Review Article

Systematic Review on Antidepressant Models

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ABSTRACT

Depression is a condition of the low state of mind and repulsion for action that can influence a man's consideration, conduct, emotions and feeling of prosperity. Depression influences 6% of adults every year and it is the main cause of suicide. Its side effects can be unbearable and unavoidable, affecting the individual patients as well as their families and the more extensive society. Depression is a possible life debilitating disorder that influences a huge number of individuals everywhere throughout the world. It can happen at any age from childhood to late life and is a colossal cost to society as this issue causes extreme trouble and interruption of life and, if left untreated, can be deadly. The lifetime majority of unhappiness is as high as 20% in the all-inclusive community worldwide with a female to a male proportion of around 5:2. The depression screening models are little hard to discover because it is the condition of mind in which the models have to work with. Screening models should help the researcher to know the right drug for the disorder. In this article, many screening models are described for the purpose of treatment and management of depression.

Keywords: Depression, Psychotic depression, Tail Suspension test, Muricide behavior in rats.

INTRODUCTION

Depression is feelings of severe despondency and dejection. Depression is normally called as Major Depressive Disorder and potentially life-threatening illness, which is caused by changes in monoamine neurotransmitter, mainly dopamine, serotonin or norepinephrine[1]. The patient is characterized by pervasive and low mood with low self-esteem and the patient may lose interest in daily social life and activities, sad mood, tiredness, guilt, sense of worthlessness, lack of concentration and suicidal thoughts. It is very common disorder and it may be less severe in some patients to most severe in patients like psychotic delusions and hallucination in some of them. Worldwide 20% of the total population is affected by depression[2]. Female are more prone to depression than males because of genetic, biochemical, environmental of some kind of psychological factor. Family history, major life change, health problems, some medicine and drugs abuser have more risk. It is estimated that in this weakening of central nervous system (CNS) synapses occur and N-methyl-D-aspartate (NMDA) and metabotropic glutamate receptors activation start. Calcium influx activates NMDA receptors and glutamate activation happens by the presynaptic mechanism[3].

Symptoms of Depression

The symptoms of depression help in diagnosis and better treatment of the affected individual. The symptoms of depression are majorly classified into four different categories.

Although depression may occur only once during your life, people typically have multiple episodes[4]. During these episodes, symptoms occur most of the day, nearly every day and may include:

- Feelings of sadness, tearfulness, emptiness or hopelessness
- Angry outbursts, irritability or frustration, even over small matters
- Loss of interest or pleasure in most or all normal activities, such as sex, hobbies or sports
- Sleep disturbances, including insomnia or sleeping too much
- Tiredness and lack of energy, so even small tasks take extra effort
- Reduced appetite and weight loss or increased cravings for food and weight gain
- Anxiety, agitation or restlessness
- Slowed thinking, speaking or body movements
- Feelings of worthlessness or guilt, fixating on past failures or self-blame
- Trouble thinking, concentrating, making decisions and remembering things
- Frequent or recurrent thoughts of death, suicidal thoughts, suicide attempts
- Unexplained physical problems, such as back pain or headaches

Types of Depression

Major depression

It is also called as Major Depressive Disorder (MDD). Weight loss or gain, insomnia, fatigue and low energy are some other symptoms. The person feels worthless and always surrounded by guilt, finds it difficult to make any decision and has suicidal thoughts[5].

Persistent depressive disorder

In this, the person is depressed for about 2 years or longer and show all the signs and symptoms of major depression. It is also called as dysthymia. It is same as major depression but the symptoms last for more time. The person suffering from this feel low self-esteem, hopeless, cannot concentrate on anything, either sleeps too much or not at all [6].

Bipolar disorder

This is also called as Maniac Depression because in this sometimes the person feels mood swings of excitation and depressions. The person feels two type of phase: first is the maniac phase in which the person gets super excited, feel a high energy, sleepless, and talk more. Second is the depressed phase, which is slightly similar to major depression and has all the symptoms. It can create a mess in the life of the affected individual, suicide is common. Medications such as mood Stabilizers and lithium are effective in this[7] .

