mTOR Activity and Brain Glucose Metabolism in Major Depression Disorder

Noha A. Mohamed [a*], Eman T. Mehanna [b], Yasser M. Moustafa [c,d], Norhan M. El- Sayed [d]

[a] Department of Forgery & Counterfeiting, Forensic Medicine, Ministry of Justice, Ismailia, Egypt; [b] Department of Biochemistry & Molecular Biology, Faculty of Pharmacy, Suez Canal University, Ismailia, Egypt; [c] Department of Pharmacology & Toxicology, Faculty of Pharmacy, Badr University, Cairo, Egypt;. [d] Department of Pharmacology &Toxicology, Faculty of Pharmacy, Suez Canal University, Ismailia, Egypt.

Abstract

Major depressive disorder (MDD) is one of the most common diseases affecting an enormous population worldwide. MDD is considered a complex mental disorder with unknown clear etiology. It has become the most common neuropsychiatric disorder. MDD affects a person's life efficiency. Numerous data support that excessive administration of glucocorticoids may lead to behavioral, biochemical, functional and morphological characteristics of depression. Depression pathogenesis involves glucose metabolism disturbance, where the concentration of glucose and glycogen in the frontal cortex and hippocampus increases during depression. The marked increase in the concentration of carbohydrates and glucose transporters is evidence of animal exposure to stress. Mammalian targets of rapamycin (mTOR) signaling pathways are involved in the pathogenesis of depression. mTOR signaling is impaired in the frontal cortex and hippocampus of an animal with MDD. This review discusses the role of brain glucose and mTOR pathways involved in controlling MDD in addition to the different therapeutic approaches for treatment of depression.

Keywords: Brain, Glucose Metabolism, mTOR, Major Depressive Disorder, Pathophysiology.

1. Introduction

1.1. Major depressive disorder

Major depression disorder (MDD) is a complex mental disorder with poorly understood causes, becoming one of the most common neuropsychiatric disorders. Numerous data support that excess glucocorticoid in experimental animals produces many behavioral, biochemical, functional, and morphological characteristics of depression (**Nemeroff & Owens, 2002**). Consequently, major depressive disorder or clinical depression causes a persistent feeling of sadness and loss of interest. It affects sense, thinking, and behavior and can lead to various emotional and physical problems. It spread by 20% among women and 12% among men. It is severe because it interferes with daily life such as working, studying, eating, and sleeping. MDD is probably a combination of factors, for example, genetics, biological, environmental, and psychological factors (**Bockaert & Marin, 2015**).

Despite a large variety of antidepressant medications and alternative therapeutic modalities, including several forms of psychotherapy (e.g., cognitive behavioral therapy) and several other

trends such as yoga, exercise, and sleep deprivation, depression suffers a vast treatment gap worldwide, whereby large numbers of individuals who require care do not receive treatment (**Lindberg et al., 2020**). Depression can cause morbidity during the life of a person of all ages. The diagnosis is always difficult in the pediatric and adolescent period (**Prager, 2009**), complicate the course of patients with chronic illness (**Evans et al., 2005**), and increase the overall medical burden in the elderly (**Lyness et al., 2006**).

2. Major depressive disorder pathogenesis

2.1. Brain glucose metabolism disturbance

Glucose is the primary source of energy for the brain. Glucose metabolism allows the proper synthesis and neurotransmitter function (**Hosokawa et al., 2009; Navale & Paranjape, 2016**). Due to its polar nature and large molecular size, glucose cannot cross the cell membrane by simple diffusion. Instead, the entry of glucose molecules into the cells is affected by a large family of structurally related transport proteins known as glucose transporters. Two main types of glucose transporters have been identified, namely, sodium-glucose-linked transporters (SGLTs) and facilitated diffusion glucose transporters (GLUTs). Sodium-glucose-linked transporter-1 (SGLT1) was the first SGLT to be discovered and extensively studied. It comprises 14 transmembrane helices of which both the COOH and NH2 terminals face the extracellular space. All members of the SGLT family are 60- to 80-kDa proteins containing 580–718 amino acids (**Navale & Paranjape, 2016**).

