12 Weeks, Non-Comparative Study of the Safety, Efficacy and Toleration of Sertraline in the Treatment of Obsessive Compulsive Disorder

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31 patients have been enrolled in this study. They were 27 females (87.1%) and 4 males (12.9%) and their ages ranged between 21 and 47 years. They all suffered from obsessive compulsive disorder (OCD) according to the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), the obsessive compulsive rating (NIMH-OC) and the clinical global impression illness severity score (CGI). The admissible screening scores were 25 or greater for the Y-BOCS and 9 or greater on the NIMH-OC scale and 5 or greater on the CGI scale. All patients were subjected to one week wash-out period before starting the active medication. At patients were subjected to one week wash-out period before starting the active medication. At baseline assessment, each patient must have a total score of 20 or greater on the Y-BOCS and 7 or greater on the NIMH-OC and 4 or greater on CGI to be randomised for active medication phase. Sertraline was given as 50 mg/day then titrated to 100 mg/day and 150 mg/day at the end of week 4 and week 8 respectively if the response was not satisfactory. Assessment was made by the Y-BOCS, NIMH-OC and CGI scales, which were considered as the primary efficacy variables. The Montgomery Asberg Depression Rating Scale (MADRS) and the Hamilton Anxiety Scale (HAM-A) were used to measure secondary variables. The HAM-A Scale was performed at screening, baseline and at the end of weeks 4,8 and 12. There were a significant decline in the mean scores of Y-BOCS ($p<0.01$) starting from the second week of treatment that recorded 28.9, 11.2 and 5 while their scores before treatment were 31.5, 10.6 and 6.0 respectively. The scores continued to decline significantly ($p<0.001$) to reach 15.7, 6.6 and 3.5 at the end of treatment. Sertraline was well tolerated by 20 patients (64.5%) and 11 patients (35.5%) expressed mild adverse events. Sertraline was proved to be effective and well tolerated in the treatment of OCD with or without comorbid depression.

(Egypt.J. Psychiat., 1999, 22: 239 -246).

INTRODUCTION

OCD is a common and disabling condition (Myers et al, 1984, Rasmussen and Eisen, 1988 and Reynold et al 1992). The familial nature of OCD has been observed since many years and some studies have provided limited evidence for the importance of genetic factors in the manifestations of obsessive compulsive disorder (Pauls, 1992). In addition to these familial data, it is found that OCD is a common neurobiological condition (Lydiard, 1994). Also there is a strong pharmacological evidence concerning the serotonergic system and the well established efficacy of potent serotonin reuptake inhibitor in the treatment of OCD(Lydiard, 1994).

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Sertraline hydrochloride is a potent ad highly selective inhibitor of serotonin reuptake in the central nervous system (Reimherr et al, 1990). It is a new naphthylamine derivative, which is in its usual clinical doses devoid of cardiovascular and anticholinergic activity (Greist et al 1995).

The half life of sertraline is long enough (25 hours) to permit once daily administration but short enough that equilibration of plasma levels occurs within one week. This property and the absence of a clinically active metabolite may give sertraline an advantage especially among the elderly (Ikasha and Asuad 1994 and Doogan and Gaillard, 1988).

AIM OF THE WORK

To evaluate the efficacy, safety and toleration of sertraline in out patient suffering from obsessive compulsive disorders.

SUBJECTS and METHODS

1) Patients

The study was conducted on 31 males and females, older than 18 years and suffering from OCD. The patients were included if they met the DSM-III-R criteria (1987) for obsessive compulsive disorder. In screening admissible scores were 25 or greater for the Yale-Brown scale, 9 or greater for NIMH-OC and 5 or greater on CGI severity scale. Patients with baseline total score of 20 or greater on the Y-BOCS and 7 or greater on the NIMH-OC and 4 or greater on the CGI illness severity score for obsessive-compulsive disorder. Each patient provided his/her informed consent prior to study entry. On the other hand patients who were pregnant, lactating, patients with any primary psychiatric diagnosis other than OCD, patients who represented a significant suicide risk, patients taking psychotropic medications (with the exception of short acting benzodiazepines or chloral hydrate for insomnia only when indicated during the study) and patients with history of drug or alcohol dependence were all excluded from the study.