Seasonal affective disorder

Feeling of depression due to lack of sunlight. This happens during the winter season due to exposer to less sunlight. This is related to the exposure of light and is, mainly found in those countries which have less sunlight in the winter season. People affected have same symptoms as of depression but during a particular time period of a year. It is may be due to a change in the biological clock or the circadian rhythm. Treatment can be done by light therapy, antidepressants and talk therapy[8].

Psychotic depression

Hallucination, delusions, paranoia conclude psychotic depression. In this, the person suffers from psychosis along with depression, which is very harmful. The person see or hear things that are not present, he may create false believes about himself and others and believes the others are trying to harm him in any way. Treatment is done with the help of antidepressants and antipsychotic medications.

Postpartum depression

Women after childbirth may have depression for weeks and months. The can be stressed due to adjustment of newborn and may cause depression, this type of depression affect the mother-son bonding. The symptoms of depression occur Baby Blue can occur; symptoms are unusual crying, irritating behavior, and anxiety. Antidepressants can help in this condition[9].

Premenstrual dysphoric disorder

Women get depressed during menstruation along with period symptoms. The symptoms of depression started with the start of a menstrual cycle. Depression symptoms alone with the feeling of mood swings, fatigue anxiety occurs. Antidepressants and contraceptive are helpful in this type of depression.

Situational depression

This type of depression occurs when a person feels difficulty in managing life events like something occur in life which they do not want to, loss of job, sudden casualty may be the reasons. This type of depression is caused due to some unwanted and undesirable situations that is happening in the person's life. Psychotherapy is most useful in this type of depression.

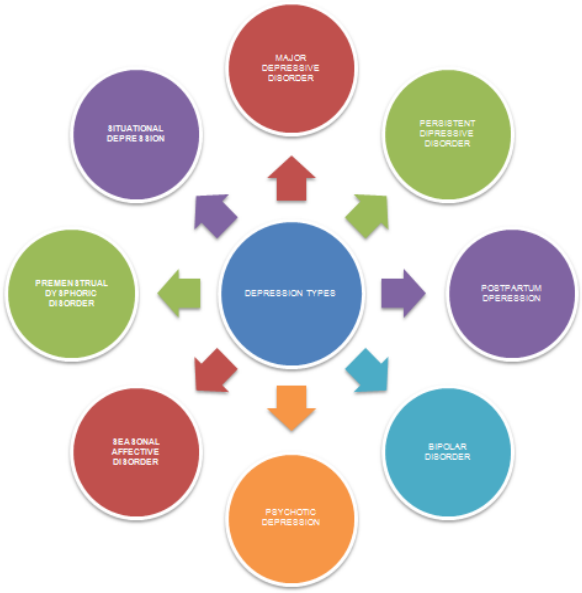


Figure 1: Types of depression.

Anti-Depressant Screening Models

Principle

The basic principle behind the testing of anti-depressant drugs is to find out the efficacy of the given drug and its effects. The test can find out how potent the drug is and the dose of anti-depressant activity because many drugs at higher or lower doses can give sedative or stimulatory action[10].

The following are the types of anti-depressant screening models in animals:

In-Vivo Screening Models	*In-Vitro* Screening Models
1. Forced swim test 2. Tail suspension method 3. Learned helplessness in rats 4. Muricidebehavior in rats 5. Amphetamine potentiation test 6. Catalepsy antagonism in chicken 7. Potentiation of NE toxicity in mice 8. Reserpine-induced hypothermia 9. Yohimbine toxicity enhancement	1. Inhibition of NE uptake in rat brain 2. Inhibition of Dopamine uptake in rat striatal

Table 1: *in vivo* and *in vitro* models of antidepressant drugs.

