Trends in major depression disorder Pharmacology.

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La depresión es un trastorno heterogéneo con un curso muy variable, una respuesta inconsistente al tratamiento y ningún mecanismo establecido.En el desarrollo de la enfermedad interviene una compleja interacción de factores genéticos, ambientales, sociales y psicológicos.

RESUMEN

La hipótesis de la deficiencia de neurotransmisores para los trastornos depresivos considera que los síntomas depresivos derivan de niveles insuficientes de dopamina (DA), norepinefrina (NE) y/o serotonina (5-HT) en el cerebro. La deficiencia de neurotransmisores está posiblemente relacionada con el agotamiento de monoaminas, la síntesis insuficiente o la secreción/reabsorción alterada de neurotransmisores en la sinapsis. Los tratamientos pueden consistir en psicoterapia centrada en la depresión, farmacoterapia, terapia electroconvulsiva o una combinación de ellas. Los ISRS siendo los tratamientos farmacoterapéuticos de referencia para el TDM. En el presente artículo, discutimos pales tendencias recientes en la farmacología para la Depresión.

Palabras clave: Depresión mental, fármacos antidepresivos, monoaminas.

ABSTRACT

The neurotransmitter deficiency hypothesis for Depressive disturbs considers depressive symptoms derived from insufficient levels of dopamine (DA), norepinephrine (NE), and/or serotonin (5-HT) in the brain. Neurotransmitter deficiency is possibly related to monoamine depletion, insufficient synthesis, or altered secretion/reuptake of neurotransmitters at the synapse. Treatments can involve depression-focused psychotherapy, pharmacotherapy, electroconvulsive therapy, or a combination of them. SSRIs remain the gold-standard pharmacotherapeutic treatments for MDD. In the present article, we discuss the recent major trends on the pharmacology for the Depression.

Key words: Mental Depression, antidepressant drugs, monoamines.

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1. Introduction

Mental depression is one of the most common psychiatric disorders worldwide, affecting about 3.8% of the general population (approximately 280 million people), or 5.0% of adults in 2019 (INSTITUTE FOR HEALTH METRICS AND EVALUATION, 2019). Stressful life events are the principal factor to induce depressive episodes (FUCHS; FLÜGGE, 2004). Research from the World Health Organization (WHO) has indicated that the COVID-19 pandemic has increased mental disorders such as anxiety and depression by more than 25%. The WHO has estimated that depression and anxiety cost the global economy the loss of 12 billion workdays and about US$1 trillion a year (WHO, 2023).

Depression differs from usual mood fluctuations that a person can experience in response to everyday challenges. The frequency of episodes and the severity of symptoms can impact the individual's ability to carry out life activities in work, education, family, personal, and social life. Depression can also lead to suicide and hence the WHO estimates that almost 700,000 people die due to suicide per year. Treatments for depression are considered effective and have been studied for the last 50 years. Nevertheless, nearly 75% of people affected by this disorder in underdeveloped countries don't receive any treatment, because of underdiagnosis, possible issues of access to treatment, and stigmatization of patients, among other causes (WHO, 2021).

2. Clinical condition

According to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, text revision (DSM-5-TR), depressive disorders can be classified into: major depression, disruptive mood dysregulation disorder, persistent depressive disorder, depressive disorder due to another medical condition, premenstrual dysphoric disorder, substance/medication-induced depressive disorder, other specified depressive disorder, or unspecified depressive disorder (AMERICAN PSYCHIATRIC ASSOCIATION, 2022). Major depression (MDD) is defined as the occurrence for at least two weeks of five or more symptoms, almost all day long and/or almost every day: (a) depressed mood; (b) loss of pleasure or interest in daily activities; (c) weight loss or gain without being on a diet, or loss or gain of appetite; (d) insomnia or hypersomnia; (e) agitation or psychomotor retardation; (f) fatigue; (g) low self-worth or excessive guilt feelings; (h) loss of concentration or thinking capability, or indecision; (i) recurrent death thoughts (AMADERA, 2019). MDD can occur with anxious distress, mixed features, melancholic features, atypical features, mood-congruent psychotic features, catatonia, peripartum onset, or seasonal patterns. A complex interaction of genetic, environmental, social, and psychological factors is involved in the development of the disease. Hamon and Blier have shown that genetic polymorphisms are present in 38% of cases of MDD (HAMON; BLIER, 2013).

