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DEPRESSION: A REVIEW ON INTRODUCTION, FACTORS AND IN-VIVO SCREENING METHODS

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ABSTRACT

Since depression is common, numerous people don't really exhibit emotional distress due to the quantity and diversity of physical and neurological clinical manifestations of major depressive disorder (MDD). Due to this significant frequency of MDD among other disorders, physicians and other healthcare providers must also identify and treat chronic depression within their patients. Depression is a prevalent mental illness. Projections suggest that 5 percent of adolescents globally struggle with depressive symptoms. Depression is the leading driver of impairment worldwide nowadays, and it contributes considerably to the global burden of disease. Depression is quite common in women than in males. Suicide can be compelled by depression. The major causes of depression include brain chemistry, genetics, stressful events in life, personality, family history, moodiness, lack of appetite, loneliness, alcoholism, and illness. The screening method's principles are as follows: a) to investigate the connection among both the psychoactive impact of diverse functional prototypes and the therapeutic effectiveness of well-known antidepressant medications and b) by constructing a correlation with both the antidepressant dosage and the sedated dosage form, the movement patterns of such tests enable evaluation of the selectivity of antidepressant efficacy. In vivo methods include the water wheel model, tail suspension test, resperpine-induced hypothermia, amphetamine potentiation, resident intruder paradigm, learned helplessness, and murderous behavior of rats.

KEYWORDS: Depression, Neurological clinical manifestations, Clinical efficacy, Behavioral impact, Antidepressant activity.

1. INTRODUCTION

Depression is a serious illness and a significant public health issue. No matter the nation, cultural group, or social economic class, many universal illnesses share identical characteristics and symptoms.[1] The symptoms of depression, which are categorized medically as a mental health issues and behavioral disease,[2] influence a person's self-esteem, enthusiasm, sentiments, perceptions, attitude, and sensation of joy.[3] Depressive moods are a key indicator of sadness because they refer to a decreased excitement and enjoyment of activities that often result in human satisfaction.[4] Unipolar melancholy and severe melancholic syndrome, among other emotional disturbances, can manifest as unhappiness,[5] it is a common, transient response to traumatic events in life, like death of a beloved; and[6] it is a negative consequence of different drugs and treatments.

The timing and course of depression are relatively rare, although many preadolescents (aged 9–12) and children in the 3-5 age groups have significant internalizing symptoms of dysphoria and distress. Whether the lifestyle factors, including determinants of depressive episodes that begin in childhood, adolescence, and adulthood[7] are exactly the same. The above question's solution is ambiguous. According to neuroscientist and behavioral evidence, both of these disorder communities typically identify similar characteristics, but not all three,[7] indicating a heterogeneous narrative of linked and semi-linked mechanisms at the start of depression at various stages of gestation. In terms of risk, developmental subtypes of depression are different. To examine the risks for purposes of biosocial research, intervention and prevention would be important, as has been shown by research on developmental subtypes of antisocial behaviors.[8] An overview on depression:

a) Specialty: Psychotherapy, Study of Mentality

b) Consequences: Brain structure, heredity, personal exposures, illnesses, and temperament.

c) Hazardous factors: The threat is associated with severe illness stereotypes.[9]

d) Therapeutic techniques: Beckman Depressive Index and Patients Wellness Assessment.

e) Prevention: Social connections; physical activity

f) Treatment: Talking therapy, Psychopharmacology

Signs and Symptoms[10]

- Hyperactivity
- Risk-taking behavior
- Stress

- Anger or irritability
- Alcohol/drug abuse
- Insomania (Sleep disturbance)
- Loss of interest

Common depression symptoms

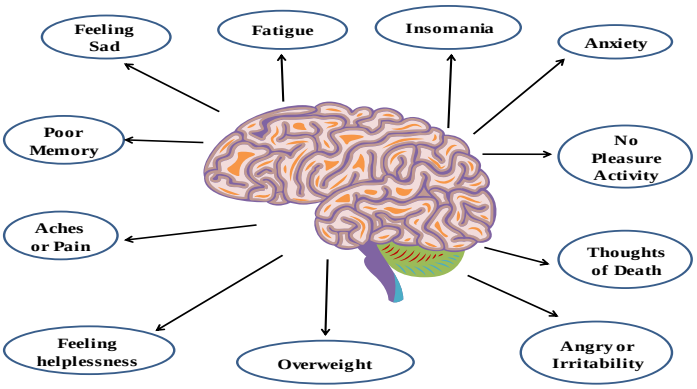

Fig. 1: Common depression symptoms.