GLUTs are proteins comprising 12 membrane-spanning regions with intracellularly located amino and carboxyl terminals. GLUT proteins' amino acid sequence has shown 28–65 % identity against GLUT 1. Based on this and multiple sequence alignment studies, three subclasses (Class I, II, and III) of facilitative transporters have been identified (**Navale & Paranjape, 2016**).

GLUT3 is mainly present in the brain. It has a high affinity for glucose, a consistent property with its function to transfer glucose into cells with a higher glucose requirement. GLUT4 is an insulin-responsive glucose transporter found in the heart, skeletal muscle, adipose tissue, and brain. It is

present in the cytoplasm of cells in vesicles from which it is translocated to the plasma membrane under the influence of insulin. Such insulin-directed recruitment of GLUT4 results in a 10- to 20-fold increase in glucose transport (**Bryant et al., 2002**).

As previous studies support that glucose/ glycogen and glucose transporter (GLUT 1- GLUT 3) concentrations are more significant in the frontal cortex and hippocampus in the brain of depressed animals than normal animals (**Detka et al., 2014**) due to the intensity of glucose uptake in depression, some theories support that the HPA axis activity's persistent stimulation increases the risk of mental, metabolic, and cardiovascular diseases. Indeed, clinical data frequently show the co-occurrence of depression with obesity, metabolic syndrome, type-2 diabetes, hypertension, and adverse coronary events (**Murgatroyd et al., 2009; Bouwman et al., 2010**). Available data indicate that the main reason for the coexistence of MDD due to metabolic disturbances resulting from excessive glucocorticoid action (**Detka et al., 2013**).

Glucose is required to provide the precursors for neurotransmitter synthesis and the ATP to fuel their actions, and the brain's energy demands are not related to signaling. Cellular partition of glucose transport and metabolism are related to local blood flow regulation, and glucose-sensing neurons govern the brain-body nutrient axis. Glucose metabolism is connected to cell death pathways by glucose-metabolizing enzymes. Therefore, any disturbance in the glucose delivery pathway and metabolism leads to debilitating brain diseases (**Mergenthaler et al., 2013**).

2.2. Mammalian target of rapamycin (mTOR)

Mammalian target of rapamycin (mTOR) is a mechanistic target of rapamycin, which regulates protein translation initiation and is expressed in dendritic development that controls new protein synthesis (**Ghosal et al., 2020**). Dysregulation of mTOR is implicated in different psychiatric disorders' etiology, including depression (**Abelaira et al., 2014**). The antidepressant effect mediated by activation of the mTOR pathway, a target downstream from AKT, the prefrontal cortex underlies the antidepressant effects (**Bockaert & Marin, 2015**) (**Figure 1**).
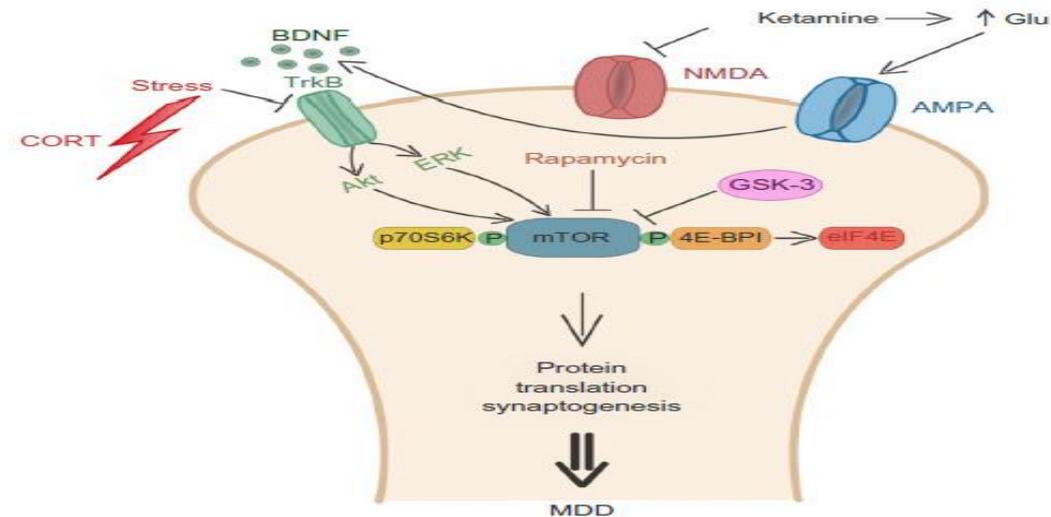
Figure 1. Role of mTOR signaling pathway in the pathophysiology of MDD **(Réus et al. 2015)**.