3. Metabolic syndromes

Depression is associated with metabolic syndromes, like obesity and diabetes, inflammation, endocrine disorders, and cardiovascular diseases. Plasma levels of cortisol are usually higher in MDD individuals (HAMON; BLIER, 2013; SHELTON; MILLER, 2010). Insulin-like growth factor (IGF) induces hippocampal neurogenesis. Studies suggest that IGF disorder is associated with depression, and antidepressants can improve hippocampal neurogenesis by glucocorticoid receptors (ANACKER et al., 2011). Inflammatory cytokines are increased during depression (SHELTON; MILLER, 2010), and anti-inflammatory drugs can be associated with antidepressants as a new strategy for MDD (ABDEL-BAKKY et al., 2021).

4. Neural circuits in MDD

Neural circuits involved in MDD can be evaluated with imaging techniques. Limbic–cortical–striatal–pallidal–thalamic (LCSPT) circuits play an important role in self-reference, fear, anxiety, visceral response, and the reward system (HAMON; BLIER, 2013). LCSPT comprehends a pathway through the prefrontal cortex, amygdala, hippocampus, striatum, pallidum, and thalamus. Positron emission tomography (PET) on monkeys has revealed that the prefrontal cortex acts in sensory integration and in the reward system; the posterior parahippocampal cortex is involved in mood and visceral reactions to emotional stimuli; and frontal hypometabolism and limbic hypermetabolism in depression (KENNEDY et al., 2001). Differences in limbic–cortical connections between antidepressant responders and non-responders show that non-responders present more abnormalities in these pathways, and this could lead to the identification of depression phenotypes, and individualization of treatment (SEMINOWICZ et al., 2004). Magnetic resonance imaging studies have shown that depressive patients present structural abnormalities in the brain, like loss of hippocampal volume or heterogeneity in certain regions of the brain. Chronic stress causes hyperactivity of the central nervous systems (CNS), which can induce cellular changes or neuroplasticity. The hippocampus

is very sensitive to stress and patients with MDD often present hyperactivity of hypothalamic–pituitary–adrenal (HPA) axis. HPA hyperactivity can induce secretion of glucocorticoids by the adrenal gland. Glucocorticoids act on the HPA feedback and modify metabolic processes during stress or depression episodes (DUMAN, 2004; FUCHS; FLÜGGE, 2004). Some authors have suggested that part of antidepressant activity is due to glucocorticoid receptors (HAMON; BLIER, 2013).

5. Neurotransmitter deficiency hypothesis

The neurotransmitter deficiency hypothesis for MDD considers depressive symptoms derived from insufficient levels of dopamine (DA), norepinephrine (NE), and/or serotonin (5-HT) in the brain (DELGADO, 2000). This hypothesis is sustained by the fact that antidepressant drugs raise the levels of one or more monoamines, and the incidence of MDD in patients with neurodegenerative diseases, such as Parkinson's, in which levels of DA and GABA are diminished (REMY et al., 2005; SANTAMARÍA; TOLOSA; VALLES, 1986). Neurotransmitter deficiency is possibly related to monoamine depletion, insufficient synthesis, or altered secretion/reuptake of neurotransmitters at the synapse. Investigations on pharmacological blockade of the enzyme tryptophan hydroxylase or reduction of dietary tryptophan have shown a reversal of the antidepressant effects of monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and NE reuptake inhibitors (NRIs) in individuals under treatment for MDD (MILLER et al., 1996; SHOPSIN et al., 1975). However, in healthy individuals an acute reduction in monoamine levels isn't enough to induce depression (HAMON; BLIER, 2013; MILLER et al., 1996). These findings indicate that a chronic deficiency in 5-HT level is needed to induce depression (HAMON; BLIER, 2013; MILLER et al., 1996). Furthermore, polymorphism in the tryptophan hydroxylase-2 gene is associated with approximately 80% of loss of 5-HT synthesis (HAMON; BLIER, 2013). Karg et al. confirmed previous evidence that polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR) modulates the relationship between depression and stress, and subjects expressing the mutation have greater sensitivity to stress and more predisposition to MDD with repeated life traumas (CASPI et al., 2003; KARG et al., 2011). Additionally, administration of subanaesthetic doses of ketamine, an N-methyl-D-aspartate (NMDA) receptor blocker, produces an antidepressant effect on treatment-refractory patients (BERMAN et al., 2000).

