The current mechanism and treatment methods for depression

Yutong Ye*

Department of Bioengineering, Tianjin University of Science and Technology, Tianjin, China
* Corresponding Author Email: yutongye@qq.com

Abstract. Depression is a very common illness that negatively affects people's lives, mental states and families. This paper explains the causes of depression from both psychological and biological perspectives, finding that it is related to negative psychology and drugs, gender, genetics, brain chemistry, and even brain structure. At the same time, this paper analyzed the differences, effects and applicability of psychological, medical and physical therapy, and found that mild depression usually does not need medical intervention; Moderate and severe depression is usually treated with a combination of psychotherapy and medication; Less sensitive people can be treated with more aggressive brain stimulation.

Keywords: Depression, Mechanism, Treatment

1. Introduction

One of the most common diseases in the United States is depression, which affects 100 million people in China, with an average of 1 in 14 people suffering from depression[1]. Depression can have a very negative impact on people's lives, their state of mind and their families. Depression patients may feel depressed and hopeless about normal daily activities, resulting in low work efficiency, self-denial and self-abasement. This paper explains the causes of depression from two aspects of psychology and biology, and finds that anyone may suffer from depression at any age. People who experience misfortune and great psychological stress are more likely to suffer from depression. Psychological factors have a great relationship with personal experience and personality. In addition to psychological factors, there are also some biological factors, such as drugs, gender, genes, brain chemistry; And even physical factors related to brain structures such as the hippocampus. Of course, depression is treatable, and statistics show that treatment has a positive effect on 80 to 90 percent of people with depression. Almost all experienced relief, and there are three treatments, depending on the severity of the illness: mild depression usually does not require medical intervention, but psychotherapy; Moderate depression requires medication; Major depression requires psychotherapy and medication, or physical brain stimulation to improve its effects. This article reviews the psychological and biological causes of depression and carefully analyzes the differences, effects and applicability of psychology, medicine and physical therapy.

2. Mechanism

People who are susceptible to depression are those who experience misfortune in their lives and bear great psychological pressure. Depression may have many reasons and many triggers. It is a disease caused by the complex interaction of psychological factors and biological factors, which brings great trouble to people's life. Almost anyone of any age can suffer from depression, psychological factors and personal experience, personality has a great relationship.

2.1. Psychology cause

(1) Early loss, abuse:

The loss of a parent or emotional or physical abuse at a young age can also trigger depression in adulthood. In one study, nearly 76% of participants with depression reported experiencing childhood trauma, and 37% of them experienced multiple types of trauma[2]. Approximately 18% of women and 5% of men were diagnosed with adult depression when they reported sexual abuse as children[3].
The overall severity of trauma and the severity of specific trauma areas are also associated with the severity of depression[4].

(2) Age
Depression is common in later life, with nearly 5 million of 31 million Americans aged 65 and older having clinically significant depressive symptoms, up to 13% of those aged 80 and older[5]. The prevalence of depression is significantly higher in older people, and older people like those who are lonely and lack social support are at higher risk of depression.

(3) Personal character
A community sample of people with depression showed that 22% of them had a personality disorder[6]. Similar to the ideal of her high and too strong or fragile self-esteem character flaws is also one of the causes of depression. High and unattainable goals and overly concerned with the eyes of others can lead to great feelings of frustration, helplessness and hopelessness.

(4) Life events
Depression is caused by the removal of positive reinforcement from the environment is an idea derived from operant reflexia[7]. Relatively noteworthy life events can also trigger depression, even good ones. Such as graduation or retirement; Getting a new job or losing one; Marriage or divorce; Move or stay longer, etc. These are all normal life events, but patients with clinical depression syndrome have abnormal emotional responses to stressful life events that can lead to depression. And rough life experiences, such as financial difficulties; Separation or conflict with relatives, partners or friends; Sadness over the death of a loved one, partner or friend can be a trigger. Freud was the first person to explain depression. He believed that depression was the result of sadness after the loss of a loved one. If this sadness cannot be expressed, it can turn into depression[8]. When one or more of these stressful life events occur in a short period of time, the feelings of sadness that follow are normal, but the risk of depression also increases.

