Mental health update – update on depression with a focus on escitalopram

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Abstract

Depression is one of the heterogenous diseases included in the International Classification of Diseases (ICD-11), published by the World Health Organization (WHO). Depression affects more than 300 million people globally. Almost 10% of the total burden of disease in sub-Saharan Africa is attributed to neuropsychiatric disorders, with depression disorders being the most diagnosed. Symptoms may include feelings of worthlessness, concentration and sleep difficulties, and suicidal ideation. There are different types of depression, with major depression being the most prevalent. The potential pathogenesis has been explored in various research, and it encompasses hypotheses from different angles such as genetics, neurotransmitters and hypothalamic-pituitary-adrenal axis, among other contributing factors. Both pharmacological and non-pharmacological treatments are effective for depression, however, antidepressant drugs (ADs) remain the primary treatment, particularly the selective serotonin re-uptake inhibitors (SSRIs), for example escitalopram. Untreated depression can result in emotional, behavioural and physical health problems that affect every area of that individual's life. This review article aims to summarise the hypotheses in the pathogenesis of depression and discuss its treatment, with particular focus on escitalopram.

Keywords: depression, escitalopram, antidepressant therapy, selective serotonin reuptake inhibitors

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Introduction

Depression, clinically known as major depressive disorder (MDD) is the most prevalent psychiatric condition globally.[1] It is characterised by persistent feelings of sadness, and lack of interest or pleasure in daily activities.[2,3] Despite effective treatments being available, depressive disorders are often overlooked and undertreated.[3,4] This under-treatment has historically been attributed to the stigma surrounding depression and inadequate assessment of symptoms.[2] However, recent data suggests that reduced social stigma and the availability of effective treatment options has led to increased rates of diagnosis.[4] Nonetheless, only a small portion of patients receive adequate treatment.[3]

Depression severely limits psychosocial functioning and diminishes quality of life.[5,6] It can cause difficulties at school and work and affect interpersonal relationships.[7] It is estimated that depression and anxiety result in the loss of 12 billion productive workdays annually, costing the global economy one trillion United States dollars.[8]

Depression is a complex mental health disorder influenced by a variety of factors. Established risk factors for depression include:[9]

- Genetic factors: heritability, specific genetic loci and gene-environment interactions contribute to the development of depression.
- Environmental factors: childhood adversities, significant life stressors and chronic medical conditions are major contributors.
- Psychosocial factors: impaired social support, loneliness and caregiver burden are significant psychosocial risk factors.
- Neuroendocrine/neurochemical factors: abnormalities in neuroendocrine systems and neurodegenerative diseases play crucial roles in the development of depression.

Given the widespread prevalence and severe impact of depression, there is a critical need for effective treatment options. Traditional treatments include pharmacotherapy, such as antidepressants, and psychotherapy, including cognitive-behavioural therapy (CBT).[9-11] Selective serotonin reuptake inhibitors (SSRIs) such as escitalopram, are preferred due to their effectiveness and better tolerability compared to the older tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). Escitalopram is regarded as an appropriate first-line antidepressant for moderate to severe major depression.[12] This review aims to provide an updated overview of the use of escitalopram in the treatment of depression.

Depressions

Depression can be characterised as a feeling of being sad, unmotivated, hopeless, irritable, as well as a general lack of interest or pleasure in life.[13] The concept explaining the etiology and pathophysiology of depression or depressive disorders is unclear, despite numerous in-depth studies.[14] Owing to its complexity, it cannot be explained using a single theory. Other than the psychological and social determinants of depression, there are various proposed biological hypotheses explaining the pathogenesis and these include genetic abnormalities, monoamines and neurotransmitter irregularities, dysfunction of the Hypothalamus-Pituitary-Adrenal (HPA) axis, neurotrophic

factors and neuroplasticity, inflammatory hypothesis and microbiome disturbances. Notably, depression may also develop because of somatic diseases or other mental conditions.[14,15]

Approximately 31–42% of depressive disorders are hereditary with 37% heritability demonstrated in twin studies.[15,16] Genetic predisposition is suspected in patients whose parents or siblings have suffered from recurrent depression in which the depression started at a relatively young age such as in childhood, teenage years or twenties. Some of the possible genetic causes include polymorphic genes, such as the serotonin transporter gene variants, related to the neurotransmission of serotonin, norepinephrine and dopamine (DA). They inhibit serotonin re-uptake, therefore predisposing individuals to depression.[15,16]