TOR (target of rapamycin) and its mammalian ortholog mTOR have been discovered to understand the mechanisms of action of the immunosuppressant drug rapamycin extracted from the Easter Island bacterium (*Rapa Nui*) soil. mTOR is a serine/threonine kinase found in two functionally distinct complexes, mTORC1, and mTORC2, which are differentially regulated by a significant number of nutrients such as glucose amino acids energy (oxygen and ATP/AMP content), growth factors, hormones, and neurotransmitters. mTOR controls many essential cellular functions such as protein synthesis, energy metabolism, cell size, lipid metabolism, autophagy, mitochondria, and lysosome biogenesis. Besides, mTOR-controlled signaling pathways regulate the nervous system's integrated physiological functions, including neuronal development, synaptic plasticity, memory storage, and cognition. Thus, it is not surprising that mTOR signaling deregulation is associated with many neurological and psychiatric disorders. Preclinical and preliminary clinical studies indicate that inhibition of mTORC1 can be beneficial for some pathological conditions such as epilepsy, cognitive impairment, and brain tumors. In contrast, stimulation of mTORC1 (direct or indirect) can help other pathologies such as depression or axonal growth and regeneration **(Bockaert & Marin, 2015) (Figure 2)**.

3. Types and symptoms

Depression is characterized by persistent sadness and a lack of interest or pleasure. It can also disturb sleep and appetite; tiredness and poor concentration are common. Depression is a leading cause of

disability worldwide and contributes significantly to the global burden of disease. The effects of depression can be long-lasting or recurrent and can dramatically affect a person's ability to function and live a rewarding life **(Bockaert & Marin, 2015).**

Depending on the number and severity of symptoms, a depressive episode can be categorized as mild, moderate, or severe **(Bockaert & Marin, 2015)**.

A key distinction is also made between depression in people who have or do not have a history of manic episodes. Both types of depression can be chronic (i.e., over an extended period) with relapses, especially if they go untreated. The recurrent depressive disorder involves repeated depressive episodes. During these episodes, the person experiences a depressed mood, loss of interest and enjoyment, and reduced energy leading to diminished activity for at least two weeks. Many people with depression also suffer from anxiety symptoms, disturbed sleep, and appetite. They may have feelings of guilt or low self-worth, poor concentration, and even signs that a medical diagnosis cannot explain **(Bockaert & Marin, 2015)**.