Depression types[11]

1.	Nounmanic-depressive illness
2.	Assorted unhappiness
3.	Unlawful activitieS
4.	Desolation depression
5.	Insignificant disorder
6.	Postpartum depression
7.	Periodic major depressive episode
8.	Climatic intuitive disorder
9.	Dysthymic disorder

Common types of depressive disorders

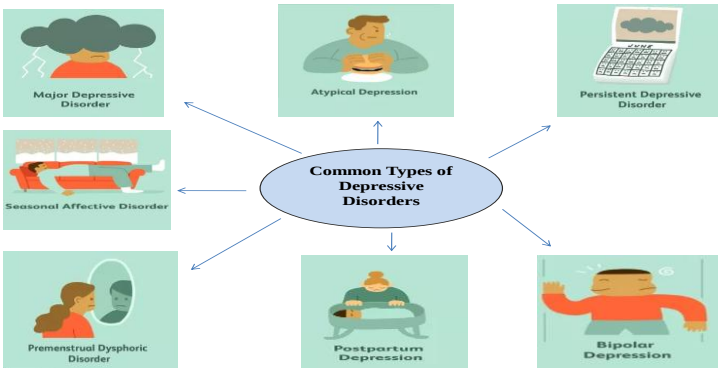

Fig. 2: Schematic presentation of depressive disorders.

2. Factors

2.1 Life events: Childhood adversity, especially both tangible and interpersonal assault, neglect, and even CSA, is a significant quasi-potential predictor for a number of cognitive and natural diseases that can manifest in children, school-age children, but also in adults.[11,12]

2.2 Temperament, personality, and copying styles: Steady differences between the sexes in babyhood are seen in authoritative parenting, showing that girls are superior at controlling their attentiveness and cause more significant problems than males do. This is in keeping with the fact that boys are more likely to try to mitigate their difficulties.[13] Males and females exhibit the same levels of perceived stress, or psychoticism, at a prematurely young age.[14] During toddlerhood, girl's antisocial trait ratings significantly rise in proportion to guy's levels, plus both higher Machiavellianism and inauspicious mood state scores are sustained for the entirety of the human life.[15] Premature gender disparities were small but constant and entailed interconnected qualities that indicated an intercultural inclination, which included friendliness, social competence, and maverick.[15,16]

A significant portion of the sexual identity discrepancy in depressive episodes was already attributed to an introspective feedback pattern, such as the propensity to apathetically and progressively scrutinise an individual's discomfort, issues, and worries despite making a move. Retrospection helps to foretell bouts of depression, but it works in conjuction with stress to do so.[18] Though it exhibits a high degree of predictability in forecasting psychotic feelings, it must be associated with negative affectivity.[19]

2.3 Alcoholism: Liquor could be a stimulant that slows both prefrontal and temporal cortical regions, among other neurological regions, and has a detrimental effect on judgement and memory.[20] Consuming high amounts of alcohol may contribute to harsher, more acute depressive symptoms.[21]

2.4 Family history: Early research[22] suggests that maniac-depressive individuals who have recently experienced stress may have less individuals of the family have mental health issues in the past. The foundational idea of these findings is that there is a lower chance of discovering significant extraneous influences in the histories of mental illness "the more defective the familial stock" (p. 530). These preliminary findings were strengthened by

further studies that concentrated especially on serious depression. For instance, in a group of depressed people,[23] we found an inverse relationship between severe psychological stress and familial rates of depression.

2.5 Bullying: When an individual is repeatedly exposed to unpleasant, degrading, or hurtful treatment in social and public life.

2.6 Medical treatments: Advancements in science and changes to the interventions and environment have influenced contemporary developments in the depression treatment field. In the last few years, newly marketed antidepressants were made available in the US: fluoxetine (Prozac), sertraline (Zoloft), paroxitine (Paxil), bupropion (Wellbutrin), nefazodone (Serzone), and citalopram (Celexa). These drugs are structurally and pharmacologically quite dissimilar from prior TCA and bradykinin oxidase blocker treatments.[24]

2.7 Substance-induced: So many addictive substances, whether used often or for extended periods of time, can worsen or induce depression. Liquor, tranquillizers (especially benzodiazepines on conventional), analgesics (including opium and pain medication), accelerators (narcotics and methamphetamine), magic mushrooms, and opiates are some of the drugs.

2.8 Non-psychiatric illness: Many communicable diseases, dietary shortcomings, neurodegenerative diseases, and pharmacological issues, including lupus, amyotrophic lateral sclerosis, parkinsonism, fibromyalgia, cerebrovascular disease, insulin resistance, and cancer, can lead to depressed mood. Such situations also include the extent to which a person has hypergonadotrophinemia (in men), extension ailment, Cushing dysfunction, thyroid issues, congenital hypothyroidism, thyroiditis, and hypercalcemia.

