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A RECENT ADVANCEMENT AND TREATMENT OVERVIEW OF DEPRESSION

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ABSTRACTS

Depression and depressive symptoms are common mental disorders that have a considerable effect on patients' health-related quality of life and satisfaction with medical care, but the prevalence of these conditions varies substantially between published studies. The purpose of this research is to carry out a comprehensive review and meta-analysis so that an accurate estimate of the number of outpatients suffering from depression or depressed symptoms may be obtained across a variety of clinical subspecialties. This review Mainly focus at the research on desvenlafaxine's usage in MDD therapy. In adults, desvenlafaxine was a successful antidepressant with good safety and tolerability. The subset of peri- and postmenopausal women with MDD showed efficacy, but not children and adolescents. Due to its metabolic nature, there is a relatively minimal risk for drug-drug interactions. While severe renal failure necessitates certain dose changes, hepatic impairment does not dramatically change dosage needs. Patients with concomitant physical ailments may benefit from desvenlafaxine. When treating MDD clients without other medical comorbidities, desvenlafaxine may be a first option. Despite the fact that these hit molecules are readily available, around 30% of depressive patients do not react to the current pharmacological regimens, and the remaining 70% do not have a full remission. Antidepressants can have a wide range of adverse effects including drug-drug and drug-food interactions. To develop more effective and secure medications to treat serious depression, various ways are being tested in this situation. One such chemical that has shown encouraging effectiveness in several animal models of severe depression is curcumin. Curcumin's antidepressant effect is thought to work by blocking the monoamine oxidase enzyme and controlling the release of serotonin and dopamine, while the exact mechanism of action is still unclear. This review examines the pharmacology and molecular mechanisms of curcumin's antidepressant impact in animal models of depression. Curcumin's antidepressant effectiveness and safety require clinical testing.

KEYWORDS: MDD (Major depressive disorder).

1. INTRODUCTION

Depression is the primary cause of disability and contributes significantly to the global disease burden. In recent decades, the global prevalence of depression and depressed symptoms has risen.[1] Depression is one of the most well-known and serious psychotic diseases, and it is characterized by a loss of confidence, difficulty concentrating, sleep disturbances, a gloomy mood, melancholy, unhappiness, and suicidal attempts as a result of a lack of interest in social activities. Depression affects roughly 16% of the population and is the leading cause of suicide in more than 60% of instances.[2] Depression is a major factor of quality of life and survival, accounting for almost half of all psychiatric consultations and a quarter of all hospital admissions.[3] The illness itself, as well as the high medical costs, inadequate medical care service, and a bad doctor–patient interaction, are all contributing factors.[4] There have been some useful systematic reviews published on specific populations of outpatients. Mitchell et al., for example, indicated that depression was present in 9.6 percent to 16.5 percent of oncology and hematology patients.[5] Outpatient depression is linked to large indirect costs due to lost productivity and unemployment. A large economic burden will result from the combination of chronic medical diseases and depression.[6] Depression will be the leading cause of disability by 2030, according to the World Health Organization.[7]

Depression has a prevalence rate of up to 20% in the general population worldwide, with a female to male ratio of about 5:2. The disease is usually recurrent, and most patients recover from major depressive episodes.[8] However, a significant proportion of patients develop severe depression, and after 5 and 10 years of prospective follow-up, 13% and 7%, respectively, are still depressed.[9] Depression appears to raise the risk of cardiac mortality regardless of baseline cardiac status; additionally, the excess mortality risk for major

depressive disorder was more than twice that of minor depression.[10] Suicide is a significant risk for mortality in depression, and the suicide rate is quite high between the ages of 15 and 24.[11]

