Vol. 1 No. 2 December 1994

An Open Non Comparative Study for the Evaluation of Efficacy and Safety of "Sertraline" in the Treatment of Major Depressive Disorder

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Abstract

The study included 30 patients fulfilling the DSM-III-R criteria for major depression, ~~selected from those attending Ain Shams~~ University Psychiatric ~~Institute~~. Patients were given sertraline after wash-out period in case previous anti-depressants were used before. Doses were to be evaluated and increased when required every two weeks. Assessments were done on days 0,14, 28, 42 and 56 using Hamilton Depression and Anxiety scales, CGI and other scales for side effects. The results showed satisfactory significant improvement as shown by scores of HAMD and CGI. The drug was found well tolerable with no report of significant serious side effect.

Introduction The selection of an "anti-depressant" in clinical practice is governed by several factors, including efficacy, tolerability and safety profile, spectrum of activity, speed of action, interaction with other drugs and cost-effectiveness.

An ideal agent is expected to be the one with high efficacy, good tolerability, wide safety margin, extended spectrum of activity, in addition to rapid onset of action and low economic cost. In fact, such a "magic" drug could hardly be found; however, continuous trials have never stopped searching for a drug which can fulfill the far possible maximum of these criteria, at least, partially. Being drugs for long term, or even life-long use, anti-depressants should bear fair safety and tolerability, and this fact explains the successively increasing introduction of new anti-depressants to the market.

The newly introduced group of anti-depressants, namely, serotonin reuptake inhibitors, or "the third generation anti-depressants show great promise in psychiatry regarding the aspect of providing effective anti-depressant activity without sedating, anticholinergic or cardiotoxic reactions observed with anti-depressants of the tricyclic standard group (*Schatzberg A.F. et al., 1987, Fuller R.W, Wong 1987; Mendels 1987; Rickls K, Schweizer E. 1990*).

Sertraline, a new naphthylamine derivative, is a highly selective blocker of serotonin reuptake in the central nervous system. Its chemical name is 1S, 4S-N-methyl 4 (Mendels J, 1987; *Rickls K, Schweizer 1990*) dichlorophenyl 1, 2, 3, 4 tetrahydro-1-naphthylamine hydrochloride. Sertraline is slowly but consistently absorbed orally, and its bioavailability is enhanced by food. The half-life of Sertraline is long enough (25 hours) to permit once daily administration, but short enough that equilibration of plasma levels occur within one week. This property and the absence of a clinically active metabolite may give Sertraline an advantage, especially among the elderly (*Fouda H.G., et al 1987; Doogan D.P., Caillard 1988*).

The treatment with "Sertraline" does not produce an increase in the body weight, as the case with classic anti-depressants such as tricycles. Sertraline lacks the cardiovascular, anticholinergic, antihistaminergic, and antidopaminergic effects associated with other classes of antidepressants (*American Psychiatric Association, 1987*).

Aim of the study The present study was designed to assess the efficacy and safety of "Sertraline" in patients suffering from major depressive disorder, according to DSM-III R criteria, for an eight-week period of treatment.

Study Description This study was an open, non-comparative one. After initial screening, patients had a single-blind wash-out period of 7 days (14 days in case of previous treatment with monoamine oxidase inhibitors).

The duration of the study was 8 weeks of active treatment with "Sertraline'-. The number and type of patients were 30 adult inpatients and outpatients, suffering from major depressive disorder, according to DSM-III R criteria, selected from the Institute of Psychiatry, Ain-Shams University, Cairo.

Subjects and Methods The inclusion criteria were males or females, aged 18-70 years and suffering from major depressive disorder, according to criteria of DM-III R (9), suitable for anti-depressant therapy . The minimum total score on the Hamilton Rating Scale for Depression
H.R.S.-D. (*Hamilton M., 1960*) is 18 on the first 17 items at the end of washout period. For females of child-bearing potential, adequate contraceptive should have been employed, otherwise, they would be excluded.

The exclusion criteria included all forms of secondary depression, including post-partum; pregnant or lactating women, taking in concurrent psychotropic medications with the exception of short acting benzodiazepines or chloral hydrate for insomnia (with exclusion of Alprazolam) only when indicated during the study.
The same applies for electro-convulsive therapy in the 7 days before the start of the study, hypersensitivity \ resistance to antidepressant drugs (resistance defined as failure to respond in the recurrent depressive episode to two or more adequate trials with two different anti-depressants for 4 to 5 weeks), treatment with lithium salts during the 4 previous weeks, poor compliance of the patients, physical or psychological dependence on drugs or alcohol, severe suicidal risk, patients treated with study drugs in the 4 previous weeks, patients with improvement > 25% of Hamilton Depression Scale, during the washout period, monoamine oxidase inhibitors, given less than 14 days prior to entry in the study, chronic renal insufficiency, and concomitant organic disease e.g. significant renal, cardiac or hepatic dysfunction or urinary retention. Patients with controlled hypertension on B-blockers and / or diuretics, controlled diabetes mellitus and controlled hypothyroidism were not excluded from the study.