Forced Swim Test

Principle

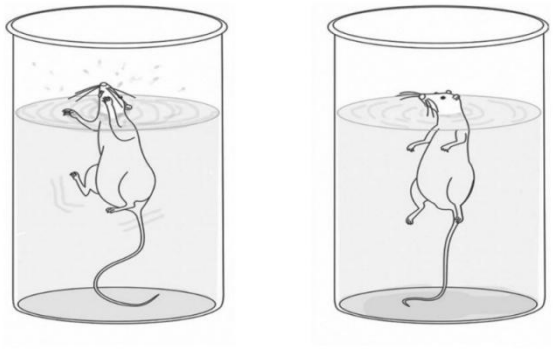
It was suggested by Porsolt *et al*. When rat or mice are subjected to force swim in a limited space with no way to escape then a characteristic immobility develops in them after some time of forced swimming. The anti-depressants drugs decrease the duration of immobility. It is the most widely used method for screening of acute antidepressants.

Procedure

Adult rats are allowed to swim in a cylinder with no escape filled with water at 25 ºC. When the rats are forced to swim in water initially it remains hyperactive, but approximately 5 min later the activity slows down and the phase of immobility starts. After 15 min the rats are removed and allowed to dry. The duration of immobility is measured. The same activity is done for standard and test groups and the drug is administered 1 h earlier when the test starts[11].

Evaluation

The duration of immobility is measured for test, control and standard groups treated with various drugs. The antidepressants drugs decrease the duration of immobility.



MOBILITY **IMMOBILITY**

Figure 2: Forced swim test

Tail Suspension Test

Principle

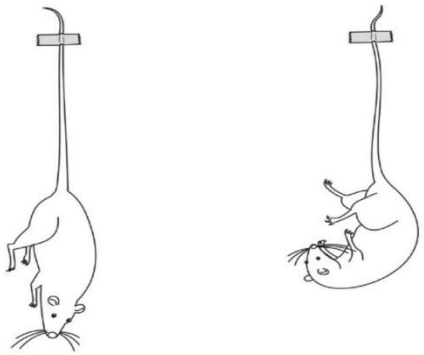
When a rat is suspended by its tail, the immobility is displayed because of inescapable stress. It reflects behavioral despair. The antidepressants drugs decrease the immobility in a tail-suspended rat.

Procedure

Three groups of rats are divided and proper food and water are given. Control, test, and standard groups are divided and are subjected to respective drugs. The rats are suspended upside down through its tail. At the start of the test, the rat tries to escape, but is unable and become immobile after some time. The readings are taken for 6 min by using CCTV camera and computer count the time for activity and immobility is recorded and compared with the test and standard groups[12].

Evaluation

The duration of immobility of standard and test is compared with control groups and decrease in duration of immobility is calculated. For different drugs, ED50 is calculated.



Immobility **Mobility**

Figure 3: Tail suspension method

Learned Helplessness

Principle

The rats are exposed to an unavoidable electrical shock for some time and after that, the animal is unable to

escape in a situation where escape is possible. An electrical grid box is constructed and the rat is placed in it and shock is given (0.7mA) for 1 hour every 10 sec per min interval. A 30 to 80% learned helplessness behavior is calculated. Antidepressants decrease the escape failure.

Procedure

Sprague Dawley rats of weight 250-300gm are used for this test. An electrical grid box is constructed on which the rat is placed. Shock is given (0.7mA) for 1 h every 10 sec per min interval. A platform is not given during the training of rats. After the training, a platform is inserted into the grid, drugs are given and a shock of 0.4mA is given for 10 sec. If any escape response occurs, the animal is allowed to enter on the platform for 10 sec and then it has to return to the grid. Readings have been taken for 10 responses for 20-sec duration[13].

Evaluation

The test and standard groups reduce the learned helplessness in comparison with the control group. The number of escape increases and the drug has considered effective antidepressants.