2.9 Psychiatric syndromes: A mental disorder is a behavioral or mental pattern that causes impairment of personal functioning.[24]

3. Measures: The lifetime history of the patient was routinely assessed by interviewing the patient carefully every session and making a uniform index of lifetime episodes. Detailed information about the patient's family is included in a comprehensive questionnaire that helps to judge the family history of depression. Life events and difficult schedules were used to operationalize life stress.[25]

4. **Animals used in experimental pharmacology education and research:** Rats and mice have been used for the bulk of trials (96%). Gerbils (13%), rabbits (18%), and nonhuman primates (19%) are other creatures that are frequently used.[26]

5. **Antidepressants:** Antidepressant medications are used to treat illnesses like major depressive disorder, anxiety disorders, and chronic pain, in addition to managing addictions.[27] Common side effects of antidepressants include dry mouth, weight gain, drowsiness, headaches, sexual dysfunction, and emotional blunting. The percentage of persons aged 12 and older using antidepressants in the United States increased from 7.7 percent of credible sources in 1999–2002 to 12.7 percent in 2011–2014, according to the Centers for Disease Control and Prevention (CDC). Antidepressants are used by around twice as many women as men.

Types of antidepressant drugs

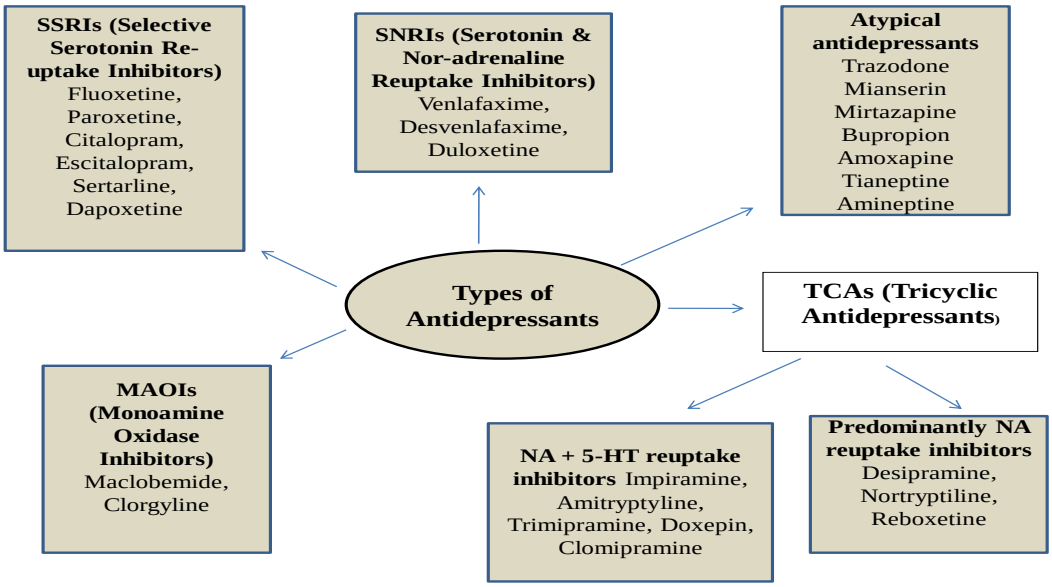

Fig. 1: Schematic diagram of antidepressant drugs.

6. **Pharmacological side effects of antidepressants**[28]

1. Anti-muscarinic Jaw clenching, indigestion, urine stagnation, impaired foresight, perceptual decline, and other ailments are examples of consequences.
2. Histamine H1 blockade: sedation, falls, cognitive impairment
3. Nor-adrenaline A-1 blockade: sexual arousal issues and hypoxia in the posture
4. Dopamine sickness, anorexia, diminished appetite, and queasiness are all manifestations of 5-HT transporter restriction.

5. Obesity reduction from 5-HT blockage
6. Diaphragm stabilization: standby mode and myocardial dysrhythmia
7. Sophisticated: swift bipolar abnormalities, myoclonic seizures, seizures, fine shaking, and perspiration

7. Withdrawal symptoms

Among all of the basic types of medicines, cessation (withdrawal) episodes can develop (29). Dopamine pickup blockers and 5-hydroxytryptamine and adrenergic receptor reintegration blocker venlafaxine have received a lot of interest lately(SNRI). According to twofold research, drawdown experiences are frequent with a few drugs. 7 of 9 (78%) venlafaxine-treated participants and two (22% of nine nonrandomized volunteers) observed the appearance of a detrimental effect in the three days after the treatment was stopped.[30] The variance in the prevalence of termination complaints among all SSRIs has been validated by a second double-blind trial.[31]

8. Uses of antidepressant drugs

1. Chemical features, professional and clinical aspects, regulations, and compensation patterns, among other things, have an impact on the decision to take an antipsychotic.[32]
2. Fatal cornerstone outcomes of antidepressants include hemorrhage, ischemic stroke, and conscience damage.[33]
3. Antidepressants are frequently used in therapeutic settings for illnesses other than sadness, including anxiety, insomnia, schizophrenia, and cluster headaches.[34]

9. Productiveness: Any antidepressant's impact may initially not become apparent for several weeks. Although patients think the drugs are ineffective, many patients quit taking them.

10. Screening method's principles: Screening methods in pharmacology focus on methods for screening substances for pharmacological activities and discussions of the organization of screening programs. Screening methods are based on two principles:

1. To investigate a potential connection with the operational efficiency of well-known pharmaceuticals, including the associated impact on diverse scientific experimental models.
2. The motor activity of these tests allows for the assessment of antidepressant specificity by formulating a dosage-to-antidepressant proportion and the sedative or stimulant dose.