DA neurons have their origin in the substantia nigra and adjacent ventral tegmental area. Dopaminergic pathways through the striatum and neocortex play a role in movements and the emotional process. NE neurons are initiated in the locus coeruleus, and connect limbic and cortical regions to the thalamus, cerebellum, and spinal cord. NE pathways regulate attention, autonomic functions, and mood. 5-HT synthesis occurs in the raphe nucleus neurons in the CNS, but mainly in the enterochromaffin cells of the gastrointestinal tract (MANOCHA; KHAN, 2012). Due to 5-HT's acidity, the molecule doesn't cross the blood–brain barrier, so its concentration in the CNS depends on the conversion of its precursor, L-tryptophan, by CNS tryptophan hydroxylase. 5-HT signalling pathways modulate emotions, memory, sleep, and thermal regulation. Serotonergic neurons are distributed through almost all areas of the brain. Some serotonergic pathways are parallel to the noradrenergic ones. Serotonergic neurons can be modulated by glutamatergic, noradrenergic, inhibitory GABAergic, and dopaminergic neurons, besides their self-regulation mostly by the 5-HT_{1A} autoreceptor. Although monoamine neurotransmitters have their origins in different brain regions and are implicated in different neuronal activities, they are connected in a net of neural circuits in the CNS (FUCHS; FLÜGGE, 2004; HAMON; BLIER, 2013).This complex net indicates that changes in 5-HT neurons can produce different alterations in even non-serotonergic ways.Thus, MDD development can be associated with multiple pathological processes, and depression treatments focusing on modulation of serotonergic activity in the brain could be a new strategy offering an alternative to those involving antidepressant drugs (CELADA et al., 2001; ŚLIFIRSKI; KRÓL; TURŁO, 2021).

6. Serotonergic receptors

At least 14 5-HT receptor subtypes are known, varying in their physiological function, and CNS regional and synaptic expression. The majority of 5-HT receptors are postsynaptic and coupled with G proteins (OHNO, 2019; ŚLIFIRSKI; KRÓL; TURŁO, 2021). 5-HT_{1A} is the most studied subtype because of its wide and frequent expression among 5-HT receptors in the brain. Presynaptic autoreceptors occur on the dendrites and cell body of raphe nuclei neurons. Stimulus of 5-HT_{1A} autoreceptors is associated with the negative feedback of the 5-HT system, to maintain homeostasis. Postsynaptic heteroreceptors are found on the dendrites and cell body of 5-HT-projecting areas, such as the prefrontal cortex, hippocampus, amygdala, and septum, besides excitatory pyramidal neurons and inhibitory

interneurons. 5-HT_{1A} heteroreceptors mediate transmission of the impulse through serotonergic pathways. They are involved in emotions like anxiety, depression, stress, fear, and cognitive function. Imaging studies have shown a reduction of 5-HT_{1A} density on postsynaptic neurons and hyperexpression on presynaptic neurons in MDD individuals. Most 5-HT_{1A} drugs can bind to both 5-HT_{1A} autoreceptors and heteroreceptors, generating opposite effects. The development of more selective 5-HT_{1A} heteroreceptor drugs could be a target to improve MDD treatments (ALBERT; LE FRANÇOIS; MILLAR, 2011; ALBERT; VAHID-ANSARI, 2019; HAMON; BLIER, 2013; ŚLIFIRSKI; KRÓL; TURŁO, 2021).