Depending on the number and severity of symptoms, a depressive episode can be categorized as mild, moderate, or severe. An individual with a mild depressive episode will have some difficulty continuing with everyday work and social activities but will probably not cease to function thoroughly. During a severe depressive episode, it is unlikely that the sufferer will continue with social, work, or
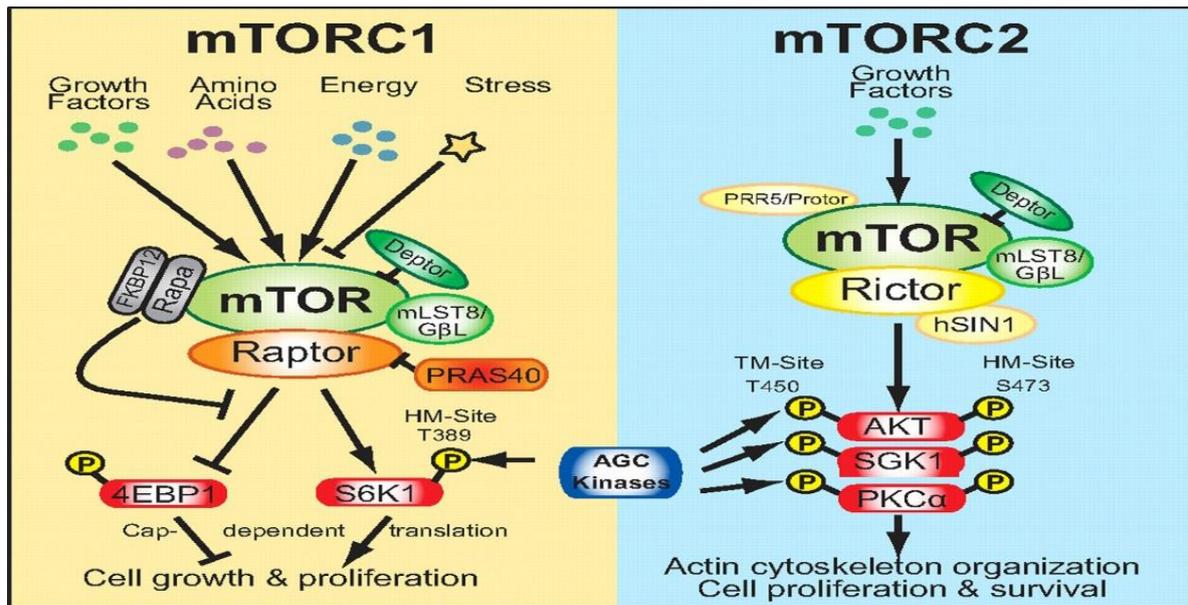
Figure 2. mTORC1 versus mTORC2. Distinct rapamycin sensitivities, partner proteins, substrates, and cellular functions distinguish the two known mTOR signaling complexes, mTORC1 and mTORC2 **(Foster & Fingar, 2010)**.

domestic activities, except to a limited extent **(Bockaert & Marin, 2015)**.

Bipolar affective disorder: this type of depression typically consists of both manic and depressive episodes separated by regular mood periods. Manic episodes involve elevated or irritable mood, over-activity, speech pressure, inflated self-esteem, and a decreased need for sleep **(Bockaert & Marin, 2015)**.

4. Contributing factors and prevention

Depression results from a complex interaction of social, psychological, and biological factors. People who have gone through adverse life events (unemployment, bereavement, psychological trauma) are more likely to develop depression. Depression can, in turn, lead to more stress and dysfunction and worsen the affected person's life situation and depression itself **(James et al., 2018)**.

There are interrelationships between depression and physical health. For example, cardiovascular disease can lead to depression and vice versa **(James et al., 2018)**.

Prevention programs have been shown to reduce depression. Effective community approaches to prevent depression include school-based programs to enhance positive thinking patterns in children and adolescents. Interventions for children with behavioral problems may reduce parental depressive symptoms and improve outcomes for their children. Exercise programs for the elderly can also be effective in depression prevention **(James et al., 2018; WHO, 2020)**.

5. Treatment of depression

There are effective treatments for moderate and severe depression. Health-care providers may offer psychological treatments such as behavioral activation, cognitive behavioral therapy (CBT) and interpersonal psychotherapy (IPT), or antidepressant medication such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs). Health-care providers should keep in mind the possible adverse effects of antidepressant medication, the ability to deliver either intervention (in terms of expertise and treatment availability), and individual preferences. Different psychological treatment formats for consideration include individual and group face-to-face psychological treatments delivered by professionals and supervised lay therapists **(WHO, 2015)**.

Psychosocial treatments are also effective for mild depression. Antidepressants can be an effective form of treatment for moderate-severe depression but are not the first line of treatment for cases of mild depression. They should not be used for

treating depression in children and are not the first line of treatment in adolescents, among whom they should be used with extra caution (**Bockaert & Marin, 2015; WHO, 2015**).