11. In-vivo screening methods

11.1 Water wheel model or forced swim test: Depending on the finding that most mammals adopt a motionless stance in an impermeable canister packed with water, "the forced-swimming test was developed". In rodent analogues of depressive research, a similar test, officially recognized as the Porsolt test, is extensively employed as a screening tool for psychiatric therapies.[35–37] Each mammal is confined in a water-filled receptacle while undergoing FST so that it is unable to escape. The animals would initially struggle to flee but eventually go limp.[38]

Principle: Whenever rodents or mice are made to float inside a small area, they show depression.

Method: Animals are put through two tests in which they must swim against their will inside an impenetrable acrylic glass cylinder filled with water. The preliminary hearing lasts 15 minutes. The second trial is for 5 minutes after 24 hours. The second trial is measured by the amount of time the test animal goes without moving other than what's been instructed to maintain its staying afloat.[39] Electroconvulsive shock and different kinds of antidepressants can also shorten this period of immobility.[40] Another typical variation of this behavioral test that is performed only on mice is a trial that lasts six minutes.[41] Because selective serotonin reuptake inhibitors have been shown to increase swimming behavior while selective nor-epinephrine reuptake inhibitors like desipramine and maprotiline have been shown to increase climbing behavior, modern test implementations evaluate swimming and climbing behaviors separately.[42]

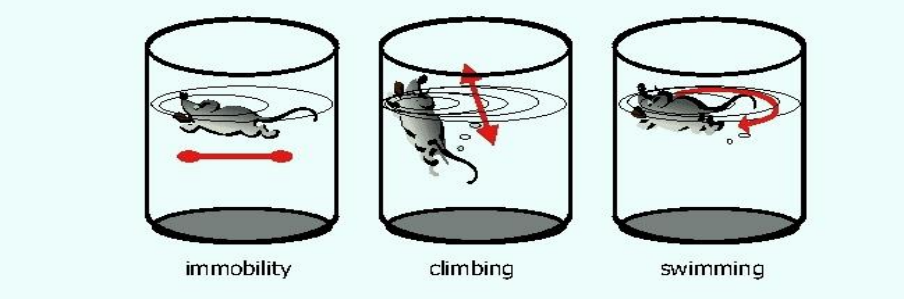

Fig. 1: Forced swim test.

11.2 Tail Suspension Test (TST): The Method, also widely recognized as the tail flick test, that earlier utilises a similar scientific foundation and attitudinal monitor with the FST is

depend on its discovery that mammals (just about invariably mice, through hamsters and rats are options to opt) develop an immobile stance well after preliminary break-free progression patterns.[43,44] As a result, the animal is immobile during the TST for distant future of time than it is during the FST, and thus the TST is a little more sensitive to the effects of antidepressants.[45] Since the animal's stiffness might have been caused by the surprise of being plunged under water, the interpolation is less than screening test. The next issue is dehydration.[46]

Principal

a) The mouse is suspended by the tail.
b) Longer periods of immobility.

Method of tail suspension test: For five minutes, the animal (male mice) is suspended by its tail from a tube at a height of around 10 cm. The animal will attempt to flee during this time and grasp for the earth. Its immobility is measured in terms of how long it lasts. A single test is administered to each animal alone, away from all other animals. Two sets of rats should be used in the experiment: the control group, which received saline injections, and the test group, which received injections of the antidepressant-like substances.[47]

Fig. 2: Schematic Representation of Tail Suspension Test (TST).

11.3 Learned Helplessness: Animals can develop a pathetic behavior called "fear of getting."[48] When faced with unavoidable unpleasant stimuli, acquired helplessness causes a restrained response in unfamiliar circumstances.[49] Learning to be helpless entails cognitive attributions that range from specific to universal, interior to exterior, and fixed to instable, which allow learned helplessness to transfer from one set of circumstances to another,[50] resulting in the emergence of personality traits.[51] Internal attributions express the idea that

the adverse condition is attributable to the person rather than to the environment. The idea of stable attribution is that unpleasant circumstances persist over time rather than changing. The adverse condition, according to global attribution, is context-specific and consistent rather than unique to a given setting.[52] While inherent lessness is a context construct that encodes a learned proclivity to behave hopelessly,[53] self-efficacy only refers to beliefs about one's ability to perform certain behaviors in specific contexts.