(5) Serious illness
People with chronic diseases may have depression caused by negative emotions. The psychological state of patients with chronic diseases has been confirmed by many scholars and found that the prevalence rate of depression in patients with chronic diseases is about 9.3% to 25%. Chronic diseases are conditions that cannot be completely cured and persist for a long time, such as chronic headache, sleep disorders, diabetes, heart disease, kidney disease, thyroid disease, AIDS, lupus erythematosus and multiple sclerosis cancer[13]. Hypothyroidism, caused by the thyroid gland not producing enough of certain hormones, mood swings from chronic headaches, and psychological stress from a deadly illness such as cancer, are all contributing factors. Up to 50% of people with depression also have anxiety symptoms suggesting that depression can be triggered by traumatic stress or anxiety.

(6) Seasonal variation
Seasonal depression affects about 5 percent of people in the U.S. each year. People in their 20s and 30s are more sensitive than other age groups, and women make up four out of five people with seasonal depression[14]. Seasonal affective disorder (SAD) is a mood disorder caused by seasonal changes, and is also commonly thought to result from disruption of the body's normal circadian rhythms[14]. The light that gets into your eyes is key. People living in cold climates who live short, dark lives are at highest risk of circadian disruption. Depression can also be triggered by decreased

(7) Malnutrition
Poor eating habits can also be a contributing factor. The risk of major depression was 15.5 times higher in malnourished patients than in non-depressed patients[15]. A diet rich in fruits, vegetables, fish and olive oil was associated with reduced symptoms of depression; A lack of many vitamins and minerals in the diet can also trigger depressive symptoms. A diet high in sugar may also be a contributing factor to depression. People who ate a lot of high-sugar, high-fat dairy products, red meat and fried foods reported more depressive symptoms than the rest of the population. Some studies have found that an unbalanced ratio of omega-6 to omega-3 fats in the diet and low levels of omega-3s in the diet may increase the risk of depression.
(8) Sleep quality
Sleep disturbances occur in 90% of patients with depression[9]. Poor sleep quality seriously affects people's mood and state in life. Poor sleep quality may worsen the symptoms of depression and increase the risk of depression.

(9) Smoking
Recent epidemiological data show that smoking rates among people with clinical depression are about twice that of the general population[16]. People with psychological problems after quitting said feeling more stable, more active life. It’s a myth that smoking relieves anxiety, but smoking is harmful and addictive, and it's probably the "stress reliever" -- cigarettes. Smoking addicts will begin to feel anxious when they for a period of time without smoking. So they light up a cigarette to relieve anxiety and cravings. After smoking, the mood is relieved and the cravings disappear temporarily, hence the myth that smoking relieves anxiety and that no cigarette makes people anxious.

2.2. Biological cause

In addition to psychological factors, depression can also occur at a biological level. Some drugs, gender, genetic inheritance levels, brain chemistry levels.

(1) Gender
Key findings in the National Center for Health Statistics (NCHS) Data Brief issued on Feb. 13 show that more than 8% of adults older than 20 years old reported having depression during a given two-week period. Women (10.4%) were almost twice as likely as were men (5.5%) to have had depression, and its incidence peaks during women's childbearing years[10].

Postpartum depression or PPD is pregnancy-related depression in women[10]. Thirteen percent of women may experience PPD between one week and one month after delivery. Women's moods are affected by constant hormonal changes at different times, with mood swings easily occurring during menstruation, pregnancy and childbirth, lowering the risk of postmenopausal depression. About 15 percent of women who give birth experience postpartum depression due to rapid hormonal changes and fluctuating postpartum hormone levels.

(2) Drug
Some drugs and alcohol can cause mood changes and fluctuations, putting you at risk for depression. Examples include isotretinoic acid, used to treat acne; Barbiturates; Benzodiazepines; Beta blocker; Antiviral drugs interferon -α, corticosteroids; Opioids like morphine and anticholinergic drugs for stomach cramps[11].

It is estimated that up to 40% of depressed patients have a history of SUD or alcohol dependence during their lifetime[12]. However, only 19% of these patients seek medical help for themselves, most of which are alcohol-dependent[12]. Recreational drugs and alcohol abuse can also cause or exacerbate depression. Although they have a certain anesthetic effect, can feel relaxed and relieve pain, but the result is to worsen the degree of depression.

(3) Gene
Genes have been found and is also one of the favorable factors of major depressive disorder[17], a study shows that twins meta-analysis research data, found that the genetic risk of depression, at 37%, and in a family data found in the study of depression in patients with depression in the direct descendants of probability are up to 2 to 3 times normal[31]. But that doesn't mean you have to be depressed just because a close relative is depressed. Depression is not like a purely genetic disease, where there is not a single gene that causes it but each gene has a small effect. Genes and environment interact in ways that trigger depression, genes may raise the risk of depression, and your likelihood of depression depends on your environment.

