Sertraline in OCD:
A Twelve Week, Non-Comparative Study of the Safety, Efficacy and Toleration of Sertraline in the Treatment of Obsessive Compulsive Disorder with or without Concurrent Depression in Outpatients

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Abstract:
30 patients of both sexes fulfilling the DSM-IV criteria for obsessive compulsive disorder with a duration of at least 6 months were enrolled into this study. Patients were selected from the Institute of Psychiatry, Ain-Shams University, Cairo. They were 13 males and 17 females. Their ages ranged from 21 to 42 years (mean age 31.76 +/- 4.85 years). After a washout period, in case of previous treatment with antidepressants, patients were given sertraline 50 mg tablets once daily. Doses were increased when required every 2 weeks up to a maximum dose of 200 mg. Assessments were done at screening, baseline, weeks 2, 4, 6, 8, and 12 using Y-BOC Scale, NIMH-OC Scale, CGI, MADRS, HAM-A Scale. Significant improvements were achieved as measured by all OC scales. Side effects were reported in 8 patients (27%) in the form of nausea, vomiting, irritability and insomnia which necessitated discontinuation in only two patients. Sertraline was found to be effective and well tolerated for the treatment of patients with OC disorders with or without concomitant depression.

Introduction

Obsessive Compulsive disorder (OCD) has recently undergone a dramatic change in status. It is no more considered as a rare example of neuroses, as it now occupies a central position in contemporary psychiatry.

Several reasons for this "renaissance in interest" could be described. The first of these, is the increased community awareness of the disorder. Results from the National Institute of Mental Health Epidemiological Catchment Area (ECA) survey indicated that the life time prevalence of the disorder was 2.5% making it the fourth most common psychiatric disorder in the United States after substance abuse, affective disorders and phobias (Myers et al., 1984; Robins et al., 1984; Kanno et al., 1988; Regier et al., 1993). Secondly, with the recent advances in management, beneficial treatment is now possible in 60-80% of patients (Perry, 1988; Goodman et al., 1992). Thirdly, findings from a number of neuroimaging and neuro-biochemical investigations have stimulated interest in understanding the biological substrates of OCD. Finally, increased knowledge of the disorder and its treatment has fostered greater public awareness, thus increasing the number of patients asking for therapy (Ricciardi, 1993).

There are several lines of evidence that suggest the presence of a specific serotonin metabolism abnormality in OCD. As early as 1968, Renyeh de Voxnie reported that the tricyclic antidepressant "clomipramine", also a potent inhibitor of serotonin reuptake, reduces obsessional symptoms, irre-
spective of the presence of depression. It is to be noted here that about two thirds of patients with OCD have a lifetime history of major depression and one third satisfies criteria for major depression at the time of first evaluation (Rasmussen and Eisen, 1992). Clomipramine has been widely used to treat OCD, but being "non selective", it has undesirable side effects including considerable anti-cholinergic activity.

Newly administered slow serotonin reuptake inhibitors SSRI, especially fluoxetine, fluvoxamine and sertraline, have been shown to be effective anti-obessional, as well as anti-depressant agents (Hyem and Koe, 1988).

Sertraline has been demonstrated to be an effective anti-depressant in several clinical controlled trials (Murdoch and McTavish, 1992). It has also been shown in other double blind placebo controlled studies, for non-depressed OCD patients, to reduce both the obsessive and compulsive core symptoms of OCD ("Chouinard et al., 1990; Greist et al., 1992; Greist et al., 1992 b).

Aim of the Work
The primary aim of this study is to evaluate the efficacy, safety and tolerability of Sertraline in a sample of Egyptian outpatients with obsessive compulsive disorder, with or without concomitant depression.

Study Description, Subjects and Methods
The study was an open non comparative one. After initial screening, patients had a single blind washout period of at least one week (14 days in case of previous treatment with monoamine oxidase inhibitors or other psychotropic drugs with long half life).

The duration of the study was 12 weeks of sertraline treatment. The subjects were 30 outpatients who met the DSM-IV criteria for obsessive compulsive disorder and have done so far at least 6 months. Patients might be depressed or not, but if so, depression was not needed to meet the DSM-IV criteria for major depression or dysthymia. Patients were selected from the Institute of Psychiatry, Ain Shams University, Cairo. Both males and females aged 18 years or older were included.

