Comparing effects of citalopram with fluoxetine on sleep quality in patients with major depressive disorder

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Abstract. – BACKGROUND: Sleep disturbance is a common complaint in major depressive disorder (MDD) including impairment of both subjective and objective parameters. All antidepressants affect sleep architecture and quality.

AIM: This trial was designed to compare the effects of short-term use of citalopram with fluoxetine on sleep quality (SQ) of patients with MDD based on Diagnostic and Statistical Manual for Mental Disorders – Text Revision 4th edition (DSM-IV-TR) criteria.

PATIENTS AND METHODS: Patients who met the study criteria entered this open-label study. Sleep quality and depression severity were evaluated by using Pittsburgh Sleep Quality Index (PSQI) and Beck Depression Inventory-II (BDI-II), respectively. Patients could not have received any antidepressant for at least one month prior entering the study. Subjects were assigned to receive either fluoxetine or citalopram for 8 weeks. The relationships between SQ and severity of depression were also studied at weeks 4 and 8. Data was analyzed by using SPSS 11.5 version.

RESULTS: Nineteen patients received fluoxetine 20-40 mg/day and 21 received citalopram 20-40 mg/day. After 4 and 8 weeks treatment with both fluoxetine and citalopram, significant improvements in SQ were noted in both groups. However, no significant difference between the two groups was observed. Additionally, a significant and positive correlation between improvements in SQ and depression was noted after 8 weeks treatment with citalopram but not with fluoxetine.

CONCLUSIONS: This study noted that both citalopram and fluoxetine improved SQ in outpatients with MDD after 8 weeks without any significant difference between the 2 groups.

Key Words:
Citalopram, Fluoxetine, Depression, Sleep quality, Pittsburgh sleep quality index.

Introduction

Impaired sleep is very common in patients with major depression. While most patients complain of insomnia, a few patients complain of hypersomnia[1]. Polysomnographic (PSG) studies have shown disturbed sleep architecture and continuity in depressed patients. These disturbances include decreased slow-wave sleep (SWS), intermittent awakenings, prolonged sleep latency (SL), shortened Rapid Eye Movement (REM) latency (RL), and elevated REM density particularly during the first REM period[2]. Moreover, Nowell and Buysse[3] noted that subjective sleep assessments with Pittsburgh Sleep Quality Index (PSQI) have shown poorer sleep quality (SQ) in patients with Major Depressive Disorder (MDD) compared to patients suffering from other sleep disorders.

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Nearly all antidepressants including selective serotonin reuptake inhibitors (SSRIs) alter sleep architecture and quality. SSRIs are commonly associated with insomnia[4]. However, higher doses may cause daytime sleepiness[5]. PSG findings have shown decrease in sleep efficiency (SE) and total sleep time (TST), increase in the number of awakenings and SL in both healthy and depressed subjects during the treatment with SSRIs[6].

Fluoxetine is a potent suppressor of REM sleep with effects such as prolonged RL, decreased REM sleep and REM density[7] and its effects are long lasting due to its long half life[8]. Increasing the number of awakenings and stage shifts have also been reported in subjects with depression[9]. Administration of fluoxetine to healthy volunteers has been shown to result in reduced SE and increased REM and sleep latencies[10].

Citalopram has been noted to be associated with acute and sub-chronic day time sedation in normal controls[11]. Another study noted that citalopram could cause significant decrease in REM sleep, increase in RL and stage II Non-Rapid Eye Movements (NREM) sleep fraction in depressed patients[12].

Blank et al[13] noted that citalopram resulted in improving SQ in patients with depression and anxiety while Koponen et al[14] have reported that SQ was worsened in patients with Obsessive Compulsive Disorders (OCD).

In our practice we noted that many psychiatrists believe that citalopram causes less sleep disturbances when compared with fluoxetine. To our knowledge, there have not been any published data on the comparison between citalopram and fluoxetine for their effects on SQ in depressed patients. Therefore, this 8-week trial was designed to compare the effects of citalopram and fluoxetine on SQ of patients with a diagnosis of MDD based on Diagnostic and Statistical Manual for Mental Disorders-Text Revision 4th edition (DSM-IV-TR)[15] criteria.