Neurotrophic factors regulate plasticity within the adult brain, and a decrease in these factors contributes to depression. This is evident in findings of volume reduction in the hippocampus and other forebrain regions seen in depressed patients.[17] The depletion of Brain-Derived Neurotrophic Factor (BDNF) appears to impair neurogenesis and, therefore, contributes to the onset of depression.[16]

Monoamines and other neurotransmitters

Neurotransmitters play an important role in depression etiology and the deficiency in monoamine neurotransmitters is the most common biochemical, neurophysiological explanation for depression. Monoamines include serotonin, noradrenaline and DA.[15,18] Serotonin (5-HT), a widely distributed neurotransmitter in the nervous system, can cause depression, phobias, anxiety and other mental health disorders when deficient. Serotonin results in depression through low 5-HT levels in the brain or altered 5-HT receptors such as upregulated 5-HT_2 and downregulated 5-HT_{1A} receptors as observed in depressed patients.

Another dominant neurotransmitter in the brain is DA, a precursor to epinephrine and norepinephrine responsible for regulating behavior.[19] In depressed patients, there is an increased level of DA transport resulting in increased reuptake of DA by presynaptic neurons.[20]

The monoamine hypothesis is confirmed through response of depressive patients to tricyclic antidepressants and monoamine reuptake inhibitors, proving an imbalance and neuromodulator deficiency in these patients.[15]

Glutamate, as the primary excitatory neurotransmitter in the brain, plays a role in synaptic plasticity, cognitive function as well as motivational and emotional behavior.[21] Elevated levels of glutamate, according to research, have been found in the blood, cerebrospinal fluid (CSF) and in the brains of patients with depression.

Gamma-aminobutyric acid (also known as GABA) is the opposite of glutamate as its primary function is inhibitory. GABA neurons participate in the regulation of anxiety, they are also involved in motivation and the reward system and play a crucial role in alleviating symptoms associated with MDD.[22]

Stress is one of the contributing factors to depression onset.[23] The hypothalamic-pituitary-adrenal axis (HPA) plays a vital role in stress response and a shift in the axis during depressive illness could be indicative of the involvement of stress. Exposure to stress triggers, leads to the release of the corticotropin-releasing hormone (CRH) from the hypothalamus. The CRH stimulates the pituitary to produce adrenocorticotrophic hormone (ACTH) that subsequently stimulates the adrenal cortex to secrete glucocorticoids.[24] Glucocorticoids elicit their effects in multiple target organs, including the HPA axis, causing feedback inhibition. This differs in depressive patients because the stress-induced HPA axis overactivity can lead to high cortisol levels with insufficient regulatory feedback.[25,26]

Immune system disturbances are involved in the development of depression.[27] It has been found by numerous early studies that depression is more common in patients who were exposed to autoimmune or infectious diseases as compared to the general population. It has been also shown that exposure to cytokines,

Table I: Overview of major depressive disorder diagnosis

Diagnostic criteria	Requires five or more specified symptoms, including depressed mood or anhedonia, over a two-week period. Chronic depression is termed persistent depressive disorder or dysthymia if symptoms last for at least two years.[29]
Symptoms	Depressed mood or anhedonia; Significant weight change or appetite disturbance; sleep disturbances; psychomotor agitation or retardation; fatigue; feelings of worthlessness, decreased ability to concentrate; recurrent thoughts of death or suicide.[30]
Screening tools	Patient Health Questionnaire-9 (PHQ-9) Hamilton Rating Scale for Depression (HAM-D) Beck Depression Inventory (BDI) Montgomery-Asberg Depression Rating Scale (MADRS) Zung Self-Rating Depression Scale[30,31]
Routine lab work	Used to exclude medical causes but not for diagnosing depression. Includes blood count, metabolic panel, thyroid function, vitamin D, urinalysis, and toxicology screening.[31]
Differential diagnosis	Depression symptoms must be differentiated from other conditions, such as bipolar disorder, anxiety disorders, schizophrenia, and bereavement. Persistent symptoms beyond typical grieving or adjustment period may indicate MDD.[29]
Primary care considerations	Many patients present with somatic complaints and may deny depressive feelings. Assessment for suicidal or homicidal ideations is crucial.[31]

in individuals who do not suffer from depression may result in those individuals' showing symptoms of depression.[28] Various pro-inflammatory cytokines, chemokines and soluble adhesion molecules, a sign of an immune-inflammatory response, are present in the peripheral blood and CSF of depressive patients. Inflammatory markers cause immune activation in the CNS, which can impact behaviors.[16,27]