2- Study Design

The study was 13 weeks, non-comparative, assessing the safety, efficacy and toleration of sertraline in the treatment of OCD. A one week single blind placebo wash-out period was scheduled following the screening phase, then sertraline 50 mg/day was administered for 4 weeks. The dose may be increased to 100 mg/day sertraline (week 4) if the patient's clinical response has not been satisfactory. If after another 4 weeks (week 8) the response remain n unsatisfactory, a second increase of dosage to 150 mg/ day is allowed. No further increase in dosage was allowed above 150mg.

Evaluation was made at screening baseline and at the end of weeks 2, 4, 6, 8 and 12.

3- Drug

After initial screening, patients had a single-blind placebo wash-out period of 7 days (14 days in case of an active medication with long half-life as in the case of monoamine oxidase inhibitor "MAOI").

Suitable subjects received initially 50 mg sertraline once daily. The dose could be titrated to 100 then to 150 mg once/ day, at the end of weeks 4 and 8 respectively, if clinically indicated.

The total duration of active treatment was 12 weeks.

4- Efficacy Measures

The psychiatric rating scales used to evaluate efficacy were the Y-BOCS, The NIMH-OC, the CGI severity and improvement, MADRS for depression and HAM-A. These scales were completed at screening, baseline and at each visit till the end point except the HAM-A which was applied at screening, baseline, visit 3 (end of week 4), visit 5 (end of week 8) and visit 6(end of week 12).

5- Cncomitant Medication and Conditions

Concomitant medication taken by the patient and any intercurrent illness occurred prior to or during the study were recorded at each visit.

RESULTS

A total of 31 patients were included into this study. Their ages ranged from 21-47 years with a mean of 33.5 years. Females were more encountered in this study, being represented by 27 patients (87.1%) and males represented by only 4 patients (12.9%). They all suffered from OCD according to DSM III-R criteria for OCD. 10 patients had a history of major depression (32.3%) as a concomitant disease.

The duration of OCD ranged between 8 months and 20 years as noted by the patient nd 2 months to 15 years since diagnosed. (table 1).

Table 1
Duration of OCD Amongst Patients

	As noted by patient	Since diagnosed
Range	8 months - 20 years	2 months - 15 years
Mean (year)	4.9	4.1
SD (year)	5.5	4.6

Clinical Efficacy

Through-out the study period the favorable response of sertraline was achieved on variable dose levels, where 5 patients (16.7%) responded to 50 mg, 9 patients (30%) responded to 100 mg and 16 patients (53.3%) responded to 150 mg.

Regarding the efficacy of the study drug on Y-BOCS, it was noticed that before sertraline therapy (baseline visit) the mean score was 31.5 then it was significantly ($P<0.01$) declined to 28.9 at visit 2 (week 2). The improvement was continued till the end of the study and the mean value of the Y-BOCS dropped significantly ($P<0.001$) to 15.7 after 12 weeks of treatment (Fig.1). Similar findings were observed for NIMH-OC, as after 2 weeks of treatment the significant changes ($p<0.01$) reached a mean value of 10.6 compared to baseline 11.2. The improvement of NIMH-OC continued significantly ($p<0.001$) to reach 6.6 after 12 weeks of treatment (Fig. 2).

The results revealed that the efficacy of the sertraline which reflected on CGI was 6.0 before starting treatment then it was significantly ($p<0.05$) im-

Table 2
Side Effects Occurred During the Study

Side effects*	Patients (%)
Nausea	7 (22.6%)
Insomnia	3 (9.6%)
Tremors	2 (6.4%)
Hypersmnia	6 (19.4%)
Night mares	1 (3.2%)
Somnolence	1 (3.2%)
Anorexia	1 (3.2%)
Agitation.	1 (3.2%)

