men and women aged ≥18 years who met the criteria for a diagnosis of USD based on the *Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition*[10] (*DSM-IV*), who stated they had somatic symptoms almost every day for at least the prior 6 months and who were not currently receiving any prescription medications to control their somatic complaint (over-the-counter [OTC] medications [eg, acetaminophen ≤2 g/d and ibuprofen ≤1.2 g/d] were allowed) were eligible for the study. In addition, women of child-bearing potential were required to use approved methods of contraception.

Exclusion criteria included previous or current psychotic disorders (eg, schizophrenia, schizoaffective disorder), bipolar disorder, or current Axis I disorder that might account for or contribute to somatic symptoms (eg, major depressive disorder, anxiety disorders, factitious disorder, malingering, or other somatoform disorders [eg, somatization disorder]). Individuals were also excluded if they experienced substance abuse or dependence in the previous 12 months, had a history of hypersensitivity to paroxetine, or were currently being treated with any psychotropic medication. Individuals who had participated in any clinical trial in the previous 30 days or were involved in health-related legal proceedings (including workers' compensation or disability claims) were ineligible. Women who were breastfeeding or pregnant were also excluded.

PSYCHIATRIC DIAGNOSIS

Axis I diagnosis was assessed by consensus between 2 board-certified psychiatrists (C.H. and B.H.L.) according to *DSM-IV* criteria[10] at screening visits.

MEDICATION

Paroxetine immediate-release (IR), (tablet) was administered using a flexible titration strategy based on clinical response and patients' tolerability. The starting dosage was 10 mg/d and the maximum dosage was 40 mg/d. No other psychotropic medications were permitted during the study, except hypnotics for insomnia and benzodiazepines for anxiety on an intermittent and temporary basis.

Prescription analgesics, muscle relaxants, and steroids were not allowed during the study. Concomitant as-needed OTC analgesics, including acetaminophen ≤2 g/d and ibuprofen ≤1.2 g/d, were permitted during the study.

ASSESSMENT

The study treatment period was 8 weeks, which consisted of visits at baseline and weeks 1, 2, 4, and 8. Assessments for effect and tolerability were done at each visit.

PRIMARY END POINT

The primary measure chosen a priori was the mean change in PHQ-15 total score[11] from baseline to the end of treatment. The questionnaire assesses 15 somatic symp-

toms or symptom clusters that account for >90% of all physical complaints (excluding upper respiratory tract symptoms) reported by outpatients. Each item is rated on a scale from 0 to 2. Scoring is simply the sum of the numbers circled and scores can range from 0 to 30.

SECONDARY END POINT

Secondary measures were the mean changes in total scores on the Beck Depression Inventory (BDI)[12] and the 12-item General Health Questionnaire (GHQ-12)[13] from baseline to the end of treatment. The BDI contains 21 questions about emotional, cognitive, motivational, physiological, and other symptoms. Each item consists of 4 statements describing increasing intensities of symptoms of depression. Items are rated on a scale from 0 to 3. The GHQ-12 consists of 12 items, each assessing the severity of a mental problem over the past few weeks using a 4-point scale (from 0–3).

TOLERABILITY MEASURES

A physical examination, electrocardiography, complete blood count, blood chemistry, urinalysis, and pregnancy test (for women of childbearing potential) were performed at baseline and the end of treatment. Vital signs were measured during each visit. Adverse events (AEs) were recorded during the study and included those determined using the Systematic Assessment for Treatment Emergent Events-General Inquiry.[14] *Treatment-emergent AEs* were defined as any AEs reported after patients were administered study medication.

STATISTICAL ANALYSIS

All patients who received ≥1 dose of study medication and had ≥1 post baseline visit assessment were included in the intent-to-treat (ITT) population. The last available post baseline measurement was assigned as an end point analysis (last observation carried forward [LOCF]). ITT with the LOCF approach was conducted for the analysis of outcomes. The primary and secondary end points relative to continuous variables were compared using paired *t* tests. Categoric variables were analyzed using descriptive statistics when appropriate.

All statistical significance was 2-tailed and set at $P < 0.05$. Statistical analysis was determined using STATA/SE version 10.0 (StataCorp, College Station, Texas).

RESULTS

PATIENTS

Forty-three patients were screened for the study. Reasons for exclusion were as follows: unwillingness to take study medication for >4 weeks (n = 9), comorbid psychiatric disorders (eg, alcohol dependence and major depressive disorder) (n = 6), and withdrawal of consent (n = 6). Twenty-two Korean patients (13 women, 9 men; mean [SD] age, 37.4 [12.4] years) were included in the study (**Table I**). Patients reported having had chronic somatic symptoms for a mean (SD) duration of 26.0 (14.8) months and 2.1 (1.5) prior clinic visits to any psychiatric or medical department for such complaints.

