Universidade de Lisboa

Faculdade de Farmácia

New Advances in Pharmacological Treatment of Depression

Matilde Vicente Nunes Dias Simões

Monografia orientada pela Professora Doutora Cristina de Mello Sampayo, Professora Auxiliar

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Acknowledgments

Thus comes the end of a long and challenging journey that has defined the last five years of my life. These years have been filled with growth, both academically and personally, and I owe much to those who have supported me along the way.

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Declaro ter desenvolvido e elaborado o presente trabalho em consonância com o Código de Conduta e de Boas Práticas da Universidade de Lisboa. Mais concretamente, afirmo não ter incorrido em qualquer das variedades de fraude académica, que aqui declaro conhecer, e que atendi à exigida referenciação de frases, extratos, imagens e outras formas de trabalho intelectual, assumindo na íntegra as responsabilidades da autoria.

Resumo

O presente trabalho explora os avanços recentes no tratamento farmacológico da depressão, com um foco particular na Perturbação Depressiva Major. Sendo uma das condições de saúde mental mais prevalentes em todo o mundo, a depressão afeta milhões de indivíduos, impondo uma carga substancial à saúde pública, tanto em termos de qualidade de vida reduzida como de custos económicos aumentados. Apesar da disponibilidade de vários tratamentos, incluindo antidepressivos e intervenções psicoterapêuticas, uma proporção considerável de doentes não responde adequadamente, sublinhando a necessidade de fármacos mais eficazes e de ação mais rápida.

Este trabalho revisa os mecanismos de ação, eficácia clínica e efeitos adversos de vários novos medicamentos, incluindo escetamina, gepirona, zuranolona, brexanolona, a combinação de dextrometorfano e bupropiom, toludesvenlafaxina e psilocibina. É dada especial atenção à psicoterapia assistida por cetamina e ao uso de psicadélicos, que têm despertado interesse pelo seu potencial em tratar a depressão resistente ao tratamento. Os desafios no desenvolvimento de novas terapias antidepressivas também são explorados, incluindo questões como o efeito placebo, a variabilidade nas respostas dos doentes e a falta de biomarcadores para diagnóstico e eficácia do tratamento.

Uma revisão dos ensaios clínicos destaca a promessa destas terapias emergentes, que mostram potencial para um alívio mais rápido dos sintomas e uma eficácia terapêutica mais ampla. No entanto, continuam a existir lacunas significativas na otimização dos resultados do tratamento, particularmente na gestão de doentes com depressão resistente ao tratamento. A monografia conclui enfatizando a necessidade de inovação contínua, especialmente no desenvolvimento de tratamentos mais personalizados e de ação rápida, para atender às necessidades não satisfeitas dos doentes que sofrem de depressão.

Palavras-chave: Perturbação Depressiva Major, antidepressivos, escetamina, terapias psicadélicas, depressão resistente ao tratamento.

Abstract

This work explores recent advances in the pharmacological treatment of depression, with a particular focus on Major Depressive Disorder. As one of the most prevalent mental health conditions worldwide, depression affects millions of individuals, imposing a substantial burden on public health through both reduced quality of life and increased economic costs. Despite the availability of various treatments, including antidepressants and psychotherapeutic interventions, a considerable proportion of patients fail to respond adequately, underscoring the need for faster-acting and more effective drugs.

Considering this context, the following sections review the mechanisms of action, clinical efficacy, and adverse effects of several novel treatments, including esketamine, gepirone, zuranolone, brexanolone, the combination of dextromethorphan and bupropion, toludesvenlafaxine, and psilocybin. Special attention is given to ketamine-assisted psychotherapy and the use of psychedelics, which have garnered interest for their potential in addressing treatment-resistant depression. Additionally, the challenges of developing new antidepressant therapies are explored, including issues such as the placebo effect, patient response variability, and the lack of biomarkers for both diagnosis and treatment efficacy.

A review of clinical trials highlights the promise of these emerging therapies, which show potential for faster symptom relief and broader therapeutic efficacy. However, significant gaps remain in optimizing treatment outcomes, particularly in managing patients with TRD. The thesis concludes by emphasizing the need for continued innovation, particularly the development of more personalized and rapidly acting treatments, to meet the unmet needs of patients suffering from depression.

Keywords: Major Depressive Disorder, antidepressants, esketamine, psychedelic therapies, treatment-resistant depression.

List of acronyms and abbreviations

1-PP: 1-pyrimidinylpiperazine

5-HT: Serotonin

ACTH: Adrenocorticotropic Hormone

ADHD: Attention Deficit Hyperactivity Disorder

ALLO: 3α-hydroxy-5α-pregnan-20-one

AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

AUC: Total Exposure

BDNF: Brain-derived Neurotrophic Factor

CF: Champalimaud Foundation

Cmax: Maximal Plasma Concentration

CNS: Central Nervous System

CBT: Cognitive-Behavioral Therapy

CRH: Corticotropin-releasing Hormone

CRP: C Reactive Protein

CYP: Cytochrome P450

DALYs: Disability-Adjusted Life Years

DA: Dopamine

DAT: Dopamine Transporter

DβH: Dopamine β-hydroxylase

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

ECT: Electroconvulsive Treatment

EDCs: Endocrine-disrupting Chemicals

ELA: Early life adversity

EMA: European Medicines Agency

ER: Extended-release

EU: European Union

EU-WMH: European Contribution to the World Mental Health

FDA: Food and Drug Administration

GABA: Gamma-aminobutyric acid

GABAARs: GABA Type A Receptors

GABABRs: GABA Type B Receptors

GDP: Gross Domestic Product

GDNF: Glial Cell-derived Neurotrophic Factor

HAMD-17: Hamilton Depression Rating Scale

HDRS-Grid: Hamilton Rating Scale for Depression

HPA: Hypothalamic-pituitary-adrenal

HSDD: Hypoactive Sexual Desire Disorder

IFN-α: Interferon-alpha

IL-1: Interleukin-1

IL-1β: Interleukin-1β

IL-6: Interleukin-6

IN: Intranasal

IV: Intravenous

KAP: Ketamine Assisted Psychotherapy

MADRS: Montgomery-Asberg Depression Rating Scale

MAO: Monoamine Oxidase

MAOIs: Monoamine Oxidase Inhibitors

MAT: Monoamine Transporter

MDD: Major Depressive Disorder

MRHD: Maximum Recommended Human Dose

mCPP: Meta-chloro-phenylpiperazine

mTOR: Mammalian Target of Rapamycin

NICE: National Institute for Health and Clinical Excellence

NE: Noradrenaline/Norepinephrine

NET: Noradrenaline Transporter

NGF: Neural Growth Factor

NMDA: N-methyl-D-aspartate

NMPA: Chinese National Medical Products Administration

NO: Nitric Oxide

NRIs: Noradrenaline Reuptake Inhibitors

nACh: Alpha-4-beta-2 Nicotinic

ODV: O-desvenlafaxine

OECD: Organisation for Economic Co-operation and Development

PAP: Psilocybin-assisted Psychotherapy

PDAC: Psychopharmacologic Drugs Advisory Committee

PPD: Postpartum depression

PRIME: PRIority MEdicines

PTSD: Post-Traumatic Stress Disorder

PUFAs: Polyunsaturated Fatty Acids

QIDS-SR: Quick Inventory of Depressive Symptomatology - Self-Report

RID: Relative Infant Dose

SARIs: Serotonin Receptor Antagonists and Reuptake Inhibitors

SD: Sprague Dawley

SERT: Serotonin Transporter

SMS: Serotonin Modulator and Stimulator

SNRIs: Serotonin and Noradrenaline Reuptake Inhibitors

SSRIs: Selective Serotonin Reuptake Inhibitors

TCAs: Tricyclic Antidepressants

TGA: Therapeutic Goods Administration

TH: Tyrosine Hydroxylase

TLR3: Toll-like Receptors 3

TLR4: Toll-like Receptors 4

TNF-α: Tumor Necrosis Factor-alpha

TRD: Treatment-resistant depression

TRI: Triple Reuptake Inhibitor

UGTs: UDP-glucuronosyltransferases

WHO: World Health Organization

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1 Introduction

Depression can be described as a passing emotional state encountered by nearly everyone at some point in their lives, and it also represents a clinical or biobehavioural syndrome commonly referred to as Major Depressive Disorder (MDD) (1). MDD is a medical condition characterized by discrete episodes that persist for a minimum of two weeks, with most episodes typically lasting beyond this duration (2), involving disruptions in affect and mood, neurovegetative functions (including changes in appetite and sleep patterns), cognitive disturbances (such as inappropriate guilt and feelings of worthlessness), and alterations in psychomotor activity (such as increased agitation or retardation) (1).