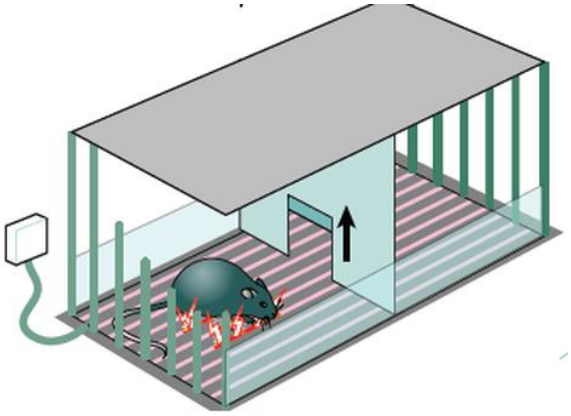


Figure 4: Learned Helplessness Test

Muricide Behavior in Rats

Principle

Some rats have the behavior of mouse killing when they are isolated for some time. This is called as muricide behavior in rats. Pre-treatment with pilocarpine can induce muricide behaviour. The rats, which consistently kill the mouse for 5 min, are used. The drugs, which cause inhibition of muricide behavior, have antidepressant action.

Procedure

Male Sprague Dawley rats of 300-350g are isolated for some weeks. The mouse is places in the rat's cage and 10-30% of rats kill the mouse by biting. The rats, which kill the mouse consistently for approx. 5 min are used for the test. Test and standard drug are injected respectively via intraperitoneal route before the test. Mice are placed in the cage for about 30, 60 and 120 min and ED50 value is calculated[14].

Evaluation

If the rats fail to kill the mouse in 5 min then the drug is considered to inhibit in Muricide behavior. ED50 value is calculated.

Amphetamine Potentiation Test

Principle

This test is done to evaluate the exploratory and locomotor activity of rats. Amphetamine when given to rats which are previously treated with antidepressants, the amphetamine effects are potentiated and are evaluated as a locomotor activity.

Procedure

Male Wistar rats of weight 200-300 g are taken for control, standard and test groups. They are kept at room temperature with 12-h light and 12-h dark cycle and fed with food and water. For a time of two weeks, the rats receive test and standard drugs respectively. When they receive the last dose of the drug 90 min later D-amphetamine (10mg/kg body weight) is injected through i.p. route. After 30 min, they are placed back and their locomotor activity is recorded and compared with control group[15].

Evaluation

Evaluation is done on the basis of their locomotor activity. Locomotor activity of control group is lowest while that receiving test and standard have more.

Catalepsy Antagonism in Chicken

Principle

This test is a method of screening of antidepressants and is done on Leghorn chickens.

Procedure

For this test, adult Leghorn Chickens are selected and divide it into test, control and standard groups. The chickens are pretested for cataleptic behavior. The chickens are grasped and turned back and hold for 1-2 min. Due to this cataleptic numbness occurs in them. The hand is removed carefully and the animal remains numb. By clapping hand around its head, the chicken jumps and run away. The test and standard drugs are given and the above test is performed for 4 times every 30 min of 2 h period[16].

Evaluation

If the occurrence of a cataleptic behavior is less than the control group, the test is positive. For 2 h period, the cataleptic behaviour is interrupted.

Potentiation of Norepinephrine Toxicity in Mice

Principle

Giving antidepressants to an animal, it blocks biogenic amines and potentiates the toxicity produced by Norepinephrine. This toxicity of NE can be lethal for mice.

Procedure

Male NMRI mice of weight 22-25g are selected randomly and divided into the groups: control, standard, and test. The test group and standard group are treated with the test drug and standard drug respectively, and control is treated with vehicle all given orally.

After 1 h, a sublethal dose of 3mg/kg body weight of NE is given via subcutaneous route. The rats are kept under supervision for 48 hours. The mortality rate is calculated[17].

Evaluation

For next 48 h the mortality rate of mice is assessed. The dose causing the death of at least 50% of the treated animal is calculated for all the respected groups. ED50 value can also be calculated.

Reserpine Induced Hypothermia

Principle

The main biogenic amine is Noradrenaline, 5HT, and Dopamine. When depletion of these occur it induce hypothermia in mice. Reserpine is given to induce hypothermia and antidepressants antagonize its action.

Procedure

Male NMRI mice of weight 20-25g is selected and grouped as test, control and standard groups. A dose of 2mg/kg body weight of reserpine is given to selected animals. Approx. 18 hours later the animals are placed in their cages. With the help of an electric thermometer recorded the initial rectal temperature. Test, standard and vehicle compound is given to respective groups via IP route. The rectal temperature is recorded every 60 min for 7 h. The difference in respective temperature is calculated[18].