5.1. Pharmacological management of depression

The selection of pharmacotherapy for patients with MDD should be guided by the patient's medication history and comorbidities, the medication's efficacy and safety profile, and the prescribing physician's familiarity with the particular drug or drugs. Pharmacotherapeutic "success" is dependent on appropriate dosing and a clearly defined duration of treatment. Once antidepressant therapy has been initiated, full therapeutic effects may take up to 8 weeks to achieve. Patients who show a partial response after 4 to 6 weeks of treatment should be maintained on their initial medication for an additional 4 to 6 weeks. Patients who show little or no response may require second-step therapy, which could include an increase in the dosage of their current medication, a switch to a different medication, or the addition of another drug to their current therapeutic regimen (**Weihs & Wert, 2011**).

The importance of using adequate doses of antidepressant medications has been illustrated by data from a long-term observational study conducted over 20 years, which demonstrated that patients who received higher doses of antidepressant medications were nearly twice as likely to recover from recurrent affective episodes as patients who were not administered these somatic treatments ($P = 0.002$) (**Leon et al., 2003**).

Table (1) lists commonly available antidepressant medications, categorized by drug class (**Weihs & Wert, 2011**). Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are considered first-line pharmacotherapeutic options for patients MDD. SSRIs constitute the antidepressant class most commonly prescribed by PCPs due partly to their reduced need for dose titration and their relatively low potential for AEs (**Weihs & Wert, 2011**). Older, less commonly prescribed antidepressant classes include tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), which may be prescribed for patients with depressive symptoms who have not responded to the first-line therapies. The use of these older drugs is limited by their treatment-limiting AEs, greater lethality in the event of overdose, higher potential for drug-drug

interactions, and the need for dietary restrictions in the case of the MAOIs (**Hillhouse & Porter, 2015**). The newer, transdermal formulation of selegiline, an MAO type B inhibitor, does not require dietary restrictions. Other individual antidepressant agents that are considered the first line include bupropion, which affects dopaminergic and noradrenergic, but not serotonergic function, and mirtazapine, which increases the release of norepinephrine and serotonin (**Sub & Saadabadi, 2022**).

6. Conclusion

Brain glucose metabolism and mTOR signaling pathway are implicated in the pathogenesis of major depression disorder and represent potential therapeutic targets that should be studied extensively in order to develop new treatment strategies of depression.

Table 1. Commonly available antidepressants **(Weihs & Wert, 2011)**

	SSRIs					SNRIs		
Chemical Name (Brand)	Citalopram (Celexa®)	Escitalopram (Lexapro®)	Fluoxetine (Prozac®)	Paroxetine (Paxil®)	Sertraline (Zoloft®)	Desvenlafaxine (Pristiq®)	Duloxetine (Cymbalta®)	Venlafaxine (Effexor®)
Notes	Slower onset of action (up to 8 weeks), sexual AEs, may promote suicidality in children, discontinuation syndrome, cytochrome P450 interactions, nausea, weight gain					Similar to SSRIs, potentially increased BP		

	TCAs							
Chemical Name (Brand)	Amitriptyline (Elavil®, Endep®)	Clomipramine (Anafranil®)	Desipramine (Norpramine®, Pertofrane®)	Doxepin (Sinequan®)	Imipramine (Tofranil®)	Nortriptyline (Pamelor®)	Protriptyline (Vivactil®)	Trimipramine (Surmontil®)
Notes	Antimuscarinic actions (ie, dry mouth, urinary retention, flushing), weight gain, hypotension, arrhythmias, cytochrome P450 interactions, suicide risk, toxicity in overdose problematic, clomipramine may increase seizure risk							

	MAOIs			
Chemical Name (Brand)	Isocarboxazid (Marplan®)	Phenelzine (Nardil®)	Selegiline (Eldepryl®, Zelapar®, EMSAM®)	Tranylcypromine (Parnate®)
Notes	Tyramine/hypertensive crisis, suicide risk			