All patients were seen at days: -7, 0, 7, 14, 28, 42 and 56. The drug was administered in increasing doses from 50 mg\day to a maximum of 200 mg\day as a single daily dose with meals, according to clinical response and safety.

The dose was titrated as follows: washout period from day -7 to day 0 (day -14 in case of previous treatment with MAOI) during which no medication was given. Patients received Sertraline 50 mg tablet once daily from day 1 to day 7 which was increased to 100 mg once daily if no side effects had occurred from day 7 to day 14. The dose was maintained as 100 mg once daily if improvement was satisfactory. If improvement was not satisfactory, the dose was increased to 200 mg once daily till the end of the study. The dose was decreased as appropriate if side effects occurred during the study.

Patients were assessed as follows:
1) At day -7 (screening) the following had been done:
History taking, physical examination including vital signs,
Hamilton Rating Scale for Depression and Anxiety (*Mendels J, 1987; Doogan D.P. & Caillord V., 1988; Reimherr, F.W. et al 1988; Cohn, C.K. et al 1990; Lapievre, 1991*) (HAM-D and HAM-A), laboratory tests (ordinary routine hematological tests, S. creatinine and liver function tests), electrocardiogram (ECG), if deemed necessary, and informed consent was taken from patients or their guardians.
2) At days 0, 14, 21, 28, 42 and 56 the following had been assessed: HAM-D and HAM-

A (only at days 28, 42 and 56), CGI, symptoms, physical examination, side effects, laboratory tests (only at day 56), ECG (only at day 56 if deemed necessary).

Results

Demographic Data and Clinical Characteristics The age of the patients ranged from 19 to 62 years with a mean age of 42.83 + 10.57. Eleven patients were females (36.66%) and 19 were males (63.33%). The weights of the patients ranged from 53 to 85 kg's with a mean of 68.7 kg's + 5.91. At the end of the study, the mean weight was 68.59 kg's ± 5.71. Systolic blood pressure ranged from 100 - 150 mmHg with a mean of 125 mmHg ± 11.66, and diastolic blood pressure ranged from 60 - 100 mmHg with a mean of 80 mmHg(±6). 16 patients had no previous history of manic or depressive episodes (53.33%), 2 patients had a history of previous manic and depressive episodes (6.66%), 9 patients had a history of previous single depressive episode (30%), 2 patients had a history of previous two depressive episodes (6.66%), and one patient had a history of previous three depressive episodes (3.33%). Family history of mood disorder was positive in 4 patients (first degree relative) (13.33%). Only one patient had a history of ischaemic heart disease and 4 patients were known to be diabetic, receiving oral hypoglycaemic agents.

Drop outs 3 patients did not complete the study, two of them discontinued treatment during the first week, because of intolerable side effects (mainly nausea, vomiting and irritability). The third patient discontinued treatment after two weeks due to lack of good response. Four other patients discontinued the treatment for few days, one of them due to the development of side effects in the second week (headache, nausea and vomiting), for which he was reassured and treatment re-started again. The other 3 patients discontinued treatment as they did not feel improvement after two weeks of therapy, but treatment was re-started again with increasing the dose, after being reassured that treatment might take sometime to be beneficial. Those patients showed satisfactory improvement on assessment in the next visits.

No single patient was maintained on 50 mg only throughout the study period. 8 patients responded to 100 mg Sertraline (from the second week) and were maintained on such a dose throughout the trial period (29.62%). 3 patients responded to 200 mg Sertraline (from the third week) and the dose was reduced to 100 mg two weeks later (11.11%). The remaining patients responded to 200 mg Sertraline from the third-fourth week and were maintained on such a dose throughout the study (59.25%).

Safety and Tolerability

Side effect	Pts. (%)	Time of occurence (in week)							
		1st	2nd	3rd	4th	5th	6th	7th	8th
Dry mouth	4(13.33)	-	2	1	1	-	-	-	-
Blurring of vision	2(6.66)	-	2	-	-	-	-	-	-
Insomnia	4(13.33)	4	-	-	-	-	-	-	-
Irritability	7(23.33)	7	-	-	-	-	-	-	-
Headache	3(10.00)	-	-	1	1	1	-	-	-
Agitation	2(6.66)	2	-	-	-	-	-	-	-
Fatigue	1(3.33)	-	1	-	-	-	-	-	-
Nausea	3(10.00)	2	1	-	-	-	-	-	-
Vomiting	4(13.33)	3	-	1	-	-	-	-	-
Anorexia	2(6.66)	-	1	-	1	-	-	-	-
Dyspepsia	1(3.33)	1	-	-	-	-	-	-	-
Sexual dysfunction	2(6.66)	-	-	1	-	1	-	-	-

Side effects were reported in 9 patients (30%), which necessitated discontinuation of treatment within two of them only. A third patient also discontinued treatment despite the side effects were short-lasting, as he did not feel satisfactory improvement after two weeks. For the other patients, the side effects were described to be mild to moderate in severity and did not necessitate discontinuing treatment. There were no complaints of postural hypotension, palpitation, confusion, somnolence, constipation, diarrhoea, micturition difficulty, allergy or obesity.