Evaluation

Evaluation is done on the basis of the difference in recorded rectal temperature. The maximum difference in recorded temperature is calculated. Amphetamine and chlorpromazine can also induce hypothermia.

Yohimbine Toxicity Enhancement

Principle

Yohimbine is a selective alpha 2 blockers. It prevents binding of NE to alpha 2 receptors. The reuptake of NE to nerve terminals is blocked by antidepressants. Yohimbine, when given with antidepressants, cause toxicity of NE and finally death of the animal.

Procedure

Male NMRI mice of weight 22-25g are taken and grouped as control, test and standard groups. Each mouse is treated with standard, test and vehicle compound respectively according to their groups. 30 min later, a sublethal dose of 25mg/kg body weight of Yohimbine is injected into each mice via the subcutaneous route. They are kept under supervision for 24 h[19].

Evaluation

After the dosing of yohimbine, the mortality of mice is assessed for 1, 2, 3, 4, 5 and 24 h. The mortality of test, standard, and control groups are compared after 24 h. ED 50 value is calculated.

Inhibition of Norepinephrine Uptake in Rat Brain

Principle

The reuptake of NE is an important physiological process. It is important for removing NE in the synaptic cleft. Antidepressants inhibit the reuptake of NE. Hypothalamus is used for this model as it is mainly responsible for the uptake of NE.

Procedure

Tissue preparation

Male Wistar rats are taken in groups. They are decapitated and their brain is removed rapidly. The hypothalamus is weighed and homogenized by using ice-cold sucrose solution with the help of Potter-Elvejhem homogenizer. Centrifugation is done at 1000g at 0-4 ºC for 10 minutes and the supernatant is decanted which is used for the experiment[20].

Assay

800µl 62.5 Nm NE and 200µl of tissue suspensionis mixed and incubated in Krebs-Henseleit bicarbonate buffer at temperature 37ºC with 20µl test or standard drug or vehicle in control. Incubation of each assay tube is done at 0ºC ice bath with the 20µl vehicle at 95% O_2 and 5% CO_2. Centrifugation is done for 10 min at 4000g. After that, firstly, the supernatant is aspirated and the pellets are dissolved in solubilizer. This is then shaken and decanted into scintillation vials. This is counted in 10 ml liquid scintillation counting cocktail. The difference between camp at 37ºC and 0ºC is the active uptake.

Evaluation

The mean of at least three determination is calculated and this is the percent inhibition at each drug concentration. From the log-probit analysis, IC50 values can be determined. Desipramine is a standard drug with an IC50 value of 20nM[21].

Inhibition of Dopamine Uptake in Rat Striatal

Principle

Dopamine has sodium-dependent transport of high affinity in various tissue preparation. Dopamine is found in high amount in Striata. Antidepressants and cocaine inhibit the uptake of dopamine.

Procedure

Tissue preparation

Male Wistar rats are taken in groups. They are decapitated and their brain is removed rapidly. The Corpora Striata is weighed and its preparation is made. Homogenization of this is done by using ice-cold sucrose solution 0.32M 9 volumes with the help of Potter-Elvejhem homogenizer. Centrifugation is done at 1000g at 0-4 ºC for 10 minutes and the supernatant is decanted which is used for the experiment[22].

Assay

900µl 55.5 Nm Dopamine and 100µl of tissue suspension are mixed and incubated in Krebs-Henseleit bicarbonate buffer at temperature 37ºC with 20µl test or standard drug or vehicle in control. Incubation of each assay tube is done at 0ºC ice bath with the 20µl vehicle at 95% O_2 and 5% CO_2. Centrifugation is done for 10 min at 4000g. After that, firstly, the supernatant is aspirated and the pellets were dissolved in 1 ml solubilizer which is 1:4 ratio of Triton X-100 + 50% ethanol. This is shaken and then decanted into scintillation vials. This is counted in 10 ml liquid scintillation counting cocktail. The difference between CMP at 37ºC and 0ºC is the active uptake.