A baseline (end of washout) total score of 20 or greater on the Yale Brown Obsessive Compulsive Scale (Y-BOCS) and 7 or greater on the National Institute of Mental Health Obsessive Compulsive Rating (NIMH-OC) and 4 or greater on the Clinical Global Impression (CGI) illness severity score for obsessive compulsive disorder, was required for enrollment.

For females of childbearing potential, adequate contraceptive had to be employed, otherwise they would be excluded.

Exclusion criteria included pregnant or lactating women, patients with other primary psychiatric diagnosis than OCD or depression (if depression was present, it could not be due to bipolar disorder), patients with significant suicidal risk and patients who have had a 25% or greater reduction in the screening total Y-BOCS or NIMH-OC scores at baseline or who have had a decrease in CGI severity of two or more points from screening at baseline.

Patients requiring additional treatment with psychotropic drugs (except infrequent use of benzodiazepines or chloral hydrate as hypnotics), electroconvulsive therapy, behaviour or intensive psychotherapy during the course of the study have been excluded.

Also patients who had been treated with depot neuroleptic drugs in the 6 months prior to entering the study or with MAOI or other antidepressants in the period of 5 times the half life of the drug concerned, were also
excluded.

Other exclusion criteria were previous history of seizure disorder, organic brain disease, concomitant medical disorder (renal, cardiac, or hepatic dysfunction, urinary retention, increased intraocular pressure, hematological and endocrinical disorders), concomitant use of reserpine, methyldopa, guanethidine, anti-coagulants, drugs with anti-cholinergic activity, any serotonergic drug as well as use of general anesthesia.

Patients with controlled hypertension, on beta blockers and/or diuretics, controlled diabetes mellitus and controlled hyperthyroidism were not excluded from the study.

Patients were seen at weeks -1 (or -2 in case of previous treatment with MAOI), 0, 2, 4, 6, 8, and 12.

The dose was titrated as follows: washout period from week -1 or -2 to week 0, during which no medication was given. Patients received "Sertraline" 50 mg tablet once daily from week 0 to week 2 and then further increase of 50 mg every two weeks is allowed according to the patient's response till a maximum of 200 mg/day. The drug is given as a single daily dose with meals.

The dose could be decreased as appropriate if side effects occurred during the study.

 Patients were assessed as follows:

1. At week -1 or -2 (screening):
   - History taking, physical examination, including weight and vital signs.
   - Yale Brown Obsessive Compulsive Scale (Y-BOCS)
   - The National Institute of Mental Health Obsessive Compulsive Rating Scale (NIMH-OC) used to measure the severity of obsessive compulsive symptoms.
   - Clinical Global Impression (CGI) scale.
   - Montgomery Asberg Depression Rating Scale (MADRS) used to measure the severity of depression.
   - The Hamilton Anxiety Rating Scale (HAM-A) used to measure the severity of anxiety.

2. At weeks 0 (baseline), 2, 4, 6, 8, and 12:
   The previous assessment was applied (HAM-A at weeks 0, 4, 8, and 12 only), in addition to assessment of the resulting side effects.

Results

A. Demographic data and clinical characteristics:

30 patients of both sexes were enrolled into this study. Their ages ranged from 21 to 42 years with a mean age of 31.76 +/- 4.85. The male to female ratio was 13 : 17.

The weight of the patients ranged from 50 to 86 kg with a mean of 71.83 +/- 7.86. At the end of the study the mean weight was 71.66 +/- 7.88 (no significant difference from the screening value.)

Systolic blood pressure ranged from 110 to 140 mmHg with a mean of 120.6 +/- 6.21 and diastolic blood pressure ranged from 60 to 90 mmHg with a mean of 80 +/- 5.0.

The pulse rate ranged from 64 to 88 with a mean of 73.66 +/- 4.93. No significant difference has been found regarding these vital data by the end of the study period.

Two patients had a past history of previous
depressive disorder (7%) and eight patients had a positive family history of psychiatric disorder (27%), 4 of them had a positive family history of probable OCD (13%). Two patients had a family history of mood disorder (depression) (7%) and one patient had a family history suggestive of a schizophrenic disorder (3%).

Only two patients had controlled diabetes mellitus, maintained on oral hypoglycemic drugs and one patient had a past history of bronchial asthma, which AIID bee controlled for years.