2. Methods to detect depression

2.1 Data research methods of functional magnetic resonance imaging

Since cognitive impairment in depression is linked to the rehabilitation of social function in people with depression, research on cognitive impairment in depression has gotten a lot of attention in recent years. Perception, attention, memory, thinking, executive function, and language understanding are just a few examples of cognitive functions. Functional magnetic resonance imaging (fMRI) is a new neuroimaging technique that uses magnetic resonance imaging to evaluate changes in hemodynamics caused by neuronal activity. It's mostly utilised to research human and animal brains and spinal cords. +e traditional data research method requires obtaining information under the task state in advance and then comparing and analysing it with subsequent data, but now, fMRI imaging technology is combined to collect the subject's fMRI data, in which we can get the difference through different regions of interest (ROI). This data analysis approach is based on the fMRI data analysis method and the ROI feature changes information under different time series, so it is no longer essential to gather information for comparison in advance.[12,13] The model-driven method is a statistical analysis-based method that requires the time-to-time images of pre-brain activity to be known. +is method is appropriate for single functional brain positioning, since it predicts the temporal image of brain activity based on the time of stimulation, and then uses the predicted temporal image of brain activity for statistical analysis and positioning.[14,15]

2.2 Resting function connection method

The BOLD signal (fMRI) of people who are awake, blinded, and relaxed was first utilized to detect abnormalities in brain structure or brain activity. Initially, scientist assumed that EEG signals at rest were random and susceptible to disturbance. EEG equipment is used to capture and magnify changes in biopotential information inside the brain on the scalp's surface, which reflects the activity state of various brain areas the capture of EEG signals is a simple and effective noninvasive method of studying brain activity. The potential fluctuations it reflects are the product of several nerve cells in the brain working together.[16]

The resting state's functional connectivity analysis, The EEG comprises mostly of three steps:

- ✓ The calculation of connectivity between different regions of the brain,
- ✓ The functional network of the brain and the analysis of related attributes are constructed using the minimum spanning tree based on the connectivity results,
- ✓ The hierarchical clustering of the minimum spanning tree is different. Using amplitude squared coherence, the coherence of all 72 electrode EEG signals at each single frequency was calculated in this study (MSC).

3. Mechanism of depression

They suppress the reuptake transport protein leads to enhance amount of serotonin and norepinephrine in the synaptic clefts, which consequently give reliefs against symptoms of depression. The graphical presentation is described in following