Depression represents a chronic, recurring and potentially life-threatening condition, posing a significant mental health burden and standing as the primary contributor to mental-health-related disability on a global scale (3). The global lifetime prevalence of MDD is approximately 12% (4), and according to the World Health Organization (WHO), MDD holds the 11th position among the leading causes of disability and mortality (5).

Projections of the burden of disease, measured in disability-adjusted life years (DALYs) and developed through epidemiological studies, estimate that by 2030, depression will rank among the top three leading causes of burden of disease (6). This disorder not only results in health declines comparable to those associated with other chronic diseases (such as angina, arthritis, asthma, and diabetes) but also significantly exacerbates mean health scores when occurring concurrently with these diseases, in contrast to when the diseases manifest independently (7). In addition, it is associated with important psychological suffering, as well as elevated rates of suicide (7,8).

In Portugal, a National Mental Health Epidemiological Study conducted by Nova Medical School identified MDD as the nosological entity with the highest estimated lifetime prevalence, reaching 16.7% (9). Furthermore, the European contribution to the World Mental Health (EU-WMH) Surveys Initiative established Northern Ireland, Portugal, and Belgium as the countries with the highest risks for mental disorders (10).

Various treatment approaches to MDD are currently available, these encompass psychotherapy, antidepressant medications, electroconvulsive treatment (ECT), and other somatic therapies (1). Antidepressants are well-supported in effectively treating MDD, especially during moderate to severe major depressive episodes (11). While psychotherapy, such as cognitive-behavioural therapy, and brain stimulation, like ECT, stand as essential alternative approaches, they come with inherent limitations, these include challenges related to availability, scalability, acceptability, cost, and tolerability (12).

Even though contemporary treatment options for depression are generally safe and effective, they fall short of being optimal. Individuals undergoing treatment with current antidepressants often encounter a waiting period of at least four weeks before experiencing any potential positive response to the medication (13). Moreover, common side effects such as sexual dysfunction, loss of libido, headache, gastrointestinal symptoms, weight gain, anxiety, and agitation, can be prevalent during this period (14), this often prompts patients to discontinue therapy frequently before experiencing the desired benefits.

Nevertheless, even with significant advances in the understanding of the pathophysiology of MDD over the last few decades, and the approval of numerous medications for its treatment, about 20-40% of the patients undergoing treatment for MDD or bipolar depression diagnosis exhibit an insufficient clinical response (15). Additionally, fewer than 50% of patients with depression achieve full remission even with optimized treatment, which includes trials with various medications, both with and without concurrent psychotherapy (13).

Managing patients with treatment-resistant depression (TRD) poses a significant public health challenge (16), given that over one-third of individuals undergoing depression treatment develop resistance to standard interventions (17). Therefore, there is still a great need for development of more rapid onset of action, improved tolerability, and the potential for greater effectiveness than current antidepressants options (14).

2 Objectives

The primary objective of this monograph is to review the recently approved drugs for the treatment of major depressive disorder, as well as those that are still under investigation. Additionally, this review aims to provide an in-depth analysis of the mechanism of action, pharmacodynamics, and pharmacokinetics of these drugs, alongside a discussion of the clinical trials that support their use. Moreover, this work will explore emerging therapies involving psychedelics, offering insights into their potential role in the future of depression treatment.

3 Materials and Methods

This monograph was developed through a comprehensive literature review focusing on recent advancements in the treatment of major depressive disorder. The primary source of information was Google Scholar (https://scholar.google.com/), where articles were searched using keywords related to new drugs, both approved and under investigation, for the treatment of major depressive disorder. The literature search was conducted from January 2024 to September 2024, with searches filtered to include peer-reviewed studies, full-text articles, and those written in English and Portuguese. The selection criteria for the articles included studies that provided empirical data on the efficacy, safety, and mechanisms of the new pharmacological treatments. Studies that lacked direct relevance to the treatment of major depressive disorder were excluded.

Additionally, key reference books, such as the Diagnostic and Statistical Manual of Mental Disorders - 5 (DSM-5) and other pharmacology textbooks, including Basic & Clinical Pharmacology by Bertram G. Katzung (14th ed., McGraw-Hill Education, 2017) and Medical Pharmacology & Therapeutics by Waller DG, Sampson AP, and Hitchings AW (6th ed., Elsevier, 2022), were consulted to provide foundational knowledge and context.

Relevant data were extracted and synthesized to provide a thorough understanding of the topic, ensuring a balanced review of both established and emerging treatments for major depressive disorder.

4 Major Depressive Disorder

4.1 Epidemiology

According to the WHO, MDD is a common mental disorder that involves a depressed mood or loss of pleasure or interest in activities for long periods of time (18). Depressive disorders rank among the most prevalent psychiatric conditions, with a prevalence rate of approximately 7-9% in Portugal (19). Notably, in 2019, Portugal had the highest percentage of individuals reporting chronic depression among European Union (EU) countries, with a rate of 12.2% (20).

The 12-month prevalence of MDD is approximately 6%, with the lifetime prevalence being about three times higher, affecting roughly one in six adults. In addition, around 20% of individuals will meet the criteria for MDD at some point in their lives. Prevalence rates are similar across high-income and low- to middle-income countries, indicating that MDD is not confined to "modern-world" health concerns (8).

The median age of onset, symptom severity, and key demographic and environmental factors associated with MDD exhibit similar patterns across diverse countries and cultures. However, a significant disparity exists in access to treatment: 50-60% of individuals with severe MDD in high-income nations receive appropriate care, while less than 10% do so in low-income countries (8).

After puberty, women are twice as likely as men to develop MDD. The median age of onset is approximately 25 years, with the highest risk occurring from adolescence to the early 40s. Common risk factors for both men and women include partner absence (e.g., divorce, widowhood), adverse life events (e.g., illness, loss of loved ones, unemployment, financial or social hardships), childhood adversity, low socioeconomic status, poor social support, and lower levels of educational attainment. Notably, childhood trauma more than doubles the risk of developing MDD and is also associated with more severe symptoms (8).

In 2013, the Global Burden of Disease Consortium ranked MDD as the second-largest contributor to the global disease burden, measured in DALYs, across both developed

and developing nations. Beyond its mental health impact, MDD significantly heightens the risk of physical conditions like diabetes, heart disease, stroke, hypertension, obesity, cancer, cognitive decline, and Alzheimer's disease. It also increases mortality by 60-80%, accounting for 10% of all-cause deaths (8).

Genetic variation plays a significant role in conferring risk for depression and other psychiatric disorders. MDD is known to have a familial component, with individuals diagnosed being three times more likely to have a first-degree relative with depression. Twin studies have been instrumental in distinguishing genetic and environmental influences, revealing that MDD is moderately heritable. Comparisons between monozygotic and dizygotic twins suggest that approximately 40% of the population risk for MDD can be attributed to genetic factors (8).

Mental health disorders impose a significant burden on both societies and economies, leading to decreased productivity, increased absenteeism, and higher healthcare costs. According to the European Commission, data from the Organisation for Economic Co-operation and Development (OECD) indicates that these issues can cost the EU up to 4% of its Gross Domestic Product (GDP) each year, exceeding €600 billion. This financial burden primarily stems from productivity losses and healthcare expenses (20).

