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# Oral Administration of Sertraline and Clozapine Affects Memory, Liver Enzymes and Function in Rats

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**Abstract** The effects of clozapine and sertraline on memory, blood chemistry and liver function were studied. Thirty male Sprague -Dawley rats were put into three groups and orally administered daily 0.5 mg/kg of clozapine or sertraline and saline, which served as control. The rats were sacrificed by decapitation on the 14, 28 and 35 days. The blood was collected, liver and brain were excised and subjected to blood chemistry, liver function tests, brain acetylcholinesterase, superoxide dismutase ( SOD) activities and reduced glutathione( GSH) level were determined. The time spent by rats administered the respective drugs in the light compartment before entering dark compartment of the shuttle box was measured. The blood chemistry and liver function show significant increase in activities of ALP, AST and ALT between clozapine administered group and control. There was no significant difference in levels of albumin, total protein, creatinine, urea, cholesterol and tri acyl glycerol, in rats administered clozapine and sertraline when compared with control. There was significant difference in the activities of SOD and GSHin rats administered clozapine, sertraline and control. Data of the study suggest that clozapine resulted in the improvement of short and long –term memory, while sertraline improved long –term memory only in rats. The elevated activities of liver enzymes, AST and AST indicate impairment of liver function in rats orally administered clozapine and sertraline in rats.

**Keywords** Sertraline, Clozapine, Memory, Blood Chemistry, Liver Enzymes, Rats

## 1. Introduction

Antidepressants help restore the chemistry of the brain, so that normal mood and behavior can be returned. They are classes of psychotherapeutic drugs that are used to treat major depression[1,2]. These include tranquilizers, sedatives, analgesics, or stimulants. They are classified into 4 groups: monoamine oxidase (MAO) inhibitors, tricyclic anti-depressants, selective serotonin reuptake inhibitors (SSRI) and atypical antidepressants[3,4]. Antipsychotic drugs act by blocking dopamine receptors in the brain. They also prevent the reuptake of norepinephrine and serotonin by brain tissue. The ability of the antipsychotics to block neurotransmitters in the brain also causes some of the common adverse effects of this drug class. Adverse effects are the same but occur in varying degrees with each drug in this group.( 3,4).

Sertraline and clozapine belong to antidepressant and antipsychotic drugs respectively. Sertraline is an oral antidepressant drug of the selective serotonin reuptake type. It increases serotonin in the CNS by inhibiting reuptake of serotonin[5]. Sertraline potentiates serotonin by inhibiting its neuronal reuptake[6,7]. Clozapine is a di-benzodiazepine derivative and a truly atypical antipsychotic drug. The therapeutic effects of clozapine are probably mediated by dopaminergic and serotoninergic activities. It appears to be most effective antipsychotic drug for treatment – resistant schizophrenia[2].

The brain is the centre or organ of memory, reason, intelligence and understanding[8]. The biochemical investigations on cellular mechanisms involved in memory and learning can be classified into 4 approaches, namely:- facilitation, transfer, interruption and correlation[9]. Acetylcholine is synthesized in neuronal terminals in a reaction catalyzed by choline acetyl transferase. The choline is derived from membrane phospholipids, while the acetylcholine is degraded into choline and acetate by acetyl cholinesterase[10]. The function of acetyl choline in the brain is less well defined, it is thought to be related to motor activity, learning and memory and controlling sleep stages. Agonists or stimulators of all these transmitters system affect learning, memory recall and cognitive process[11]. The function of acetylcholine in the peripheral nervous systems is well documented in the autonomic nervous system and the neuromuscular junction. Acetyl cholinesterase is an important enzyme which regulates the effect of acetylcholine at cholinergic synapses.