Patients and Methods

Participants

Fifty outpatients with a diagnosis of MDD based on DSM-IV-TR criteria were selected from Roozbeh Hospital Clinic and from one psychiatrist private office. The inclusion criteria included patients between 18 to 55 years of age with a diagnosis of MDD who were not receiving any antidepressants for at least one month prior to the initiation of the study. The exclusion criteria included pregnancy and lactation, history of substance abuse during the past six months, severe medical conditions (cancer, cardiovascular and cerebrovascular diseases, thyroid disorders), other DSM-IV-TR Axis I disorders and mental retardation. Subjects who were working at night shifts for at least one month prior to the study were also excluded. All patients gave their signed informed consent. The study was approved by the Ethics Committee of the Faculty of Pharmacy at Tehran University of Medical Sciences (TUMS) and was conducted in accordance with the Declaration of Helsinki 1975 as revised in 2000.

Study Design

Each patient involved in this investigation was assessed for depression severity utilizing Beck Depression Inventory-II (BDI-II) and for SQ using PSQI at baseline. The patients were then assigned to receive either fluoxetine or citalopram (each 20-40 mg/day) for 8 weeks. Both drugs started at the dose of 10 mg/day. The dosages were gradually increased to 20 mg within 3 to 7 days of treatment and could be further increased to 40 mg/day if needed clinically per decision of the psychiatrist in charge. Changes in SQ and severity of depression were obtained at weeks 4 and 8 of the treatment using PSQI and BDI-II. It should be noted that the person who was evaluating patients' SQ was not aware of each patient medication.

Measures

The Pittsburgh Sleep Quality Index

Pittsburgh Sleep Quality Index is an effective tool for subjective assessment of sleep in adults over the past month. It is a self-report questionnaire that measures seven components of sleep. These seven areas include: subjective SQ (component 1), SL (component 2), sleep duration (component 3), habitual SE (component 4), sleep disturbances (component 5), using sleep medications (component 6), and daytime dysfunction (component 7). For each component, scores can be assigned from 0 to 3 with three reflecting the greatest problem. The PSQI has the reliability coefficient (Cronbach's alpha) of 0.83 for its seven components[16]. Originally, the scale is in English; however, in this study the Persian translation of the scale was used. The Persian version of PSQI has shown good psychometric properties (Cronbach's alpha of 0.82; test-retest reliability, r=0.88).

The Beck Depression Inventory-II

Beck Depression Inventory is a common self-administered scale for measuring severity of depression. This scale contains 21 items. Each consists of four statements describing symptom severity over the past week. The BDI-II has good psychometric properties (Cronbach's alpha of 0.92; test-retest reliability, r=0.93) in previous work[17]. The Persian translation of the scale was used in the present study.

Statistical Analysis

Analysis of data was performed utilizing SPSS 11.5 software (SPSS Inc., Chicago, IL, USA). General Linear Model (GLM), mixed repeated measures was used to detect changes in BDI-II and PSQI scores at weeks 0, 4 and 8 between the two groups. The test was also used to determine the differences within the two groups. Changes in the scores of the 16th item of the BDI-II (sleep item) and PSQI components were detected using Friedman test with Wilcoxon as post hoc test. Between groups differences were determined using Mann-Whitney test. The relation between improvement of SQ and depression severity was analyzed using bivariate correlation and Pearson correlation coefficient. A value of $p < 0.05$ was established as minimal level of statistical significance.

Results

Demographic Characteristics

Demographic characteristics of the patients in both groups are shown in Table I. Fifty patients met the inclusion criteria for the study. Ten patients (3 in citalopram and 7 in fluoxetine group) did not complete the study. The drop-outs were due to adverse drug reactions (gastrointestinal disturbances and somnolence) and 2 patients in the fluoxetine did not follow the study and we could not find them. Forty participants completed the study. Twenty one patients were prescribed citalopram (15 females and 6 males); the mean age ± standard deviation (SD) of these patients was 32.48 ± 10.18. Nineteen patients were prescribed fluoxetine (15 females and 4 males); the mean age ± SD of patients in this group was 28.89 ± 7.06. Results of two-independent sample T-test and Chi square test analyses showed no significant difference between the two groups with respect to age (F=2.65, $p = 0.21$) and gender ($p = 0.721$).

Depression Severity

The results of GLM test on BDI-II and PSQI scores for both treatments are shown in Table II. Two patients in the citalopram group received trifluoperazine 1 mg and risperidone 1 mg every night. In order to investigate the effects of trifluoperazine and risperidone on sleep scores the statistical analysis of the data was done once with and once without the data on these two patients. We should also not that all of the patients received benzodiazepines equivalent to 1 mg/day lorazepam due to restlessness and anxiety. Based on the statistical analysis, the results were not affected by exclusion of these patients. Analysis of the BDI-II scores using GLM showed no significant difference between the two treatments

Table I. Baseline demographic and clinical characteristics of the patients.