The COVID-19 crisis, along with the restrictive measures implemented by governments to limit virus transmission, significantly exacerbated mental health symptoms and led to a deterioration in the overall mental well-being of the public compared to the pre-pandemic period. In 2019, approximately 84 million individuals in the EU were affected by mental health problems, and these numbers have worsened since the onset of the pandemic. Not only did the crisis increase the prevalence of mental health issues, but it also intensified the challenges faced by those already struggling, worsening existing conditions. The unpredictability and uncertainty surrounding the pandemic contributed to a rise in psychosocial issues, such as depression, and heightened known risk factors for mental health disorders (20,21).

4.2 Pathophysiology

4.2.1 The Monoaminergic Hypothesis

The monoaminergic hypothesis, which emerged in the 1950s, was initially based on observations from the use of reserpine, an antihypertensive drug. Reserpine had the notable side effect of inducing depressive symptoms, which dissipated once the drug was discontinued. In studies involving rats treated with reserpine, significant reductions in brain serotonin levels were observed, along with an increase in serotonin metabolites in the urine, suggesting enhanced neurotransmitter degradation. Further research revealed that reserpine not only reduced serotonin levels but also dopamine and norepinephrine, leading to the hypothesis that these neurotransmitters are crucial in regulating mood and affective functions. A reduction in their concentrations was proposed to underlie the development of depressive symptoms (22).

Additionally, the antibacterial agent iproniazid was found to improve mood in patients with depressive symptoms by inhibiting the enzyme monoamine oxidase (MAO). This inhibition increased presynaptic levels of monoamines, particularly serotonin and norepinephrine. However, the monoamine hypothesis faced challenges, such as explaining the delay in clinical effects. While antidepressants appeared to improve symptoms after several weeks of treatment, animal studies demonstrated an increase in monoamine levels within hours of drug administration, and side effects were evident shortly after (22).

4.2.2 The Neurotrophic Hypothesis

The neurotrophic hypothesis, which appeared in the 1990s, aimed to address the limitations of the monoaminergic hypothesis. This theory highlighted how antidepressants affect neurotrophins, molecules that support neuron development, function, and regeneration. The first neurotrophin identified was neural growth factor (NGF). Antidepressants promote neuronal trophism, leading to axon growth and increased dendritic arborization and spine density, which are typically reduced in animal models of MDD. These drugs also stimulate genes encoding NGF, brain-derived neurotrophic factor (BDNF), and glial cell-derived neurotrophic factor (GDNF). However, these changes take weeks to manifest, explaining the delayed clinical effects

of antidepressants. This suggests that efficacy is not limited to monoamine levels but also involves restoring proper neuronal function through neurotrophic factors (22).

Additionally, long-term antidepressant treatment has been shown to restore the volume of brain regions involved in mood regulation, such as the hippocampus, prefrontal cortex, and nucleus accumbens, which are reduced in MDD due to neuronal loss (22).

4.2.3 The Neurodevelopmental Hypothesis

The neurodevelopmental hypothesis suggests that depressive disorders may stem from early life neurodevelopmental changes. Early life adversity (ELA), such as childhood abuse and stress, is strongly linked to a higher risk of anxiety and mood disorders in adulthood. Animal studies show that stress can alter the hypothalamic-pituitary-adrenal (HPA) axis, affecting corticotropin-releasing hormone (CRH) expression and the response to adrenocorticotropic hormone (ACTH) and cortisol (22).

At the neurochemical level, changes in CRH, dopamine, norepinephrine, Gamma-aminobutyric acid (GABA), and neurotrophic factors like BDNF support the link between the neurodevelopmental and neurotrophic hypotheses. Similar alterations are observed in MDD patients with a history of ELA. The neurodevelopmental hypothesis also ties to the monoaminergic hypothesis, as serotonin is crucial for brain development. Early disruptions in serotonin can impact brain pathways, affecting stress sensitivity and emotional regulation (22).

4.2.4 The Glutamatergic Hypothesis

Glutamate is the primary excitatory neurotransmitter in the central nervous system (CNS). The glutamatergic hypothesis of depression dates back to the early 1990s, when initial studies revealed that antagonists of the N-methyl-D-aspartate (NMDA) glutamate receptor produced antidepressant-like effects. Glutamate plays a critical role in nearly all brain functions, and growing evidence suggests that dysregulation of the glutamatergic system contributes to cognitive and mood dysfunctions. Studies in patients with MDD have shown altered glutamate levels in brain regions responsible for these functions (22). Excess extracellular glutamate is neurotoxic, primarily through overactivation of post-synaptic glutamate receptor. This phenomenon is often linked to

stress-related reductions in astrocyte numbers in the hippocampus, leading to glutamate accumulation and subsequent structural brain changes. Additionally, other glutamate receptors, such as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, also play a role in these processes. This is evident in the mechanism of action of ketamine, an anaesthetic drug that has recently gained attention as a rapid-acting antidepressant (22).

4.2.5 The GABAergic Hypothesis

GABA is recognised as the primary inhibitory neurotransmitter in the CNS and has been implicated in MDD. The GABAergic hypothesis suggests that impairments in GABAergic inhibition may contribute to MDD pathophysiology (22). Studies show that MDD patients exhibit reduced brain GABA levels and altered subunit composition of GABA-A receptors, which mediate inhibitory GABAergic transmission. This transmission is essential for regulating hippocampal neurogenesis and neural maturation—key processes in antidepressant action. GABAergic neurons, which make up 20–40% of all neurons, balance excitatory neurotransmission, including in monoaminergic and cholinergic systems (23).

GABA exerts its effects through two main receptor types: ionotropic GABA-A receptors (GABAARs) and metabotropic GABA-B receptors (GABABRs). GABAARs are linked to anxiety control, as evidenced by the anxiolytic effects of benzodiazepines, which act as positive allosteric modulators. Growing evidence points to significant alterations in GABAAR signalling in both anxiety and mood disorders. GABABRs, part of the G-protein coupled receptor family, are also involved in mood regulation, with pharmacological and genetic studies in mice linking these receptors to anxiety- and depression-like behaviours (23).

Furthermore, the effectiveness of antidepressant treatments may depend on their capacity to restore proper GABAergic transmission. Chronic stress in rodents leads to behavioural changes associated with reduced density and functionality of GABAergic synapses. Mechanisms that enhance GABAergic inhibition have been found to confer resilience to stress. Notably, mice with reduced or blocked production of specific GABA receptor subunits exhibited depression-like behaviours, supporting the idea that

disruptions in GABA neurotransmission may influence MDD development by affecting the body's stress response (22).

4.2.6 The Inflammatory/Immune Hypothesis

The concept that depression may be linked to inflammation has gained increasing attention in recent years. This idea is supported by evidence showing that patients with MDD often exhibit elevated levels of genes and proteins linked to innate immunity and pro-inflammatory markers, including C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α), and toll-like receptors 3 (TLR3) and 4 (TLR4). Additionally, depressive-like behaviours have been experimentally induced by administering interferon-alpha (IFN-α), a potent pro-inflammatory cytokine (22,24).

Although the exact mechanisms remain unclear, an increase in pro-inflammatory cytokines is thought to impair neuronal plasticity and contribute to neurodegeneration. Furthermore, pro-inflammatory cytokines can interfere with the activity of growth factors, leading to reduced neurogenesis. These immune-mediated changes may cause damage to glial cells and neurons, exacerbating the effects of depression (22,24).