B. Premature Discontinuation

Three patients (3%) did not complete the study, two of them due to the development of intolerable side effects nausea and vomiting) which occurred during the first two weeks of treatment. The third patient discontinued treatment after 4 weeks due to insufficient clinical response.

Temporary discontinuation for few days was found in one patient, because of the development of some irritability and insomnia during the first two weeks of treatment.

The patient responded to simple reassurance and treatment was re-started again and he showed satisfactory improvement on the next assessment.

No single patient was maintained on sertraline 50 mg/day throughout the study period as the study required rapid titration of the dose every two weeks if no response was observed.

Seven patients improved on 100 mg/day of sertraline from the 3rd week and were maintained on this dose throughout the study (27%). Fifteen patients improved on 200 mg/day sertraline starting from the 7th week (50%).

C. Side effects:

Side effects were reported in 8 patients (27%), which necessitated discontinuation of treatment in only two of them, with temporary discontinuation in a third one, for a few days. Nausea, vomiting, irritability and insomnia were the most frequently reported side effects.

D. Clinical efficacy:

Results on the Y-BOCS from baseline to the last visit are shown in Table (1) and figures 1, 2 and 3.

Significant improvement of obsession subtotal scores (at week 2) was earlier than that for compulsions subtotal scores (at week 4).

Obsessional items showed earliest improvement in time occupied by obsessive thoughts and degree of control over obsessional thoughts.

Results on other efficacy measures (NIMH-OC, MADRS, HAM-D, CGI) from baseline to the last visit are shown in Table (2) and figures 4, 5, 6, 7, and 8. Significant improvement was apparent at week 4 (p=0.002, 0.001, 0.003, 0.004, 0.005) for NIMH-OC, MADRS, HAM-A and CGI impression of severity and improvement scores respectively.

Overall response to treatment is shown in Table (3). Significant improvement was apparent at week two for overall and obsessional subtotal scores. For compulsion subtotal scores, depression and CGI, significant improvement was apparent later at week four.
Table (1)
Results on the Y-BOCS

<table>
<thead>
<tr>
<th>Week</th>
<th>Item</th>
<th>-2</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time occupied by obsessions</td>
<td>03.33±0.47</td>
<td>03.36±0.48</td>
<td>02.84±0.32</td>
<td>02.26±0.61</td>
<td>02.07±0.40</td>
<td>01.79±0.67</td>
<td>01.43±0.68</td>
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<td></td>
<td>Interference due to obsessions</td>
<td>02.86±0.33</td>
<td>02.86±0.33</td>
<td>02.67±0.44</td>
<td>02.44±0.74</td>
<td>01.92±0.56</td>
<td>01.66±0.69</td>
<td>01.37±0.70</td>
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<td></td>
<td>Distress with obsessions</td>
<td>02.96±0.23</td>
<td>02.93±0.22</td>
<td>02.85±0.22</td>
<td>02.62±0.63</td>
<td>02.11±0.58</td>
<td>01.77±0.66</td>
<td>01.51±0.70</td>
</tr>
<tr>
<td></td>
<td>Resistance to obsessions</td>
<td>02.76±0.52</td>
<td>02.83±0.47</td>
<td>02.71±0.56</td>
<td>02.44±0.65</td>
<td>02.00±0.48</td>
<td>01.85±0.63</td>
<td>01.48±0.87</td>
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<tr>
<td></td>
<td>Control over obsessions</td>
<td>03.03±0.10</td>
<td>03.03±0.10</td>
<td>02.75±0.43</td>
<td>02.33±0.60</td>
<td>02.00±0.63</td>
<td>01.66±0.68</td>
<td>01.22±0.74</td>
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<tr>
<td></td>
<td>Obsessive subtotal score</td>
<td>15.03±1.43</td>
<td>15.06±1.46</td>
<td>13.92±1.57</td>
<td>11.55±2.33</td>
<td>09.22±2.29</td>
<td>07.62±2.83</td>
<td>05.81±2.88</td>
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<tr>
<td></td>
<td>Time spent on compulsions</td>
<td>07.00±0.66</td>
<td>2.06±0.63</td>
<td>0.92±0.51</td>
<td>01.66±0.53</td>
<td>01.62±0.59</td>
<td>01.16±0.69</td>
<td>01.07±0.77</td>
</tr>
<tr>
<td></td>
<td>Interference due to compulsions</td>
<td>02.00±0.66</td>
<td>02.06±0.63</td>
<td>02.00±0.51</td>
<td>01.74±0.85</td>
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<td>01.46±0.75</td>
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<td>Distress with compulsions</td>
<td>02.06±0.70</td>
<td>02.16±0.74</td>
<td>02.00±0.50</td>
<td>01.66±0.52</td>
<td>01.62±0.54</td>
<td>01.48±0.32</td>
<td>01.14±0.74</td>
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<td>Resistance to compulsions</td>
<td>01.80±0.56</td>
<td>01.96±0.58</td>
<td>01.89±0.66</td>
<td>01.77±0.68</td>
<td>01.48±0.32</td>
<td>01.48±0.32</td>
<td>01.25±0.15</td>
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<tr>
<td></td>
<td>Control over compulsions</td>
<td>01.90±0.58</td>
<td>02.03±0.62</td>
<td>01.92±0.64</td>
<td>01.62±0.53</td>
<td>01.59±0.48</td>
<td>01.44±0.38</td>
<td>01.07±0.70</td>
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<td>Compulsive subtotal score</td>
<td>09.29±3.66</td>
<td>10.13±2.80</td>
<td>09.60±2.44</td>
<td>07.48±3.31</td>
<td>06.66±0.50</td>
<td>06.00±0.43</td>
<td>04.51±2.24</td>
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<tr>
<td></td>
<td>Total Y-BOCS Score</td>
<td>24.63±3.56</td>
<td>25.26±2.43</td>
<td>23.67±3.69</td>
<td>19.33±4.25</td>
<td>15.29±6.00</td>
<td>13.57±5.48</td>
<td>10.03±4.36</td>
</tr>
</tbody>
</table>