* More than one side effect could be reported in one patient

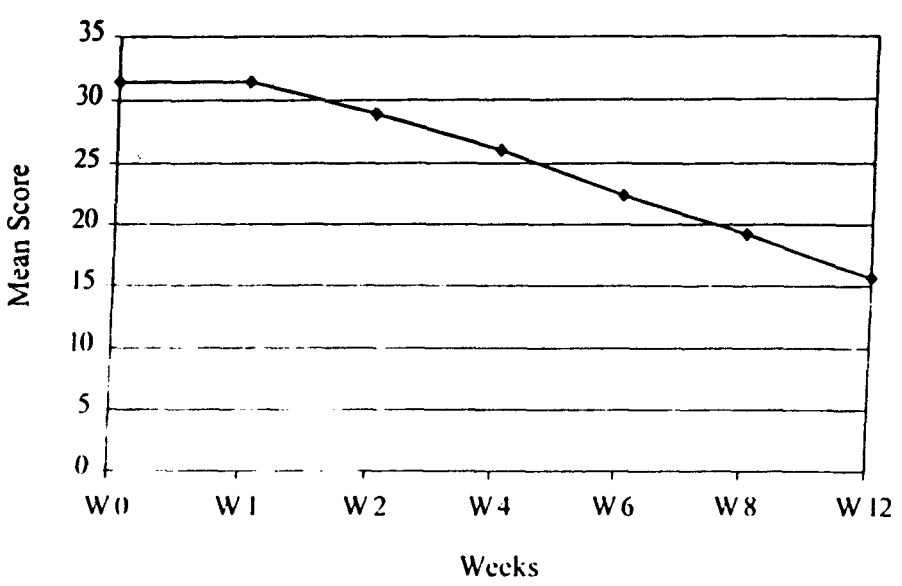

Figure 1

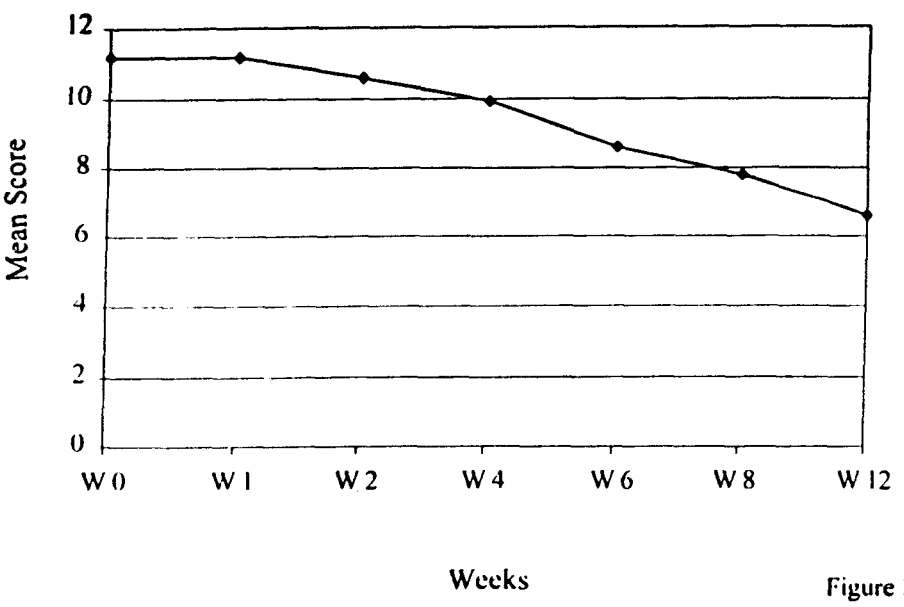

Figure 2

Effect of Sertraline on CGI

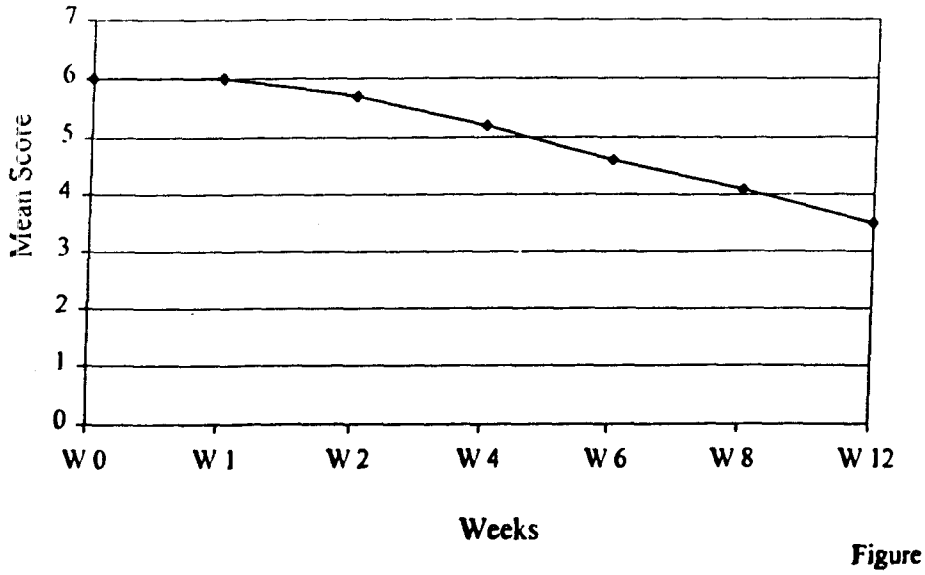

Figure 3

Effect of Sertraline on MADRS