4.2.7 The Endocrine Hypothesis

The endocrine hypothesis links MDD to hyperactivity of the HPA axis, evident in increased CRH secretion and elevated glucocorticoids. Interleukin-1β (IL-1β) activates the HPA axis via nitric oxide (NO), an inflammatory mediator. During stress, IL-1β induces NO synthase, leading to NO production and depressive symptoms. Studies in chronically stressed rats revealed alterations in prolactin and somatostatin levels, both neurohormones involved in regulating emotional processes, which were restored to normal physiological levels with antidepressant treatment. Recent epidemiological data suggest that prenatal exposure to endocrine-disrupting chemicals (EDCs), associated with nervous system disorders, can impair cognitive development in children and increase the incidence of depression in adulthood (22).

4.2.8 The Role of Fatty Acids

The shift in the balance of omega-3 to omega-6 polyunsaturated fatty acids (PUFAs) in the Western diet over the past 150 years is believed to contribute to the pathogenesis of various inflammatory-related diseases, including depressive disorders (22,25).

PUFAs, especially omega-3 and omega-6, are crucial for proper brain function, as they are key components of cellular and neuronal membranes. They also play an essential role in regulating inflammation and the HPA axis activity. Since these fatty acids are not synthesized by the body, their availability is highly dependent on dietary intake. Research has shown that a deficiency in omega-3 can impair neuronal function, particularly affecting serotonergic and dopaminergic neurotransmission (22,25).

Epidemiological studies have consistently demonstrated a significant inverse correlation between the consumption of oily fish, rich in omega-3, and the prevalence of depression and bipolar disorders. Regions with higher fish consumption tend to have lower rates of psychiatric disorders, underscoring the potential protective role of PUFAs in mental health (22,25).

Although the precise mechanisms by which omega-3 may prevent psychiatric conditions are still under investigation, there is growing evidence suggesting its protective effects against MDD. In recent years, omega-3 supplementation has shown increasing efficacy as a tertiary prevention strategy for depression. However, conclusive recommendations regarding its routine use in depression therapy remain elusive, pending further research (22,25).

4.2.9 The Role of the Gut Microbiota

The role of the microbiota in mediating gut-brain axis functions has only recently become a focus of research. It is now understood that this interaction involves bidirectional neuroimmunological and neuroendocrine mechanisms (22,26).

Microbial populations in the gut communicate with the CNS through endocrine, nervous, and immune signalling mechanisms. Intestinal microorganisms, particularly bacteria, influence the nervous system by releasing chemical messengers that can cross

the blood-brain barrier and affect brain functions. Many of these bacteria produce neurotransmitters such as serotonin, dopamine, adrenaline, and their metabolites, as well as short-chain fatty acids. Changes in the microbiota have been linked to inflammatory processes, and in conditions characterized by high inflammation, a connection between microbiota composition and depressive symptoms has been observed (22,26).

While the precise mechanism through which gut microbiota influences depression-like behaviours remains debated, the anti-inflammatory effects of Lactobacillus and Bifidobacterium may provide a key explanation. Probiotics containing these bacteria have been shown to significantly alleviate symptoms in patients with MDD, as well as reduce the inflammatory states often associated with depression (22,26).

4.3 Psychotherapy Approaches

Research indicates that the combination of psychotherapy and pharmacotherapy is significantly more effective than either treatment alone in improving both functioning and quality of life (27). For mild to moderate MDD, depression-focused psychotherapy is typically considered the first-line treatment. For more resistant forms of depression, a combination of medications, psychotherapy, and somatic therapies remains the most effective approach to management (28).

Psychotherapy interventions are widely used in the treatment and prevention of various psychiatric disorders, including depression. The choice of a specific psychotherapy approach (Cognitive-Behavioural Therapy or Psychoanalysis therapy) depends on the patient's preferences, the clinician's expertise, and resource availability. For patients with depression, psychotherapy fosters a strong therapeutic alliance, helps them monitor their mood, enhances daily functioning, deepens their understanding of symptoms, and equips them with practical tools to manage stressful events effectively (28).

Cognitive-Behavioral Therapy (CBT) is a widely recognized and effective treatment for MDD, recommended as a first-line intervention in most clinical guidelines. CBT targets irrational beliefs and distorted thinking patterns that sustain depressive

symptoms, aiming to challenge and modify them. Its effectiveness largely depends on the patient's ability to identify and alter their own thoughts and behaviours (28).
CBT typically involves strategies to change behavioural patterns, such as confronting fears, using role-playing to prepare for challenging interactions, and practicing relaxation techniques. Patients are taught coping skills to help modify negative thinking, emotions, and behaviour (29).

Psychoanalysis is both a theory and a method for understanding human psychological development and functioning, particularly emotions. Its primary goal is to alleviate mental symptoms and life challenges by uncovering and addressing conflicting emotional forces rooted in unconscious mental representations formed during childhood, including wishes, fears, and attitudes (30).

Psychoanalytic therapy is a modified form of psychoanalysis with a similar goal: relieving mental suffering through understanding psychological processes. It is often better suited for patients with limited mental resilience, such as those with depression, panic attacks, or social anxiety. This approach emphasizes interpreting internal conflicts while supporting defences and self-esteem, aiming to repair rather than reconstruct mental functioning (30).

5 Pharmacology of Antidepressants

5.1 Sites of Central Nervous System Drug Action

Virtually, all drugs with CNS effects target specific receptors that modulate synaptic transmission. Moreover, the communication between neurons in the CNS primarily takes place via chemical synapses. These actions dependent on neurotransmitters can be categorized as either presynaptic or postsynaptic (31).

Drugs targeting the synthesis, storage, metabolism, and release of neurotransmitters, fall under the presynaptic category. Blockading transmitter synthesis or storage can depress synaptic transmission. In addition, drugs have the capacity to alter transmitter release (31).

In the postsynaptic region, the transmitter receptor serves as the principal site of drug action. Drugs can act as neurotransmitter agonists, such as dopamimetic drugs used in Parkinson's disease, enhancing receptor function, or as antagonists, blocking receptor activity—a common mechanism among CNS drugs. Some drugs can also act directly on the ion channel of ionotropic receptors, such as ketamine, which acts as an antagonist of the NMDA subtype of glutamate ionotropic receptors, blocking them by binding to the ion channel pore. Additionally, various antidepressants can enhance neurotransmitter levels by inhibiting either their pre-synaptic transporters or the degradation of monoamines. This last class of drugs works by blocking the enzymes responsible for the breakdown of key neurotransmitters, thereby increasing their availability and prolonging their action at synaptic sites (31).

The selectivity of CNS drug action hinges on two primary drug factors: Firstly, different neurotransmitters are released by various neuron groups. Secondly, multiple receptors for each neurotransmitter exhibit divergent cellular distributions throughout the CNS, enabling the development of drugs that selectively target specific receptors and CNS functions (31).

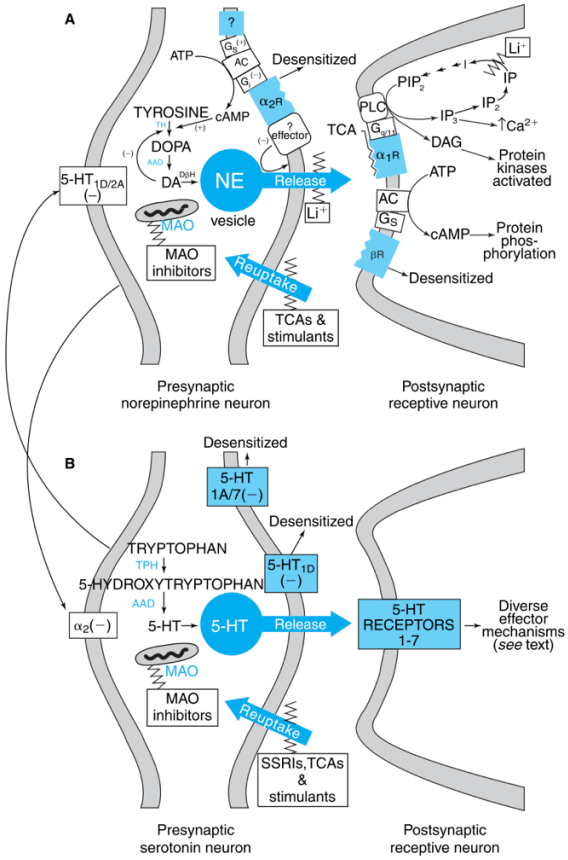

Figure 1. Sites Of Action of Antidepressants (32)

A. In varicosities of noradrenaline (NE) neurons projecting from the brainstem to the forebrain, L-tyrosine is converted to dopamine (DA) by tyrosine hydroxylase (TH) and stored in vesicles, where dopamine β-hydroxylase (DβH) converts DA to NE. Following depolarization and Ca2+ presence, NE is released and interacts with postsynaptic α and β adrenergic receptors and presynaptic α2 autoreceptors, which regulate NE release. Reuptake into presynaptic terminals inactivates trans-synaptic communication, inhibited by tricyclic antidepressants (TCAs) and stimulants, with subsequent deamination by MAO. Initially, TCAs block NE inactivation, reducing firing rates and transmitter release, but α2 autoreceptor response diminishes over time. Postsynaptically, β receptors activate the GS-adenylyl cyclase pathway, while adrenergic α1 receptors activate the phospholipase C pathway.