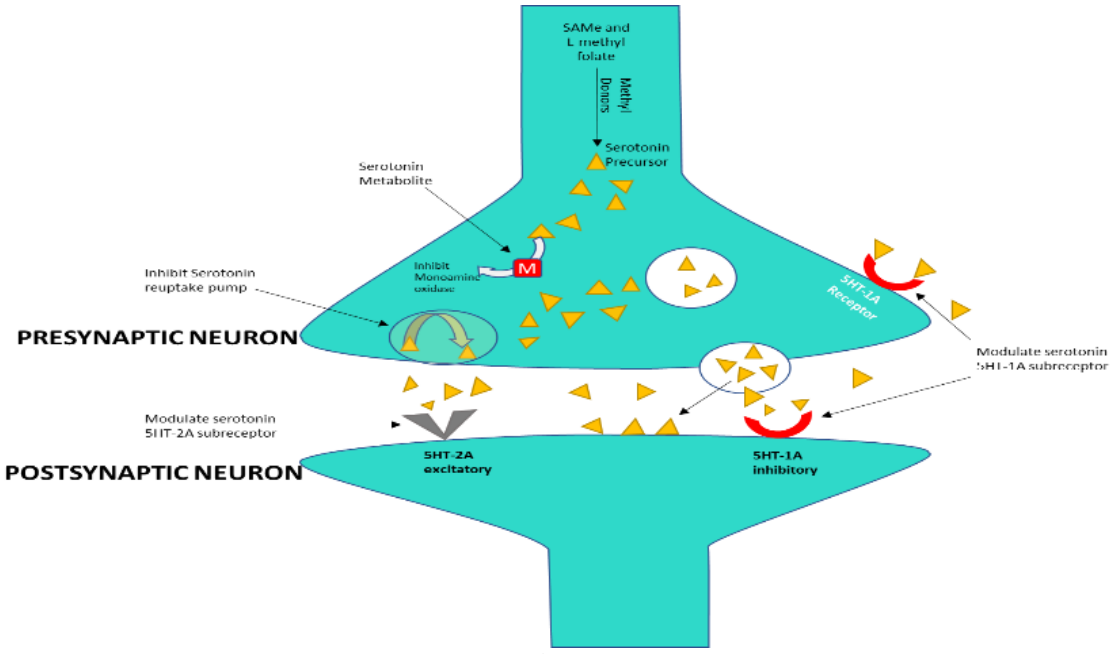

Fig. 1

Non tricyclic serotonin and nor epinephrine reuptake inhibitors are the agents having dual serotonin and norepinephrine reuptake inhibition (SNRIs). Ant it is also proven by supportive studies (Clinical) that drugs which elevate the amount of both norepinephrine and serotonin in the synaptic cleft are better than single acting agents, especially in the treatment of depression. The decrement in chances of side effects is due to lower affinity of SNRIs at neuronal receptors of the other neurotransmitters, compared with the TCAs.

3.1 Stages involved in depression

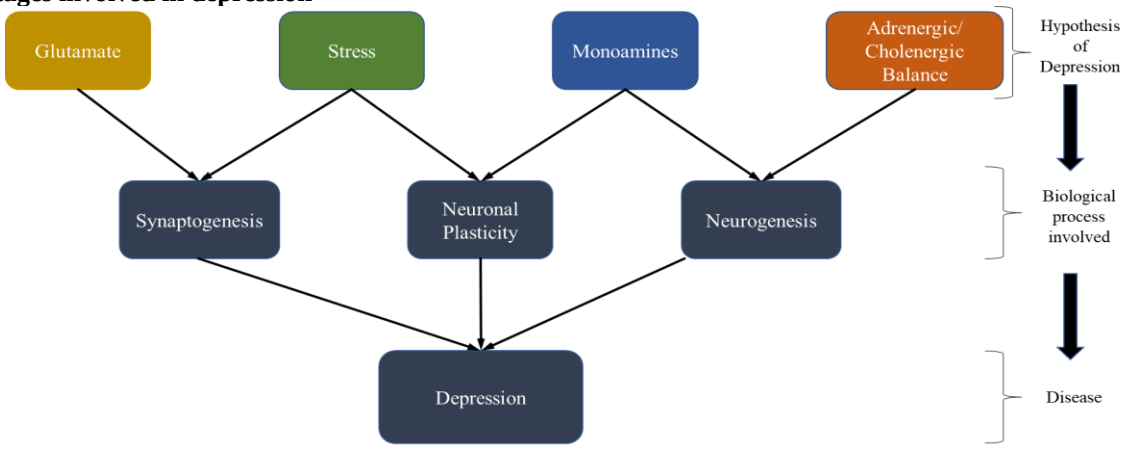

Figure 2: Summary of current hypotheses of depression. Proposed hypotheses of depression and their associated drug targets are shown in the top Row. Several biological processes involved in the etiology of depression are listed in the middle Row. The bottom Row represents human depression.

3.2 Symptoms of depression

Although depression can occur only once in a lifetime, most people experience multiple episodes. Symptoms occur most of the day, nearly every day, during these episodes, and may include:

I. Feelings of sadness, tearfulness, emptiness or hopelessness
II. Loss of interest or pleasure in most or all normal activities, such as sex, hobbies or sports
III. Sleep disturbances, including insomnia or sleeping too much
IV. Tiredness and lack of energy, so even small tasks take extra effort
V. Suicidal thinking or feelings, especially in older men
VI. Memory difficulties or personality changes
VII. Physical aches or pain[17]