Results of Laboratory Findings

Test		Results before treatment (Mean value)	Results before treatment (Mean value)
Urea	mg / dl	29.30 +/- 7.89	30.05 +/- 8.16
Creatinine	mg / dl	0.64 +/- 0.236	0.66 +/- 0.218
Bilirubin	u/L	0.63 +/- 0.156	0.62 +/- 0.116
S.G.O.T.	U/L	20.20 +/- 13.41	17.30 +/- 6.83
S.G.P.T.	U/L	19.10 +/- 14.67	17.80 +/- 12.44
S. Alkaline Phoshatase	U/L	42.80 +/- 10.67	42.20 +/- 9.18
Hb	%	85.25% +/- 5.85	85.5% +/- 5.23
W.B.C.	count x1000 /mm3	5.68 +/- 1.66	5.98 +/- 1.43

Clinical Efficacy The clinical efficacy of Sertraline is shown in figures 1 to 10.

Discussion Despite the relatively small size of patients included in this open trial study, the results do confirm the satisfactory efficacy of "Sertraline" as an anti-depressant for patients with major depressive disorder, fulfilling the criteria of DSM III-R diagnosis, which is consistent with other several studies.

Significant improvement occurred from as early as the first week of treatment, as evidenced by the significant reduction in total scores of HAM-D Scale ($P<0.01$) (figures 1,2) and as observed from CGI scores(figures 3,4), which suggests a fair rapidity in the start of action of the drug. However, as it is normally the case with antidepressants, the maximal improvement occurred by the end of the study period.

Analysing the "differential efficacy" of "Sertraline"' in specific depressive symptoms showed the following:

A) Effect on "Psychological" Symptoms (figure 5) (mood, guilt, helplessness, hopelessness and worthlessness). Significant satisfactory improvement was observed from the first week, increasing gradually throughout the following week, which means that the drug has an early beneficial effect in reducing the core psychological symptoms of major depressive disorder.

B) Effect on' "Physiological" symptoms" (figure 6) (sleep, weight, diurnal variation). Significant improvement on these items occurred by the 28th day with more significant improvement by the end of study period, but no significant difference from the baseline was noted by the first week even slight increase was observed, though statistically insignificant. Such slight initial worsening of insomnia might be due to the fact that the drug has no sedative effect and improvement in insomnia is coinciding with improvement of the original depressive disorder, which takes several days to be significant.

C) Effect on "Behavioural" symptoms (figures 7,8) (activities, retardation, and "anxiety-agitation"). Significant improvement in 'anxiety-agitation" factor scales, despite the last visit evaluation revealed significant improvement in patients with high baseline anxiety level, yet at day 7 initial increase is occasionally observed, although not reaching the level of statistical significance. The explanation of such an occasional initial increase in the level of anxiety

might be also attributed to the natural course of the depressive disorder before the start of good therapeutic effect of the drug, rather than being a side effect of the drug itself. Comparing the scores of the agitated-anxious" group and the "retarded group", at day 28 revealed no significant difference regarding improvement between both groups, meaning that "Sertraline" is of help for both types of depression, once the therapeutic effect is reached.

D) Effect on "Somatization"(figure 10). Significant improvement in the scores related to somatization has been found by the end of study period.

E) Effect on "suicidality"(figure 10). The scores of this factor showed significant improvement from day 28 onwards, but it is worth mentioning that patients with severe suicidal risk were excluded from the study.

Regarding tolerability and side effects, the drug was found well tolerable with few side effects, most of which are related to the gastro-intestinal tract (nausea, vomiting), irritability, occasional insomnia and dry mouth.

Most of these symptoms especially vomiting, irritability and insomnia occurred by the first week of treatment, and the latter two (irritability and insomnia) could be manifestations of the original depressive illness, that tend to improve with completion of the therapeutic action of the drug. For those patients, adjutant benzodiazepine therapy, a just reassurance, if symptoms were mild, could be of benefit especially in the first one or two weeks. As regards body weight, no significant difference was found between the initial and final (after treatment) mean weights indicating that the drug has no weight gain producing effect. The mean final weight was even less than the initial weight (before treatment), though not reaching the level of statistical significance. The satisfactory safty profile of "sertraline" has been suggested also by several other studies (*Reimherr F.W. et al 1988; Cohn C.K. et al 1990; Doogan D.P. 1991; Lapievre, 1991*).

Conclusion The findings in this trial, in addition to the previous studies on "Sertraline" indicate that the drug is an effective anti-depressant with good safety and tolerability profile.

It is not only an alternative to the classic anti-depressants, but it could be also of special benefit as a first choice drug for major depressive disorder, especially in the following conditions:

1. Depression secondary to medical illness (safe and effective drug).

2. Elderly patients (safe and effective drug).

3. Depression with psychomotor inhibition (of special 'activating" efficacy).

4. Depressed patients who ought to be "ambulant" (non-sedative drug).

5. Obesity minded depressed patients (it does not produce weight gain).

6. Moderately severe depression in a hypochondriacal or somatizing patient (it is well tolerable and given only as a single dose, hence, better compliance is expected).