B. Selective serotonin reuptake inhibitors (SSRIs) act similarly to TCAs on serotonin-containing neurons. Serotonin is synthesized from L-tryptophan, and upon release, it interacts with various postsynaptic 5-HT (serotonin) receptors. Inhibitory autoreceptors like 5-HT1A and 5-HT1D become desensitized with prolonged SSRI treatment. The adrenergic and serotonergic systems influence each other through complementary heteroceptor mechanisms.

5.2 Antidepressant Drug Action

Most antidepressant drugs target mechanisms concerning the control of monoamine neurotransmitter turnover or monoamine receptor function. Prolonged treatment with antidepressants enhances both the structural and functional integrity of neural circuits responsible for mood regulation (33).

The primary mechanism of action for most drugs used in depression treatment involves the **enhancement of neurotransmission by CNS monoamines**, notably serotonin, along with noradrenaline and dopamine. This increased noradrenergic activity further boosts serotonergic transmission by stimulating somatodendritic α_1-adrenoceptors on serotonergic neurons. However, despite the rapid increase in synaptic monoamine levels, clinical improvement is delayed. This delay may occur due to a gradual reduction in the number of upregulated somatodendritic and presynaptic 5-HT_1 inhibitory autoreceptors in individuals with depression (33).

Antidepressant drugs exert **effects on postsynaptic monoamine receptor expression and signalling**. During antidepressant treatment, there is a gradual increase in responsiveness to serotonin within the prefrontal cortex. Moreover, these medications enhance the response to monoamine receptor stimulation, thereby increasing the expression of BDNF and its receptor. Consequently, this stimulation facilitates the differentiation of progenitor cells into neurons and enhances neuronal survival (33).

Long-term administration of antidepressants **regulates CRH production**, leading to the normalization of excessively expressed CRH secretion. This process may be related to upregulation of CNS glucocorticoid receptors, with feedback inhibition of CRH (33).

Lastly, through the **antagonism of NMDA receptors**, antidepressants can target specific sites within NMDA receptor-associated ion channels, particularly in critical regions such as the hippocampus and cerebral cortex. This interaction plays a vital role in protecting cells from stress-induced glutamate excitotoxicity, a phenomenon strongly linked to the pathophysiology of depression (33).

5.3 Antidepressant Drugs

5.3.1 Tricyclic Antidepressants (TCAs)

TCAs were once considered the cornerstone in the treatment of MDD, but they have since been largely superseded by other antidepressant drug classes, particularly the SSRIs (33). Nowadays, TCAs are predominantly prescribed for refractory patients who have not responded to more commonly used antidepressants, such as SSRIs or SNRIs (Serotonin and Noradrenaline Reuptake Inhibitors). Their loss of popularity rose from relatively lower tolerability compared to newer agents, difficulty of use and lethality in overdose (34).

TCAs exert their therapeutic effects by inhibiting the reuptake of monoamine neurotransmitters into the presynaptic neuron. This occurs through competitive inhibition of monoamine transporter (MAT) proteins, particularly the noradrenaline transporter (NET) and the serotonin transporter (SERT) (33).

The side effects of TCAs arise from their antagonistic action on various postsynaptic receptors, which does not contribute to their antidepressant action (33).

Common side effects of TCAs include sedation, which results from blocking histamine H1 receptors and α1-adrenoceptors. Additionally, antimuscarinic effects lead to dry mouth, while constipation, urinary retention, and visual disturbances occur less frequently. Peripheral α1-adrenoceptor blockade induces postural hypotension, particularly problematic for older individuals. Furthermore, weight gain due to histamine H1 receptor blockade and sexual dysfunction are among the most prevalent effects experienced (33).

Following oral administration, all TCAs are rapidly absorbed and bind strongly to plasma albumin (90–95% at therapeutic plasma concentrations) (35), these exhibit long half-lives (34) (ranging from 8 to 90 hours) and undergo extensive first-pass metabolism in the liver, forming active metabolites that contribute to the variable effective half-lives of these drugs (33).

5.3.2 Selective Serotonin Reuptake Inhibitors (SSRIs)

Selective Serotonin Reuptake Inhibitors (SSRIs) reduce the reuptake of serotonin by its presynaptic transporter protein, with little or no effect on noradrenaline reuptake (33),

or blocking actions on adrenergic and cholinergic receptors (34) . Due to their high tolerance and wide-ranging effectiveness, they are prescribed as a first-line medication for individuals of various ages suffering from depression (36).

Unlike the TCAs, SSRIs have few antimuscarinic effects, causing little sedation or weight gain (33). However, since they enhance serotonergic tone not only in the brain but throughout the body, this increased serotonergic activity often leads to gastrointestinal disturbances such as nausea, upset stomach, and diarrhoea, which typically manifest early in treatment but tend to alleviate after the first week. Other side effects associated with SSRIs are diminished sexual function and interest, increase in headaches, insomnia (34), agitation or restlessness (32).

SSRIs require careful consideration in children and adolescents due to their association with increased risk of suicidal thoughts and self-harm, particularly among individuals under 25 years of age during the initial phases of treatment (33).

Serotonin syndrome, characterized by the rapid onset of neuromuscular hyperactivity, autonomic dysfunction and altered mental state due to excessive serotonin levels, is an adverse effect associated with SSRIs. While rare, it can present life-threatening risks, with symptoms typically emerging after an increase in SSRI dosage or concurrent administration of drugs with serotonergic activity (33).

All SSRIs require hepatic metabolism (34). Fluoxetine has a half-life of 1 to 4 days while its active metabolite, norfluoxetine, exhibits a half-life of 7 to 15 days. Other SSRIs half-lives range from 15 hours (fluvoxamine) and 36 hours (citalopram). The key distinction lies in their potential for drug-drug interactions: Paroxetine, fluoxetine and norfluoxetine strongly inhibit CYP2D6, while fluvoxamine inhibits CYP1A2 and CYP2C19. Concomitant administration of these SSRIs with drugs that are substrates of the inhibited enzymes holds potential for great harm, unless properly recognised and managed (37).

5.3.3 Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs)

Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs) bind to SERT and NET transporters (34), yet the potency of their binding to each of these and their selectivity ratios differ (38). SNRIs distinguish themselves from TCAs by their minimal impact

on peripheral receptors including histamine H1, muscarinic, or α-adrenergic receptors, which are significantly blocked by TCAs (34).

Venlafaxine exhibits a stronger affinity for the 5-HT transporter compared to the noradrenaline transporter. At lower doses, it predominantly inhibits the 5-HT transporter, mimicking the action of SSRIs. It's only at higher doses that significant noradrenaline reuptake inhibition occurs. In contrast, Desvenlafaxine, the primary metabolite of venlafaxine, demonstrates approximately tenfold greater potency in inhibiting 5-HT uptake compared to noradrenaline uptake (39).