(4) Physics and biochemistry
An underlying biological root cause of depression is an imbalance in neurotransmitters involved in mood regulation. Levels of dopamine, serotonin, norepinephrine and so on are important for mood regulation, 'they are the neurotransmitters that make people feel good. Neurotransmitters help different areas of the brain communicate with each other. If they are out of balance, they can directly
affect people's happiness. Not only can depression occur, but too low levels can lead to depression, impulsivity, violence and aggression.

Depression is associated not only with neurotransmitter imbalances, but also with the physical structure and chemistry of the brain. The reason why symptoms of depression don't go away when patients take drugs to restore neurotransmitter balance is that the effects of depression on brain structures don't go away. Studies have shown that depressed people have different brain structures from normal people, particularly in the prefrontal cortex (PFC) and hippocampus[18]. Some depressed people have a smaller hippocampus, which is an important part of long-term memory. Serotonin, as a neurotransmitter, is one of many brain chemicals that can rely on cross-electrical communication to process emotions. Connections between brain cells are broken, and the ability of cells to communicate is reduced, and the number of neurotransmitters is reduced. The smaller hippocampus has fewer serotonin receptors and is less able to process emotions, leading to depression. Studies have shown that constant exposure to stress impairs the growth of nerve cells in this part of the brain[19]. Depressed people produce too much of the stress hormone cortisol, and the hippocampus shrinks because it is inhibited by its toxic properties. It's also possible that depressed people are born with a smaller hippocampus.

3. Treatment

Depression is treatable, though it can often lead to feelings of hopelessness and extreme behavior such as suicide. The data suggest that treatment has a positive effect on 80 to 90 percent of patients with depression, with almost all patients experiencing relief. According to different severity, there are drug therapy, psychological therapy, physical therapy, this, three kinds of treatment means. Mild depression usually do not need to be drug intervention, psychological treatment can; Moderate depression requires medication; Major depression needs psychotherapy and medication, or physical brain stimulation to improve its effects.

3.1. Psychology

Mild depression is often treated with psychotherapy, also known as "talking therapy." Medication can only alleviate depression, and to cure depression, it needs to be targeted at the way the patient perceives and processes things. Psychotherapy is to change the patient's thinking mode and improve the coping skills, try to perceive and change the negative thoughts and behaviors, adjust the correct mentality and actively face the pressure and frustration in life.

(1) Cognitive behavioral therapy

Cognitive behavioral therapy (CBT) is a good psychological intervention that can help you identify the unhelpful thought patterns that lead to depression and lead people to find sources of happiness in life. Although these strategies place a strong emphasis on cognitive factors, there is meta-analysis data showing that physical, emotional and behavioral factors are also believed to play a role in maintaining disease[20]. It is also one of the most effective treatments for depression. CBT improves emotional regulation, changes negative and distorted perceptions, helps you develop more positive thoughts and behaviors, and provides personal solutions and development strategies for current problems. CBT also has a role in preventing relapse of depression.

(2) Interpersonal therapy

Interpersonal therapy (IPT) is a structured form of psychotherapy that focuses on skills needed to cope with relationships and is based on the idea that depression may have something to do with our relationships. Because relationship problems are a major cause of depression, they have a big impact on people's mood. IPT can help you become a good language artist, learn how to deal with sadness and solve social problems.

(3) Cognitive therapy for mindfulness

MBCT aims to teach the patient the ability to be present and to pay attention to what is happening to the patient at the moment. Unlike other approaches, MBCT no longer aims to change patients'
perceptions, but to focus on them for better or worse. This draws the patient's mind back from the future or past, focusing only on the present and not worrying too much about other things. In meditation, exploring negative experiences and not making them worse is what you should do, so that strong emotions can be handled well and not be exacerbated by negative past experiences. It also means you'll be able to spot signs of depression earlier, making it easier to treat as a way to prevent depression. In a trial of 123 patients with major depression in remission or recovery, the MBCT group had a significantly lower recurrence rate at 15 months than the monotherapy group. MBCT was also shown to be associated with reduced depressive and comorbid symptoms and improved quality of life[21].

(4) Psychodynamic therapy
Short-term psychodynamic psychotherapy has proved to be efficacious in depression[22]. It is designed to help patients explore and understand past experiences, such as injuries and trauma. And understanding what role these experiences play in the development of depression, and understanding the relationships between these experiences and events. This helps doctors understand and address them so they can return to a positive attitude towards life.

