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# Comparative Effects of Paroxatine and Clomipramine on Locomotor Behaviour in Mice

*Mfem CC[1], Oyama SE[2], Seriki SA[3], Nyoro IK[1]*

1. Department of Human Physiology, College of Medical Sciences, University of Calabar, Nigeria
2. Department of Family Medicine, University of Alberta, Canada
3. Department of Human Physiology, College of Medical Sciences, Edo State University, Uzairue, Nigeria

**ABSTRACT**

BACKGROUND/AIM: The present study investigates behavioral parallels between stress-induced mice and stress-induced mice that are treated with antidepressants (paroxatine and clomipramine). This is to determine the effect of these drugs on the locomotor behaviours of mice exposed to stress. METHOD: Twenty eight (28) Swiss Mice were divided randomly into four groups of 6 in each group; i.e. group one (control), group two (stressed), group three (stressed and then treated with paroxatine) and group four (stressed and then treated with clomipramine). Mice in all the groups were given normal rat chew and water throughout period of experiment. The four groups were then subjected to tests in both open field and elevated-plus maze apparatus. Open field apparatus and elevated-plus maze test were the method used to determine locomotor behaviour. These were determined in the frequency of line crossing, centre-square entry, centre-square duration in the open field apparatus, and open arm entry frequency and duration. RESULTS: Mice that were stressed without treatment with antidepressant had reduced locomotor activity when compared with Mice in control group. The stressed groups treated with paroxatine and clomipramine showed significant increase in locomotor activity($P < 0.05$) compared to the stressed non-treated group. The stress group treated with paroxatine had significant improved locomotor activitywhen compared to the stressed group treated with clomipramine ($P < 0.05$). CONCLUSION: Paroxatine and clomipramine administration result in significant improved locomotor activity in stressed mice. Paroxatine however caused a more significant improvement inlocomotor activity than clomipramine in mice recovering from stress when the two agents were compared.

***Keywords: Locomotor activities, Stress, Paroxatine and Clomipramine***

***Corresponding author: seriki.samuel@edouniversity.edu.ng***

## INTRODUCTION

Stress is the body's reaction to any change that requires an adjustment or response. The body reacts to these changes with physical, mental, and emotional responses. When stressed, a chemical reaction occurs in the body that allows it to act in a way to prevent injury. This reaction is known as "fight-or-flight," or the stress response. During stress response, heart rate increases, breathing quickens, muscles tighten, and blood pressure rises.Stressful events can have a damaging effect on normal physiological functions leading to a variety of diseases. Many of the diseases of the modern life like hypertension, diabetes, behavioral disorders have been suggested as some of the many deteriorating effects of stress**[1].**

Experimental models are required to better understand the progression of the diseases which elaborate new therapy. Exposure to stressful stimuli produces widespread physiological and behavioral effects in animals including man **[2].**Stress is an important factor of depression that causes the changes in various body systems. Animal health including human has been shown to be affected by the stressful events of life including situation which alters cognition, learning, memory and emotional responses, causing mental disorders like depression and anxiety.

Depression is a state of low mood and aversion to activity that can affect a person's thoughts, feelings, behavior and sense of well-being**[3].**However, many of these effects are mediated by stress-induced neurochemical and hormonal abnormalities that are often associated with oxidative stress **[4].**People with depressed mood may be notably sad, anxious, or empty; they

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may also feel hopeless, helpless, dejected or worthless. Other symptoms expressed may include senses of guilt, irritability or anger. These individuals may express a further feeling of shamefulness or an expressed restlessness. They may notably lose interest in activities that they once considered pleasurable to family and friends or otherwise experience either a loss of appetite or overeating. Experiencing problems like concentrating, remembering general facts or details, otherwise making decisions or experiencing relationship difficulties may also be notable factors in these individuals' depression and may also lead to their attempting or actually committing suicide **[5].**

Antidepressants are drugs used for the treatment of major depressive disorder and other conditions, including dysthymia, anxiety disorders, obsessive compulsive disorder, eating disorders, chronic pain, neuropathic pain and, in some cases, dysmenorrheal, snoring, migraine, attention-deficit hyperactivity disorder, addiction, dependence, and sleep disorders**[6].**

The most important classes of antidepressants are the selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (TeCAs), and noradrenergic and specific serotonergic antidepressant**[7].** Antidepressants are recommended by the National Institute for Health and Care Excellence (NICE) as a first-line treatment of several depressions and for the treatment of mild-to-moderate depression that persists after conservative measures such as cognitive therapy. There has been controversy regarding the efficacy of antidepressants in treating depression depending on its severity and duration. Two meta-analyses published in 2008 found that in mild and moderate depression, the effect of SSRIs is small or none compared to placebo, while in very severe depression the effect of SSRIs is between 'relatively small' and 'substantial' **[8].**