11.4 Chronic mild stress: Chronic Mild Stress Paradigm, also known as persistent unexpected, shifting, or irregular stress, is a popular rat model that requires accurate recognition of and exposure to a variety of minor stressors that change and are unpredictable over an extended period (1–8 weeks).[54] Chronic moderate stress, which is based on the animals losing their ability to respond to rewards after being exposed to a number of diverse stressors, is a corroborate and often used animal model. After earlier researchers found that rats exposed to a variety of quite severe stressors did not raise their hydration status when sucrose or sugar substitutes were added to normal drinking water, the CMS model was created in the late 1980s.[55]

11.5 Muricidal test: Pharmacological investigation employs the muricidal test. This term comes from the Latin word for "mouse slaying". The test gauges a rat’s propensity to attack mice brought into its cage at home or during another sitting.[56] The mouse is not always actually killed in the laboratory use of this test.[57] This test is occasionally used for antidepressant inspection, investigation of aggression, and other psychotropic agents. Considering that many antidepressants have serotonergic pathways that inhibit muricidal behavior. The test may be helpful in finding antidepressants. Although lithium has antidepressant qualities, it doesn’t prevent suicidal behavior, suggesting a potential drawback to using it as a screening tool for antidepressants.

11.6 Reserpine-Induced hyperthermia: Human H+-coupled vesicle norepinephrine channels VMAT1 and VMAT2 are permanently blocked by reserpine. By inhibiting cortical VMAT2, active metabolites slow reception while also decreasing storage of neurotransmitters such as noradrenaline, endorphins, zoloft, and urticaria in the secretory cleft of synapses.[58] Psychiatric drugs counteract the drop in skin temperature brought about by reserpine. "All investigations used healthy Swiss oxidative stress markers mice (20-24 g) by CERJ-General St. Isle 53940 in France". Mice were kept in groups of ten in a room thermostatically kept at 211°C with either a 12-hour photoperiod or a 24-hour photoperiod.

There was no scarcity of food or liquid. The rectal temperature is recorded every hour. Every session, the thermal deviation beyond the vessel's regulations is assessed, and even the highest deviation receives a penalty. Antidepressant medications don't always cause anaemia to repeat itself. Methamphetamine and amiodarone may also impair the body's ability to regulate its temperature.

11.7 Social defeat stress: A framework called "social defeat" is applied to study the biological and pathological effects of aggressive dialogues between mating pair creatures or people in a dyad or group contexts, with the potential to have very significant effects on resource exploitation, mate connection directly, and status groups. In actual life, mammals (especially mankind) must deal with pressure brought on by encounters with cospecifics, particularly owing to ongoing conflicts over the ownership of scarce resources, partners, and economic class.[59] Additionally, studies suggest that neuroendocrine processes involving serotonin, dopamine, adrenaline, noradrenaline, the anterior pituitary axis, locus nested, and limbic regions regulate the referred behavioural consequences.[59] Studies on both animals and humans show that the cultural environment has a significant impact on the stress-related effects. These observations appear to be particularly true for social pressures like professional rejection.[59]

11.8 Marble burying test: The mammal paradigm for perfectionism or anxiety behaviour is the practice of burying marbles. It derives from rodents burying both dangerous and non-harmful items in their nests.[60] Despite being frequently utilized, there is considerable disagreement over how to perceive the data. Rodents are kept for 30 minutes in a typical cage containing 10 marbles evenly dispersed across the bedding, which is 5 cm deep and made of wood chips. Within thirty minutes, the pebbles are tallied that have been buried. In this technique, a stone is considered buried if bedding covers at least two-thirds of it. There must be two animal groups in the study: one that received saline injections and the other that received injections of the substance under investigation. This test comes in a variety of forms. While some studies employ more marbles, other variations arrange the marbles in a unique way. While conducting this experiment, it’s crucial to maintain silence in the lab to prevent unforeseen outcomes. The maturity of the rodents being examined must be identical since younger animals will bury marbles more quickly than older mice.[61]

12. CONCLUSION

Although there are many animal models of depression, there are also lot of coveates and limitations that constrain their usefulness. It is known that translating human affective disorders into relevant tests utilizing rodents is problematic. Nonetheless, scientists still attempt to establish an ideal animal model of depression that displays strong face, construct and predictive validity. This paper provides a description of the most widely used animal models of depression currently utilized in evaluating anti-depressives and in understanding the depressive state. Moreover, it presents a discussion of the advantages and drawbacks of each model. As revealed, the more rapid and acute antidepressant-responsive assays, such as the FST and TST, are useful tools which allow the quick and economical detection of compounds with potential anti-depressant-like activity in which the mechanism of action is similar to older known drugs. The identification of novel antidepressant mechanism is made possible by using models that can recreate critical process operative in depression. Since critical processes are still not deeply known, models that employ stress exposure, time-dependent induction and treatment response are the most appropriate in exploring the mechanisms underlying depression and its treatment.