(5) Problem solving therapy
Problem solving therapy is a kind of therapy in which the doctor helps the patient to identify the most urgent and important problems and guide the patient to solve them. Of course, the doctor may suggest a variety of ways to solve them and help the patient to get rid of the sadness. The doctor helps the patient analyze the possibilities of several options and choose the best one.

(6) Family or couples therapy
Family or couples therapy is a good way to address situations where depression affects others in the family. This type of treatment is based on educating your loved one about depression and how it affects the sufferer. Couples home therapy can help resolve problems within the family or that are troubling your partner.

(7) Group therapy
Treating patients in a group setting can also help them get rid of their grief. It is also a good way to communicate more and get to know and interact with others who have similar experiences.

(8) Dialectical behavior therapy
Dialectical behavior therapy (DBT) is aimed at emotional problems such as anger and cutting such emotional behavior to improve, can effectively reduce the symptoms of patients with personality disorders.

3.2. Drug
People with moderate and severe depression can take medication to relieve their depression. Medication is used to improve depression symptoms by improving the balance of neurotransmitters in the brain. The antidepressant SSRI, as a selective serotonin reuptake inhibitor, can affect the increase or decrease of neurotransmitters, regulating the receptors that neurochemicals bind to[23]. Combining drugs with therapy is a good way to get the most out of drugs. Medication can effectively relieve sad feelings, suicidal thoughts, insomnia, loss of appetite and other problems.

SSRIs relieve depression by inhibiting serotonin reuptake, which also disrupts serotonin activity. Tryptophan depletion studies have shown a strong relationship between serotonin and anxiety and depression[25]. The serotonin transporter (SERT) at the end of presynaptic axons is also inhibited by SSRIs, which allows serotonin (serotonin or 5HT) to remain in the synaptic cleft and stimulate postsynaptic receptors for a longer time[26]. More than 15 different serotonin receptors from seven families have been identified[27]. Serotonin receptors are ubiquitous in the hippocampus, cortex, and raphe nucleus, and activating them has both short-term and long-term implications.

For example, serotonin receptors 5-HT 1A are common and widely used, and downregulation of the hippocampus and 5-HT 1A receptor often has an impact on anxiety and depression[28]. Presynaptic autoreceptors negatively regulate serotonin activity while postsynaptic heteroreceptors in the forebrain mediate serotonin response in this target tissue. Two receptor types act through...
hyperpolarized membranes and reduced neuronal excitability and their agonists have been shown to have anti-anxiety effects in mice[28]. In addition, studies have shown that 5-HT 1A receptor is also involved in the process of cognitive decline, and emotional disorders are usually associated with cognitive decline (Sarnyai Z,2000)[29].

It could also suggest that the serotonin system plays a big role in regulating mood, but it can also have some side effects. For example, stimulation of receptors may cause nausea, but sexual dysfunction, weight gain and sleep disturbances are more important[30].

1)Selective serotonin reuptake inhibitors

The most commonly used drugs for depression are selective serotonin reuptake inhibitors (SSRIs), such as Prozac (fluoxetine), Paxil (Paroxetine), Zoloft (sertraline), Celexa (citalopram) and Luvox (fluvoxamine)[24].

Both major and non-major depression can be treated with selective serotonin reuptake inhibitors, which have relatively few side effects.

2)Serotonin and norepinephrine reuptake inhibitors

Serotonin and norepinephrine reuptake inhibitors (SNRI) have similar effects to SSRIs. The main difference is that they also block the body’s reuptake of norepinephrine, one of the neurotransmitters involved in mood.

Examples are Effexor (venlafaxine), Cymbalta (duloxetine) and Pristiq (norramaxine).

3)Ketamine

Ketamine is a very commonly used anesthetic, but is now available to suppress resistant depression. It works by blocking the non-monoamine neurotransmitter glutamate, the activity of all other neurotransmitters affected by glutamate. It is usually given intravenously and can relieve symptoms in a matter of hours. Depression patients with suicidal ideation problems are well suited for ketamine, which makes it a promising use in emergency psychiatry. Esketamine, a variant of ketamine, is a nasal spray that has a calming effect but can also be an out-of-body experience. So, its use needs to be in a specific location and regulated.