The 2008 meta-analysis combined 35 clinical trials submitted to the Food and Drug Administration (FDA) before licensing of four newer antidepressants (including the SSRIs paroxatine and flouxatine, the non-SSRI antidepressant nefazodone, and the SNRI venlafaxine). The authors attributed the relationship between severity and efficacy to a reduction of the placebo effect in severely depressed patients, rather than an increase in the effect of the medication. SSRIs are recommended by the National Institute for Health and Care Excellence (NICE) for the treatment of generalized anxiety disorder (GAD) that has failed to respond to conservative measures such as education and self-help activities. Among the SSRIs, paroxatine has the highest specificity for serotonin. Paroxatine affects chemicals in the brain that may be unbalanced in people with depression, anxiety, or other disorders. It is effective in depression that has proved resistant to other antidepressants and in depression complicated by anxiety **[8].**

Paroxatine is used to treat depression, obsessive-compulsive disorder, anxiety disorders, post-traumatic stress disorder (PTSD), and premenstrual dysphonic disorder (PMDD).Commonn side effects of paroxatine may include: vision changes; weakness, drowsiness, dizziness; sweating, anxiety, shaking; sleep problems (insomnia); loss of appetite, constipation; dry mouth, yawning; or decreased sex drive, impotence, or difficulty having an orgasm. Other antidepressants used in the treatment of obsessive-compulsive disorder, major depressive disorder, panic disorder, are the tricyclic antidepressants (TCAs). Clomipramine belongs to this group and is a highly selective inhibitor of serotonin reuptake**[9].** It is also an antagonist/inverse agonist at the histamine H1 receptor, the muscarinic acetylcholine receptors and the α1 adrenergic receptor. These last three actions likely contribute to its adverse effects **[9].**

The nervous system is a coordinating system that controls all the activities of the body. It receives millions of bits of information from the different sensory organs and then integrates all

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these to determine the responses to be made by the body. It is a communication network that allows an individual to interact appropriately with the environment. The nervous system consists of sensory and motor divisions. The sensory division initiates most of its activities emanating from sensory receptors whether visual, auditory, and tactile on the surface of the body or other kinds of receptors. The motor division controls the various body activities like contraction of skeletal muscles, smooth muscles in the internal organs and secretion of both endocrine and exocrine organs**[10].** These are collectively called the motor functions of the nervous system. Primarily, the nervous system is divided into two parts namely, the central nervous system and the peripheral nervous system. The central nervous system includes the brain and spinal cord. It is formed by neurons and the supporting cells called neuroglia. The functions of the central nervous system among others include organizing reflexes and other behavioural responses responsible for cognition, learning and memory and plans and executes voluntary movements. Memory refers to the storage mechanisms for what is learned, learning and memory are special forms of information processing that permit behaviour to change appropriately in response to environmental challenges based on past experiences. The peripheral nervous system is formed by the neurons and their processes present in all regions of the body. These consist of cranial nerves from the brain and spinal nerves from the spinal cord. It is further subdivided into the somatic nervous system and autonomic nervous system.

The somatic nervous system controls the movements of the body by acting on the skeletal muscles while the autonomic nervous system is concerned with regulation of visceral or vegetative functions **[10].** Behaviour consists of the totality of the organism's responses to its environment.

## METHODS

### Experimental animals and drugs

Twenty eight (28) Swiss mice, obtained from the Department of Pharmacology, University of Calabar, Nigeria with body weight of between 180 to 250g were used for the experiment. The mice were divided into four groups (n=7).

- Group 1: The control.
- Group 2: Stressed group (stressed but not treated).
- Group 3: Stressed and then treated with paroxetine (10mg/kg body weight, for 2 weeks)
- Group 4: Stressed and then treated with clomipramine (10mg/kg body weight, for 2 weeks)

All animals were allowed acess to feed and water.

### Drug administration protocol

The doses of drugs, the duration of the administration were done according to previous studies**[11].**

### Administration of paroxatine and clomipramine

A 20mg and a 10mg capsule of paroxatine and clomipramine was dissolved in 20ml and 10ml of distilled water to form a stock solution of 0.02mg/20ml and 0.01/10ml respectively. Each of the solution was administered at the dose of 10mg/kg body weight orally, once daily for two weeks.

### Stress regimen

This procedure was done through social isolation (prolonged social deprivation), confinement to small cages and exposure to bright light at night for the period of five weeks**[12].**

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**Apparatus and experimental protocol**

*The open field maze*

The large open field (72 × 72 cm, with 36cm high walls) constructed of plywood was used following the protocol of Brown *et al* **[13].** Each trial was recorded using a video cassette recorder (VCR) connected to a camcorder. This was for rescoring of behaviour.