Duloxetine, unlike venlafaxine, maintains a balanced inhibition of both neurotransmitters across its dosing range. Additionally, Duloxetine is regarded as a less potent inhibitor of dopamine reuptake (39).

Milnacipran stands out as the most balanced reuptake inhibitor among the current SNRIs, exhibiting nearly equipotent inhibition of both serotonin and noradrenaline reuptake (40). This balanced effect remains consistent across all doses, with an equivalent and simultaneous impact on the reuptake inhibition of both neurotransmitters (41). Levomilnacipran, the more active enantiomer of Milnacipran, exhibits a two-fold higher potency for inhibiting noradrenaline reuptake in comparison to serotonin reuptake (42).

Among SNRIs, the most common side effects encompass nausea, anxiety, sweating, drowsiness, reduced appetite, constipation, tremors, dizziness, dry mouth, insomnia, and sexual dysfunction (38). Venlafaxine is particularly associated with elevated blood pressure, which is dose-dependent and more pronounced with the immediate-release formulation (43)

SNRIs hold relatively short half-lives. Venlafaxine undergoes hepatic metabolism primarily through the cytochrome P450 (CYP) isozymes, while Desvenlafaxine experiences minimal first-pass metabolism in the liver (38). Both Venlafaxine and Desvenlafaxine exhibit the lowest protein binding among antidepressants, estimated at 27–30% (34).

Duloxetine is predominantly metabolized by the enzymes CYP2D6 and CYP1A2 (38), and has a half-life of approximately 12.5 hours, with hepatic metabolism being the main route of elimination (39).

Milnacipran is rapidly and extensively absorbed and has a high bioavailability, boasting a relatively short half-life of 12 hours (39), it has not been shown to interact with CYP enzymes (38) Levomilnacipran sharing the same half-life as Milnacipran, primarily undergoes metabolism via the 3A4 isoenzyme pathway, resulting in inactive metabolites (44).

5.3.4 Noradrenaline Reuptake Inhibitors (NRIs)

Reboxetine, the first selective noradrenaline reuptake inhibitor , exhibits a high affinity to the human and rat noradrenaline transporter. It is a weak serotonin inhibitor, with a marked 124-fold selectivity for the noradrenalin reuptake over the serotonin reuptake (45), lacks dopamine activity and has no significant affinity for adrenergic, histaminergic, or cholinergic receptors (46). Its inhibition of noradrenaline reuptake triggers an immediate rise in synaptic noradrenaline levels (46), while concurrently downregulating NET and β1 receptors without affecting SERT (45).

The absence of binding to histamine H_1 receptors suggests a reduced likelihood of weight gain in patients (45), though it is associated with increased sweating, constipation, and dry mouth (47).

Following oral administration, reboxetine is rapidly absorbed, with an oral bioavailability exceeding 92%. It undergoes extensive hepatic metabolism via cytochrome CYP3A4 with an elimination half-life averaging 12-13 hours (46).

5.3.5 Noradrenergic and Specific Serotonergic Antidepressant (NaSSA)

Mirtazapine, a tetracyclic compound, has a distinct mechanism of action setting it apart from other antidepressants (39). Mirtazapine inhibits the central presynaptic alpha-2-adrenergic receptors, which elevates noradrenergic and 5-HT_{1A}-mediated serotonergic neurotransmission. This is achieved by its dual action as an antagonist at central α_2-adrenergic autoreceptors and heteroreceptors, coupled with postsynaptic blockade of 5-HT2 and 5-HT3 receptors (48).

Known for its potent histamine H_1 receptor antagonism, mirtazapine, when administered at low doses, is associated with excessive sedation and drowsiness, alongside an increase in appetite and weight gain. Unlike SSRIs, it typically doesn't lead to sexual side effects; however, it may still induce dry mouth and constipation (48).

Extensively metabolized in the liver by the enzymes CYP2D6, CYP3A4 and CYP1A2, mirtazapine exhibits a half-life ranging between 20-40 hours (39). Like many antidepressants with a therapeutic latency, mirtazapine may require 2–4 weeks for its therapeutic benefits to manifest fully, and notably lacks an active metabolite (48).

5.3.6 Serotonin Receptor Antagonists and Reuptake Inhibitors (SARIs)

Trazodone, a phenylpiperazine and triazolopyridine derivate, has a unique dual mechanism of action, acting as both a 5-HT_2 receptor antagonist and a selective serotonin reuptake inhibitor. This unique pharmacological profile provides trazodone with multiple benefits in addressing comorbidities often seen alongside major depression, such as anxiety and insomnia. Moreover, trazodone exhibits antagonistic effects on α_1 and α_2 adrenergic receptors, along with H_1 receptor antagonism. Notably, it distinguishes itself from tricyclic antidepressants with its reduced anticholinergic properties and minimal impact on cardiac conduction (49,50).

The most common side effects associated with 5-HT_2 antagonists include sedation, notably prominent in trazodone, and gastrointestinal disturbances, which tend to be dose-dependent and milder compared to those observed with SNRIs or SSRIs (49). Additionally, cardiovascular effects may manifest as orthostatic hypotension, particularly prevalent among the elderly and individuals with pre-existing cardiac conditions. Notably, trazodone stands out due to its association with priapism, an urological emergency occurring at rates ranging from 1 in 1,000 to 1 in 10,000, typically within the initial 28 days of treatment at doses of 150mg/day or less (50,51).

Trazodone is well absorbed after oral administration and exhibits a high protein-binding, ranging from 89% to 95%. Its immediate release formulation boasts a relatively short half-life of approximately 7 hours. Within the liver, it undergoes extensive metabolic transformation via oxidative cleavage, with less than 1% unchanged in the urine. The primary metabolite, produced by the CYP3A4, is meta-

chloro-phenylpiperazine (mCPP), known for its potent antagonistic effect on 5-HT_2 receptors (49,50).

5.3.7 Monoamine Oxidase Inhibitors (MAOIs)

Monoamine oxidase inhibitors (MAOIs) can be categorized into two main groups: irreversible inhibitors such as phenelzine, tranylcypromine, and isocarboxazid, and second-generation selective and reversible MAOIs such as moclobemide, an inhibitor of MAO-A, and selegiline, targeting MAO-B. The latter is predominantly used in the treatment of Parkinson's disease (52).

5.3.7.1 Irreversible Monoamine Oxidase A and B Inhibitors

The early MAOIs were characterized by their irreversible mode of action, meaning they bind permanently to MAO for the enzyme's life, 14 to 28 days. Consequently, a waiting period of 7 to 14 days is necessary for new enzyme generation and the return of MAO activity. In Portugal, medications like Phenelzine, Tranylcypromine, and Isocarboxazid were never introduced commercially, contrasting with the United States where the American Psychiatric Association guidelines restrict the use of these nonselective MAOIs to patients who have not responded to other treatments. Due to dietary restrictions and the associated risk of serious adverse effects related to tyramine-laden foods, irreversible MAOIs are often considered as third, fourth, or even fifth-line treatments in current depression treatment guidelines (53).

The National Institute for Health and Clinical Excellence (NICE) guidelines, reserve irreversible MAOIs such as phenelzine, for individuals with chronic depressive symptoms that significantly impair personal and social functioning, who have not responded to SSRIs or SNRIs. However, these medications are only prescribed by mental health specialists (54).

Most common early side effects reported with oral MAOIs include insomnia, sedation, orthostatic hypotension, dizziness, and nausea, while later side effects may manifest as weight gain, edema, muscle pain, myoclonus, paresthesia, and sexual dysfunction (53).

However, the most severe potential side effects of MAOIs are hypertensive crisis, due to dietary tyramine metabolism, and serotonin syndrome, which can occur due to

interactions with medications with potent serotonergic effects, such as certain antidepressants, synthetic opioids, and specific migraine medications (53).