Diagnosis

Diagnosing depression involves a comprehensive approach that integrates diagnostic criteria, symptom assessment and screening tools. The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) outlines specific criteria for MDD, including the presence of five or more symptoms over a two-week period, with at least one being depressed mood or anhedonia.[11,29] Challenges in diagnosing depression often arise due to overlapping symptoms, comorbid conditions, and variability of clinical presentations.[29] For a detailed overview of diagnostic criteria, tools, limitations, and other considerations please refer to Table I.

Management of depression

Non-pharmacological measures

There are various approaches in the management of depression including pharmacotherapy, psychotherapy and somatic therapy often used for treatment resistant depression.[32]

Somatic therapy: Somatic therapy for depression is a device-based approach that consists of introducing transient electric or magnetic current onto the scalp or to anatomically deep brain structures. The mechanism of action is largely attributed to increasing the level of neurotransmitters and sensitisation of post-synaptic receptors through changing the neuronal firing in the regions involved.[18] Electroconvulsive therapy (ECT) is the first effective somatic therapy to be used for the treatment of mental disorders with a widespread clinical use to date.[33]

Transcranial magnetic stimulation (TMS) is another type of somatic treatment which induces depolarisation of cortical neurons by the use of magnetic current that passes through a metal coil applied to the scalp of the patient, making it non-invasive.[34]

Pharmacological treatment

Majority of the available antidepressant drugs work by modulating the brain monoamine neurotransmission. The primary mechanism of these drugs is increasing the overall synaptic concentration of monoamines (serotonin, norepinephrine and dopamine).[32] They achieve this either by binding to the respective neurotransmitter transporter and blocking their reuptake into the presynaptic neuron or through inhibition of the monoamine degrading enzyme MAO.[35]

Tricyclic antidepressants act primarily by elevating serotonin and norepinephrine levels via reuptake inhibition. However, as they also antagonise muscarinic acetylcholine receptors, they are prone to anticholinergic side effects (e.g. dry mouth, blurry vision, constipation and urinary retention), which often limit their usefulness in the clinical practice setting. In addition, TCAs are known to cause prominent weight gain and sedation and can block cardiac sodium channels, which, in the case of an overdose, may lead to sudden cardiac death.[35]

Monoamine oxidase inhibitors inhibit the activity of the enzyme, monoamine oxidase, and thereby preventing the breakdown of the monoamine neurotransmitters. Two enzyme isoforms exist, namely MAO-A and MAO-B, which preferentially degrade different amines.[36]

This class has potentially lethal interactions with food, particularly foods rich in tyramine (e.g. aged cheese), and with other medications. Fatal serotonin syndrome or a hypertensive crisis may develop due to the inappropriate use of these agents. In fact, MAOIs should not be used together with SSRIs due to a potentially lethal increase in serotonin levels, known as the so-called serotonin syndrome. MAOIs are also known to promote weight gain and cause fatigue and hypotension.[36]

Some newer MAOIs such as selegiline and the reversible MAOI, moclobemide, have proven to be safer options.[35]

Selective serotonin re-uptake inhibitors are the preferred choice of treatment for depression. Unlike the TCAs, these agents only have selective serotonin reuptake-inhibition property and therefore avoid many of the other side effects of the TCAs such as anticholinergic and cardiac side effects. Additionally, they do not require dietary and drug-related restrictions as the MAOIs do. These agents block the serotonin reuptake pumps, acutely raising this transmitter in neuronal synapses.[36]

SSRIs may cause headaches, gastrointestinal disturbance, insomnia and fatigue, but are generally better tolerated than other antidepressants. Paroxetine eventually may allow more weight gain and may be the most sedating along with citalopram. Furthermore, sertraline may have more adverse gastrointestinal effects.[35]