* P = < 0.01

Table (2)
Results on other assessment tools

<table>
<thead>
<tr>
<th>Week</th>
<th>Item</th>
<th>-2</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NIMH - OC</td>
<td>10.36±0.16</td>
<td>10.46±0.11</td>
<td>10.00±0.96</td>
<td>08.70±0.03</td>
<td>07.70±0.14</td>
<td>06.92±0.11</td>
<td>05.74±0.44</td>
</tr>
<tr>
<td></td>
<td>MADRS</td>
<td>19.43±0.75</td>
<td>19.1±0.96</td>
<td>15.00±0.20</td>
<td>12.20±0.62</td>
<td>08.11±0.40</td>
<td>06.33±0.27</td>
<td>04.14±0.77</td>
</tr>
<tr>
<td></td>
<td>HAM - A</td>
<td>12.73±0.36</td>
<td>12.6±0.40</td>
<td>08.80±0.29</td>
<td>04.70±0.29</td>
<td>04.25±0.14</td>
<td>03.83±0.14</td>
<td>03.43±0.14</td>
</tr>
<tr>
<td></td>
<td>CGI (A) Impression of severity</td>
<td>05.53±0.60</td>
<td>05.56±0.61</td>
<td>05.35±0.75</td>
<td>04.70±0.88</td>
<td>04.25±0.88</td>
<td>03.83±0.88</td>
<td>03.43±0.88</td>
</tr>
<tr>
<td></td>
<td>CGI (B) Improvement scores</td>
<td>04.06±0.06</td>
<td>03.82±0.17</td>
<td>03.48±0.61</td>
<td>03.00±0.25</td>
<td>02.44±0.57</td>
<td>02.07±0.57</td>
<td>02.07±0.57</td>
</tr>
</tbody>
</table>

232
Discussion

The findings obtained in the present study suggest that sertraline is an effective treatment for patients 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). This supports previous findings reported by other investigators as Chouinard et al. (1990), Greist et al. (1992a), Greist et al. (1992b), Piccinelli et al. (1995) and Greist et al. (in press).

In addition to improvement in obsessive compulsive symptoms, sertraline was also found effective in relieving the associated depressive and anxiety symptoms as suggested by the significant improvement in the scores related to both depression and anxiety.

Response in OCD is more gradual and delayed relative to major depression. However, significant improvement was observed (as shown by Y-BOCS) from as early as the first assessment (i.e. two weeks following start of treatment), which indicates a relatively rapid onset of action. Maximal improvement occurred by the end of the study period, indicating that like most antidepressants, full therapeutic response may take several weeks to be achieved.

Significant improvement was observed earlier for obsession subtotal scores of YBCOS, reported with the first assessment at week 2 (p<0.01).