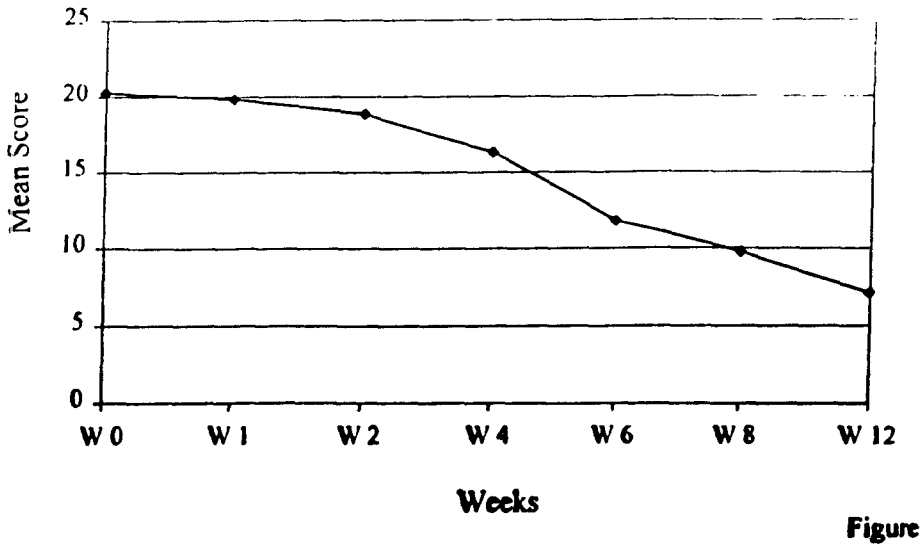

Figure 4

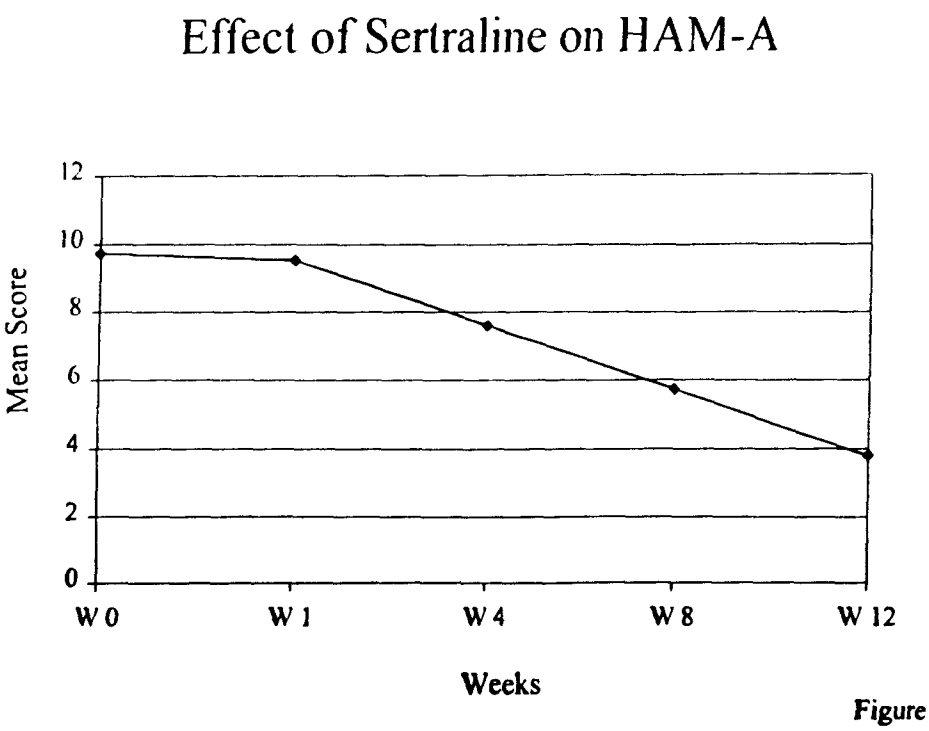

Figure 5

provement in MADRS started after 4 weeks of treatment. The mean value of MADRS was 19.9 at baseline then decreased significantly 9p<0.001) to 7.1 at the end of the treatment period (Fig. 4).