REFERENCES

1. Sartorius, Norman & WHO Collaborative Study on Standardized Assessment of Depressive Disorders. Depressive disorders in different cultures: report on WHO Collaborative Study on Standardized, 1983. Assessment of Depressive Disorders/N. Sartorius … [et al.]. World Health Organization. https://apps.who.int/iris/handle/10665/37139
2. de Zwart PL, Jeronimus BF, de Jonge P. Empirical evidence for definitions of episode, remission, recovery, relapse and recurrence in depression: a systemic review. Epidemiol Psychiatr Sci, 2019; 28(5): 544-562. doi:10.1017/S2045796018000227. Epub2018 May 17. PMID: 29769159; PMCID: PMC7032752.
3. Gilbert P. Psychotherapy and counseling for depression Los Angeles: Sage, 2007; 3. ISBN 978-1849203494. OCLC 436076587.
4. American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders Arlington, VA: American Psychiatric Publishing, 2013; 5.
5. Kaufman J, Martin A, King RA, Charney D. Are child-, adolescent-, and adult-onset depression one and the same disorder? Bio Psychiatry, 2001; 15, 49(12): 980-1001. doi: 10.1016/s0006-3223(01)01127-1. PMID: 11430841.

6. Moffitt, T. E. Life-course-persistent versus adolescence-limited antisocial behavior. In D. Cicchetti & D.J. Cohen (Eds.), Developmental psychopathology: Risk, disorder, and adaptation John Wiley & Sons Inc, 2006; 570 - 598.
7. Martin LA, Neighbors HW, Griffith DM. The experience of symptoms of depression in men vs women: Analysis of the National Comorbidity Survey Replication, JAMA Psychiatry, 2013; 70(10): 1100-6. doi: 10.1001/jamapsychiatry.2013. 1985. PMID: 23986338. http://archpsy.jamanetwork.com/ by a University of St. Andrews Library
8. Orvaschel H, Thompson WD, Belanger A, Prusoff BA, Kidd KK. Comparison of the family history method to direct interview. Factors affecting the diagnosis of depression. J Affect Disord, 1982; 4(1): 49-59. doi: 10.1016/0165-0327(82)90019-2. PMID: 6461687
9. Shrivastava A, Bureau Y, Rewari N, Johnston M. Clinical risk of stigma and discrimination of mental illness: Need for objective assessment and qualification. Indian J Psychiatry, 2013; 55(2): 178-182. doi:10.4103/0019-5545.111459
10. Brown V, Smith D. Mouse models of madness. Mol psychiatry, 1999; 4(50): 400-2. PMID: 10523206
11. Benazzi F. Various forms of depression. Dialogues Clin Neurosci, 2006; 8(2): 151-161. doi:10.31887/DCNS.2006.8.2/fbenazzi
12. Heim C, Shugart M, Craighead WE, Nemeroff CB. Neurobiological and psychiatric consequences of child abuse and neglect. Dev Psychobiol, 2010; 52(7): 671-90. doi: 10.1002/dev.20494. PMID: 20882586
13. Wegman HL, Stetler C. A meta-analytic review of the effects of childhood abuse on medical outcomes in adulthood. Psychosom Med, 2009; 71(8): 805-12. doi: 10.1097/PSY.0b013e3181bb2b46. Epub 2009 Sep 24. PMID: 19779142.
14. Else-Quest NM, Hyde JS, Goldsmith HH, Van Hulle CA. Gender differences in temperament: a meta-analysis. Psychol Bull, 2006; 132: 33-72. doi: 10.1037/0033-2909. 132.1.33. PMID: 16435957.
15. Costa PT, Terraciano A, McCrae RR. Gender differences in personality traits across cultures: robust and surprising findings. J Pres Soc Pyschol, 2001; 81(2): 322-331. doi: 10.1037/0022-3514.81.2.322. PMID: 11519935
16. Zahn-Waxler C, Shirtcliff EA, Marceau K. Disorders of childhood and adolescence: gender and psychopathoogy. Annu Rev Clin Psychol, 2008; 4: 275-303. doi: 10.1146/annurev.clinpsy.3.022806.091358. PMID: 18370618
17. Nolen-Hocksema S, Watkins ER. A Heuristic for Developing Transdiagnostic Models of Psychopathology: Explaining Multifinality and Divergent Trajectories. Perspect Psychol