Ebuehi *et al.,* (12) previously reported that intraperitoneal administration of imipramine or amitriptyline produced a more pronounced effect on brain serotonin, activities of liver

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derived enzymes in serum and blood chemistry of rabbits compared tosertraline or clozapine. In the past, some biochemical studies using non-oral administration of antidepressants have been reported (12, 13). From the wealth of literature, there is dearth of information as to whether oral administration of sertraline and clozapine affect memory, liver enzymes and functions in rats. Due to the use of some antidepressants, such as sertraline and clozapine in the management of psychiatric disorders, it is therefore imperative to ascertain whether sertraline and clozapine affect memory, liver enzymes and function in rats. The results of the present study could be extrapolated to humans and will be useful in biological psychiatry.

## 2. Materials and Methods

### 2.1. Drugs

Sertraline and clozapine were purchased from reputable government pharmacy in Lagos, Nigeria. Tablets of sertraline (50mg) were manufactured by Pfizer Italian S.P.A, Latina, Italy under authority of Pfizer Inc, New York, USA. Tablets of clozapine (100mg) were manufactured by Novartis Pharmaceuticals and marketed as clozaril, leopnes and fazaclo.

Ten tablets of 50mg of sertraline were homogenized and dissolved in 1 litre of saline to produce 0.5mg/ml drug solution. 5 tablets of 100mg clozapine were homogenized and dissolved in 1 litre of saline. 2ml of 0.5mg/ml sertraline or clozapine solution were administered per 100g body weight of rats, using buccogastric canulla. The drug was orally administered daily for 35 days.

Thirty-six male virgin Sprague – Dawley rats (125.46 ± 3.87g) were equally divided into 3 groups. The rats were kept in a room with a temperature of $28 \pm 2^oC$, illuminated for 12h per day (0700-1900h). The rats were housed 3 in a metallic cage and fed commercial rat chow and water *ad libitum*, to acclimatize for 14 days. Care of all animals was in accordance with the natural law on animal care and use [14].

After 14 days of acclimatization, Group A rats comprising 12 rats were orally administered 2ml of 0.5mg/ml sertraline per 100mg body weight daily fed rat chow and water *ad libitum* for 35days. Group B rats comprising 12 rats were orally administered clozapine, rat chow and water *ad libitum* daily for 35days. Group C contained 12 rats which were fed rat chow and water *ad libitum* for3 5days and served as the control.

### 2.2. Training Procedure

The training apparatus of rats used for the study to assess short-term and long-term memory was the shuttle box[15]. It consisted of two wooden compartments of identical dimensions (28cm by 15cm). The two compartments were separated by a door in the middle part of this apparatus of the two compartments, one was illuminated and the other was dark[16]. The door could be raised to permit entry of the rats into any of the two compartments. The floor consisted of 6mm diameter wire rods were connected to a set down transformer with a regular diameter which could be switched on and off to deliver an instant scrambled foot shock to either compartments.

The training task commenced after rats were acclimatized. At day 14 ($1^{st}$ day of training), all rats were placed in the shuttle box and had access to the light or dark compartment for 1h. One day 2 of training, rats from each group were placed in the illuminated compartment and 30sec later the door was raised. Upon entering the dark compartment, the door was closed and a 1.5mA constant current shock was applied for 2sec, after 20sec, the rats were removed from the dark compartment and placed in their home cages.

For short-term memory, 24h after trainingon day 2, each rat from the 3 groups was placed in illuminated chamber and 30 sec later the door was raised and the time spent in the light compartment before entering the dark compartment was recorded. The training procedure was repeated on days 9, 16 and 23 training skills acquired on days 16 and 23 depicted long-term memory.

### 2.3. Plasma and Brain Analysis

At the end of the training or learning procedure carried out on days 2, 9, 16 and 23, after the acclimatization of the rats, using the shuttle box, 3 rats from each group were sacrificed by decapitation in each of these days. Blood was taken into heparinized tubes and centrifuged at 2500g for 10min. Plasma was carefully collected and used for further analysis. Brains were excised, wiped dry of blood, weighed and thoroughly perfused in ice-cold phosphate buffered saline, pH 7.4, until further analysis.

Brain tissues were homogenized with 5 volumes of ice-cold 50mm Tris HCl (pH 7.4) containing 30mM sucrose. The homogenate was centrifuged at 1500 x g for 10min to remove nuclei and cell debris. The resulting supernatant was then used for total protein determination, reduced glutathione level, superoxide dismutase and acetyl cholinesterase activities.