4. Classification of antidepressants

4.1 Antidepressant drug

a) Selective Serotonine Reuptake Inhibitor (SSRI):
i) Fluoxetine
ii) Citalopram
iii) Fluvoxamine
b) Selective Serotonine and Noradrenaline Reuptake Inhibitor (SNRI's):
i) Desvenlafaxine
ii) Venlafaxine
iii) Duloxetine
c) Tricyclic and Tetracyclic Antidepressant (TCAs):
i) Clomipramine
ii) Desipramine
d) Others:
i) Tianeptine
ii) Tryptophan

4.2 Mood stabilizers

a) Lithium Salts
b) Antiepileptics

4.3 Non-Chemical therapies

a) Light Therapy
b) Magnetic Stimulation
c) Deep Brain Stimulation

4.4 Psychotherapy

a) Cognitive Therapy
b) Problem Solving Therapy
c) Interpersonal Psychotherapy [18].

5. Treatment of depression

5.1 SNRIs (Desvenlafaxine)

Desvenlafaxine is a phenethylamine bicyclic derivative that is the primary active metabolite of venlafaxine: O-desmethyl-venlafaxine (see Box 1). Because the molecule has a chiral centre, it is reasonable to expect that, like venlafaxine, desvenlafaxine will exhibit enantio-selective effects on noradrenaline and serotonin presynaptic reuptake.[19]

Desvenlafaxine succinate is a serotonin–norepinephrine reuptake inhibitor (SNRI) that is approved for the treatment of MDD in adults at a dose of 50 mg per day.[20] it rapidly penetrated the brain and increased hypothalamic noradrenaline concentrations, but not dopamine concentrations, according to in vivo micro

dialysis studies.[21] Nine fixed-dose, short-term, placebo-controlled studies in adult outpatients with MDD revealed statistically significant improvements with desvenlafaxine 50 and 100 mg/day versus placebo for all efficacy end points.[22] A few head-to-head studies have also shown that desvenlafaxine and escitalopram have comparable efficacy and safety.[23,24] For patients with hepatic difficulties, the Australian and New Zealand College of Psychiatrists 2015 practice guidelines preferred desvenlafaxine above other antidepressants that are metabolized by the liver.[25]

5.1.1 Metabolism

Desvenlafaxine (or O-desmethylvenlafaxine) is the major active metabolite of the SNRI venlafaxine after metabolism by CYP2D6. This metabolite has antidepressant properties, and its salt, desvenlafaxine succinate, is a prescription medication.[26] Renal excretion is a significant route of desvenlafaxine elimination, with approximately 45 percent excreted unchanged in urine.[27] The hepatic metabolism has been shown to perform a limited role in the elimination of desvenlafaxine, indicating a relatively simple metabolism.[28] However, urinary recovery of total desvenlafaxine and its metabolites in renally impaired patients is comparable to that in healthy patients. Pharmacokinetic studies have shown that the systemic clearance of a single oral dose of 100 mg desvenlafaxine decreases with the severity of renal impairment.[29]

5.2 Add-ons to SSRIs and SNRIs in MDD:

5.2.1 Atypical antipsychotics as an augmenting strategy

Several atypical antipsychotics (olanzapine, risperidone, quetiapine, aripiprazole, paliperidone, etc) have been tested in clinical MDD trials as an adjunct to SSRIs/SNRIs, and some have received label claims for the treatment of MDD.[30] The synergistic effect of atypical antipsychotics and SSRIs/SNRIs is most likely due to inhibition of 5-HT reuptake and antagonism of 5-HT2A/C receptors, resulting in an increase in 5-HT levels above what an SSRI achieves. Surprisingly, there is very little clinical evidence to support the use of selective 5-HT2 receptor antagonists as a stand-alone therapy.[31] Cariprazine, a partial agonist of the DA D2, DA D3, and 5-HT1A receptors,[32] is currently being tested in clinical trials as an adjunctive treatment for MDD.[33]