**Experimental procedure in the open field maze:**

Mice were carried to the neuro-behaviour laboratory in their home cages from the animal house and were handled by the base of their tails at all times. Each mouse of the four groups was exposed to the open field maze by placing it in the centre square of the maze and allowed to explore the apparatus for 5 minutes. The mouse behaviour was scored within this period and the mouse returned to its home cage while the open field was cleaned with 70% ethyl alcohol and then allowed to dry between tests. This was to eliminate olfactory cue.

**Behaviour scores in the open field**

The behaviours score **[13];**

1. Line crossing: Number of times the mouse crossed a line drawn on the floor with all its four paws.
2. Rearing: Frequency with which the animal stands on its hind legs or leans against the wall with front paws.

**Elevated plus maze**

Experimental procedure in the elevated plus maze

The mouse was picked by the base of its tail from the home cage and placed in the center square between the open and closed arms facing an open arm. Each mouse was allowed to explore the maze for 5 minutes and the behaviours scored within thisperiod and then returned to its home cage. The apparatus was cleaned with 70% ethyl alcohol and then allowed to dry between tests in order to eliminate olfactory cue.

**Behaviour scores in the elevated plus maze**

1. Rearing: Frequency with which the animal stands on its hind legs or leans against the wall with front paws.
   **[13]**

**Statistical analysis**

Values for the result are expressed as mean ± SEM. The statistical analysis was done using the analysis of variance (ANOVA) and the post/hoc Newmann Keul's test. The computer software was Microsoft excel and SPSS for window.

Differences between means were tested at 0.05 level of significance.

**RESULTS**

**Frequency of line crossing for control, stressed, stressed + paroxatine, and stressed + clomipramine groups in the open field maze**

The frequency of line crossing for control, stressed, stressed+Paroxatine and stressed+Clomipramine groups were, 72 ± 3.0, 56 ± 2.0, 89 ± 4.7, and 73 ± 2.3 respectively. The

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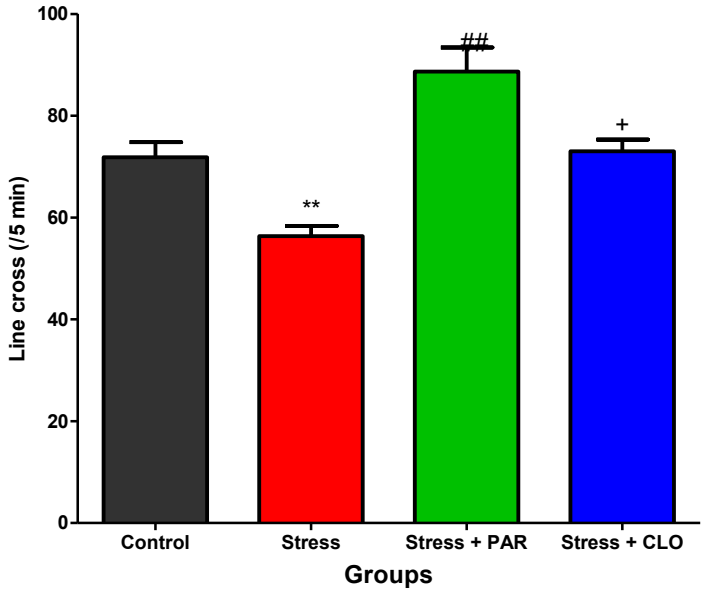
stressed group mice showed a significant decrease (P<0.01) in the frequency of line crossing compared to control group.

There was a significantly higher(P<0.05) line crossing frequency in stressed+paroxatine and stressed+clomipramine group of mice compared to stressed group. The frequency of line crossing in the stressed+paroxatine group was significantly higher (P<0.05) compared to that of the control group. The result also showed a significant increase(P<0.05) in the frequency of line crossing in the stressed+paroxatine group of mice compared with the stressed+clomipramine group Fig.1. However, there was no significant difference in the frequency of line crossing between the stressed+clomipramine group and control.




*** - Significant at p< 0.01 vs control; + - Significant at p< 0.05 vs stress + par; ## - Significant at p< 0.01 vs control*

**Fig.1: Line cross in the open field maze**

**Frequency of rearing in the open field for the control, stressed, stressed+paroxatine and stressed+clomipramine groups**

The frequency of rearing in the open field for the control, stressed, stressed+paroxatine, and stressed+clomipramine were, 23 ± 2.0, 15 ± 0.7, 8.8 ± 0.6, and 8.8 ± 0.6 respectively. There was a significant decrease (P<0.01) in the rearing frequency of stressed group and stressed-treated groups compared to control group. It was also noted that there was a significant higher difference in stressed+paroxatine rearing frequency compared to stressed+ clomipramine. Fig 2