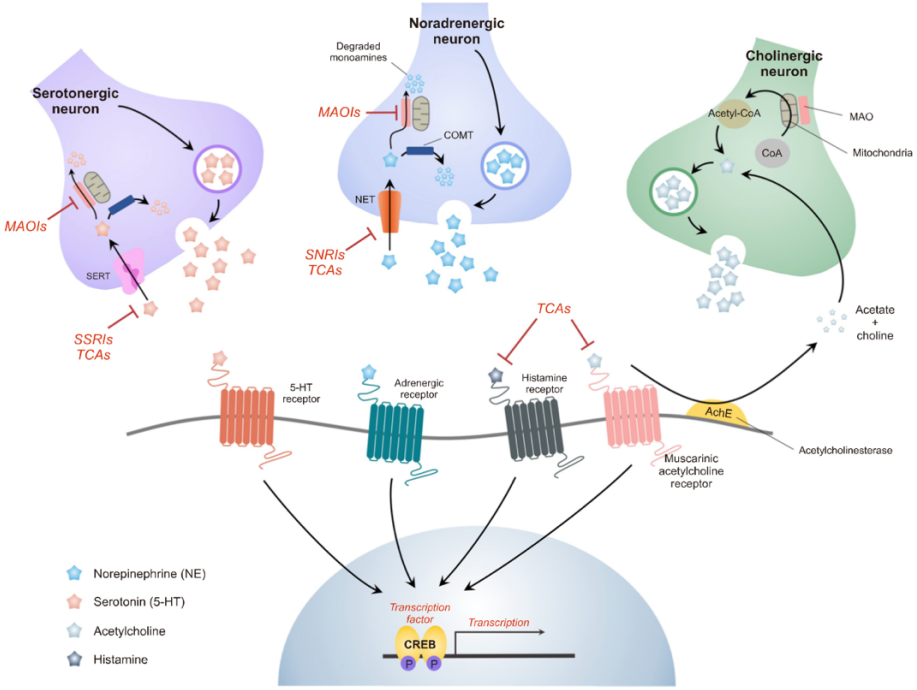

Figure 2 – Key mechanisms of action for the antidepressants: SSRIs, SNRIs, TCAs and MAOIs (55)

MAOIs increase brain amine levels by disrupting nerve-ending metabolism, leading to enhanced vesicular storage of NE and 5-HT. When nerve activity releases these vesicles, the levels of neurotransmitters rise. TCAs immediately affect neurotransmitter function at post-synaptic receptors by blocking the reuptake mechanism that terminates NE and 5-HT activity in the brain. SSRIs specifically target SERT by allosterically blocking it through non-serotonin binding sites, with minimal inhibition of the NE transporter and potential blockage of adrenergic and cholinergic receptors. SNRIs enhance the activity of both neurotransmitters by binding to SERT and NET, without significantly blocking peripheral receptors such as histamine H1, muscarinic, or adrenergic receptors, unlike TCAs.

5.3.7.2 Reversible Inhibitors of Monoamine Oxidase A

To fully harness the recognised efficacy of traditional irreversible MAOIs in addressing atypical and treatment-resistant depression, drug development began to focus on selective and reversible MAOIs, aiming to enhance safety and convenience. Reversible MAO-A inhibitors, unlike their irreversible counterparts, do not bind directly to the MAO in the gut, allowing tyramine to displace these medications, significantly reducing the risk of blood pressure elevation. Moclobemide, as a reversible MAO-A

inhibitor, maintains its therapeutic effect even after dissociating from the enzyme (52). This is suggested to be due to the time-dependent binding of moclobemide to MAO-A, which reflects its relatively slow dissociation from the enzyme (56).

In contrast to many older antidepressants, moclobemide offers a favourable side effect profile, lacking anticholinergic, sedative, and cardiovascular effects. Moreover, it exhibits fewer gastrointestinal issues compared to SSRIs and is not associated with sexual dysfunction. Common side effects associated with moclobemide include dizziness, nausea, and insomnia/sleep disturbance (56).

Following oral administration, moclobemide is rapidly absorbed and undergoes substantial first-pass metabolism in the liver, yielding at least 19 different metabolites, two of which possess moderate MAO-A inhibitory activity. The drug's elimination half-life ranges from approximately 1 to 2 hours, with renal excretion being the primary route for metabolite elimination (33,56).

5.3.8 Noradrenaline-dopamine reuptake inhibitor (NDRI)

Bupropion’s mechanism of action in treating MDD is not fully yet understood. However, it is known to function as an inhibitor of dopamine and noradrenaline transporters (DAT and NET respectively). This inhibition leads to a reduction in the reuptake of dopamine and noradrenaline in the synaptic cleft, without significantly affecting other neurotransmitters or their receptors. Although bupropion exhibits low affinity for DAT and NET, suggesting alternative modes of action, its efficacy in treating MDD is well-established (57).

Moreover, bupropion functions as a nicotinic acetylcholine receptor antagonist. Its approval in Portugal extends beyond MDD treatment to include smoking cessation. In other countries, it is also prescribed for Attention Deficit Hyperactivity Disorder (ADHD) (57).

Following oral administration, bupropion is well-absorbed by the gastrointestinal tract, even if subjected to significant first-pass metabolism, which reduces its bioavailability. CYP2B6 primarily metabolizes bupropion into its most active metabolite,

hydroxybupropion, followed by erythrohydrobupropion and threohydrobupropion. With an elimination half-life of approximately 21 hours, bupropion is primarily excreted through urine (57).

The most frequently reported side effects associated with bupropion treatment typically occur during initial treatment. These may include dry mouth, constipation, headache, nausea, agitation, insomnia, and weight loss (58). Notably, bupropion's pharmacological profile lacks activity on antihistamine, anticholinergic and serotonin reuptake inhibitory activity, sparing patients from common side effects such as sexual dysfunction, weight gain, and sedation, often experienced with TCAs. However, it is crucial to recognize that seizures represent a potentially severe adverse effect of bupropion usage. Patients with a lower seizure threshold, either due to comorbid conditions or concomitant use of other seizure-lowering medications, should be carefully monitored and advised about this risk (41).

5.3.9 Serotonin Modulator and Stimulator (SMS)

Vortioxetine has a unique mechanism of action with a distinct clinical profile. As a multimodal antidepressant, vortioxetine targets serotonin receptors and transporters, showcasing a diverse pharmacological approach (59).

Acting as a 5-HT_{1A} receptor agonist, 5-HT_3, 5-HT_7, and 5-HT_{1D} receptor antagonist, 5-HT_{1B} receptor partial agonist, and a SERT inhibitor, vortioxetine exerts its antidepressant activity by modulating neurotransmission across various systems. These encompass serotonin, noradrenaline, dopamine, acetylcholine, histamine, glutamate, and gamma-aminobutyric acid systems, highlighting its influence on mood modulation (59).

The most common adverse effects reported included dose-related nausea, typically manifesting within the initial week of treatment, along with headaches, dry mouth, and dizziness. Vortioxetine has minimal impact on weight, likely due to its unique mechanism of action that promotes balanced serotonergic modulation. Sexual side effects, when present, are primarily associated with the 20 mg dosage. This may be explained by vortioxetine’s dose-dependent binding affinity, where increasing the dose

leads to greater receptor binding—approximately a 15% increase for every 5 mg, up to the maximum dosage (49,60).

Vortioxetine is well absorbed orally and underdoes extensive metabolism primarily through oxidation via CYP enzymes, followed by glucuronic conjugation via uridine diphosphate glucuronosyltransferase, with CYP2D6 being the principal enzyme responsible for its metabolism. This process yields six metabolites, with the major one, Lu AA34443, being pharmacologically inactive and not binding to the main 5-HT receptors related to effectiveness. Therefore, the clinical efficacy of vortioxetine is attributed solely to the parent compound. Although other metabolites have been detected, they are considered pharmacologically irrelevant due to their concentrations and inability to cross the blood-brain barrier. Vortioxetine exhibits a half-life of approximately 57 hours and is predominantly excreted through urine (59,61).