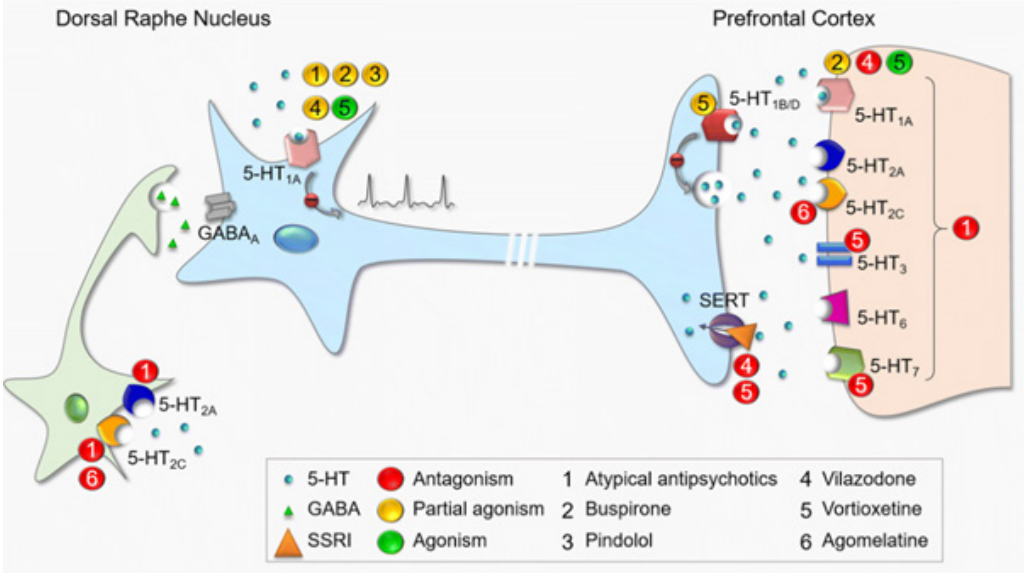

Figure 1. *Monoaminergic system and depression. (Extract from "Monoaminergic system and depression"; (PEREZ-CABALLERO et al., 2019) doi: 10.1007/s00441-018-2978-8).*

PET scanning of antidepressant-naive patients with MDD shows an inverse correlation between binding affinity to 5-HT_{1A} and response to treatment, when compared to subjects treated with antidepressants or healthy individuals. This suggests an overall reduction in 5-HT signalling pathways in MDD. Thus, hyperactivity of the HPA axis can elevate the secretion of cortisol, which can act by decreasing transcription of the 5-HT_{1A} receptor-encoding gene and downregulating the HPA axis. The lack of modulation of the hormone cortisol and consequently an upregulation of 5-HT_{1A} autoreceptors are associated with MDD and suicide (ALBERT; LE FRANÇOIS; MILLAR, 2011).

The 5-HT_{1B} receptors are pre- and postsynaptic receptors in the LCSPT axis. The 5-HT_{1B} autoreceptors are located on serotonergic axons, modulating 5-HT synthesis and secretion (LI et al., 2020). Postsynaptic receptors are expressed in the centres of motor control, like basal ganglia, modulating other neurotransmitter systems. The 5-HT_{1B} receptors are involved in locomotor activities, aggressive behaviour, anxiety, depression, and migraines (HAMON; BLIER, 2013).

Like 5-HT_{1B} receptors, 5-HT_{2A} receptors are pre- and postsynaptic receptors. They are expressed mostly in the neocortex. Some studies have found 5-HT_{2A} receptors in the GABAergic interneurons of the cortex, as well as in glutamatergic projection neurons in the brain (DE ALMEIDA; MENGOD, 2007).