4)Norepinephrine and dopamine reuptake inhibitors

Norepinephrine and dopamine reuptake inhibitors (NDRI) are a method of reducing depression by blocking norepinephrine and dopamine transporters. Examples are Focalin (dextrophenidate), Ritalin (methylphenidate) and Wellbutrin (Wellbutrin).

5)Tricyclic antidepressants

Tricyclic antidepressants (TCAs) and SSRIs can effectively inhibit chronic depression and dysthymia, and are one of the earliest depression drugs developed. Examples include Elavil (amitriptyline), Tofranil (imipramine) and Pamelor (nortriptyline). Tricyclic antidepressants are more effective than other drugs, but may also have more side effects.

6)Monoamine oxidase inhibitors

Monoamine oxidase inhibitors (MAOIs) have in common with tricyclic drugs that they are not usually the preferred treatment, but the more difficult treatment of depression requires their involvement. Reactions that may lead to hypertension if MAOI are used unchecked may be created, and interactions with certain other medications such as SSRIs must be noted. Examples are Marplan (isocarboxylhydrazine), Nardil (phenylhydrazine) and Parnate (trans-cyclopropylamine).

3.3. Physical

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3.4. The same
The treatment of depression is fundamentally to improve the patient's mood through psychological, drug and physical methods. In addition to psychological therapy for the patient's mood and thoughts, drugs and physical therapy are basically to reconnect neurons in the brain for the purpose of treatment.

4. Conclusion
The review found that mild depression usually does not require medical intervention, except regular psychotherapy and appropriate exercise to boost mood. Moderate and major depression is usually treated with a combination of psychotherapy and medication, and most patients can get relief. Patients with severe depression who are not sensitive to the first two treatments will be treated with more invasive brain stimulation.

Although depression treatment has been developed very mature, there is still a high proportion of depression patients in the world who do not respond to medication. For example, treatment-resistant depression (TRD) is expected to have certain development in the future in the field of depression drugs targeting TRD.
References

[1] NIMH. (2022). Transforming the understanding and treatment of mental illnesses.

[2] Negele, A., Kaufhold, J., Kallenbach, L. And Leuzinger-Bohleber, M. (2015). Childhood trauma and its relationship with chronic depression in adults. Depression research and treatment, 2015, 650804. https://doi.org/10.1155/2015/650804

[3] Hill, J. (2003). Childhood trauma and depression. Current Perspectives in Psychiatry, 16(1). https://journals.lww.com/psychiatry/Abstract/2003/10000/Childhood_trauma_and_depression_2.aspx

[4] Humphreys, KL, LeMoult, J., Wear, JG, Piersiak, HA, Lee, A., & Gotlib, IH (2020). Child abuse and depression: a meta-analysis of studies using the Child trauma Questionnaire. Child abuse and neglect, 102, 104361. https://doi.org/10.1016/j.chiabu.2020.104361

[5] Blazer, D.G. (2009). Depression in late life: Review and commentary. FOCUS, 7(1), 118-136.

[6] Casey P, Birbeck G, McDonagh C, Horgan A, Dowrick C, Dalgard O, Lethenen V, Ayuso-Mateos JL, Dunn G, Page H, Wilkinson C, Wilkinson G, Vazquez-Barquero JL; ODIN Group. Personality disorder, depression and functioning: results from the ODIN study. J Affect Disord. 2004 Oct 15;82(2):277-83. doi: 10.1016/j.jad.2003.11.009. PMID: 15488258.

[7] Lewinsohn, P. M. (1974). A behavioral approach to depression.

[8] Freud, S. (1917). Mourning and melancholia. Standard edition, 14(19), 17.

[9] Franzen, P. L., & Buysse, D. J. (2008). Sleep disturbances and sleep debt: risk relationships for subsequent depression and therapeutic implications. Dialogues in clinical neuroscience, 10(4), 473-481. https://doi.org/10.31887/DCNS.2008.10.4/plfranzen

[10] NIMH. (2017). Depression’s “Transcriptional Signatures” Differ in Men vs. Women.

[11] Oliva F, Nibbio G, Vizzuso P, Jaretti Sodano A, Ostacoli L, Carletto S, Picci RL. Eur Addict Res. (2018) Gender differences in anxiety and depression before and after alcohol detoxification: anxiety and depression as gender-related predictors of relapse. 2018; 24:163-172.

[12] Danzo S, Connell AM, Stormshak EA. J Adolesc. (2017). Associations between alcohol-use and depression symptoms in adolescence: examining gender differences and pathways over time. 2017; 56:64–74.