7. The following symptoms in the context of a depressive syndrome give good and early response to Sertraline:
- Hypersomnia. - Hyperphagia.

8. Depression mixed with obsession or anxiety (the drug does affect both symptoms).

It is to be mentioned finally that severe melancholic depression or psychotic depression actually needs other lines of treatment in additional to anti-depressant pharmacotherapy (i.e. electroconvulsive therapy or neuroleptics).

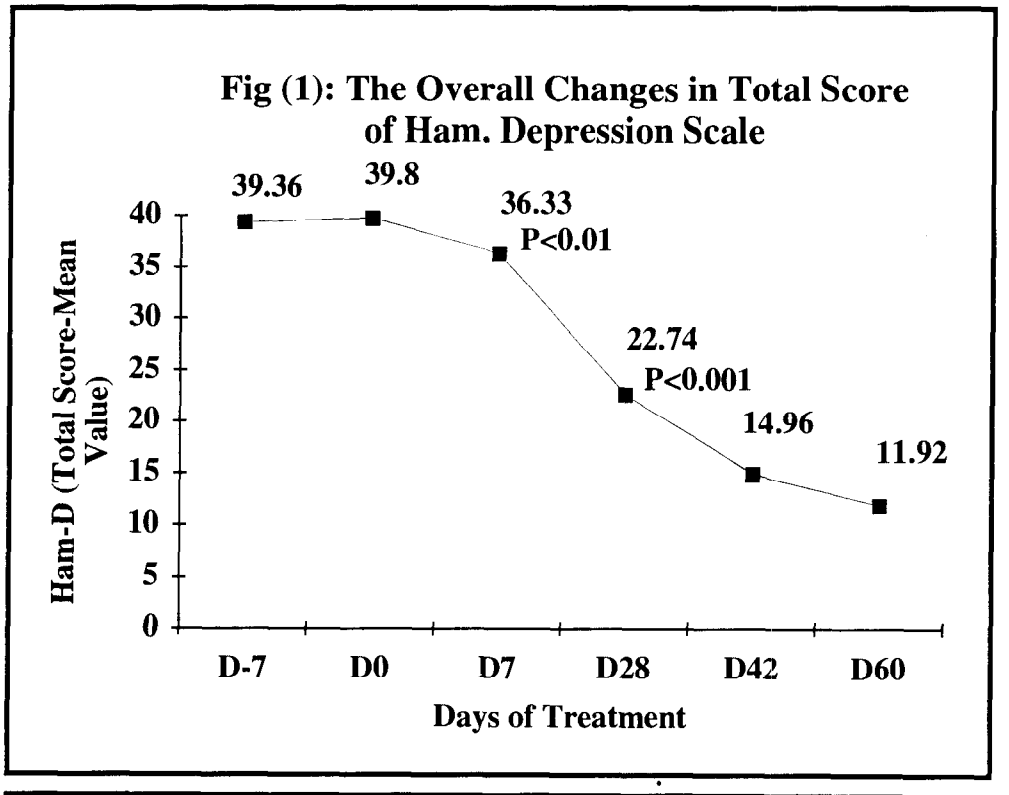


Fig (1): The Overall Changes in Total Score of Ham. Depression Scale
39.36
39.8
36.33
P<0.01
22.74
P<0.001
14.96
11.92
Ham-D (Total Score-Mean Value)
40
35
30
25
20
15
10
5
0
D-7
D0
D7
D28
D42
D60
Days of Treatment