7. Pharmacotherapy

The American Psychiatric Association recommends MDD treatment should be personalized according to the clinical situation. Treatments can involve depression-focused psychotherapy, pharmacotherapy, electroconvulsive therapy, or a combination of them. SSRIs remain the gold-standard pharmacotherapeutic treatments for MDD (KARROURI et al., 2021; ŚLIFIRSKI; KRÓL; TURŁO, 2021). For most patients, an SSRI, a serotonin-norepinephrine reuptake inhibitor (SNRI), bupropion, or mirtazapine is effective. MAOIs are recommended to be restricted to non-responder subjects ("TREATING

MAJOR DEPRESSIVE DISORDER A Quick Reference Guide", 2006). Differences in the pharmacological activity between antidepressant drugs of the same class can make the management of treatment difficult (HAMON; BLIER, 2013).

Antidepressant administration increases 5-HT extracellular levels in the raphe nuclei, activating 5-HT_{1A} autoreceptors, and consequently decreases the efficacy of the drug. Chronic treatment with antidepressants leads to desensitization of 5-HT_{1A} autoreceptors, which is attributed to be the cause of the latency of action of these drugs (HAMON; BLIER, 2013; ŚLIFIRSKI; KRÓL; TURŁO, 2021). Animal studies suggest neuroadaptive changes induced by chronic antidepressant treatments (HAMON; BLIER, 2013).

MAOIs and TCAs are nonspecific agents against MDD, and their therapeutic benefits are associated with many side effects. Although more selective agents like SSRIs and NRIs are better tolerated than TCAs and MAOIs, discontinuation of treatment is up to 15% in SSRI therapy, against 19% in MAOI regimens. Despite drug selectivity and the long period of research about MDD, to date there is still no curative treatment for this disease (HAMON; BLIER, 2013).

Although fluoxetine, paroxetine, and sertraline are classified as SSRIs, they also present binding affinity to DA and NE transporters, when present in higher blood concentrations than those used for SSRI activity. Paroxetine also acts in muscarinic receptors, which is associated with some of the drug's side effects. DA transporter affinity minimizes stimulation of prolactin secretion. Common side effects of this class are anxiety, food intolerance, nausea, diarrhoea, fatigue, and sexual dysfunction (HAMON; BLIER, 2013; ŚLIFIRSKI; KRÓL; TURŁO, 2021).

In the same way, the dual SNRIs, like venlafaxine and duloxetine, at minimal effective doses act as a 5-HT reuptake inhibitor. Upgrades of doses are associated with NE reuptake inhibition (SHELTON, 2019; ŚLIFIRSKI; KRÓL; TURŁO, 2021). Minalcipran presents a higher binding affinity to NE transporter (NET) than to serotonin transporter (SERT) (HAMON; BLIER, 2013; SHELTON, 2019). Bupropion is a dual DA-NE reuptake inhibitor, which presents more effective antidepressant properties than SSRIs (ŚLIFIRSKI; KRÓL; TURŁO, 2021).