Total brain protein levels were determined according to Lowry *et al.,*[17], using bovine serum albumin. The concentration of reduced glutathione (GSH) was determined using the method of Ellman *et al.,*[10]. Acetyl cholinesterase activity in the brain homogenate was assayed as described by Ellman *et al.,*[10] and its specific activity expressed as increase in absorbance per min / mg protein.

The superoxide dismutase activity was assayed by its ability to inhibit the auto-oxidation by its epinephrine, determined by the increase in absorbance at 480nm[18]. The plasma creatinine level was measured using a creatinine test kit (Sigma creatinine No. 555–A kit). Protein concentrations were assayed by the method of Lowry *et al.,*[17]. Plasma and tissue cholesterol and triacyl glycerol concentrations were determined using Synchron CX5 auto analyzer. The activities of plasma aspartate amino transferase (AST, EC 2.6.1.1), alanine amino transferase (ALT, EC 2.6.1.2) and alkaline phosphatase (ALP, EC 3.1.3.1) were assayed at 37℃, according to the recommended principles and using commercial kits manufactured by Boehringer, Mannheim, Germany and Roche, Switzerland.

### 2.4. Statistical Analysis

Data were analyzed using Microsoft Excel office 2003 and expressed as Mean ± S.D of triplicate determinations. The Student's t-test for independent samples was used to analyze the difference between the mean. Probability values less than 0.01 were considered as highly significant (P < 0.0101).

## 3. Results

The concentration of rat brain homogenates administered clozapine, sertraline and saline for 14,, 28 and 35 days respectively, is presented in Table 1. The brain protein levels of rat administered clozapine or sertraline were significantly (P<0.01) higher than in rats administered saline or control rats. There was significant difference in the brain proteins of all rats administered the different drugs or saline after 14,28 and35days.

The blood chemistry of rats administered clozapine, sertraline and saline for 35 weeks is presented in Table 2. There were no significant (P>0.01) differences in the plasma creatinine, uric acid, HDL and LDL levels of rats administered clozapine or sertraline or saline, for 35 weeks. However, the plasma triglyceride, cholesterol and albumin levels of rats administered clozapine or saline were significantly (P< 0.01) higher than rats administered sertraline.

The activities of aspartate amino transferase, alanine amino transferase and alkaline phosphatase in plasma of rats administered clozapine, sertraline and saline are shown in Table 3.

There were no significant (P>0.01) differences in the activities of plasma aspartate amino transferase and alkaline phosphatase of rats administered clozapine, sertraline or saline for 14, 28 or 35 days. The activities of plasma AST and ALT of rats administered sertraline or saline were significantly (P<0.01) increased with duration of drug administration. From 14 to 35 days, while there was no significant difference in the plasma ALP activity of rats administered sertraline or saline (Table 3).

The time spent in the light compartment before entering the dark compartment by rats orally administered clozapine, sertraline or saline during after 14, 28 and 35days is presented in Table 4. There was no significant (P>0.01) difference in the time spent in the light compartment by rats orally administered clozapine or saline as the duration administration increase from 14 to 35days. However, increase in the duration administered of sertraline from 14 to35days significant increased the time spent in the light compartment.

On the other hand, the time spent on the different training session after 14, 28 and 35days of drug administration, was significantly (P<0.01) higher in rats administered clozapine or sertraline as compared to rats administered saline. The time spent after 14days of training rats administered clozapine or sertraline did not differ significantly (P>0.01) (Table 4).