[13] Ingle VK, Pandey I, Singh AR, Pakhare A, Kumar S. (2017). Screening of patients with chronic medical disorders in the outpatient Department for Depression Using Handheld Computers as Interface and patient health Questionnaire-9 as a tool. Int J Appl Basic Med Res. 2017;7(2):129–33. https://doi.org/10.4103/2229-516X.205809.

[14] Rosenthal NE, Sack DA, Gillin JC, Lewy AJ, Goodwin FK, Davenport Y, Mueller PS, Newsome DA, Wehr TA. (1984). Seasonal affective disorder. A description of the syndrome and preliminary findings with light therapy. Arch Gen Psychiatry. 1984 Jan;41(1):72-80.

[15] Vafaee, Z., Movahedi, H., Sadooghi, Z., Meamar, R., Chitsaz, A., & Moeini, M. (2013). Malnutrition is associated with depression in rural elderly population. Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences, 18(Suppl 1), S15–S19.

[16] Grant BF, Hasin DS, Chou SP, Stinson FS, Dawson DA. (2004) Nicotine dependence and psychiatric disorders in the United States: Results from the national epidemiologic survey on alcohol and related conditions. Arch Gen Psychiatry. 2004;61(11):1107–15.

[17] Menke A, Klengel T, Binder EB. (2012) Epigenetics, depression and antidepressant treatment. Curr Pharm Des.2012,18:5879–89. 10.2174/138161212803523590

[18] Zhang, F. F., Peng, W., Sweeney, J. A., Jia, Z. Y., & Gong, Q. Y. (2018). Brain structure alterations in depression: Psychoradiological evidence. CNS neuroscience & therapeutics, 24(11), 994–1003. https://doi.org/10.1111/cns.12835

[19] McEwen BS. (1999). Stress and hippocampal plasticity. Ann Rev Neurosci. 1999; 22:105–122.

[20] Hofmann, S. G., Asnaani, A., Vonk, I. J., Sawyer, A. T., & Fang, A. (2012). The Efficacy of Cognitive Behavioral Therapy: A Review of Meta-analyses. Cognitive therapy and research, 36(5), 427–440. https://doi.org/10.1007/s10608-012-9476-1
[21] MacKenzie, M.B., & Kocovski, N.L. (2016). Mindfulness-based cognitive therapy for depression: trends and developments. Psychology research and behavior management, 9, 125–132. https://doi.org/10.2147/PRBM.S63949

[22] Malhi, G.S., Bell, E., Bassett, D., et al. (2021) The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Australian and New Zealand Journal of Psychiatry 55: 7–117.

[23] DeLucia, V., Kelsberg, G., Safranek, S. (2016) Which SSRIs most effectively treat depression in adolescents? J Fam Pract. 2016, Sep;65(9):632-4.

[24] Coleiro, B., Marshall, S.E., Denton, C.P., Howell, K., Blann, A., Welsh, K.I., Black, C.M. (2001) Treatment of Raynaud's phenomenon with the selective serotonin reuptake inhibitor fluoxetine. Rheumatology (Oxford). 2001 Sep;40(9):1038-43.

[25] Gordon, J.A., Hen, R. (2004). Annu Rev Neurosci. 2004; 27:193.

[26] Young, E.A., Lopez, J.F., Murphy-Weinberg, V., Watson, S.J., Akil, H. (2003). Arch Gen Psychiatry. 2003;60(1):24.

[27] Taylor, C., Fricker, A. D., Devi, L. A., & Gomes, I. (2005). Mechanisms of action of antidepressants: from neurotransmitter systems to signaling pathways. Cellular signalling, 17(5), 549–557. https://doi.org/10.1016/j.cellsig.2004.12.007

[28] Gross, C., Santarelli, L., Brunner, D., Zhuang, X., Hen, R. (2000) Biol Psychiatry. 2000;48(12):1157.

[29] Sarnyai, Z., Sibille, E.T., Pavlides, C., Fenster, R.J., McEwen, B.S., Toth, M. (2000) Proc Natl Acad Sci U S A. 2000;97(2):14731.

[30] Ferguson, J. M. (2001). SSRI Antidepressant Medications: Adverse Effects and Tolerability. Primary care companion to the Journal of clinical psychiatry,3(1),22–27. https://doi.org/10.4088/pcc.v03n0105

[31] Sullivan, P.F., Neale, M.C., Kendler, K.S. (2000). Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry 2000,157:1552–62. 10.1176/appi.ajp.157.10.1552