Escitalopram

Escitalopram is one of the most commonly prescribed newer SSRIs worldwide.[37] Escitalopram is the racemic form of citalopram and is a more potent inhibitor of serotonin reuptake It has been found to be more than twice as potent as citalopram in the inhibition of serotonin uptake in in vitro binding studies.[38] It is more effective with a higher response rate than the other SSRIs and fewer side effects.[36] It was also shown to have less withdrawal symptoms compared to the other SSRIs.[39] Just like citalopram, escitalopram can cause significant QTc prolongation, potentially increasing the risk of ventricular arrhythmias, however at a less rate than the other antidepressants. Escitalopram is rapidly absorbed and reaches maximum plasma concentrations in approximately 3–4 hours. Escitalopram has low protein binding (56%) and it is unlikely to cause interactions with highly protein-bound drugs.[38]

Table II: Pharmacokinetic and pharmacodynamic properties of escitalopram[40,41]	
Pharmacokinetics	
Absorption	Rapid absorption with peak plasma concentrations (C_max) reached within 3–4 hours post-dose.
Bioavailability	Approximately 80%
Distribution	Widely distributed in the body, volume of distribution is approximately 12–26 L/kg
Plasma protein binding	About 56%
Metabolism	Metabolized primarily in the liver by CYP2C19, CYP2D6, and CYP3A4 enzymes
Elimination half-life	Approximately 27–32 hours
Excretion	Mainly excreted via urine; around 8% unchanged and the rest as metabolites
Steady-state concentration	Achieved within 1 week of consistent dosing
Pharmacodynamics	
Mechanism of action	Selective serotonin reuptake inhibitor (SSRI); increases serotonin levels in the synaptic cleft
Allosteric modulation	Unique allosteric interaction with the serotonin transporter (SERT)
Binding affinity	High affinity for the serotonin transporter
Selectivity	Highly selective for serotonin transporter with minimal effect on norepinephrine and dopamine
Therapeutic effects	Improvement in depressive symptoms, anxiety reduction
Side effects	Common: nausea, insomnia, fatigue, dry mouth; less common: sexual dysfunction, increased sweating

A summary of the pharmacokinetic and pharmacodynamic properties of escitalopram is available in Table II.

Escitalopram has been demonstrated to be superior to other antidepressants for the acute phase treatment of major depressive disorder in terms of efficacy, acceptability, and tolerability.[37,42]

Special populations

Escitalopram is well tolerated by elderly patients with MDD and should be used preferentially in this population as other SSRIs have interactions or adverse effects due to their additional mechanisms.[43] However, the use of multiple medications in this population increases the risk of drug interactions and side effects. Dosage adjustments are typically recommended with gradual titration to minimise side effects and regular monitoring of electrolytes and renal function is recommended.[40,41] Escitalopram is also approved for use in children and adolescents due to its favourable efficacy and safety profile, however there is increased risks of suicidal ideation in this population.[44] Thus, monitoring of emergent suicidal thoughts or behaviours is necessary, combined with family/caregiver involvement in treatment plans to assist with adherence and improve outcomes.

The use of escitalopram during pregnancy and breastfeeding requires a careful risk-benefit analysis. While untreated depression poses significant risks to both the mother and the foetus, SSRIs, including escitalopram, have been associated with potential risks such as preterm birth, low birth weight, and persistent pulmonary hypertension of the newborn[45] Thus, if treatment with escitalopram is deemed necessary, the lowest effective dose should be used. Close monitoring throughout pregnancy and the postpartum period is advised to manage potential risks to both the mother and the infant.

Important interactions between escitalopram and other medications or foods are detailed in Table III.

Serotonin Norepinephrine reuptake inhibitors inhibit serotonin and norepinephrine reuptake pumps, allowing treatment of a wide range of depressive symptoms. Some of the side effects include initial increase in anxiety, insomnia, and restlessness, as

Table III: Medication/food interactions with escitalopram[46,47]	
Medication/Food	**Interaction**
Monoamine oxidase inhibitors	Risk of serotonin syndrome. Avoid use within 14 days of discontinuing MAOIs.
Other SSRIs	Increased risk of serotonin syndrome. Avoid concurrent use unless closely monitored.
Tricyclic Antidepressants (TCAs)	Can increase TCA plasma levels, risking toxicity. Monitor TCA levels and adjust dosages.
NSAIDs and Anticoagulants	Increased bleeding risk. Use with caution and monitor for bleeding.
CYP2C19 and CYP3A4 Inhibitors	Can increase escitalopram levels. Adjust escitalopram dosage if used with inhibitors.
Alcohol	Can exacerbate side effects like drowsiness. Limit or avoid alcohol consumption.
Lithium and Triptans	Increased risk of serotonin syndrome. Use with caution and monitor closely.
Antiepileptic Drugs (AEDs)	May affect plasma levels of AEDs. Monitor levels and adjust doses as needed.
Grapefruit juice	Can inhibit CYP3A4 enzyme, increasing escitalopram levels. Avoid excessive consumption.
Caffeine	High intake can increase anxiety and insomnia. Advise moderation of caffeine.