Sci, 2011; 6(6): 589-609. doi: 10.1177/1745691611419672

18. Gowin J. "Your Brain and Alcohol". Psychology Today, 2010.
19. Fergusson DM, Boden JM, Horwood LJ. Tests of causal links between alcohol abuse or dependence or major depression. Arch Gen Psychiatry, 2009; 66(3): 260-6. doi: 10. 1001/archgenpsychiatry.2008.543. PMID: 19255375
20. Lyubomirsky S, Layous K, Chancellor J, Nelson SK. Thinking about rumination: the scholarly contributions and intellectual legacy of Susan-Nolen-Hocksema. Annu Rev Clin Psychol, 2015; 11: 1-22. doi: 10.1146/annurev-clinspy-032814-112733. Epub 2015 Jan 2. PMID: 25581241
21. Klein DN, Kotov R, Buffered SJ. Personality and depression: explanatory model and review of the evidence. Annu Rev Clin Psychol, 2011; 7: 269-95. doi: 10. 1146/annurev-clinpsy-032210-104540. PMID: PMC3518491.
22. Edward AS. A preliminary study of the precipitating situation in two hundred cases of mental disease. American Journal of Psychiatry, 1922; 4: 503-36. doi: 10.1176/ajp.78.4.503.
23. Pollitt, J. Relationship between genetic and precipitating factors in depressive illness. Br J Psychiatry, 1972; 121(560): 67-70. doi:10.1192/bjp.121.1.67. PMID: 5047173.
24. Bolten D. What is Mental Disorder? An essay in philosophy, science, and values. Oxford University Press, Oxford, 2008. https://doi.org/10.1093/med/9780198565925.001.0001
25. Goldman LS, Nielson NH, Champion HC. Awareness, diagnosis and treatment of depression. J Gen Intern Med, 1999; 14(9): 569-80. doi: 10.1046/j.1525-1497.1999.03478.x. PMID: 10491249; PMCID: PMC1496741.
26. Monroe SM, Slavich GM, Gotlib IH. Life stress and family history for depression: The moderating role of past depressive episodes. J Psychiatr Res, 2014; 49: 90-5. doi: 10.1016/j.jpsychires.2013.11.005. Epub 2013 Nov 19. PMID: 24308926; PMICD: PMC3918432.
27. Jennings L. Chapter 4: Antidepressants. In Grossberg GT, Kinsella LJ (eds). Clinical psychopharmacology for neurologists: a practical guide. Springer, 45-71. doi: 10.1007/978-3-319-74604-3_4.
28. Cookson J. Side-effects of antidepressants. Br J Psychiatry Suppl, 1993; (20): 20-24. PMID: 8252912.
29. Lejoyeux, M., Ades, J., Mourad, S. et al. Antidepressant Withdrawal Syndrome. CNS Drugs, 1996; 5: 278-292. https://doi.org/10.2165/00023210-199605040-00006
30. Fava M, Mulroy R, Alpert J, Nierenberg AA, Rosenbaum J F. Emergence of adverse

events following discontinuation of treatment with extended-release venlafaxine. Am J Psychiatry, 1997; 154(12): 1760-2. doi: 10.1176/ajp.154.12.1760. PMID: 9396960.

31. Michelson D, Fava M, Amesterdam J, Apter J, Londberg P, Tamura R, Tepner RG. Inerruption of selective serotonin reuptake inhibitor treatment: Double-blind, placebo-controlled trial. Br J Psychiatry, 2000; 176: 363-368. doi: 10.1192/bjp. 176.4.363. PMID: 10827885.
32. Forns J, Pottegard A, Reinders T, Pablador-Plou B, Morros R, Brandt L, Caizos-Achirica M, Hellfritzsch M, Schink T, prados-Torres A, Giner-Soriano M, Hagg D, Hallas J, Cortes J, Jaquot E, Deltour N, Perez-Gutthann S, Pladevall M, Reutfors J. Antidepressant use in Denmark, Germany, Spain, and Sweden between 2009 and 2014: Incidents and comorbities of antidepressant intiators. J Affect Disord, 2019; 15, 249: 242-252. doi: 10.1016/j.jad.2019.02.010. Epub 2019 Feb 6. PMID: 30780117.
33. Coupland C, Dhiman P, Morris R, Arthur A, Barton G, Hippisley-Cox J. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. BMJ, 2011; 343(7819): d4551.
34. Noordam R, Aarts N, Verhamme KM, Sturkenboom MCM, Stricker BH, Visser LE. Prescription and indication trends of antidepressant drugs in the Netherlands between 1996 and 2012: a dynamic based population study. Eur J Clin Pharmacol, 2015; 71(3): 369-75. doi: 10.1007/s00228-014-1803-x. Epub 2015 Jan 6. PMID: 25560052
35. Varty GB, Cohen Williams ME, Hunter JC. The antidepressant-like effects of neurokinin NK 1 receptor agonists in a gerbil tail suspension test, Behav Pharmacol, 2003; 14(1): 87-95. doi:10.1097/00008877-200302000-00009. PMID: 12576885.
36. Chermat R, Thierry B, Mico JA, Steru L, Simon P. Adaptation of the tail suspension test to the rat. J Pharmacol, 1986; 17(3): 348-50. PMID: 3795979.
37. Lucki I. The forced swimming test as a model for core and component behavioral effects of antidepressant drugs. Behav Pharmacol, 1997; 8(6-7): 523-32. doi: 10.1097/00008877-199711000-00010. PMID: 9832966.
38. Yankelevitch-Yahav R, Franko M, Huly A, Doron R. The forced swim test as a model of depressive-like behavior. J Vis Exp, 2015; 2(97): 52587. doi:10.3791/52587. PMID:25867960; PMCID:PMC4401172.
39. Porsolt RD, Bertin A, Jalfre M. Behavioral despair in mice: a primary sceening test for antidepressants. Archives Internationales de Pharmacodynamic et de Therapie, 229(2): 327-36.
40. Porsolt RD, Le pichon M, Jalfre M. Depression: a new animal model sensitive to

antidepressant treatments. Nature, 1977; 21, 266(5604): 730-2. doi: 10.1038/266730a0. PMID: 559941.