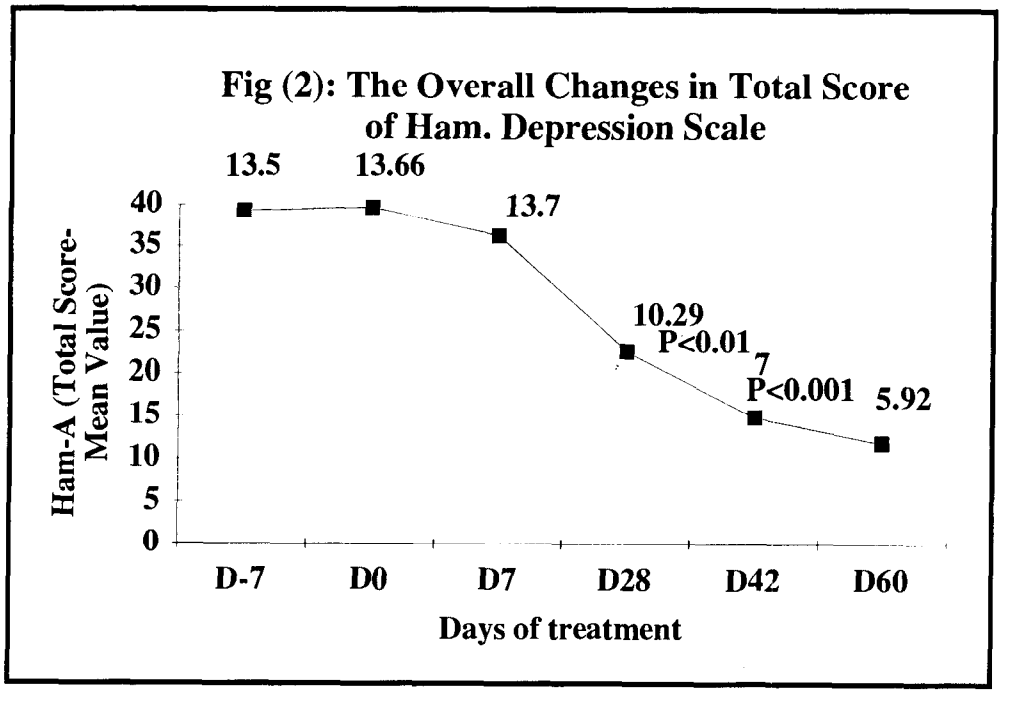


Fig (2): The Overall Changes in Total Score of Ham. Depression Scale
13.5
13.66
13.7
10.29
P<0.01
7
P<0.001
5.92
Ham-A (Total Score-Mean Value)
40
35
30
25
20
15
10
5
0
D-7
D0
D7
D28
D42
D60
Days of treatment

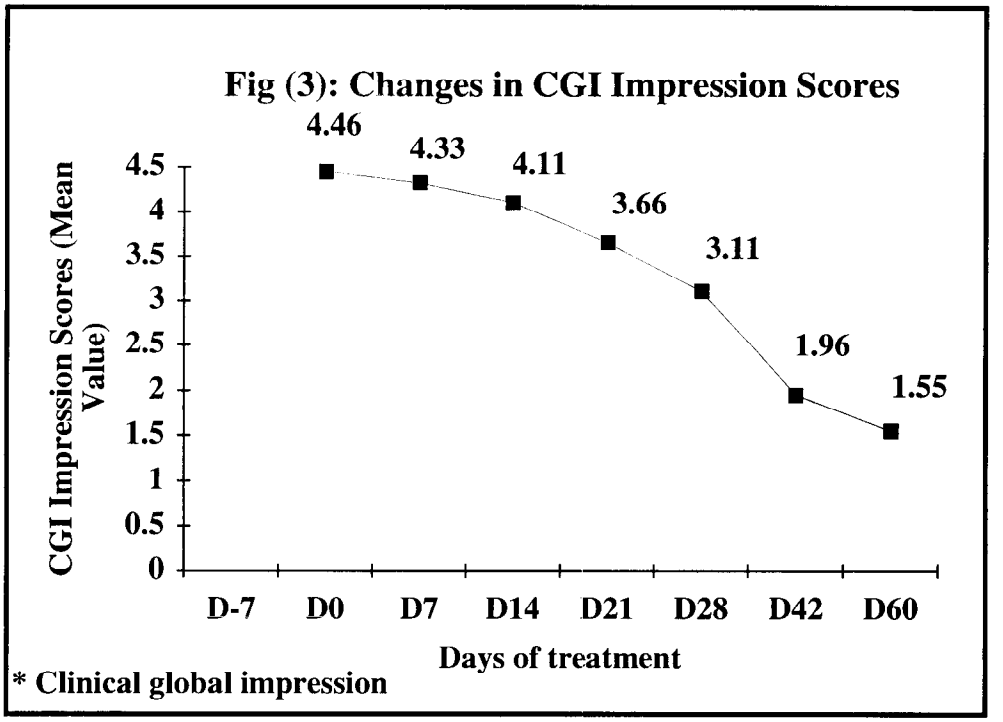


Fig (3): Changes in CGI Impression Scores
CGI Impression Scores (Mean Value)
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
4.46
4.33
4.11
3.66
3.11
1.96
1.55
D-7
D0
D7
D14
D21
D28
D42
D60
Days of treatment
* Clinical global impression