Table I. Baseline demographic and clinical characteristics of the study patients with undifferentiated somatoform disorder (N = 22).

Characteristic	Value
Age, mean (SD), y	37.4 (12.4)
Sex, no. (%)	
Female	13 (59.1)
Male	9 (40.9)
Income status*	
High	1 (4.5)
Middle	18 (81.8)
Low	3 (13.6)
Marital status†	
Married	14 (63.6)
Single	5 (22.7)
Divorced	1 (4.5)
Education, no. (%), y	
≤12	15 (68.2)
>12	7 (31.8)
Alcohol use, no. (%)†	
Never	7 (31.8)
Once per week	14 (63.6)
≥2 per week	1 (4.5)
Smoking history, no. (%)	
No	19 (86.4)
Yes	3 (13.6)
Admission history, no. (%)§	
No	19 (86.4)
Yes	3 (13.6)
Duration of somatic symptoms, mean (SD), mo	26.0 (14.8)
Prior clinic visits, mean (SD), no.‖	2.1 (1.5)
Somatic symptoms at baseline, mean (SD), no.	3.2 (2.0)
Baseline PHQ-15 score, mean (SD)	17.2 (5.4)
Baseline BDI score, mean (SD)	12.8 (10.5)
Baseline GHQ-12 score, mean (SD)	16.2 (8.0)

PHQ-15 = Patient Health Questionnaire; BDI = Beck Depression Inventory; GHQ-12 = General Health Questionnaire.

*Monthly income based on 2007 analysis by Kookmin Bank, Seoul, South Korea (in approximate US$): high = ≥$5000; middle = ≥$2000 to <$5000; low = <$2000.

† Data missing for 2 patients.

‡ No patient met alcohol abuse or dependence criteria based on the *Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition*.[10]

§ Admisson for the evaluation and treatment of somatic symptoms in any department.

‖ Visits to any psychiatric or medical departments.

Twenty of the 22 enrolled patients (90.9%) completed the study; 2 patients were lost to follow-up (second and final visits, respectively). No patient discontinued due to AEs. All patients returned for ≥1 post baseline follow-up visit, yielding an LOCF ITT population of 22.

MEDICATION

The mean (SD) dosage of paroxetine was 19.5 (11.5) mg/d (range, 10–40 mg/d) during the study. Twelve patients (54.5%) were administered lorazepam or alprazolam concomitantly as needed for temporary control of mild anxiety, as deemed clinically appropriate by the clinical experience of the study physicians and the status of the patients.

PRIMARY END POINT

The mean total score on the PHQ-15 decreased significantly from baseline to the end of treatment (17.2 vs 4.3; $P = 0.001$). The mean reduction in PHQ-15 total score from baseline was 11.0%, 19.8%, 43.0%, and 75.0%, at weeks 1, 2, 4, and 8, respectively (**Figure**). No patient had an increase in PHQ-15 total score at the end of treatment compared with baseline.

SECONDARY END POINTS

The mean total score on the BDI from baseline to the end of treatment decreased significantly by 50.8% ($P < 0.001$), while the mean reduction in the score on the GHQ-12 (13.0%) was not significant.

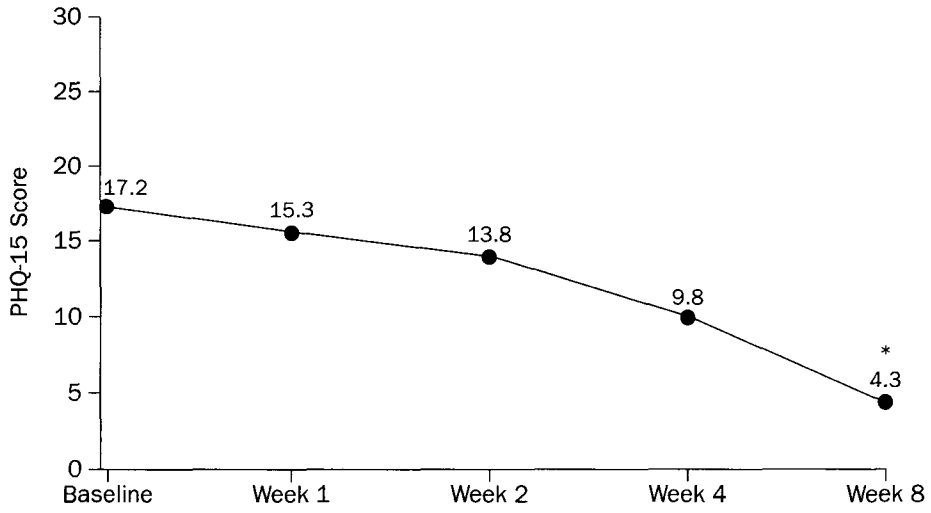

Figure. Change in mean Patient Health Questionnaire (PHQ-15) score from baseline to the end of treatment (week 8) in patients with undifferentiated somatoform disorder administered paroxetine 10 to 40 mg/d. *$P < 0.001$.