However, by week 4 the improvement in both obsession and compulsion subtotal scores was quite significant. So it seems that the drug initially attacks the obsessive symptoms or it might be that the improvement in compulsions is secondary to an improvement in an underlying obsession i.e. the improvement in thinking. analysing the subitems of "obsessions". The earliest improvement was found in items related to "time occupied by obsessive thoughts" and "degree of control over obsessive thought". This means that the improvement in "quality of life" or "adaptation to obsessive thoughts" seems to precede the disappearance or reduction of thoughts themselves.

Improvement in obsessive and compulsive
Symptoms seem unrelated to the level of depression found in these patients, as evidenced by these two observations:

First, the significant improvement in depression scores (MADRS) was delayed until week 4, although improvement in total scores of obsessive compulsive symptoms (Y-BOCS) was significantly noted from week 2. It appears that the improvement in depression is secondary to the improvement in obsessive compulsive symptoms.

Second, improvement in OC symptoms was noted in both groups of patients with and without high levels of depression, indicating that the drug anti-obsessional effect is not related to its anti-depressant effect. This is not consistent with what has been previously shown by other researchers as Thosen et al. (1980) and Mark et al. (1982) who found that the level of depression is a good predictor for drug response in OCD patients.

The improvement in anxiety symptoms was observed at the same time of improvement of OC symptoms. This finding may indicate that the improvement in OC symptoms was not just a mere result of improvement in anxiety symptoms.

Sertraline was found to be well tolerated, with few side effects, mostly related to gastrointestinal tract and insomnia. These side effects were observed in the first few weeks of treatment, and tended to improve in subsequent weeks. Considering drug dosage, most patients in the present study responded to relatively moderate-to-high doses (150 or 200 mg/day), although other investigators reported the effectiveness of a dose as low as 50 mg/day. This is reasonable in light of the fact that the study protocol necessitated the rapid increase of drug dosage before a sufficient trial at lower doses had been achieved.

Greater improvement at lower dose levels of sertraline (50 - 100 mg/day) may have been observed if patients are maintained on the lower dose levels for longer intervals of time i.e. four weeks. The study did not properly test the therapeutic effect of the low dosages of sertraline.

Conclusion
Findings in the present study indicate that:
1- Sertraline is an effective treatment for patients with OCD.
2- The anti-obsessional effect of Sertraline is not related to its anti-depressant effect, i.e. the drug is useful in both depressed and non-depressed patients.
3- Although the drug has an initial therapeutic effect for "obsessions", yet on the long run, it is effective for both "obsessions" and "compulsions".
4- Sertraline has a good safety and tolerability profiles.

References


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السيرترالين في علاج الوسواس القهري

قام الباحثون بعمل دراسة غير مقارنة عن أمان وكفاءة واحتمال السيرترالين في علاج اضطراب الوسواس القهري مع و بدون اكتساب د ورسي العيادة الخارجية

تم دراسة ثلاثين مريض يعانون من اضطراب الوسواس القهري تم تشخيصهم تبعا للتقسيم الأمريكي الرابع.

اختيرت العينة من مركز الطب النفسي بجامعة عين شمس وكانت تتكون من 17 رجل و 12 امرأة، تتراوح اعمارهم ما بين 21 و 44 سنة. وفي حالة المرضى الذين كانوا يعانون مضادات الاكتساب تم اجراء البحث عليهم بعد مرور فترة خالية من العلاج.

تم علاج جميع المرضى بعقار السيرترالين بجرعة 50 مجم في اليوم، وتم زيادة الجرعة عند الحاجة كل أسبوعين بعد اقصي 220 مجم في اليوم.

تم تقسيم الحالات بعد أسبوعين من بداية البحث ثم بعد اربعة وستة وثمانية اسابيع وذلك باستخدام مقياس البيل بران للاضطراب القهري. وقد لوحظ ملحوظ مع العلاج في حالة الغالبية من المرضى مع العلم ان اعراض جانبية قد ظهرت على ثمانية من المرضى وتمثلت في شعور بالغثيان وقى واضطرابات في النوم. وقد كانت الأعراض الجانبية خفيفة في غالبية الأحيان ولم يضبط سوى اثنين من المرضى تأثير العلاج بسبيها.

هذا وقد وجد ان السيرترالين عقاقر مؤثر وفعال في علاج الوسواس القهري.
The First International Congress on Psychiatric Education for the 21st Century

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