**Table 1.** Total protein concentrations of brain homogenates of rats administered clozapine, sertraline and saline for 14, 28 and 35days respectively[1,2]

| Drug of Administration | Total Protein Conc (mg/ml) | | | |
|---|---|---|---|---|
| | After 0day | After 14days | After 28days | After 35days |
| Clozapine | 10.94 ±0.69 | 13.26 ± 1.06[a] | 15.31 ± 1.09[b] | 12.46 ± 1.23[a] |
| Sertraline | 10.89±1.57 | 13.24 ± 1.23[a] | 14.82 ± 1.21[b] | 12.23 ± 1.04[a] |
| Saline | 11.07±0.86 | 11.25 ± 1.25[b] | 10.52 ± 1.29[a] | 9.56 ± 1.25[b] |

*[1] Values are expressed in mean ± S.D of three determinations*
*[2] Values carrying different superscripts horizontally are significantly different (P<0.01)*

**Table 2.** Blood chemistry of rats administered clozapine, sertraline and saline for 35days[1,2]

| Blood Chemistry parameter | Drug Administered | | |
|---|---|---|---|
| | Clozapine | Sertraline | Saline |
| Triacylglycerol (mmol/l) | 0.65 ± 0.03[a] | 0.92 ± 0.04[b] | 0.58 ± 0.02[a] |
| Cholesterol (mmol/l) | 3.24 ± 0.18[a] | 3.46 ± 0.15[b] | 3.6 ± 0.14[c] |
| Albumin (g/l) | 35.84 ± 2.91[a] | 44.23 ± 5.11[b] | 28.25 ± 2.17[a] |
| Creatinine (mmol/l) | 52.03 ± 2.48[a] | 51.07 ± 2.05[a] | 50.03 ± 2.62[a] |
| Uric acid (mmol/l) | 2.05 ± 0.11[a] | 2.08 ± 0.06[a] | 2.42 ± 0.12[b] |
| HDL (mmol/l) | 0.93 ± 0.06[a] | 0.92 ± 0.03[a] | 0.95 ± 0.02[a] |
| LDL (mmol/l) | 4.03 ± 0.12[a] | 4.01 ± 0.25[a] | 4.06 ± 0.15[a] |

*[1] Values are expressed in mean ± S.D of three determinations*
*[2] Values carrying different superscripts horizontally are significantly different (P<0.01)*

**Table 3.** Activities of (umol/l) of aspartate amino transferase (AST), alanine amino transferase (ALT) and alkaline phosphatase (ALP) in plasma of rats orally administered clozapine, sertraline and saline for 14, 28 & 35days respectively [1,2]

| Drug / Duration of Administration | Serum Enzyme Activities | | |
|---|---|---|---|
| | AST | ALT | ALP |
| **Clozapine** | | | |
| 0day<br>14days | 110.5±3.92<br>131.9 ± 2.74[a] | 124.6 ±2.75<br>147.6 ± 2.13[a] | 68.8±3.05<br>85.2 ± 1.78[a] |
| 28 daysweek | 130.2 ± 7.25[a] | 155.1 ± 2.35[a] | 87.5 ± 1.46[a] |
| 35days | 140 .1 ± 2.26[b] | 158.2 ± 1.38[a] | 93.3 ± 1.96[a] |
| **Sertraline** | | | |
| 0day<br>14days | 108.6± 2.46<br>120.1 ± 1.72[c] | 89.4±1.52<br>108.5 ± 1.76[e] | 102.6±2.13<br>124.5 ± 1.82[g] |
| 28days | 121.3 ± 1.35[c] | 158.4 ± 2.51[f] | 126.4 ± 1.37[g] |
| 35days | 135.4 ± 1.26[d] | 162.5 ± 2.81[f] | 120.5 ± 1.26[g] |
| Saline | | | |
| 0day<br>14days | 18.1±0.75<br>23.6 ± 1.94[h] | 23.5±2.17<br>26.3 ± 1.98[j] | 25.1±1.19<br>29.9 ± 1.37[m] |
| 28days | 34.1 ± 0.58[i] | 34.8 ± 2.50[k] | 32.4 ± 1.60[m] |
| 35days | 36.7 ± 1.78[i] | 16.01 ± 1.49[j] | 31.5 ± 1.77[m] |

*[1]Values are expressed in mean ± S.D of three determinations*
*[2]Values carrying different superscripts horizon tally are significantly different (P<0.01)*