TOLERABILITY

All reported AEs were considered treatment-emergent AEs. The most common AEs reported during the 8-week treatment period were nausea and dry mouth (both, 5 [22.7%]) (**Table II**). No serious AEs occurred, and no patient withdrew from the study due to AEs. There were no clinically significant changes in laboratory or vital sign parameters during the study.

DISCUSSION

This is the first published study to assess the effect of paroxetine over 8 weeks in patients with USD. Paroxetine was associated with significantly reduced PHQ-15 total score from baseline to the end of treatment. The magnitude of improvement in PHQ-15 total score was 75.0%, with a decrease of 12.9 points from baseline to the end of treatment. Although conclusions are limited by the absence of a placebo arm in the present study, it should be noted that the magnitude of improvement on the PHQ-15 exceeded the typical placebo response rate (~30.0%) observed in clinical trials.[15]

Few studies have investigated the effectiveness of SSRIs for USD using change in PHQ-15 total score as a primary end point. A 12-week, randomized, double-blind, placebo-controlled trial[15] in 112 patients with multisomatoform disorder with comorbid anxiety or depression investigated the effect of venlafaxine extended-release (ER) (75–225 mg/d) on PHQ-15 score. Venlafaxine ER treatment yielded significantly better scores compared with placebo on the PHQ-15 pain subscale ($P = 0.03$); however, improvement in PHQ-15 total score was not significant compared with placebo. These data suggest that venlafaxine ER reduced the pain associated with multisomatoform disorder but did not improve the whole symptom domain.

In a series of studies,[16–19] paroxetine was reported to be effective for somatic symptoms associated with major depressive disorders, as determined by improvements on somatic and anxious symptom items of depression rating scales. Additionally, paroxetine was found to be effective for various somatic syndromes, including noncardiac chest pain,[20] fibromyalgia,[21] irritable bowel syndrome,[22] and rheumatoid arthritis.[23]

Table II. Treatment-emergent adverse events (AEs) reported in patients with undifferentiated somatoform disorder treated with paroxetine* 10 to 40 mg/d (N = 22).

AE	No. (%)
Nausea	5 (22.7)
Dry mouth	5 (22.7)
Somnolence	4 (18.2)
Sweating	3 (13.6)
Dizziness	3 (13.6)
Yawning	2 (9.1)
Headache	1 (4.5)

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A large literature review[24] of paroxetine use in physical illness with and without comorbid depression concluded that paroxetine may be particularly effective for treating somatic symptoms.

We found a significant reduction in total BDI scores from baseline to the end of treatment. The reduction in BDI scores might have been due to the effects of paroxetine on subsyndromal depressive symptoms. We excluded patients with current depressive and anxiety disorders from study participation to reduce the confounding factors of antidepressant/anxiolytic effects. Therefore, we posited that the improvement observed in somatic symptoms in the present study was not due solely to improvement in depressive or anxiety disorders. In accordance with this notion, there is copious evidence that antidepressants have a direct analgesic effect on somatic symptoms in patients with a variety of somatic syndromes.[5,25–27] Caution in interpreting the results of our trial is advised until more evidence-based clinical data are available.

Nevertheless, our study may at least contribute to psychopharmacologic treatment for patients with USD by providing a tolerability profile of paroxetine, although the open-label study design does not provide definite information about the efficacy of a certain medication for a specific disease due to the lack of a placebo group. Our study suggested that subsequent clinical trials for the treatment of USD are needed, because we observed some utility of paroxetine in treating USD. Further research into the pathophysiology of somatic syndromes and antidepressant mechanisms of action may clarify the interface between somatic syndromes and depressive/anxiety disorders with regard to their treatment responses. Finally, this study was the first trial of paroxetine for USD that suggested a preliminary possibility for control of USD. Additional clinical trials should expand our understanding of the utility of paroxetine and other antidepressants for somatic syndromes.