	SDRIs		Other		
Chemical Name (Brand)	Bupropion hydrobromide (Aplenzin™)	Bupropion hydrochloride (Wellbutrin®)	Buspirone (BuSpar®)	Mirtazapine (Remeron®)	Trazodone (Desyrel®)
		SR XL			
Notes	Minimal drug interactions	Reduced seizure threshold	Slower onset of action	Tetracyclic antidepressant (similar to TCAs), sedating	Discontinuation syndrome

References

Abelaira, H. M., Réus, G. Z., Neotti, M. V., & Quevedo, J. (2014). The role of mTOR in depression and antidepressant responses. Life Sciences, 101(1–2), 10–14. https://doi.org/10.1016/j.lfs.2014.02.014

Bockaert, J., & Marin, P. (2015). MTOR in Brain Physiology and Pathologies. Physiological Reviews, 95(4), 1157–1187. https://doi.org/10.1152/physrev.00038.2014

Bouwman, V., Adriaanse, M. C., van 't Riet, E., Snoek, F. J., Dekker, J. M., & Nijpels, G. (2010). Depression, Anxiety and Glucose Metabolism in the General Dutch Population: The New Hoorn Study. PLoS ONE, 5(4), e9971. https://doi.org/10.1371/journal.pone.0009971

Bryant, N. J., Govers, R., & James, D. E. (2002). Regulated transport of the glucose transporter GLUT4. Nature Reviews. Molecular Cell Biology, 3(4), 267–277. https://doi.org/10.1038/nrm782

Detka, J., Kurek, A., Basta-Kaim, A., Kubera, M., Lasoń, W., & Budziszewska, B. (2013). Neuroendocrine link between stress, depression and diabetes. Pharmacological Reports: PR, 65(6), 1591–1600. https://doi.org/10.1016/s1734-1140(13)71520-2

Detka, J., Kurek, A., Basta-Kaim, A., Kubera, M., Lason, W., & Budziszewska, B. (2014). Elevated Brain Glucose and Glycogen Concentrations in an Animal Model of Depression. Neuroendocrinology, 100(2–3), 178–190. https://doi.org/10.1159/000368607

Evans, J., Heron, J., Lewis, G., Araya, R., Wolke, D., & ALSPAC study team. (2005). Negative self-schemas and the onset of depression in women: Longitudinal study. The British Journal of Psychiatry: The Journal of Mental Science, 186, 302–307. https://doi.org/10.1192/bjp.186.4.302

Foster, K. G., & Fingar, D. C. (2010). Mammalian Target of Rapamycin (mTOR). Conducting the Cellular Signaling Symphony. The Journal of Biological Chemistry, 285(19), 14071-14077, https://doi.org/10.1074/jbc.R109.094003

Ghosal, S., Duman, C. H., Liu, R.-J., Wu, M., Terwilliger, R., Girgenti, M. J., Wohleb, E., Fogaca, M. V., Teichman, E. M., Hare, B., & Duman, R. S. (2020). Ketamine rapidly reverses stress-induced impairments in GABAergic transmission in the prefrontal cortex in male rodents. Neurobiology of Disease, 134, 104669. https://doi.org/10.1016/j.nbd.2019.104669

Hillhouse, T. M., & Porter, J. H. (2015). A brief history of the development of antidepressant drugs: from monoamines to glutamate. Experimental and clinical psychopharmacology, 23(1), 1–21. https://doi.org/10.1037/a0038550

Hosokawa, N., Hara, T., Kaizuka, T., Kishi, C., Takamura, A., Miura, Y., Iemura, S., Natsume, T., Takehana, K., Yamada, N., Guan, J.-L., Oshiro, N., & Mizushima, N. (2009). Nutrient-dependent mTORC1 association with the ULK1-Atg13-FIP200 complex required for autophagy. Molecular Biology of the Cell, 20(7), 1981–1991. https://doi.org/10.1091/mbc.e08-12-1248