**Table 4.** Time spent in the light compartment before entering the dark compartment by rats orally administered clozapine, sertraline and saline during training after 14,28 and 35days respectively [1,2]

| Drug Administered | Time (Sec) spent on different training | | | |
|---|---|---|---|---|
| | 0day | 14days | 28days | 35days |
| **Clozapine** | 34.6 ± 1.42 | 41.3 ± 2.40[a] | 42.0 ± 2.58[a] | 42.6 ± 1.71[a] |
| **Sertraline** | 18.4 ± 1.10 | 21.1 ± 1.70[b] | 47.3 ± 1.43[a] | 45.6 ± 2.15[a] |
| **Saline** | 18.1 ± 0.63 | 21.6 ± 1.95[b] | 21.3 ± 2.41[b] | 20.3 ± 2.58[b] |

*[1]Values are expressed in mean ± S.D of three determinations*
*[2]Values carrying different superscripts vertically are significantly different (P<0.01)*

**Table 5.** Specific activities of brain acetyl cholinesterase (AChE) superoxide dismutase (SOD) and levels of reduced glutathione of rats orally administered clozapine, sertraline and saline during training after 14, 28 and35days respectively [1,2]

| Drug Administered | AChE (mol/min/mg) | SOD (mol/min/mg) | GSH (mol/mg) |
|---|---|---|---|
| **Clozapine** | | | |
| 0day<br>14days | 0.94 ±0.06<br>1.20 ± 0.04[a] | 3.96 ±0.24<br>4.62 ± 0.31[a] | 0.232 ±0.015<br>0.209 ± 0.031[a] |
| 28days | 1.34 ± 0.01[a] | 5.02 ± 0.06[a] | 0.186 ± 0.015[b] |
| 35days | 1.21 ± 0.03[a] | 6.04 ± 0.044[a] | 0.163 ± 0.012[b] |
| **Sertraline** | | | |
| 0day<br>14days | 2.47 ±0.62<br>2.03 ± 0.07[b] | 3.71 ±0.35<br>3.44 ± 0.15[a] | 0.194 ±0.025<br>0..163 ± 0.012[b] |
| 28days | 1.41 ± 0.03[a] | 3.26 ± 0.21[a] | 0.135 ± 0.012[c] |
| 35days | 1.34 ± 0.01[a] | 4.54 ± 0.71[a] | 0.127 ± 0.016[c] |
| **Saline** | | | |
| 0day<br>14days | 1.68 ±0.08<br>1.34 ± 0.05[b] | 4.75 ±0.14<br>4.02 ± 0.66[a] | 0.184 ±0.024<br>0.154 ± 0.052[a] |
| 28days | 0.92 ± 0.02[a] | 5.64 ± 0.08[a] | 0.140 ± 0.027[c] |
| 35days | 0.91 ± 0.03[a] | 4.87 ± 0.69[a] | 0.132 ± 0.016[c] |

*[1]Values are expressed in mean ± S.D of three determinations*
*[2]Values carrying different superscripts vertically are significantly different (P<0.01)*

The specific activities of brain acetyl cholinesterase (AChE), superoxide dismutase (SOD) and reduced glutathione level of rats administered clozapine, sertraline and saline during training after 14,28 and 35days are shown in Table 5. The specific activities of AChE of rats administered sertraline or saline after 14days of training were significantly higher than in rats administered clozapine. There were also no significant (P>0.01) differences in the activities of SOD of rats administered clozapine, sertraline or saline after 14, 28 and 35days of training. The reduced glutathione levels of rats administered clozapine or saline after 14days of training were significantly higher than in rats administered sertraline. However, there were no significant differences in the levels of GSH of rats administered those respective drugs after 28 or 35days of training.

There was no significant difference in the time spent in the light compartment by rats administered sertraline after 14days training session as compared with the control.

## 4. Discussion

The duration of time spent in the light compartment of the shuttle box by the rats before entering the dark compartment was affected by sertraline and clozapine. There was significant (P<0.01) difference in the time spent in the light compartment in rats administered clozapine for 14, 28 and 35days of training and control, respectively. However, significant differences existed only in the light compartment by the rats administered sertraline for 28 and 35days of training session as compared to the control.