5.2.2 Augmentation mechanisms

For patients who have not responded adequately to SSRI/SNRI therapy, it is common practice to prescribe a second drug as an adjunctive treatment in an attempt to either increase the efficacy of the first antidepressant or treat residual symptoms. Clinical studies involving SSRIs and pindolol, a 5-HT1A receptor partial agonist and a adrenoceptor antagonist, revealed a faster onset of antidepressant effect than SSRIs alone, fueling interest in this research area.[34]

5.3 Multimodal antidepressants

Another approach to enhancing 5-HT transmission beyond what an SSRI achieves has been to target 5-HT receptors in tandem with SERT inhibition in a single molecule.[35] Vilazodone, a 5-HT1A receptor partial agonist and SERT inhibitor and vortioxetine, a 5-HT1A receptor agonist, 5-HT1B receptor partial agonist, 5-HT3, 5-HT7, and 5-HT1D receptor antagonist and SERT inhibitor, are two multimodal antidepressants that have recently been approved for the treatment of MDD.[36]

5.4 Agonmelatine

Another strategy for treating depression symptoms has been to target 5-HT beyond reuptake. Agonmelatine, a melatonin MT1 and MT2 receptor agonist and 5-HT2C receptor antagonist, is one example.[37] In the pineal gland, 5-HT is catabolized into melatonin in a two-step enzymatic process.[38] Agomelatine was well accepted, with no severe serotonergic side effects,[39,40] no withdrawal syndrome,[41] and only minor sexual dysfunction. The main negative effect was increase in serum transaminase levels in some of the subjects, which could be indicative of liver damage.[42]

5.5 Ketamine and Other NMDA receptor modulators

Berman et al seminal clinical study demonstrating that a single intravenous dose of the NMDA open channel blocker ketamine can produce immediate and long-lasting antidepressant effects in patients with TRD case of emerging interest in the role of glutamatergic transmission in depression.[43] Ketamine is a glutamatergic NMDA receptor non-competitive open-channel blocker. It binds to open NMDA receptors, becomes trapped inside the channel pore when the receptor closes, and slowly dissociates when the receptor is reactivated by its endogenous ligand.[44]

6. Natural treatment of depression

6.1 Green Tea and Green tea catechins

The tea plant, Camellia sinensis L., is one of the significant plant species in the Theaceae family, and it is utilized as a popular herbal beverage all over the world. Catechins, flavanols, theaflavins, and thearubigins are only a few of the bioactive natural compounds found in tea which are very useful, which possess potent antioxidant activity and can inhibit lipid peroxidation.[45,46]

Green tea administration has been shown to have a positive effect on depressive-like behavior in several in vitro investigations. Exogenous infusion of green tea polyphenols significantly decreased monoamine oxidase activity in the C6 glial cell line.[47]

It was found that green tea treatment has an effect on a mouse model of depression caused by lipopolysaccharide. Green tea extracts have been shown to suppress the activity of COX which is a cyclooxygenase enzyme that plays a critical function in depression.[48]

6.2 Cocoa

Cocoa is one of the most important and common sources of natural bioactive substances in the human diet, including polyphenols.[49,50]

Taking cocoa for a month improved mood states on the Bond–Lader Visual Analogue Scale.[51]

A cross-sectional study of 1018 adults yielded similar results. Chocolate consumption was also linked to lower depression scores on the Depression Scale.[52]

6.3 Vitamins B

A lack of vitamin B has been linked to a variety of neuropsychiatric disorders. Epidemiological studies have revealed an inverse relationship between serum B vitamin levels and the risk of depression.[53]

Several epidemiological studies have found that raising folate, B12, and B6 levels by dietary intervention can vastly reduce depression symptoms.[54]

When compared to antidepressant monotherapy alone, folate supplementation is a cheap and safe therapeutic drug that can improve the therapeutic success of SSRIs.[55,56]

7. Disease associated with depression

7.1. Epilepsy

MDD is the most common psychiatric illness in epilepsy patients, with a lifetime prevalence rate of 17.4 percent.[57,58] Phenytoin, carbamazepine, and barbiturates are strong inducers of CYP enzymes and UGTs, minimizing antidepressant exposure. Valproic acid inhibits a wide range of enzymes, including CYPs and some UGTs [59]. Many antidepressants, on the other hand, inhibit CYP metabolism to varying degrees and can raise antiepileptic-drug levels. Some antidepressants may interact with antiepileptic drugs, potentially lowering seizure thresholds and exacerbating seizure attacks.

