

Switching to tianeptine in patients with antidepressant-induced sexual dysfunction

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Sexual side effects are frequent and are recently being considered as effects of antidepressant treatment. One method to improve the sexual dysfunction associated with the use of antidepressants is to change to another antidepressant. In the present work, the consequences of switching to tianeptine in patients with antidepressant-induced sexual dysfunction were studied. The study group comprised 23 patients with major depressive disorder who experienced antidepressant-induced sexual dysfunction. These antidepressants were stopped and switched to tianeptine (12.5 mg × 3/day). All patients were screened by using the clinical global impression-improvement scale (CGI-I), the Hamilton depression rating scale (HAM-D) and the Arizona sexual experience scale (ASEX) at the beginning of the study, and at weeks 4 and 8. No patient failed to tolerate 37.5 mg of tianeptine or to complete the study except for one patient becoming pregnant. Paired *t*-tests revealed a significant difference between baseline and week 4 or week 8 in scores on both the HAM-D and ASEX. At 8 weeks, six patients were rated as very much improved (CGI-I = 1) and ten patients were rated as much improved (CGI-I = 2). Thus, with a CGI-I score of 2 or less used to indicate a positive response, 72.7% of the patients were responders. *The results suggest that switching to tianeptine appears to be useful for alleviating sexual dysfunction caused by other antidepressants.* Copyright © 2003 John Wiley & Sons, Ltd.

KEY WORDS—tianeptine; sexual dysfunction; SSRI; depression; open-label study

INTRODUCTION

Sexual side effects including decreased libido, orgasm inhibition, erectile dysfunction and priapismus related to the use of antidepressant drugs are currently being strongly focused on because of their negative effects on patients' compliance to the antidepressant treatment. Sexual dysfunctions are common side effects reported with most of the available antidepressant drugs. Because of the nonspecific effects, old antidepressants, tricyclic antidepressants (TCA) and irreversible monoamine oxidase (MAO) inhibitors are thought to be responsible for almost all the sexual dysfunctions (Margolese and Assalian, 1996). Despite the limited number of available studies comparing the frequency of sexual side effects related to the use of different antidepressant drugs, selective serotonin reuptake inhibitors (SSRIs) have been thought to have

a greater tendency to cause these side effects. Studies not specifically designed to determine antidepressant-induced sexual side effects reported 5%–10% sexual dysfunction for patients using TCAs, while this rate was 10%–30% for patients using SSRI (Hsu and Shen, 1995; Shen and Hsu, 1995; Montejo-Gonzalez *et al.*, 1997). On the other hand, bupropion, not available in Turkey, and the reversible MAO inhibitor moclobemide were reported to have no sexual side effect (Gardner and Johnston, 1985; Philipp *et al.*, 1993). Clayton *et al.* (2002) have recently examined the prevalence of sexual side effects of the newer antidepressant drugs and found between 22% and 43%. It should be noted that the apparent incidence has been dependent upon the method of inquiry. One approach used to address antidepressant-induced sexual dysfunction is to change to another antidepressant (Shen *et al.*, 1999). Tianeptine is an antidepressant agent that, in contrast with classical TCA or SSRIs, enhances presynaptic serotonin uptake (Wilde and Benfield, 1995). Beyond its anxiolytic properties and favourable tolerability profile in terms of anticholinergic, sedative and cardiovascular adverse events, it seems not to bind any

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of the 5-HT receptors, α_1 and α_2 and muscarinic receptors which may be associated with antidepressant-induced sexual dysfunction (Vaugeois *et al.*, 1999).

Therefore, the present study aimed to investigate whether switching to tianeptine would be useful for alleviating sexual dysfunction caused by other antidepressants.

METHODS

A total of 23 married patients (18 males and 5 females) who had applied to the Firat University School of Medicine Department of Psychiatry and had been diagnosed with major depressive disorder according to DSM-IV criteria, had been treated with an antidepressant drug at least for 4 weeks and had experienced antidepressant-induced sexual dysfunction were enrolled in this study. All patients were heterosexual. *Seven of them were inpatients and the others were outpatients.* The mean age of the patients was 30.4 years (SD = 6.2; range = 23–44 years). All gave written informed consent after a complete description of the study. The study protocol was approved by the Local Ethics Committee of the Firat University School of Medicine.