The mean dose of paroxetine used in this study (19.5 mg/d) was somewhat lower than the dose ranges approved in the treatment of major depressive disorder and anxiety disorders by the US Food and Drug Administration.[28] Research has supported using a low dose (~20 mg/d) of paroxetine in patients with somatic disorder.[24] However, a fixed-dose trial will be necessary to confirm our dose finding.

Common AEs seen in the present study were similar to those seen in randomized clinical trials of paroxetine IR.[19,29,30] Because no serious AEs were reported and no patients discontinued the study due to AEs, we concluded that paroxetine was well-tolerated in this patient population.

One of the chief limitations of this study was its open-label design; the lack of a placebo group makes conclusions about the efficacy of paroxetine for USD speculative. It is possible that the observed reductions in PHQ-15 scores reflect natural improvement in the course of somatic symptoms as opposed to a specific treatment effect of paroxetine. Nevertheless, this study was the first trial of paroxetine for USD; the data are encouraging and suggest that further research into the potential effectiveness of paroxetine and other SSRIs for somatic syndromes is warranted. Additionally, our study found that paroxetine had a favorable effect in this patient population.

A challenge to further research in patients with USD is the need for a large sample size to provide statistical power to detect a significant difference between treatment groups. Power analysis based on a placebo-controlled clinical trial found that >100 patients would be needed in each group (treatment and placebo) to provide 90% power to detect an effect size of 0.66.[31] In the present study, the sample size of 22 provided 80% power to detect an observed difference in PHQ-15 score of 12.9 points from baseline to end point, corresponding to an effect size of 0.63. Therefore, large-scale, placebo-controlled studies are needed to determine whether our effect size of 0.63 should be translated into clinical significance.

The PHQ-15 is prone to subjective rating bias because it is entirely self-administered. However, the self-report feature of the PHQ-15 makes it efficient to use in primary care settings. The PHQ-15 has been extensively used as an outcome measure of somatic symptom severity and has been validated in >6000 patients[11,25]; however, the correlation between clinical improvement and changes in the PHQ-15 has not been clearly established. An additional source of potential bias in the current study was the lack of a structured interview to establish the absence of exclusionary comorbid psychiatric disorders. We strictly assessed patients based on *DSM-IV* criteria, but we could not completely exclude the impact of hidden comorbid psychiatric symptoms on the positive effect of paroxetine on the outcome measures. An exclusion of comorbid psychiatric disorders was another limitation on the ability to generalize our results and on the subgroup analysis based on mood and anxiety symptoms, given the frequent mood and anxiety disorder comorbidity in somatic syndromes.

An additional limitation of the study was its short duration. Because somatic syndromes tend to be chronic and recurrent,[1] treatments must be associated with effectiveness in long-term studies to be applicable in real clinical practice settings.

CONCLUSION

This open-label pilot study found that paroxetine IR was generally well-tolerated and was associated with a significant decrease in the severity of somatic symptoms measured by PHQ-15 from baseline to the end of treatment. Large, double-blind, placebo-controlled, long-term studies are needed to assess the efficacy and safety of paroxetine IR in the treatment of patients with USD.

REFERENCES

1. Khan AA, Khan A, Harezlak J, et al. Somatic symptoms in primary care: Etiology and outcome. *Psychosomatics.* 2003;44:471–478.
2. Katon W, Lin E, Von Korff M, et al. Somatization: A spectrum of severity. *Am J Psychiatry.* 1991;148:34–40.
3. Smith GR Jr, Monson RA, Ray DC. Patients with multiple unexplained symptoms. Their characteristics, functional health, and health care utilization. *Arch Intern Med.* 1986;146:69–72.
4. Kroenke K. Patients presenting with somatic complaints: Epidemiology, psychiatric comorbidity and management. *Int J Methods Psychiatr Res.* 2003;12:34–43.
5. O'Malley PG, Jackson JL, Santoro J, et al. Antidepressant therapy for unexplained symptoms and symptom syndromes. *J Fam Pract.* 1999;48:980–990.