well as possible sexual dysfunction and headaches. Compared to the SSRI class, the SNRI class tends to induce more nausea, insomnia, dry mouth, and in rare cases, elevated blood pressure.[36]

Atypical antidepressants

There are other antidepressants that do not fall into any of these categories and are considered unique or atypical antidepressants, such as mirtazapine and bupropion.

Mirtazapine inhibits norepinephrine's alpha-2 auto-receptors, allowing more norepinephrine to be released from nerve terminals. It also blocks 5-HT_{2A} receptors, thus allowing more serotonin, dopamine, and norepinephrine modulation in the cortex. As such, it achieves greater neurotransmitter levels via a different mechanism of action than the SNRI or SSRI drug classes. This also explains its different side-effect profile. It does, however it causes severe drowsiness and because of that, the use of mirtazapine is limited.[36]

Trazodone can be viewed as a mixed serotonergic agonist–antagonist and is more widely referred to by clinicians as a serotonin antagonist and reuptake-inhibitor (SARI). It acts as a serotonin agonist at high dosages and a serotonin antagonist at low dosages. It is considered, like mirtazapine, as a sedating agent.[36]

Bupropion has no effect on serotonin. It is a norepinephrine–dopamine reuptake-inhibitor (NDRI), due to its dual mechanism that raises both DA and norepinephrine levels. This gives it a unique side-effect profile characterised by no sexual dysfunction or weight gain. In fact, as it promotes weight loss, it is contraindicated in patients with eating disorders.[36]

Conclusion

Depression is widely associated with a decline in neurotransmitter concentrations, like serotonin and noradrenaline, in the CNS. Hence, treatment is aimed at restoring these neurotransmitter levels to normal, to enhance daily functioning and alleviate the symptoms that these patients suffer from. Escitalopram's consistent efficacy and favourable tolerability profile and fewer adverse events makes it a valuable tool in the management of MDD and GAD. It appears to be suitable as first-line antidepressant treatment. Clinicians should remain vigilant about monitoring and managing side effects, ensuring that patients receive the maximum benefit from this medication. As the landscape of mental health treatment evolves, escitalopram's role will likely remain significant, supported by continued research and clinical practice innovations.