To exclude organic sexual dysfunctions, the fasting glucose level, urine analysis, complete blood count, sex hormones and prolactin levels were obtained. Exclusion criteria were the following: being over 45 years old (no patient was already over 45 years; range 23–44 years); a concurrent medical illness affecting sexual function; being treated with a combination of an antidepressant and another psychotropic drug (except for benzodiazepines); previous or current alcohol and substance abuse or dependence; the presence of any endocrinological disorder; receiving treatment with hormones or any other drug capable of interfering with sexual relations; a history of pre-existing sexual dysfunction not related to antidepressant treatment but related to depression. The presence of antidepressant-induced sexual dysfunction was established by means of a semi-structured interview schedule designed for this purpose by the authors and that contained questions about the following: decreased libido, erectile dysfunction, delayed ejaculation and orgasm, inability to ejaculate and anorgasmia.

The antidepressive drugs that the patients received and then developed sexual dysfunction were clomipramine ($n = 8$, 150–225 mg/day), paroxetine ($n = 7$, 40–60 mg/day), sertraline ($n = 4$, 100–200 mg/day) and fluoxetine ($n = 4$, 20–80 mg/day). These antidepressants were stopped and switched to tianeptine

(12.5 mg \times 3/day) after a 2-week (4-week for fluoxetine) washout period. No concomitant psychotropic medication except for benzodiazepines or formal behaviour therapy was administered.

All subjects were evaluated by a semi-structured questionnaire form which was arranged by the authors in accordance with the clinical experience and available information sources to determine sociodemographical and clinical characteristics. All patients were screened by using the Hamilton depression rating (HAM-D) (Hamilton, 1960) and the clinical global impression-improvement (CGI-I) scales at weeks 4 and 8. Additionally, changes in general sexual functions were examined using the Arizona sexual experience scale (ASEX) (McGahuey *et al.*, 1997). This scale includes five items with a score ranging from 1 to 6.

Data were statistically analysed using the paired *t*-test in SPSS Microsoft Windows 9.05.

RESULTS

Prior to switching to tianeptine, the most frequently experienced sexual dysfunction associated with the use of antidepressants was decreased libido in 11 patients (47.8%; four patients receiving paroxetine, four patients receiving clomipramine, two patients receiving fluoxetine and one patient receiving sertraline), followed by erectile dysfunction in seven male patients (38.9% of the males; three patients receiving paroxetine, two patients receiving clomipramine and two patients receiving sertraline), delay of orgasm or ejaculation in five patients (21.7%; two patients receiving clomipramine, two patients receiving paroxetine and one patient receiving fluoxetine), anorgasmia or no ejaculation in three patients (13.1%; one patient receiving clomipramine, one patient receiving sertraline and one patient receiving fluoxetine), and lubrication disorder in one patient receiving clomipramine (20.0% of females) (Table 1). The proportion of patients who reported sexual dysfunction spontaneously was low ($n = 4$, 17.4%) when compared with those who were asked direct questions according to the sexual dysfunction questionnaire designed by authors ($n = 19$, 82.6%). All of the spontaneously self-reporting patients were inpatients.

Of the patients who switched to tianeptine, only one withdrew from the study after becoming pregnant. For the remaining 22 patients, the mean HAM-D score was 17.4 (SD = 3.7) at baseline, 14.2 (SD = 3.2) at the evaluation of week 4, and 11.1 (SD = 2.6) at the evaluation of week 8. Paired *t*-tests revealed a significant difference between baseline and week 4

Table 1. Demographic data and some characteristics of the patient group

Demographic characteristics	
Total patients: 23	
Sex: 18 males (78.3%); 5 females (21.7%)	
Age: 30.4 ± 6.2 (range 23–44)	
Status of admission: Inpatients 7 (30.4%); outpatients 16 (69.6%)	
Education: 8 (34.8%) from first school; 7 (30.4%) from elementary school; 4 (17.4%) from high school and university and 3 (17.4%) uneducated	
Type of sexual dysfunction before enrolled into study	
Decreased libido	
Paroxetine	(n = 4)
Clomipramine	(n = 3)
Fluoxetine	(n = 2)
Sertraline	(n = 1)
Erectile dysfunction	
Paroxetine	(n = 3)
Clomipramine	(n = 2)
Sertraline	(n = 2)
Delayed orgasm	
Paroxetine	(n = 2)
Clomipramine	(n = 2)
Fluoxetine	(n = 1)
Anorgasmia	
Sertraline	(n = 1)
Clomipramine	(n = 1)
Fluoxetine	(n = 1)
Lubrication disorder	
Clomipramine	(n = 1)