Variable	Citalopram (n = 21)	Fluoxetine (n = 19)	p (2-tailed)
Age			
Mean ± SD	32.48 ± 10.18	28.89 ± 7.06	0.21*
Age range	17-55	18-45	
Gender			
Female (n) %	(15) 71%	(15) 79%	0.721**
Marital status (n) %			
Married	(14) 67%	(8) 42%	
Never married	(6) 28%	(11) 58%	
Divorced	0	0	
Widowed	(1) 5%	0	
Depression severity			
BDI-II score (Mean ±S D)	23.24 ± 7.29	23.05 ± 10.31	0.95*
Sleep quality			
PSQI score (Mean ± SD)	10.62 ± 3.97	10.74 ± 4.40	0.93*

BDI: Beck Depression Inventory; PSQI: Pittsburgh Sleep Quality Index; SD: Standard deviation. *Two-independent Sample T-test; **χ^2 Square test.

Table II. Effects of fluoxetine and citalopram on sleep quality and depression severity.

Measures	Between groups (F; p)	Within groups (F; p)
Sleep Quality (Mixed Repeated Measures)	0.611; $p = 0.439$	8.904; $p = 0.001$
Depression Severity (Mixed Repeated Measures)	0.220; $p = 0.641$	31.108; $p < 0.001$

(F=0.220, $p = 0.641$). However, within group differences were significant for both drugs (F=31.108, $p < 0.001$) (Figure 1).

Sleep Quality

PSQI

At the end of week 8, citalopram and fluoxetine were equally effective in improving PSQI scores and again no significant difference was seen between the two drugs (F=0.611, $p = 0.439$) (Table II). However, within group differences were significant (F=8.904, $p = 0.001$) (Figure 2).

Beck Sleep Item (BSI)

The results of Friedman, Wilcoxon and Mann-Whitney tests on scores of BSI and PSQI components of the patients are shown in Table III. Results of Wilcoxon test showed that the difference in BSI scores was significant between weeks 4 and 8 (χ^2=19.118, $p = 0.001$). SQ was improved by the consumption of both drugs.

PSQI Components

There was a significant difference in component 1 (SQ) (χ^2=25.252, $p < 0.001$), component 2 (SL) (χ^2=18.206 $p = 0.004$), component 5 (sleep disturbances) (χ^2=17.288 $p = 0.001$),

component 6 (use of sleep medications) (χ^2=13.447 $p = 0.003$) and component 7 (daytime dysfunction) (χ^2=9.945 $p = 0.007$) scores between weeks 0 to 4. However, Mann-Whitney test results showed a significant difference only for component 6 between the two treatments at weeks 4 and 8 (Z= –3.382 $p = 0.001$) (Table III).

Correlation Between Improving SQ and depression

There was a significant and positive correlation between improving SQ and depression in citalopram group ($p = 0.007$, r=0.568). However, no such correlation was observed in the fluoxetine group ($p = 0.87$, r=0.403) (Table IV).