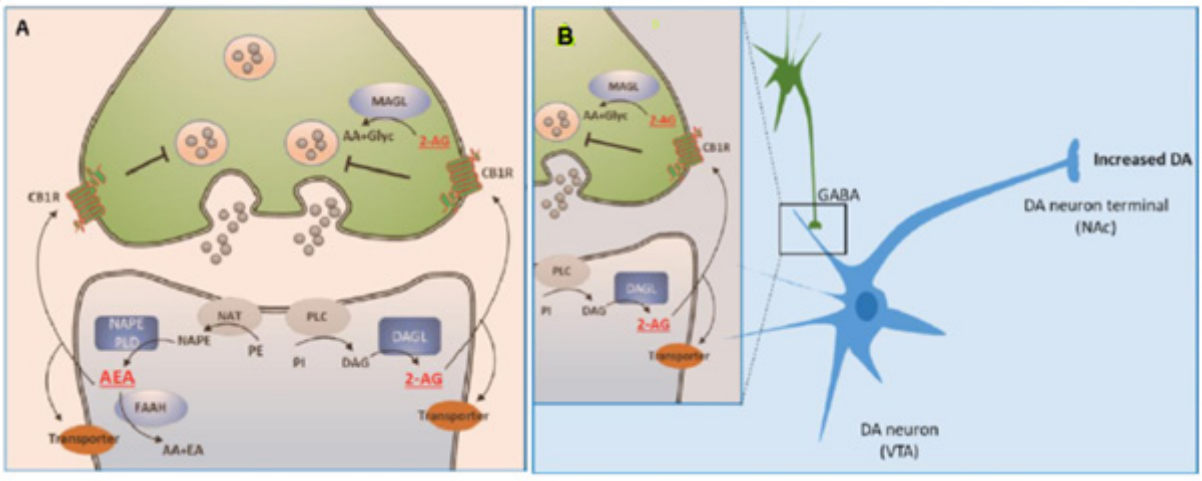

Figure 1. *Figure 2. Schematic representation of the endocannabinoid signaling system. (A) Endocannabinoids (eCBs) 2AG (2-arachidonoylglycerol) and AEA (anandamide) are synthesized in postsynaptic neurons and act pre-synaptically at their receptors (CB1Rs) in a retrograde mode. (B) Endocannabinoids modulate neuronal activity as illustrated for dopamine (DA) neurons with cell bodies in the ventral tegmental area (VTA). CB1 receptors on GABAergic terminals can facilitate dopaminergic activity through suppression of the inhibitory input onto the GABA receptors present on DA neurons, leading to an increase of DA release. Adapted from (HASBI; MADRAS; GEORGE, 2023).*

The inclusion of a 5-HT_{1A} receptor agonist can accelerate the therapeutic effects of SSRIs by a faster desensitization of 5-HT_{1A} autoreceptors. Buspirone is an anxiolytic drug with 5-HT_{1A} receptor agonist properties. Pindolol exhibits beta-adrenergic partial agonism and 5-HT_{1A} receptor antagonism properties. The combination of pindolol with SSRIs results in a shorter time to response to treatment compared with SSRIs alone. This drug association improvement is attributed to a decrease in the 5-HT_{1A}-autoreceptor-mediated inhibitory feedback of serotonergic pathways by pindolol (HAMON; BLIER, 2013; SHELTON, 2019). Mirtazapine exhibits affinity for α2-adrenoceptors and 5-HT_{2A} receptors. The association of mirtazapine with SSRIs potentiates the clinical response of treatment-resistant individuals, by blockage of 5-HT_{2A} receptors. Vilazodone is a 5-HT_{1A} receptor partial agonist with inhibitory activity against SERT. Vortioxetine is a multimodal drug with affinity for 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{3}, and 5-HT_{7} receptors, and SERT. Sexual dysfunction with the use of vilazodone is less common than with SSRIs (ŚLIFIRSKI; KRÓL; TURŁO, 2021).

Antidepressants with a triple reuptake inhibition mechanism (SSRI/SNRI/SDARI), or a combination of drugs with different 5-HT receptor subtype affinity, are some of the potential therapeutic targets for improving MDD treatment (SHELTON, 2019; ŚLIFIRSKI; KRÓL; TURŁO, 2021).