7.2. Chronic liver disease

In patients with chronic liver disease, the overall prevalence of depression was found to be 23.6 percent (27.2 percent in nonalcoholic fatty liver disease, 29.8 percent in hepatitis C, and 3.7 percent in hepatitis B).[60] Depression is another common side effect of IFN treatment (found in 30%–70% of treated patients).[61] Directly acting antivirals can also inhibit the activity of CYP enzymes which plays role in depression.[62] Boceprevir, simeprevir, and telaprevir are all CYP3A4 substrates and inhibitors.[63] The 2015 practice guidelines of the Australian and New Zealand College of Psychiatrists For patients with hepatic impairments,[64] recommended desvenlafaxine over other antidepressants (which are metabolized by the liver).

7.3. Migraine

Depression seems to be nearly three times more common in patients suffering from severe headaches/migraine.[65] Because sumatriptan and zolmitriptan are metabolized by monoamine oxidase A (MAOA), coadministration with MAOIs can increase triptan side effects.[66,67] The US Food and Drug Administration suggested in 2010 that patients taking a triptan and an SSRI/SNRI be alerted of the chance of serotonin syndrome.[68] Due to the severity of serotonin syndrome, clinicians are still recommended to be on the lookout for signs of toxicity.[69] When desvenlafaxine is combined with serotonergic agents such as triptans, serotonin syndrome should be avoided.[70]

7.4. Cardiovascular conditions

Cardiovascular disease (CVD) and depression frequently exist simultaneously.[71] CYP enzymes, including CYP2D6, extensively metabolize-blockers such as propranolol, timolol, metoprolol, and carvedilol. Antidepressants that are strong CYP2D6 inhibitors, such as paroxetine, fluoxetine, duloxetine, and bupropion, have been shown to cause additional heart rate reductions when combined with propranolol.[72] There is a risk of hypotension and bradycardia when calcium-channel blockers are combined with CYP3A4 inhibitors. DDIs in hypercholesterolemia treatment use similar PK mechanisms. When CYP3A4 inhibitors suppress statin metabolism, the risk of myopathy increases.[73] Patients with CV or lipid-metabolism disorders should exercise caution, as clinical studies with desvenlafaxine have shown an increase in blood pressure, heart rate, and cholesterol levels.

CONCLUSION

The results of the experiments indicate that the research on the mechanism of depression through brain function imaging analysis of depression patients and normal humans that is proposed in this article is more intelligent and scientific in monitoring than other methods that have been used in the past to study the mechanism of depression. In the last half-century, the discovery of antidepressant medications and the subsequent research into their pharmacology have brought about a sea change in the profession. There are now hundreds of antidepressant medications that have been authorized for use. These medications fall into one of four distinct categories: tricyclic medicines, selective serotonin reuptake inhibitors, MAO inhibitors, and other antidepressants. The effectiveness of each medication is around sixty percent.

On the other hand, the preclinical data that was presented in this review provides an explanation for the antidepressant effect of curcumin and, as a result, adds a new facet to the extensive therapeutic advantages that it offers. It is known that the molecule will alter the amounts of neurotransmitters in the brain, and it will also boost the levels of neurotrophic factors, which will further enhance neuronal survival. In order to move the

process of developing antidepressant drugs forward, it is necessary to test this natural treatment on people since the experimental studies predicted favorable effects from the use of the remedy on animals.

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