Discussions

Several mechanisms are involved in the effects of antidepressants on sleep architecture. For example, activation of 5-HT$_{1A}$ receptors may cause REM suppression[18]; stimulation of 5-HT$_2$ receptors may cause sleep fragmentation and, therefore, result in sleep disturbances[8]. Another observation is that 5-HT$_2$ blockers (nefazodone) are less sleep disruptive than SSRIs[7].
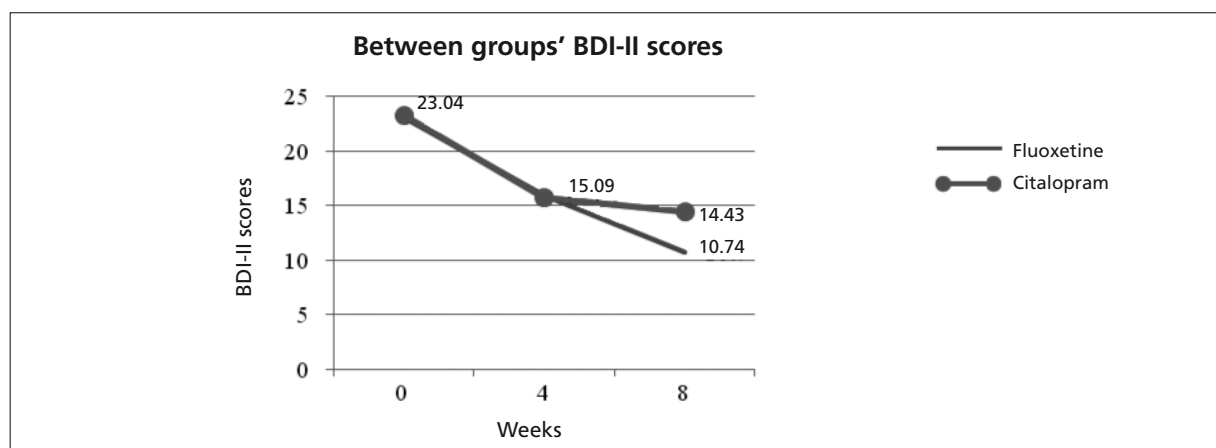
Figure 1. Effects of fluoxetine vs citalopram on depression severity (BDI-II) scores at weeks 0, 4 and 8.
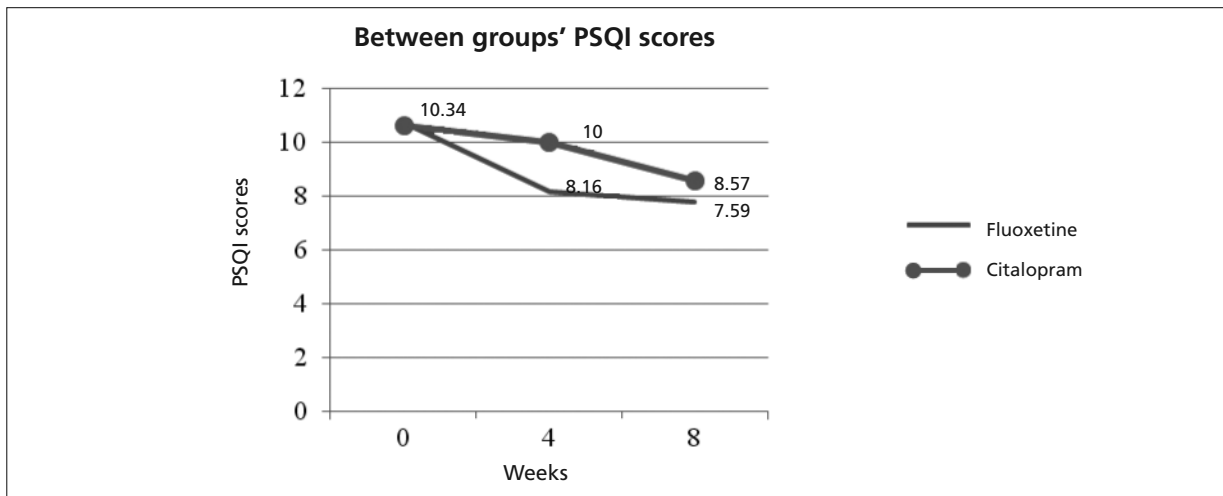
Figure 2. Effects of fluoxetine vs citalopram on sleep quality (PSQI scores) at weeks 0, 4 and 8.

In this work the effects of fluoxetine and citalopram on SQ of patients with major depression were evaluated. The effectiveness of both drugs in improving SQ was similar after 4 and 8 weeks of treatment based on PSQI and BSI scores. Similar results were obtained in studies comparing fluoxetine or citalopram with placebo. Dossenbach et al[19] observed SQ of 424 patients with MDD had improved according to Leeds Sleep Evaluation Questionnaire (LSEQ) and sleep items (items 4, 5 and 6) of Hamilton Depression Rating Scale (HAMD) scores. Moreover, Trivedi et al[20] reported improvement of scores of HAMD sleep items in 58 depressed patients on fluoxetine compared to placebo. Sleep quality has also shown improvement with citalopram comparing with placebo[12,21].

Table III. Effects of citalopram and fluoxetine on PSQI components and BSI.