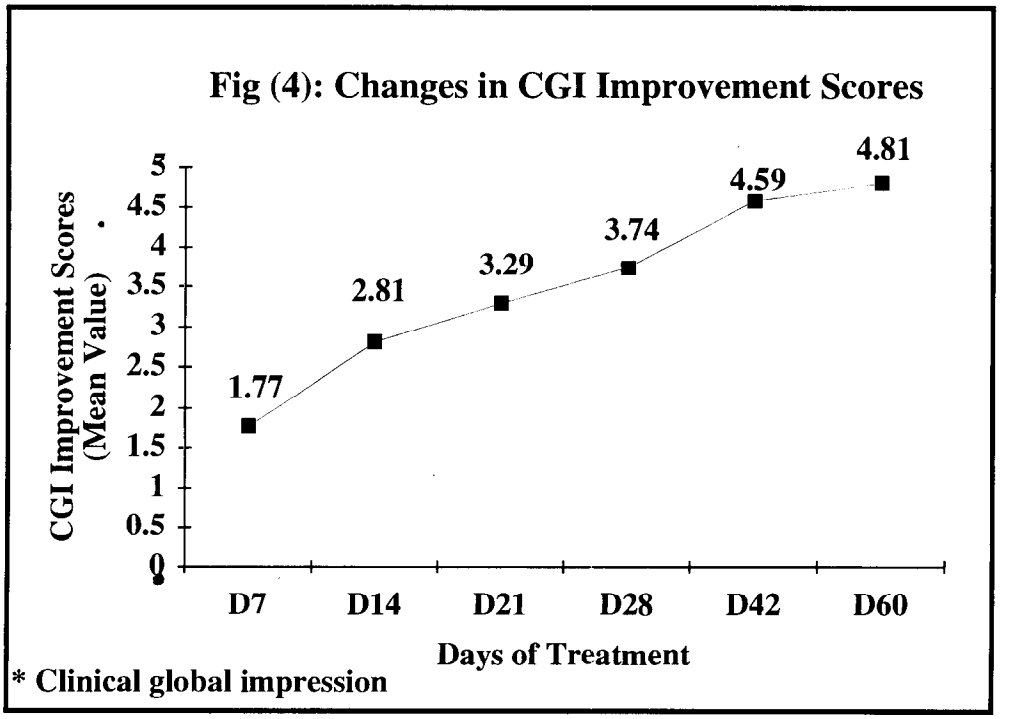


Fig (4): Changes in CGI Improvement Scores
CGI Improvement Scores (Mean Value)
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
1.77
2.81
3.29
3.74
4.59
4.81
D7
D14
D21
D28
D42
D60
Days of Treatment
* Clinical global impression

Fig (5): Changes in HAM-D-Scale Scores on Psychological Symptoms of Depression

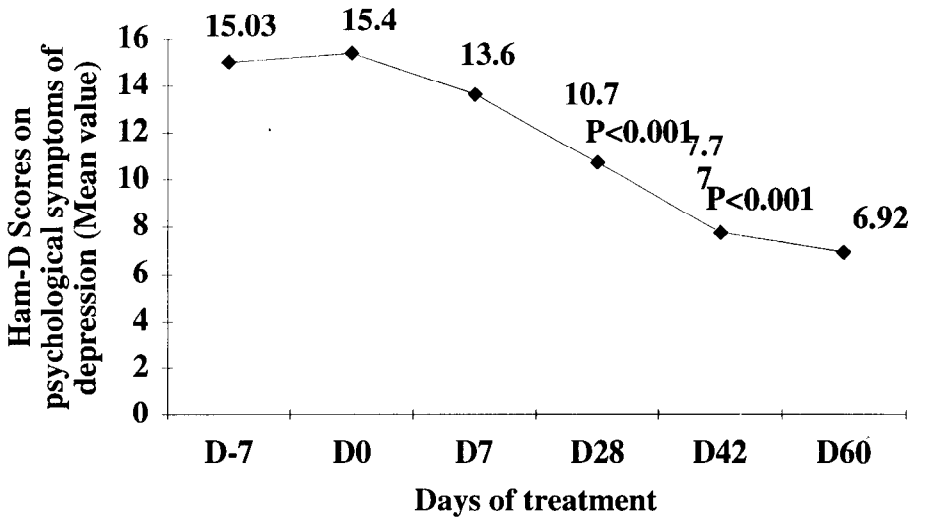
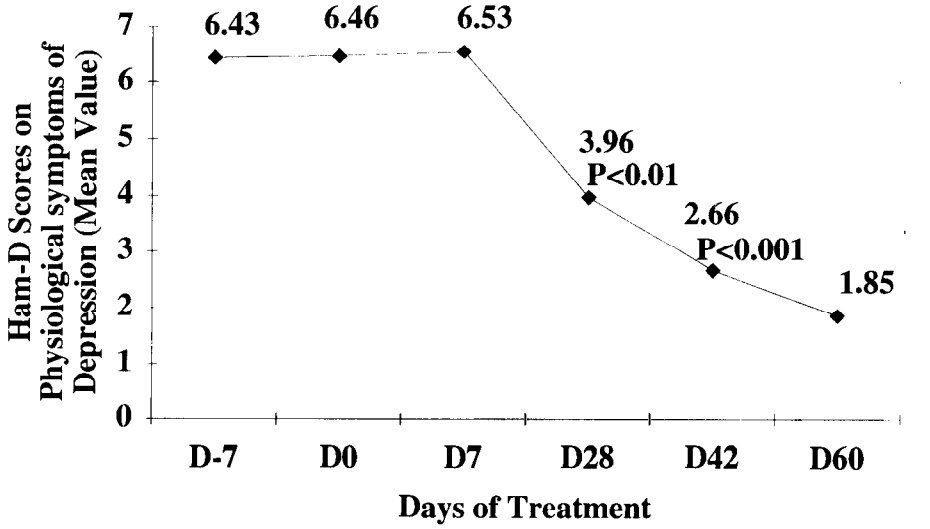