8. Cannabis and MDD

In the first decade of the 2000s, some evidence for the role of the endocannabinoid system in depression came into the literature, especially from the fact that cannabis consumers present mood alterations, and the use of a CB1 receptor antagonist for obesity causes depression and anxiety as adverse effects. The activation of cannabinoid receptors can increase monoaminergic neurotransmission (Figure 2). Electroconvulsive shock and some antidepressant treatments are associated with higher CB1 activation (HILL et al., 2009). The legalization of medicinal or recreational use of cannabis in some countries has favoured its consumption, as well as studies about its therapeutic potential. Cannabis contains several cannabinoid compounds, such as delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), which have different pharmacological activity in the endocannabinoid system (SCHOELER et al., 2018). Evidence suggests that the use of cannabis for the psychiatric population is associated with either therapeutic or harmful effects (LOWE et al., 2019). A 40-year cohort study has found a correlation between cannabis use and a higher risk of MDD diagnosis (SCHOELER et al., 2018). Nevertheless, studies on cannabis have often focused on pain and multiple sclerosis, which makes it difficult to examine its association with depression. Also, the differences in composition and via of administering the cannabis products in the studies could explain the different results obtained (BRIGHT; AKIRAV, 2022).

9. Revisiting the serotonergic hypothesis in MDD

Recently, a systematic umbrella review, conducted by Moncrieff et al. (2022), re-evaluated the 5-HT theory of depression from the levels of 5-HT or its metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the blood or in the cerebrospinal fluid. The authors also evaluated 5-HT_{1A} receptor density, tryptophan depletion, and SERT availability, activity, and polymorphism. Moncrieff et al. found an association between antidepressants and lower levels of 5-HT independently of depression, but no correlation between 5-HIAA and depression, or no difference or lower levels in 5-HT_{1A} receptors between depressive and control individuals. The authors considered 5-HT_{1A} receptors only as autoreceptors, ignoring the postsynaptic 5-HT_{1A}. SERT availability or activity suggests a possible reduction of SERT binding in some brain regions, although the small number of individuals and the heterogeneity of methodologies used in each study could lead to a high risk of bias for the meta-analysis included in the review. Results on SERT polymorphism were inconclusive, because recent studies didn't show an association between SERT polymorphism and depression, or SERT polymorphism and stress in depression, although earlier studies indicated the association between 5-HTTLPR and depression in some ethnic groups, or the interaction between the SERT polymorphism, stress, and depression. Tryptophan depletion was suggested to have no effect on mood. Briefly, the authors found "no convincing evidence that depression is associated with, or caused by, lower serotonin concentrations or activity" (MONCRIEFF et al., 2022). This conflicting result prompted an expert reaction published on Science Media Centre. Professor Gitte Moos Knudsen, of Copenhagen University Hospital, Denmark, and Doctor Michael Bloomfield, Consultant Psychiatrist and UKRI Principal Clinical Research Fellow, Translational Psychiatry Research Group Head, UCL, considered the main misconception of the review was depression as a single disease caused by a single biochemical deficiency. Doctor Michael Bloomfield mentioned the evidence of antidepressant drug efficacy, and that patients must have evidence-based treatments. Professor Phil Cowen, from University of Oxford, said that it would be surprising

if a widely spread neurotransmitter such as 5-HT wasn't involved in the complex depression disorders. Also, he questioned the methodology of the review, because the authors didn't include a meta-analysis published in the same journal in 2021 with different conclusions about 5-HT. Professor Allan Young, Director of Centre for Affective Disorders, Institute of Psychiatry, Psychology & Neuroscience, King's College London, said that the authors have forgotten that 5-HT_{1A} receptors can be either presynaptic autoreceptors or postsynaptic heteroreceptors (SCIENCE MEDIA CENTRE, 2022).

10. Conclusions

Considering all the above discussion, the past decades of research on major depression have brought to light the highly interconnected brain systems and neuroplasticity that can occur in response to a person's chemical deficiency or environmental circumstances (SCIENCE MEDIA CENTRE, 2022). The effectiveness of antidepressant drugs might not only be due to their activity directly on 5-HT machinery, and multimodal therapies associating them with other classes of drugs, like anti-inflammatory drugs, dual or triple reuptake inhibitors, and endocannabinoid system modulators, could become a way to provide pharmacological treatments for MDD that are more effective and have fewer side effects. Especially in stressful times, like Covid-19 pandemic for instance, researches on evidence-based treatments for major depression become crucial in order to improve human mental health.

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