Components (Com)	Friedman (χ^2; *p*)	Wilcoxon (Z; *p*)	Mann-Whitney (Z; *p*)
Com 1	25.252; $p < 0.001$	(w0-w4): -3.592; $p < 0.001$ (w4-8): -1.337; $p = 0.181$	0:-1.153; $p = 0.249$ 4:-1.070; $p = 0.284$ 8:-0.338; $p = 0.735$
Com 2	18.206; $p < 0.001$	(w0-w4): -2.874; $p = 0.004$ (w4-w8):-1.038; $p = 0.299$	0:-0.183; $p = 0.855$ 4:-1.048; $p = 0.29$ 8:-0.145; $p = 0.88$
Com 3	2.923; $p = 0.232$	(w0-w4):-1.512; $p = 0.131$ (w4-w8):-0.980; $p = 0.327$	0:-0.552; $p = 0.581$ 4:-0.200; $p = 0.841$ 8:-0.392; $p = 0.695$
Com 4	2.956; $p = 0.228$	(w0-w4):-0.655; $p = 0.512$ (w4-w8):-1.941; $p = 0.052$	0:-0.360; $p = 0.719$ 4:-0.518; $p = 0.604$ 8:-1.488; $p = 0.137$
Com 5	17.288; $p < 0.001$	(w0-w4):-3.266; $p = 0.001$ (w4-w8):0; $p = 1$	0:-0.722; $p = 0.470$ 4:-0.616; $p = 0.538$ 8:-1.475; $p = 0.140$
Com 6	13.477; $p = 0.001$	(w0-w4):-2.961; $p = 0.003$ (w4-w8):-0.577; $p = 0.564$	0:-0.141; $p = 0.888$ 4:-3.425; $p = 0.001$ 8:-3.115; $p = 0.002$
Com 7	9.945; $p = 0.007$	(w0-w4):-2.688; $p = 0.007$ (w4-w8):-0.224; $p = 0.823$	0:-0.522; $p = 0.602$ 4:-1.348; $p = 0.178$ 8:-1.001; $p = 0.317$
BSI	19.118; $p < 0.001$	(w0-w4):-1.191; $p = 0.234$ (w4-w8):-3.382; $p = 0.001$	0:-0.540; $p = 0.590$ 4:-0.716; $p = 0.474$ 8:-0.054; $p = 0.957$

BSI: Beck Sleep Item; W: Week:

Table IV. Correlation between depression severity and sleep quality.

Groups	r	p (2-tailed)
Citalopram	0.568	0.007
Fluoxetine	0.403	0.87

r: Pearson correlation; Co-efficient.

In another report, Aguglia et al[22] evaluated efficacy and safety of sertraline and fluoxetine in 108 depressed outpatients for 8 weeks. Significant improvement in LSEQ scores were observed for both groups. No significant difference was seen between the two groups. Similar findings were seen in another double-blind trial designed by Bennie et al[23]. However, sertraline was associated with fewer reports of difficulty in initiating sleep in this study when compared with fluoxetine.

Our study showed that SL could be improved with both fluoxetine and citalopram. No significant difference in SL was observed between the two groups. Fava et al[24] observed no significant differences between paroxetine, sretraline and fluoxetine with regard to worsening or improvement of insomnia. Sleep items of HAMD were used to evaluate sleep disturbance in patients with MDD. Dalery and Honig[25] showed that sleep disturbance has significantly improved based on scores of HAMD sleep items between weeks 4 and 6 with fluvoxamine compared to fluoxetine in 184 outpatients with MDD.

Lader et al[26] showed that escitalopram caused significant improvements on the 4th item of Montgomery-Asberg Depression Rating Scale (sleep item) scores compared to citalopram or placebo at weeks 1, 4, 6 and 8.

There is controversy in the results of different investigations that compared the effects of fluoxetine or citalopram with tricyclic antidepressants on sleep. De Ronchi et al[27] found no significant difference between amitriptyline and fluoxetine in 65 elderly depressed patients based on LSEQ scores after 10 weeks. Whereas Versiani et al[28] found significant improvement in scores of HAMD sleep items for amitriptyline after 8 weeks of treatment in 157 depressed patients.

Gillin et al[29] compared the effects of fluoxetine and nefazodone on sleep architecture of 43 depressed patients in a double-blind randomized 8-week treatment. The results showed significant improvement in clinician-rated as well as patient-rated sleep disturbance scores in patients on both drugs; however, nefazodone caused greater improvement than fluoxetine in most measures. In another clinical trial designed by Armitage et al[30], nefazodone caused significantly better improvement in sleep disturbances than fluoxetine did after 8 weeks. Winokur et al[31] compared the effects of fluoxetine and mirtazapine on sleep parameters in 19 depressed patients with insomnia. Both drugs showed significant improvement in SQ according to HAMD sleep items between weeks 2 and 8 but PSG findings suggested longer TST and better SE with mirtazapine. The difference between the results of Winokur et al[31] and the present investigation may be due to the fact that PSG (a more accurate way of evaluation) was not utilized in our study.

This study had some limitations. Benzodiazepines that may cause sedation were also allowed as needed for anxiety. However, to lessen the effects of these medications, patients were not given any doses below 1 mg/day of lorazepam or its equivalent.

Conclusions

This study suggests that fluoxetine and citalopram are similarly effective in improving SQ in outpatients with MDD. Improvements in both SQ and depression were correlated in the citalopram group but not in the fluoxetine group. More randomized controlled trials with larger sample sizes and/or more accurate ways of assessing SQ may be needed to confirm these findings.

Conflict of Interest

None declared.

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