41. Can A, Dao DT, Arad M, Terrilion CE, Piantadosi SC, Gould TD. The mouse forced swim test. J Vis Exp, 2012; 29(59): e3638. doi: 10.3791/3638. PMCID: PMC3353513.
42. Detke MJ, Rickles M, Lucki I. Active behaviors in the rat forced swimming test differentially produced by serotonergic and noradrenergic antidepressants. Psychopharmacology (Berl.), 1995; 121(1): 66-72. doi:10.1007/BF02245592. PMID: 8539342.
43. Porsolt RD. Animal models of depression: utility for transgenic research, Rev Neurosci, 2000; 11(1): 53-8. doi: 10.1515/revneuro.2000.11.1.53. PMID: 10716655.
44. Hitzemann R. Animal models of psychiatric disorders and their relevance to alcoholism. Alcohol Res Health, 2000; 24(3): 149-58. PMID: 11199284;PMCID: PMC6709740.
45. Cryan JF, Mombereau C, Vassout A. The tail suspension test as a model for assessing antidepressant activity: review of pharmacological and genetic studies in mice. Neurosci Biobehav Rev, 2005; 29(4-5): 571-625. doi: 10.1016/j.neubiorev.2005.03.009. PMID: 15890404.
46. Liu X, Peprah D, Gershenfield HK, Tail-suspension induced hyperthermia: a new measure of stress reactivity. J Psychiatry Res, 2003; 37(3): 249-259. doi: 10.1016/s0022-3956(03)00004-9 PMID: 12650744.
47. Schatzberg AF, Nemeroff CB, 5th edtn, American Psychiatric Press Textbook of Psychopharmacology. Washington DC: American Psychiatric Press, 89-131. ISBN 978-1-58562-523-9
48. Overmier JB, Leaf RC. Effects of discriminative Pavlovian fear conditioning upon previously or subsequently acquired avoidance responding. J Comp Physiol Psychol, 1965; 60(2): 213-7. doi: 10.1037/h0022340. PMID: 5832346.
49. Hiroto, Donald S. Locus of control and learned helplessness. J Exp Psychol, 1974; 102(2): 187-93. doi: 10.1037/h0035910.
50. Abramson LY, Seligman M E, & Teasdale JD. Learned helplessness in humans: Critique and reformulation. J Abnorml Psychol, 1978; 87(1): 49-74. doi: 10.1037/0021-843X.87.1.49 PMID: 649856.
51. Quinless FW, Nelson MA. Development of a measure of learned helplessness. Nurs Res, 1988; 37(1): 11-5. PMID: 3340571.
52. Miller WR, Seligman ME. Depression and learned helplessness in man. J Abnorm Psycholol, 1975; 84(3): 228-38. doi: 10.1037/h0076720. PMID: 1169264.

53. Stretcher VJ, DeVellis BM, Becker MH, Rosenstock IM. The role of self-efficacy in achieving health behavior change. Health Educ Q, 1986; 13(1): 73-92. doi: 10.1177/109019818601300108. PMID: 3957687.
54. Hill MN, Hellemans KG, Verma P, Gorzalka BB, Weinberg J. Neurology of chronic mild stress: parallels to major depression. Neurosci Biobehav Rev, 2012; 36(9): 2085-117. doi: 10. 1016/j.neubiorev.2012.07.001. Epub 2012 Jul 7. PMID: 22776763; PMCID: PMC4821201.
55. Katz RJ. Animal model of depression: pharmacological sensitivity of a hedonic deficit. Pharmacol Biochem Behav, 1982; 16(6): 965-8. doi: 10. 1016/0091-3057(82)90053-3. PMID: 7202217.
56. Karli, Pierre. The Norway rat's killing response to the white mouse: an experimental analysis. Behavior, 1956; 10: 81-103.
57. Miachon SM, Jouvenet M, and Vallon JJ. Cholestrol and triglyceride level in the serum of muricidal male Wistar rats: Indices of mitochondrial benzodiazepine receptors?" Brain Res Bull, 2000; 1, 51(1): 57-61. doi: 10.1016/s0361-9230(99)00210-5. PMID: 10654581.
58. Yaffe D, Forrest LR, Schuldiner S. The ins and outs of vesicular monoamine transporters. J of Gen Physiol, 2018; 150(5): 671-682. doi: 10. 1085/jpg.201711980.
59. Bjorkqcvist K. Social defeat as a stressor in humans. Physiol Behav, 2001; 73(3): 435-42. doi: 10.1016/s0031-9384(01)00490-5. PMID: 11438372.
60. Deacon RM. Digging and marble burying in mice: simple methods for in vivo identification of biological impacts. Nat Proto, 2006; 1(1): 122-4. doi: 10.1038/nprot.2006.20. PMID: 17406223.
61. Gulinello, Maria. Behavioral Core Protocols and Training: Marble Burying. Biobserve. Albert Einstein College of Medicine, 2016; 5.