Conflict of interest

The authors declare that there are no conflicts of interest

Ethical approval

Ethical approval was not required

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References

1. Kraus C, Kadriu B, Lanzenberger R, Zarate CA, Kasper S. Prognosis and improved outcomes in major depression: a review. Transl Psychiatry [Internet]. 2019;9(1). https://doi.org/10.1038/s41398-019-0460-3.
2. Cassano P, Fava M. Depression and public health. Int Rev Psychiatry. 1996;8(4):289-94. https://doi.org/10.1016/S0022-3999(02)00304-5.
3. Ghoneim MM, O'Hara MW. Depression and postoperative complications: An overview Visceral and general surgery. BMC Surg [Internet]. 2016;16(1):1-10. https://doi.org/10.1186/s12893-016-0120-y.
4. McCarter G. Depression Overview. MD Conf Express. 2007;7(2):28-9. https://doi.org/10.1177/155989770700213.
5. Kupferberg A, Hasler G. The social cost of depression: Investigating the impact of impaired social emotion regulation, social cognition, and interpersonal behavior on social functioning. J Affect Disord Reports [Internet]. 2023;14:100631. https://doi.org/10.1016/j.jadr.2023.100631.
6. Malhi GS, Bell E, Boyce P, Mulder R, Porter RJ. Unifying the diagnosis of mood disorders. Aust N Z J Psychiatry. 2020;54(6):561-5. https://doi.org/10.1177/0004867420926241.
7. WHO. 2022. https://www.who.int/news-room/fact-sheets/detail/depression).
8. Chodavadia P, Teo I, Poremski D, Fung DSS, Finkelstein EA. Prevalence and economic burden of depression and anxiety symptoms among Singaporean adults: results from a 2022 web panel. BMC Psychiatry [Internet]. 2023;23(1):1-9. https://doi.org/10.1186/s12888-023-04581-7.
9. Riedl D, Schüßler G. Factors associated with and risk factors for depression in cancer patients - A systematic literature review. Transl Oncol. 2022;16. https://doi.org/10.1016/j.tranon.2021.101328.
10. VandenBerg A. Chapter 88: Depressive Disorders. In 2022. p. 1-4. https://accesspharmacy.mhmedical.com/content.aspx?bookid=3097&sectionid=268013768.
11. Pepa PA, Lee KC. Chapter 60: Depression. 2024;1-14.
12. Cipriani A, Santilli C, Furukawa TA, et al. Escitalopram versus other antidepressive agents for depression. Cochrane Database Syst Rev. 2009;(2). https://doi.org/10.1002/14651858.CD006532.pub2.
13. Tomlinson G, Slater D. Types of Depression. Depression. 2018;6(1):157-61. https://doi.org/10.4324/9781315171616-21.
14. Ding W, Wang L, Li L, et al. Pathogenesis of depression and the potential for traditional Chinese medicine treatment. Front Pharmacol. 2024;15. https://doi.org/10.3389/fphar.2024.1407869.
15. Dobrek L, Głowacka K. Depression and its phytopharmacotherapy - A narrative review. Int J Mol Sci. 2023;24(5). https://doi.org/10.3390/ijms24054772.
16. Tian H, Hu Z, Xu J, Wang C. The molecular pathophysiology of depression and the new therapeutics. MedComm. 2022;3(3):1-36. https://doi.org/10.1002/mco2.156.
17. Wang JQ, Mao L. The ERK pathway: Molecular mechanisms and treatment of depression. Mol Neurobiol. 2019;56(9):6197-205. https://doi.org/10.1007/s12035-019-1524-3.
18. Karrouri R, Hammani Z, Otheman Y, Benjelloun R. Major depressive disorder: Validated treatments and future challenges. World J Clin Cases. 2021;9(31):9350-67. https://doi.org/10.12998/wjcc.v9.i31.9350.
19. Zhao F, Cheng Z, Piao J, Cui R, Li B. Dopamine receptors: Is it possible to become a therapeutic target for depression? Front Pharmacol. 2022;13:1-25. https://doi.org/10.3389/fphar.2022.947785.
20. Duval F, Mokrani MC, Erb A, et al. Neuroendocrine assessment of dopaminergic function during antidepressant treatment in major depressed patients. Brain Sci. 2021;11(4). https://doi.org/10.3390/brainsci11040425.
21. Zaghmi A. Development of therapeutic bioconjugates for neuroprotection in ischemic stroke. Theses. October 2020.
22. Ghosal S, Bang E, Yue W, et al. Activity-dependent brain-derived neurotrophic factor release is required for the rapid antidepressant actions of Scopolamine. Biol Psychiatry [Internet]. 2018;83(1):29-37. https://doi.org/10.1016/j.biopsych.2017.06.017.
23. Tan X, Zhang L, Wang D, et al. Influence of early life stress on depression: from the perspective of neuroendocrine to the participation of gut microbiota. Aging. 2021;13(23):25588-601. https://doi.org/10.18632/aging.203746.
24. Sukhareva EV. The role of the corticotropin-releasing hormone and its receptors in the regulation of stress response. Vavilovskii Zhurnal Genet Selektsii. 2021;25(2):216-23. https://doi.org/10.18699/VJ21.025.
25. Qin DD, Rizak J, Feng XL, et al. Prolonged secretion of cortisol is a possible mechanism underlying stress and depressive behaviour. Sci Rep [Internet]. 2016;6:1-9. https://doi.org/10.1038/srep30187.
26. Mikulska J, Juszczyk G, Gawrońska-Grzywacz M, Herbet M. Hpa axis in the pathomechanism of depression and schizophrenia: New therapeutic strategies based on its participation. Brain Sci. 2021;11(10). https://doi.org/10.3390/brainsci11101298.
27. Köhler CA, Freitas TH, Stubbs B, et al. Peripheral alterations in cytokine and chemokine levels after antidepressant drug treatment for major depressive disorder: Systematic review and meta-analysis. Mol Neurobiol. 2018;55(5):4195-206. https://doi.org/10.1007/s12035-