($p < 0.05$) or week 8 ($p < 0.01$) in scores on the HAM-D. The mean ASEX score was 21.9 (SD = 3.6) at baseline, 17.2 (SD = 3.1) at the evaluation of week 4 and 12.4 (SD = 2.7) at the evaluation of week 8. Paired *t*-tests revealed a significant difference between baseline and week 4 ($p < 0.05$) or week 8 ($p < 0.01$) in scores on the ASEX (Table 2).

There was no correlation between a decrease in HAM-D scores and that in ASEX scores ($r = 0.12$, $p > 0.05$). At 8 weeks, when CGI was used to measure overall response to treatment, six patients (27.3%) (mean ASEX score reduced from 22.8 ± 3.2 to 8.8 ± 2.1) were rated as very much improved (CGI-I = 1), and ten patients (45.4%) (mean ASEX score reduced from 20.7 ± 4.1 to 12.6 ± 3.6) were rated as much improved (CGI-I = 2). Thus, using a CGI-I

Table 2. HAM-D, ASEX and CGI-I scale scores during treatment

Weeks	HAM-D	ASEX	CGI-I
0	17.4 ± 3.7	21.9 ± 3.6	—
4	14.2 ± 3.2 ^a	17.2 ± 3.1 ^a	3.1 ± 0.9
8	11.1 ± 2.6 ^b	12.4 ± 2.7 ^b	2.1 ± 0.8 ^b

Paired *t*-test (statistical significance of change according to baseline) was used; ^a $p < 0.05$; ^b $p < 0.01$.

change score of 2 or less to indicate a positive response, 72.7% of the patients were responders.

No patient failed to complete the study owing to side effects. However, one patient discontinued because of becoming pregnant. Tianeptine was well tolerated. There were 16 reports of side effects from ten patients. The most frequently reported side effects were nausea ($n = 5$) and dry mouth ($n = 4$).

DISCUSSION

This prospective study demonstrates that tianeptine produced a great improvement in patients experiencing various sexual dysfunctions caused by antidepressant use.

In this study, only 17.4% of the patients spontaneously self-reported sexual side effects of antidepressant drugs, while the remaining 82.6% required persistent detailed inquiry to report any experienced sexual side effects. Monteiro *et al.* (1987) mentioned that sexual side effects could be easily missed without a structured interview. All of the spontaneously self-reporting patients were inpatients. The finding of a higher proportion of inpatients' spontaneous self-report about their sexual dysfunction may result from encouragement from the closer relation with the physicians during hospital treatment.

To improve sexual dysfunction associated with the use of antidepressants, several methods have been proposed including waiting for spontaneous remission over time, reducing the dose of antidepressants, changing to another antidepressant, and adding pharmacological antidotes to address the sexual dysfunction (Shen *et al.*, 1999).

It has been reported that an enhanced dopaminergic transmission may play a role in the antidepressant efficacy of tianeptine, although it is devoid of amphetamine-like activity and does not interact with the neuronal carrier of dopamine. An indirect facilitating action on dopaminergic transmission in the brain is demonstrated by the reversion of its stimulant locomotor effects by the D₂ receptor antagonist haloperidol (Vaugeois *et al.*, 1999). In a multicentre study (Montejo-Gonzalez *et al.*, 1997), a great improvement was noted in patients who switched to amineptine because of experiencing SSRI-induced sexual dysfunction. Tianeptine's chemical structure resembles that of the older antidepressant amineptine (Vaugeois *et al.*, 1999). On the other hand, serotonin seems to play an important role in the occurrence of sexual dysfunction and this effect of serotonin may be due to inhibiting the activity of dopamine in the central nervous system and increasing the release of prolactin

is well documented (Remy, 1986). Tianeptine is an antidepressant drug which differs from conventional antidepressants in its unique feature of increasing 5-HT uptake in the synaptic cleft (Wilde and Benfield, 1995). On the other hand, the peripheral blockade of alpha-adrenergic receptors impairs the sexual excitation process (Sorscher and Dilsaver, 1986). However, the increased responsiveness of alpha₁-adrenergic receptors following repeated administration of tianeptine is likely to result from the overall reduction in the serotonergic neurotransmission induced by this drug (Rogoz *et al.*, 2001). These different properties of tianeptine may account for its usefulness in antidepressant-induced sexual dysfunctions caused by other antidepressants.