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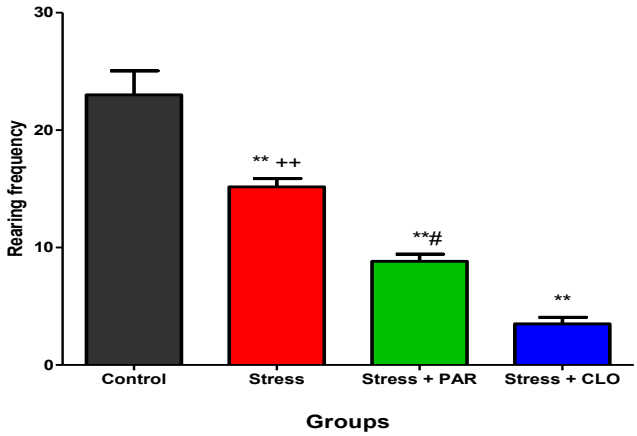


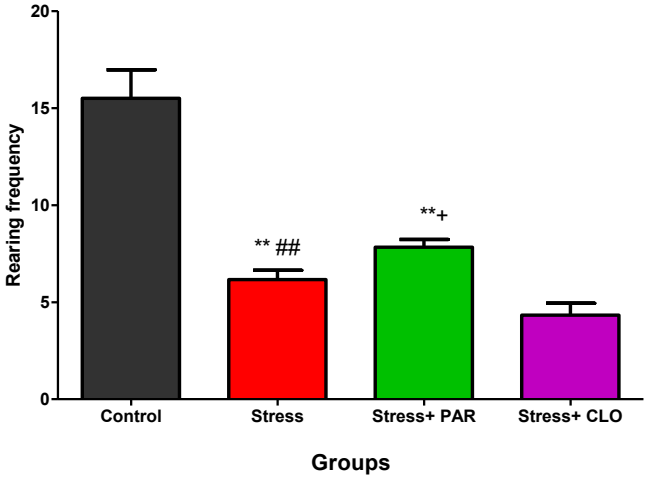

** - Significant at p< 0.01 vs control; # - Significant at p< 0.05 vs stress + clo;
++ - Significant at p< 0.01 vs stress + par.

**Fig 2: Rearing frequency in the open field maze**

**Frequency of rearing in the EPM**

The rearing frequency in the EPM for control, stressed, stressed+paroxatine, and stressed+clomipramine group of mice were,16± 1.5, 6.2± 0.48, 7.8±0.40, and 4.3±0.61 respectively. There was a significant decrease in rearing frequency in stressed, stressed+paroxatine, and stressed+clomipramine group of mice compared to the control group at P<0.01.

There was a significant increase (p<0.01) in rearing frequency in stressed+paroxatine group of mice compared to that of stressed group and stressed+clomipramine group at p<0.01 and p<0.05 respectively. Fig 3.




** - Significant at p< 0.01 vs control; ## - Significant at p< 0.01 vs treated groups;
+ - Significant at p< 0.05 vs stress+clo

**Fig3: Rearing frequency in the EPM**

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## DISCUSSION

### Locomotor behavior

The comparative effect of two antidepressants (paroxatione and clomipramine) on locomotor behavior in stressed mice was studied using open field test and elevated plus maze.

The behavior score in the open field test such as line crossing and rearing are measures of locomotor behavior. The scored behavior that is measures of locomotor behavior in the elevated-plus maze also include line crossing and rearing. High frequency in line crossing and rearing indicates an increased locomotor behavior.

The study showed a significant reduction in these indices of locomotor activity in stressed mice and a significant increase in the stress-treated with paroxatine and clomipramine groups of mice as compared with the control for the two neurobehavioural tests. The study further revealed an improved locomotor activity in stress-treated mice with paroxatine when compared with stress-treated mice with clomipramine. This increase in locomotor activity of the stress-treated mice with paroxatine could be due to hyper stimulation of motor areas of the brain including motor cortex and cerebellum as well as the discrete areas in the midbrain such as mesencephalic locomotor region that turns on the central pattern generators in the spinal cord that result in locomotor behaviorby paroxatine **[14].** Since drugs like norepinephrine precursor, L-dopa can turn on the central pattern generators for walking in spinal animals **[14],** and that a single dose of SSRI induces hyper activationof the primary sensorimotor cortex involved in movement **[15],** it is reasonable to think that drugs that stimulate generators and areas that control them can increase locomotor behavior. It is possible that paroxatine may improve the stimulation of generators and motor areas that control locomotor behavior in mice compared to clomipramine.

## CONCLUSION

Paroxatine and Clomipramine administration generally increases locomotor activitysignificantly, but paroxetine does it morethan clomipramine. This hyper effect could be due to the selectivity properties of paroxatine which do not affect other neurotransmitters like histamine and acetylcholine, thereby causing the blockage of histaminic and cholinergic receptor sites. Paroxatine may therefore be recommended as the first line of treatment for enhancing locomotor behavior and minimizing anxiolytic effects.

**No conflicts of interest among the authors over the manuscript**

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