017-0632-1.
28. Lee CH, Giuliani F. The role of inflammation in depression and fatigue. Front Immunol. 2019;10:1696. https://doi.org/10.3389/fimmu.2019.01696.
29. Malhi GS, Mann JJ. Depression. Lancet. 2018;392(10161):2299-312. https://doi.org/10.1016/S0140-6736(18)31948-2.
30. Serretti A. Anhedonia and depressive disorders. Clin Psychopharmacol Neurosci. 2023;21(3):401-9. https://doi.org/10.9758/cpn.23.1086.
31. Mughal AY, Devadas J, Ardman E, et al. A systematic review of validated screening tools for anxiety disorders and PTSD in low to middle-income countries. BMC Psychiatry. 2020;20(1):1-18. https://doi.org/10.1186/s12888-020-02753-3.
32. Fekadu N, Shibeshi W, Engidawork E. Major depressive disorder: Pathophysiology and clinical management. J Depress Anxiety. 2017;06(01). https://doi.org/10.4172/2167-1044.1000255.
33. Li M, Yao X, Sun L, et al. Effects of electroconvulsive therapy on depression and its potential mechanism. Front Psychol. 2020;11:1-13. https://doi.org/10.3389/fpsyg.2020.00080
34. Fitzgerald PB. Targeting repetitive transcranial magnetic stimulation in depression: do we really know what we are stimulating and how best to do it? Brain Stimul [Internet]. 2021;14(3):730-6. https://doi.org/10.1016/j.brs.2021.04.018.
35. DiPiro JT, Talbert RL, Yee GC, et al. Pharmacotherapy: A pathophysiologic approach. 12 edition 2014. https://accesspharmacy.mhmedical.com/book.aspx?bookID=3097.
36. Santarsieri D, Schwartz TL. Antidepressant efficacy and side-effect burden: A quick guide for clinicians. Drugs Context. 2015;4:1-12. https://doi.org/10.7573/dic.212290.
37. Yin J, Song X, Wang C, Lin X, Miao M. Escitalopram versus other antidepressive agents for major depressive disorder: a systematic review and meta-analysis. BMC Psychiatry [Internet]. 2023;23(1):1-14. https://doi.org/10.1186/s12888-023-05382-8.
38. Rao N. The clinical pharmacokinetics of escitalopram. Clin Pharmacokinet. 2007;46(4):281-90. https://doi.org/10.2165/00003088-200746040-00002.
39. Feng RF, Ma R, Wang P, et al. Efficacy of escitalopram for poststroke depression: a systematic review and meta-analysis. Sci Rep. 2022;12(1):1-10. https://doi.org/10.1038/s41598-022-05560-w.
40. FDA. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2003/21323se1-003,se8-007,21365se8-001,se1-004_lexapro_lbl.pdf
41. Drugbank. Available from: https://go.drugbank.com/drugs/DB01175
42. Jensen JB, du Jardin KG, Song D, et al. Vortioxetine, but not escitalopram or duloxetine, reverses memory impairment induced by central 5-HT depletion in rats: Evidence for direct 5-HT receptor modulation. Eur Neuropsychopharmacol [Internet]. 2014;24(1):148-59. https://doi.org/10.1016/j.euroneuro.2013.10.011.
43. Lenze EJ, Ajam Oughli H. Antidepressant treatment for late-life depression: Considering risks and benefits. J Am Geriatr Soc. 2019;67(8):1555-6. https://doi.org/10.1111/jgs.15964.
44. Fagan HA, Baldwin DS. Pharmacological treatment of generalised anxiety disorder: Current practice and future directions. Expert Rev Neurother [Internet]. 2023;23(6):535-48. https://doi.org/10.1080/14737175.2023.2211767.
45. Delaney SR, Malik PRV, Stefan C, et al. Predicting escitalopram exposure to breastfeeding infants: Integrating analytical and in silico techniques. Clin Pharmacokinet [Internet]. 2018;57(12):1603-11. https://doi.org/10.1007/s40262-018-0657-2.
46. Anderson PO. Antidepressants and breastfeeding. Breastfeed Med. 2021;16(1):5-7. https://doi.org/10.1089/bfm.2020.0350.
47. Medscape. Lexapro (escitalopram) dosing, indications, interactions, adverse effects, and more. 2024. Available at: https://reference.medscape.com/drug/lexapro-escitalopram-342961. Accessed: 24 July 2024.