The findings should be considered as preliminary and subject to some limitations. First of all, the sample is small. *In addition, the present study was an open label study and therefore had the restrictions of such a study design. Thus, double blind studies are needed in order to evaluate the findings of this study. Furthermore, the fact that no control group was used makes it difficult to eliminate the influence of the depression itself on sexual dysfunction.* Actually, in the present study, no correlation was found between the decrease in HAM-D scores and that in ASEX scores. Therefore, it appears that the improvements in sexual functions are independent of the decrease in depressive state.

In conclusion, the results of our study indicate that switching to tianeptine may provide great improvements in patients with antidepressant-induced sexual dysfunction. However, controlled studies to ascertain the activity of this drug in relation to sexual function are required.

REFERENCES

- Clayton AH, Pradko JF, Croft HA, *et al.* 2002. Prevalence of sexual dysfunction among newer antidepressants. *J Clin Psychiatry* **63**: 357–366.
- Gardner EA, Johnston A. 1985. Bupropion: an antidepressant without sexual pathophysiological action. *J Clin Psychopharmacol* **5**: 24–29.
- Hamilton M. 1960. A rating scale for depression. *J Neurol Neurosurg Psychiatry* **23**: 56–62.
- Hsu JH, Shen WW. 1995. Male sexual side effects associated with antidepressants: a descriptive clinical study of 32 patients. *Int J Psychiatry Med* **25**: 191–201.
- Margolese HC, Assalian P. 1996. Sexual side effects of antidepressants: a review. *J Sex Marital Ther* **22**: 209–217.
- McGahuey CA, Gelenberg AJ, Laukes CA, *et al.* 1997. The Arizona Sexual Experience Scale: validity and reliability. *Proceedings of the Annual Meeting of the American Psychiatric Association, San Diego, May 17–22*. American Psychiatric Press: Washington DC.
- Monteiro WO, Noshirvani HF, Marks IM, Lelliott PT. 1987. Anorgasmia from clomipramine in obsessive-compulsive disorder: a controlled trial. *Br J Psychiatry* **151**: 107–112.
- Montejo-Gonzalez AL, Liorca G, Izoquerdo JA, *et al.* 1997. SSRI-induced sexual dysfunction: fluoxetine, paroxetine, sertraline and fluvoxamine in a prospective, multicenter, and descriptive clinical study of 344 patients. *J Sex Marital Ther* **23**: 176–193.
- Philipp MR, Kohlen R, Benkert O. 1993. A comparison study of moclobemide and doxepine in major depression with special reference to effects on sexual dysfunction. *Int Clin Psychopharmacol* **7**: 123–132.
- Remy L. 1986. The effect of selective 5HT re-uptake inhibitors on 5-methoxy-N, N-dimethyltryptamine induced ejaculation in the rat. *Br J Pharmacol* **87**: 639–648.
- Rogoz Z, Skuza G, Dlaboga D, Maj J, Dziedzicka-Wasylewska M. 2001. Effect of repeated treatment with tianeptine and fluoxetine on the central α_1 adrenergic system. *Neuropharmacology* **41**: 360–368.
- Shen WW, Hsu JH. 1995. Female sexual side effects associated with selective serotonin reuptake inhibitors: a descriptive clinical study of 33 patients. *Int J Psychiatry Med* **25**: 239–248.
- Shen WW, Urosevich Z, Clayton DO. 1999. Sildenafil in the treatment of female sexual dysfunction induced by selective serotonin reuptake inhibitors. *J Reprod Med* **44**: 535–542.
- Sorscher SM, Dilsaver SC. 1986. Antidepressant-induced sexual dysfunction in men: due to cholinergic blockade? *J Clin Psychopharmacol* **6**: 53–55.
- Vaugeois JM, Corera AT, Deslandes A, Costentin J. 1999. Although chemically related to amineptine, the antidepressant tianeptine is not a dopamine uptake inhibitor. *Pharmacol Biochem Behav* **63**: 285–290.
- Wilde MI, Benfield P. 1995. Tianeptine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depression and coexisting anxiety and depression. *Drugs* **49**: 411–439.