HAM-A scale, recorded 9.7 at baseline then it decreased significantly (p<0.001) to 3.8 at the end of treatment (Fig. 5).

Drop out:

Mild to moderate side effects were reported in 11 patients (35.5%) which did not necessitate discontinuation of treatment (table 2). Only one patients did not complete the study, as he was lost to follow-up.

DISCUSSION

OCD is an anxiety disorder that was once viewed as rare and very difficult to treat. Controlled trials demonstrating the efficacy of pharmacologic treatment in OCD did not appear until the 1980s. The availability of potentially effective treatments, combined with the awareness of prevalence rates for the disorder that are higher than previously believed, led to considerable interest in OCD. Also it was observed that drugs that act by inhibiting serotonin uptake, such as clomipramine, fluvoxamine, fluoxetine and sertraline were effective in treating symptoms of OCD. Also it was observed that drugs that act by inhibiting secretion uptake, such as clomipramine, fluvoxamine, fluoxetine and sertraline were effective in treating symptoms of OCD(Perse et al, 1988, Chouinard et al, 1990, Deveagh et al 1991). On the other hand because of the chronicity character of the OCD and because of requiring long-term treatment the pharmacological management of this disorder required the use of agents which are not

only efficacious and well tolerated, but also are unlikely to cause pharmacokinetic drugdrug interactions with concomitant administered medications which the patient is receiving or may receive in the future. The SSRIs are very potential for drug-drug interactions via the inhibition of cytochrome P-450 isoenzyme, on the contrast sertraline as one of the SSRIs was not known to produce clinical inhibition of any iso enzymes (Lane 1996).

The finding obtained in the present study are supportive to a previous trial with the same suffering from OCD as shown by the significant improvement in scores of Y-BOCS, NIMH-OC scale, as well as CGI (severity and improvement scales) (Ikasha et al 1994).

In addition, it was also observed that response in OCD is more gradual and delayed relative to major depression, however, significant improvement was observed (as shown by Y-BOCS) from the early assessment which indicates a relatively rapid onset of action. The maximum improvement occurred by the end of the study indicating that full therapeutic response may take several weeks to be achieved (Ikasha et al, 1994).

Also this study proved that other associated anxiety and depressive symptoms were relieved by sertraline.

An additional point which is very important, that the drug anti-obsessional effect is not related to its anti-depressant effect and this was proved by Okasha (Okasha and Assad, 1994), while it is not consistent with what has been previously shown by other researchers as Thosen et al. (1980) (Thoren et al, 1980) and Mark et al. (1982) (Marks et al 1980) who found that the level of depression is a good predictor for drug response in OCD patients.

It was also found that sertraline is well tolerated, as adverse events repoted during this study were mild to moderate in severity and mainly related to the gastrointestinal tract and sleep disturbances.

Conclusion

Sertraline proved to be effective, safe and well tolerated in the treatment of OCD, with or without comorid depression.

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دراسة حرة لتقييم مدى كفاءة وأمان عقار السرترالين في علاج الوسواس القهرى

تناولت الدراسة ٣١ مريضا تتراوح أعمارهم بين ٢١ و ٤٧ سنة ويعانون من الوسواس القهرى، وقد تم علاجهم بعقار السرترالين بجرعة تراوحت من ٥٠ ملليجرام إلى ١٥٠ ملليجرام جرعة واحدة يوميا.

وقد تم تقييم المرضى عن طريق مقاييس بيل-براون للوسواس القهرى (Y-BOCS) وهاميلتون للقلق والإكتئاب وكذلك بإستخدام مقياس التقييم الاكلينيكى الكلى CGI وغيره من الإختبارات الأخرى وقد بينت النتائج تحسنا إيجابيا كما أثبتت النتائج شدة تحمل المرضى للعقار.