Evaluation

The mean of at least three determinations is calculated and this is the percent inhibition at each drug concentration. From the log-probit analysis, IC50 values can be determined. Nomifensine is a standard drug with an IC50 value of 460nM[23].

Table 2: Recent activities reported using different antidepressant models

S.No.	Model(S) Used	Activity	Year	Reference
1	Forced Swim Test	Altered Responsiveness to Cocaine and Increased Immobility in the Forced Swim Test Associated with Elevated cAMP Response Element-Binding Protein Expression in Nucleus Accumbens	2018	24
2	Forced Swim Test and Tail suspension test	Central irisin administration affords antidepressant-like effect and modulates neuroplasticity-related genes in the hippocampus and prefrontal cortex of mice	2018	25
3	Tail suspension test	The effect of ethanolic extract of Thymus kotschyanus on cancer cell growth in vitro and depression-like behavior in the mouse	2018	26
		The involvement of monoaminergic neurotransmission in the antidepressant-like action of scopolamine in the tail suspension test	2017	27
4	Forced Swim Test and Tail suspension test	Antidepressant effects of oleuropein in male mice by forced swim test and tail suspension test.	2018	28
		Chronic treatment with caffeine and its withdrawal modify the antidepressant-like activity of selective serotonin reuptake inhibitors in the forced swim and tail suspension tests in mice. Effects on Comt, Slc6a15 and Adora1 gene expression	2017	29
5	Learned helplessness	Effects of a single bilateral infusion of R-ketamine in the rat brain regions of a learned helplessness model of depression	2017	30
		Mice subjected to uncontrollable electric shocks show depression-like behaviors irrespective of their state of helplessness	2017	31
6	Muricide behavior in rats	Bupropion induces social anxiety in adolescent mice: Influence of housing conditions	2017	32
		Amprolium-induced thiamine deficiency in mice: evaluation of a practical model by oral administration	2017	33
7	Amphetamine potentiation test	Pramipexole restores depressed transmission in the ventral hippocampus following MPTP-lesion	2017	34
		Memantine improves memory impairment and depressive-like behavior induced by amphetamine withdrawal in rats	2016	35
8	Catalepsy antagonism in chicken	Muscarinic Acetylcholine Receptors Inhibit Fyn Activity in the Rat Striatum *In Vivo*	2018	36
		Protective effects of pituitary adenylate cyclase activating /polypeptide against neurotoxic agents	2017	37
9	Potentiation of norepinephrinetoxicity in mice	Antidepressant effect of linseed oil on various behavioral and pharmacological models of depression in Swiss albino mice	2018	38

10	Reserpine induced hypothermia	The antidepressant-like effect of trans-astaxanthin involves the serotonergic system	2017	39
11	Yohimbine toxicity enhancement	The possible mechanisms of protocatechuic acid-induced central analgesia	2018	40
12	Inhibition of norepinephrine uptake in rat brain	Atomoxetine, a selective norepinephrine reuptake inhibitor, improves short-term histological outcomes after hypoxic-ischemic brain injury in the neonatal male rat.	2018	41
		The Neurotoxin DSP-4 Induces Hyperalgesia in Rats that is Accompanied by Spinal Oxidative Stress and Cytokine Production	2018	42
13	Inhibition of dopamine uptake in rat striatal	Interactions between insulin and diet on striatal dopamine uptake kinetics in rodent brain slices.	2018	43
		Sodium sensitive cocain binding to rat striatal membrane: possible relationship to dopamine uptake sites.	2018	44

CONCLUSION

Depression is a serious mood disorder and its need to be treated carefully and properly. Depression occurs due to a deficiency in the biogenic monoamine such as serotonin, dopamine and noradrenaline. The treatment with antidepressants is done on the basis of their ability to improve monoaminergic transmission. Behaviour, thoughts, genetics, and environment plays a vital role in depression. Psychotherapy is very useful in treating depressed patients. The screening models can help to find out the efficacy of a novel drug with respect to a standard drug. It can also be used to find out the efficacy of a pre-existing drug which will eventually lead to better treatment and management of the ailment.

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