The time spent in the light compartment by rats administered clozapine increased at the 14th, 28th and 35$^{th}$ days of memory training when compared with the control. The observation was different for the rats administered sertraline, in which there was an increase in time spent at the light compartment only after 28th and 35thdaysweek of training session.

Ebuehi and Akande[16] classified memory into short-term memory, lasting 14days and while long-term memory, lasted for 28days. It therefore follows that from the present study, a training memory between day 9 and day 16 could be regarded as short-term memory, while that of between day 23 and day 30 could be termed long term memory.

It could be opined that in this study, the longer the time spent in the light compartment, the higher the training skills. The findings concur previous findings which reported that clozapine improved passive and active training in rats administered sertraline intraperitoneally (1.25mg/kg/day) for 23 days[5]. Agranoff [19] earlier reported that sertraline had improving effects on memory tests in a Y-maze training session, when administered intraperitoneally (0.05mg/kg) for 3 days.

The present study indicates that clozapine had improving effects on both short and long-term memory, while sertraline only improved long-term memory in rats. The rats which spent longer time in the light compartment where they received an instant scramble foot shock during training, were reported to have attained higher training skills. Post-stress exposure treatment with sertraline reduced the prevalence rate of extreme behavioural disruption[20]. The activities of plasma ALP, AST and ASP of rats administered clozapine and sertraline were significantly elevated than in the levels of plasma TG, Chol, Albumin, creatinine, uric acid, HDL, and LDL. Chan *et el.,*[21] and Ebuehi *et al.,*[12] have previously reported that the activities of plasma AST, ALP and ASP were elevated in rats administered atypical antipsychotics (clozapine or haloperidol) (1.25mg / kg) for 20 days. Additionally, Cohen and Nonacs[23] reported that anti-psyc hotics commonly cause asymptomatic increase in liver enzymes' activities and bilirubin level in mice and rats. The activity of the endogenous oxidative stress enzyme, superoxide dismutase and the levels of glutathione were reduced in rats administered sertraline and clozapine. Buchanan *et al.,*[24] earlier showed that clozapine caused oxidative brain damage in rats.

The present data suggest that rats administered clozapine improved short and long term memory, while those administered sertraline exhibit long-term memory. Acetyl cholinesterase is a biochemical marker of acetylcholine, which is one of the good indicators of learning and memory [23]. Oral administration of both sertraline and clozapine for14,28 and 35days increased on memory skill improves and therefore concurs with the findings of Angelucci *et al.,*[26], who linked acetylcholine to memory improvement.

Acetylcholine had been linked to memory storage, since elderly people present a progressive decline in brain acetylcholine levels[11]. Acetylcholine has been implicated to function in learning, training, memory, motor activity and control of sleep[19,27], especially as drugs that deplete acetylcholine or complete for its receptor sites to reduce performance of memory tasks. Acetyl cholinesterase is an important enzyme which regulates the effects of acetylcholine at cholinergic synapses. The major function of this enzyme is to terminate the effect of acetylcholine after its release post-synaptically [23].

Ebuehi *et al.,*[4] previously reported that oral administration of sertraline and haloperidol may alter neural functions mediated by adreninergic neurotransmission. It was also reported that oral administration of sertraline and thioridazine may alter some neuronal functions mediated by serotoninergic neurotransmission[2]. In addition, Ebuehi *et al*.,[12] previously reported that intraperitoneal administra tion of imipramine or amitryptyline in rabbits produced a more pronounced effect on brain serotonin, liver enzymes' activities and blood chemistry as compared in rabbits administered sertraline or clozapine. The present study therefore reports a novel contribution that oral administration of sertraline and clozapine affects memory, liver enzymes and function in rats. This is paucity of information on the effect of antidepressants on memory in humans and animals(12, 14 ).

## 5. Conclusions

Data of the present study indicate that sertraline improved only long-term memory, while clozapine improved both short term and long term memory. It is suggestive that sertraline and clozapine could find therapeutic significance in alleviating learning and memory problems.


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