James, S. L., Abate, D., Abate, K. H., Abay, S. M., Abbafati, C., Abbasi, N., Abbastabar, H., Abd-Allah, F., Abdela, J., Abdelalim, A., Abdollahpour, I., Abdulkader, R. S., Abebe, Z., Abera, S. F., Abil, O. Z., Abraha, H. N., Abu-Raddad, L. J., Abu-Rmeileh, N. M. E., Accrombessi, M. M. K., … Murray, C. J. L. (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. The Lancet, 392(10159), 1789–1858. https://doi.org/10.1016/S0140-6736 (18)32279-7

Leon, A. C., Solomon, D. A., Mueller, T. I., Endicott, J., Rice, J. P., Maser, J. D., Coryell, W., & Keller, M. B. (2003). A 20-year longitudinal observational study of somatic antidepressant treatment effectiveness. The American Journal of Psychiatry, 160(4), 727–733.

https://doi.org/10.1176/appi.ajp.160.4.727

Lindberg, L., Hagman, E., Danielsson, P., Marcus, C., & Persson, M. (2020). Anxiety and depression in children and adolescents with obesity: A nationwide study in Sweden. BMC Medicine, 18(1), 30–30. https://doi.org/10.1186/s12916-020-1498-z

Lyness, J. M., Heo, M., Datto, C. J., Ten Have, T. R., Katz, I. R., Drayer, R., Reynolds, C. F., Alexopoulos, G. S., & Bruce, M. L. (2006). Outcomes of minor and subsyndromal depression among elderly patients in primary care settings. Annals of Internal Medicine, 144(7), 496–504. https://doi.org/10.7326/0003-4819-144-7-200604040-00008

Mergenthaler, P., Lindauer, U., Dienel, G. A., & Meisel, A. (2013). Sugar for the brain: The role of glucose in physiological and pathological brain function. Trends in Neurosciences, 36(10), 587–597. https://doi.org/10.1016/j.tins.2013.07.001

Murgatroyd, C., Patchev, A. V., Wu, Y., Micale, V., Bockmühl, Y., Fischer, D., Holsboer, F., Wotjak, C. T., Almeida, O. F. X., & Spengler, D. (2009). Dynamic DNA methylation programs persistent adverse effects of onrly-life stress. Nature Neuroscience, 12(12), 1559–1566. https://doi.org/10.1038/nn.2436

Navale, A. M., & Paranjape, A. N. (2016). Glucose transporters: Physiological and pathological roles. Biophysical Reviews, 8(1), 5–9. https://doi.org/10.1007/s12551-015-0186-2

Nemeroff, C. B., & Owens, M. J. (2002). Treatment of mood disorders. Nature Neuroscience, 5 Suppl, 1068–1070. https://doi.org/10.1038/nn943

Prager, L. M. (2009). Depression and Suicide in Children and Adolescents. Pediatrics in Review, 30(6), 199–206. https://doi.org/10.1542/pir.30-6-199

Réus G, Quevedo J, Rodrigues AL. mTOR signaling in the neuropathophysiology of depression: current evidence. Journal of Receptor, Ligand and Channel Research. 2015;8:65-74 https://doi.org/10.2147/JRLCR.S70351

Rodrigues, A. L., Réus, G., & Quevedo, J. (2015). mTOR signaling in the neuropathophysiology of depression: Current evidence. Journal of Receptor,

Ligand and Channel Research, 65. https://doi.org/10.2147/JRLCR.S70351

Sub Laban T, Saadabadi A. Monoamine Oxidase Inhibitors (MAOI). Treasure Island (FL): StatPearls Publishing; 2022 https://www.ncbi.nlm.nih.gov/books/NBK539848/

Weihs, K., & Wert, J. M. (2011). A Primary Care Focus on the Treatment of Patients with Major Depressive Disorder. The American Journal of the Medical Sciences, 342(4), 324–330. https://doi.org/10.1097/MAJ.0b013e318210ff56

WHO (2015). WHO | Antidepressant medication in comparison with psychological treatment for moderate-severe depressive disorder. World Health Organization.