Fig (6): Changes in HAM-D-Scale Scores on Physiological Symptoms of Depression



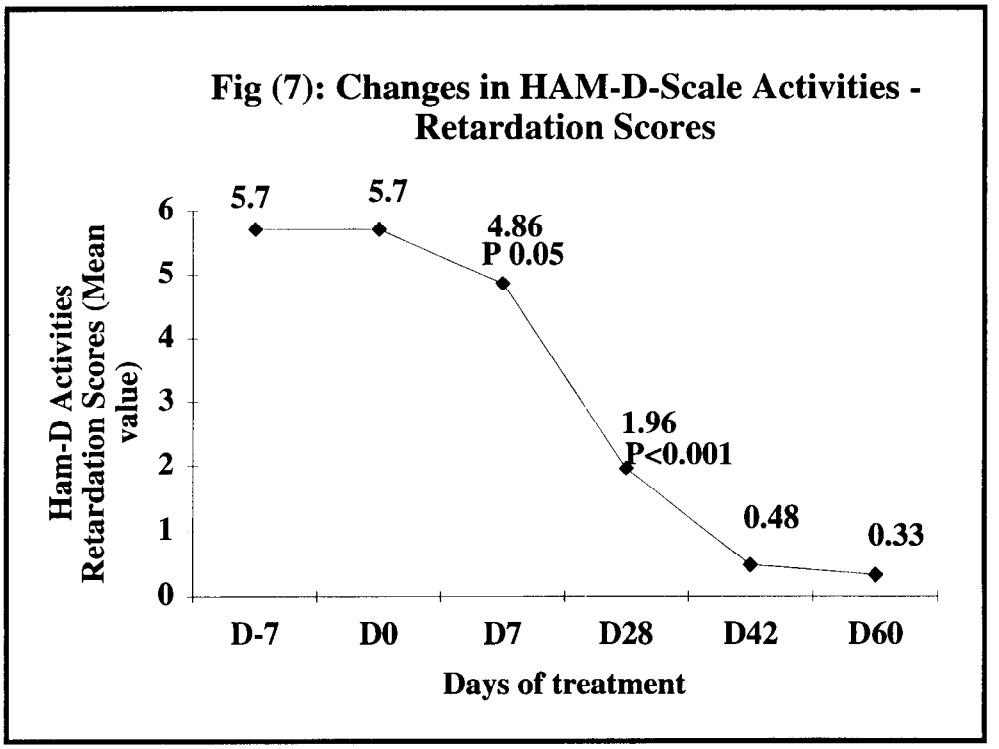


Fig (7): Changes in HAM-D-Scale Activities - Retardation Scores
Ham-D Activities Retardation Scores (Mean value)
0
1
2
3
4
5
6
5.7
5.7
4.86
P 0.05
1.96
P<0.001
0.48
0.33
D-7
D0
D7
D28
D42
D60
Days of treatment

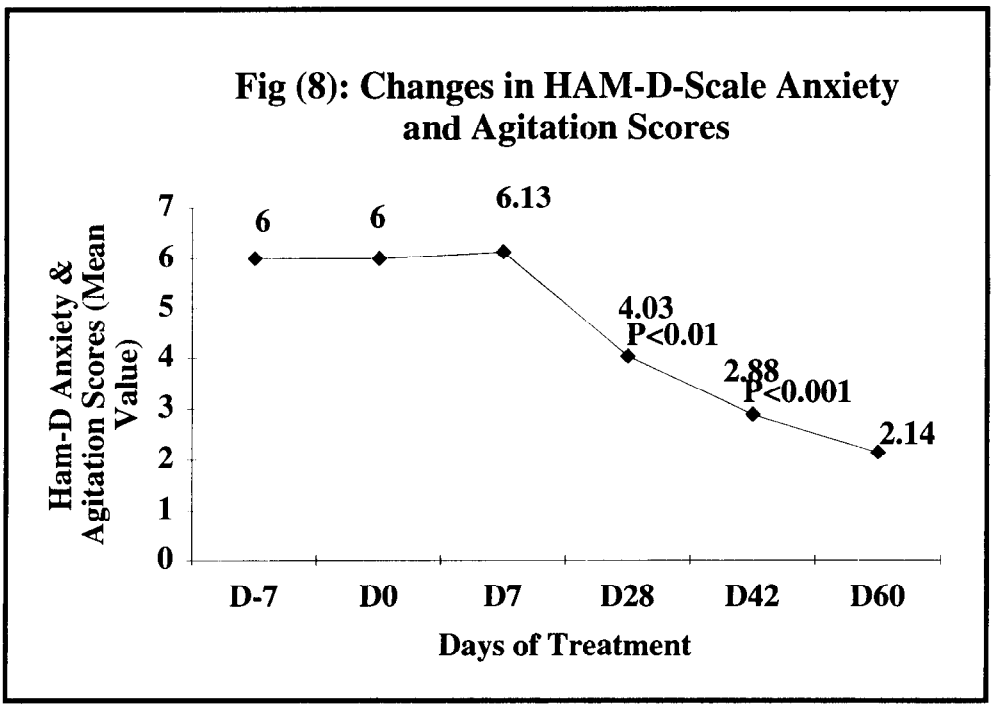


Fig (8): Changes in HAM-D-Scale Anxiety and Agitation Scores
Ham-D Anxiety & Agitation Scores (Mean Value)
0
1
2
3
4
5
6
7
6
6
6.13
4.03
P<0.01
2.88
P<0.001
2.14
D-7
D0
D7
D28
D42
D60
Days of Treatment