6. O'Malley PG, Balden E, Tomkins G, et al. Treatment of fibromyalgia with antidepressants: A meta-analysis. *J Gen Intern Med.* 2000;15:659–666.
7. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. *Cochrane Database Syst Rev.* 2007;4:CD005454.
8. Tomkins GE, Jackson JL, O'Malley PG, et al. Treatment of chronic headache with antidepressants: A meta-analysis. *Am J Med.* 2001;111:54–63.
9. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: The PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. *JAMA.* 1999;282:1737–1744.
10. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition.* Washington, DC: American Psychiatric Association Press; 1994.
11. Kroenke K, Spitzer RL, Williams JB. The PHQ-15: Validity of a new measure for evaluating the severity of somatic symptoms. *Psychosom Med.* 2002;64:258–266.
12. Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. *Arch Gen Psychiatry.* 1961;4:561–571.
13. Goldberg DP, Blackwell B. Psychiatric illness in general practice. A detailed study using a new method of case identification. *Br Med J.* 1970;1:439–443.
14. Rabkin JG, Markowitz JS, Ocepek-Welikson K, Wager SS. General versus systematic inquiry about emergent clinical events with SAFTEE: Implications for clinical research. *J Clin Psychopharmacol.* 1992;12:3–10.
15. Kroenke K, Messina N III, Benattia I, et al. Venlafaxine extended release in the short-term treatment of depressed and anxious primary care patients with multisomatoform disorder. *J Clin Psychiatry.* 2006;67:72–80.
16. De Wilde J, Spiers R, Mertens C, et al. A double-blind, comparative, multicentre study comparing paroxetine with fluoxetine in depressed patients. *Acta Psychiatr Scand.* 1993;87:141–145.
17. Fabre LF. A 6-week, double-blind trial of paroxetine, imipramine, and placebo in depressed outpatients. *J Clin Psychiatry.* 1992;53(Suppl):40–43.
18. Tignol J. A double-blind, randomized, fluoxetine-controlled, multicenter study of paroxetine in the treatment of depression. *J Clin Psychopharmacol.* 1993;13(Suppl 2):18S–22S.
19. Cohn JB, Crowder JE, Wilcox CS, Ryan PJ. A placebo- and imipramine-controlled study of paroxetine. *Psychopharmacol Bull.* 1990;26:185–189.
20. Doraiswamy PM, Varia I, Hellegers C, et al. A randomized controlled trial of paroxetine for noncardiac chest pain. *Psychopharmacol Bull.* 2006;39:15–24.
21. Patkar AA, Masand PS, Krulewicz S, et al. A randomized, controlled, trial of controlled release paroxetine in fibromyalgia. *Am J Med.* 2007;120:448–454.
22. Creed F, Fernandes L, Guthrie E, et al, for the North of England IBS Research Group. The cost-effectiveness of psychotherapy and paroxetine for severe irritable bowel syndrome. *Gastroenterology.* 2003;124:303–317.
23. Bird H, Broggini M. Paroxetine versus amitriptyline for treatment of depression associated with rheumatoid arthritis: A randomized, double blind, parallel group study. *J Rheumatol.* 2000;27:2791–2797.
24. Masand PS, Narasimhan M, Patkar AA. Paroxetine for somatic pain associated with physical illness: A review. *Prim Care Companion J Clin Psychiatry.* 2006;8:122–130.
25. Greco T, Eckert G, Kroenke K. The outcome of physical symptoms with treatment of depression. *J Gen Intern Med.* 2004;19:813–818.
26. Panerai AE, Monza G, Movilia P, et al. A randomized, within-patient, cross-over, placebo-controlled trial on the efficacy and tolerability of the tricyclic antidepressants chlorimipramine and nortriptyline in central pain. *Acta Neurol Scand.* 1990;82:34–38.

27. Onghena P, Van Houdenhove B. Antidepressant-induced analgesia in chronic non-malignant pain: A meta-analysis of 39 placebo-controlled studies. *Pain.* 1992;49:205–219.
28. GlaxoSmithKline. Paxil (paroxetine hydrochloride) Tablets and Oral Suspension: Prescribing information. http://us.gsk.com/products/assets/us_paxil.pdf. Accessed June 1, 2008.
29. Feighner JP, Boyer WF. Paroxetine in the treatment of depression: A comparison with imipramine and placebo. *J Clin Psychiatry.* 1992;53(Suppl):44–47.
30. Rickels K, Amsterdam J, Clary C, et al. The efficacy and safety of paroxetine compared with placebo in outpatients with major depression. *J Clin Psychiatry.* 1992;53(Suppl):30–32.
31. Cohen J. *Statistical Power Analysis for the Behavioral Sciences.* Hillsdale, NJ: L. Erlbaum Associates; 1988:8–14.

ADDRESS CORRESPONDENCE TO: Chi-Un Pae, MD, Department of Psychiatry, Kangnam St. Mary's Hospital, The Catholic University of Korea College of Medicine, Seoul 137-701, South Korea. E-mail: pae@catholic.ac.kr

or

Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, 2218 Elder Street, DUMC Box 3419, Durham, NC 27705. E-mail: chiun.pae@duke.edu