Fig (9): Changes in HAM-D-Scale Somatization Scores

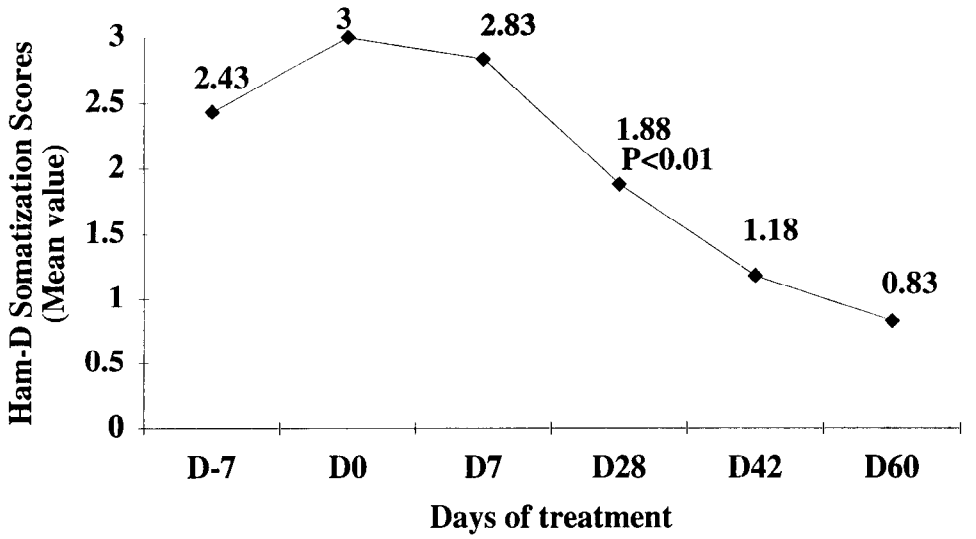
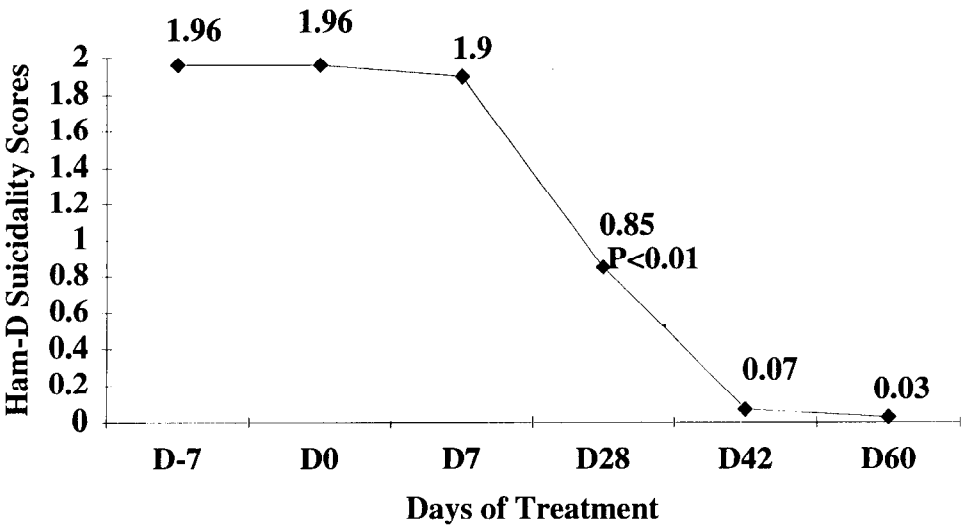


Fig (10): Changes in HAM-D-Scale Suicidality Scores



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دراسة حرة مقارنة لتقييم مدى كفاءة وأمان عقار "السرترالين" فى علاج الإكتئاب الجسيم

تناولت الدراسة ٣٠ مريضا استوفوا شروط DSM-III-R للاكتئاب الجسيم، من مرضى مركز الطب النفسى بجامعة عين شمس. وتم إعطاؤهم السرترالين بعد التأكد من أن أجسامهم قد تخلصت من أى آثار لعقاقير أخرى مضادة للاكتئاب كانوا يتناولونها قبل ذلك. وتم تقدير الجرعات وزيادتها بعد ذلك حسب الإحتياج كل أسبوعين.

وتم تقييم المرضى فى الأيام التالية: ٠، ١٤، ٨، ٤٢، ٥٦ بإستخدام مقاييس هاميلتون للقلق وللاكتئاب، وكذلك بإستخدام إختبار CGI وغيره من الإختبارات لمعرفة الآثار الجانبية للعقار .

وبينت النتائج تحسنا إيجابيا دالا كما أتضح من درجات مقاييس هاميلتون و CGI. كما وجد أن درجة تحمل عقار السرترالين حسنة وليست له آثار جانبية تذكر.