5.3.10 Melatonin Receptor Agonist and Serotonin Receptor Antagonist

Agomelatine offers a distinctive pharmacological approach for the management of depressive disorders. Its mechanism involves dual action: activating melatonin receptors while simultaneously blocking a serotonin receptor. Functioning as agonist at MT_1 and MT_2 receptors, it exhibits a binding affinity similar to melatonin. Additionally, it acts as an antagonist at 5-HT_{2C} receptors, further contributing to its therapeutic profile (62).

Melatonin, a hormone secreted by the pineal gland at nighttime, plays a role in regulating and synchronizing the circadian rhythm. Abnormal circadian function may be involved in the etiology of MDD, thus the interest in developing antidepressants with chronobiotic effects, such as agomelatine (62).

Under normal physiological conditions, the release of noradrenaline and dopamine is regulated by the tonic release of serotonin onto 5-HT_{2C} receptors. By antagonizing this receptor and subsequently disrupting this tonic inhibition, agomelatine induces a state of 'disinhibition', thereby augmenting noradrenaline and dopamine neurotransmission (63).

In contrast to SSRIs, agomelatine exhibits a more favorable side-effect profile, particularly concerning sexual functioning, weight gain, and gastrointestinal

disturbances, while avoiding the manifestation of discontinuation symptoms. The typical side effects associated with agomelatine, such as nausea and dizziness, are generally mild and transient, often emerging within the initial two weeks of treatment. Notably, agomelatine may lead to an elevation in serum hepatic transaminases, with levels rising to three times the upper limit of the normal range in about one percent of individuals. However, prompt discontinuation of the medication has been observed to normalize hepatic transaminase levels (64).

Following oral administration, agomelatine is well absorbed, with approximately 95% of the drug binding to plasma proteins in the systemic circulation. It boasts a short plasma half-life ranging from1 to 2 hours. Metabolism primarily occurs via CYP450 1A2, with up to 80% of the drug eliminated in urine. Notably, individuals with hepatic impairment experience a significant increase in the drug's bioavailability, thus warranting caution and contraindicating its use in patients with cirrhosis or active liver disease (63).

Table 1. Approved therapeutic indications of antidepressants according to the British National Formulary (65)

Antidepressant Drugs	Approved Therapeutic Indications
Tricyclic Antidepressants	Major depression disorder; Abdominal pain or discomfort; Neuropathic pain; Migraine prophylaxis; Chronic tension(type headache prophylaxis); Emotional lability in multiple sclerosis; Phobic and obsessional states; Adjunctive treatment of cataplexy associated with narcolepsy; Nocturnal enuresis (Imipramine in children from 6-17 years); Neuropathic pain.
Selective Serotonin Reuptake Inhibitors	Depressive Illness; Panic disorder; Anxiety disorders; Obsessive-compulsive disorder; Bulimia nervosa; Menopausal symptoms, particularly hot flushes, in women with breast cancer; Post-traumatic stress disorder;

Table 1. (cont.)

Antidepressant Drugs	Approved Therapeutic Indications
Serotonin and Noradrenaline Reuptake Inhibitors	Major depressive disorder; Anxiety disorders; Diabetic neuropathy; Moderate to severe urinary incontinence; Panic disorder; Menopausal symptoms, particularly hot flushes, in women with breast cancer
Noradrenaline Reuptake Inhibitors	Major depression.
Noradrenergic and Specific Serotonergic Antidepressant	Major depression.
Serotonin Receptor Antagonists and Reuptake Inhibitors	Depressive Illness (particularly where sedation is required); Anxiety.
Irreversible Monoamine Oxidase A and B Inhibitors	Depressive Illness.
Reversible Inhibitors of Monoamine Oxidase A	Depressive Illness; Social anxiety disorder.
Noradrenaline-dopamine Reuptake Inhibitor	Major depression; Smoking cessation.
Serotonin Modulator and Stimulator	Major depression.
Melatonin Receptor Agonist and Serotonin Receptor Antagonist	Major depression.

6 Addressing the Need: Challenges in Developing New Antidepressant Drugs

Current treatments for MDD face significant challenges, including low efficacy rates, prolonged therapeutic timeframes for treatment response, and undesirable side effects (66). This delay in clinical response is crucial, as it exposes patients to risks such as medication discontinuation, self-harm or suicide, and ongoing neural impacts of the illness (67). Antidepressants, such as SSRIs which remain the gold-standard treatment for depression, require several weeks to months of administration before a therapeutic response is obtained. Moreover, their effectiveness is limited, with only about a third of patients responding to initial prescriptions. Many individuals undergo multiple trials over months or even years before finding an effective treatment, with approximately one-third eventually labelled as TRD after failing two or more first-line antidepressant regimens (66).

Given the significant personal and economic consequences and the projected increase in rates of MDD, there is an urgent demand for more effective and fast-acting treatments. Present pharmacological interventions, although generally safe and helpful for certain individuals, fall short of the ideal standard and are predominantly insufficient (66).

One of the major challenges in the development of new therapeutic agents for MDD treatment lies in the complexity and heterogeneity of the illness. MDD is widely acknowledged as a syndrome encompassing diverse subtypes and etiological factors. While genetic heritability plays a role, environmental influences such as stress and trauma frequently intertwine with genetic predispositions, amplifying the complexity of the condition (66).

Among the difficulties that mental health faces are a lack of consensus concerning classification, diagnosis and treatment that stems from an incomplete understanding of the processes underlying these disorders (68). The diagnosis and treatment of MDD rely on subjective evaluations of diverse symptoms representing multiple

endophenotypes. However, the underlying biological mechanisms responsible for the diverse manifestations of MDD are still poorly understood (69).

An ongoing problem is the lack of a good biomarker of depression or treatment response. The abundance of potential biomarkers complicates the field of psychobiology, as discerning their specific implications and relevance for individuals remains ambiguous. Moreover, the limited investigation into these biomarkers within the context of depression increases the challenge. Consequently, the precise roles of most biomarkers in both healthy and clinical populations remain poorly understood (68).

One of the challenges confronting researchers involves the placebo effect when evaluating novel drugs. Placebo responses exhibit considerable variability across studies and consistently demonstrate significant impacts on depression measures. Over recent decades, these responses have been on the rise, complicating the task of distinguishing treatments that are notably superior to placebos (66).

Nevertheless, finding the perfect animal model for studies of depression or antidepressant action remains a challenge. This is especially crucial as antidepressants do not elevate mood in healthy humans. Further complicating matters is the challenge of delineating depression from anxiety, a distinction that remains unclear in both human patients and animal models (13).

One logical step towards the development of more efficient treatments is to better understand the etiology of the disease. Further characterization of MDD and its subtype-specific pathophysiology, alongside the development of biomarkers, will lead to treatments that target specific abnormalities with greater efficacy and fewer side effects (66).

The therapeutic limitations of current agents have led to the investigation of several mechanisms of action beyond the already known deficits in monoamine neurotransmitter systems, such as antagonism, inhibition of the reuptake of neurotransmitters, and modulators of glutamate receptors (28,66).

7 New Wave of Antidepressants

7.1 Esketamine

Esketamine, the S(+) enantiomer of ketamine is an NMDA glutamate receptor antagonist that has been demonstrated to produce rapid antidepressant and anti-suicidal efficacy, sustained well beyond its half-life (70). In March 2019, for the first time in 30 years, the Food and Drug Administration (FDA) approved a drug belonging to a new class of antidepressants. Based on the positive results of phase III clinical trials, intranasal esketamine in conjunction with an oral antidepressant was approved for use in adults in TRD (71). Esketamine was subsequently approved by the European Medicines Agency (EMA) in 2021.

7.1.1 Mechanism of action

Esketamine is a more potent NMDA receptor antagonist than its enantiomer R-ketamine, with a complex mechanism of action that remains not fully understood. According to the disinhibition hypothesis, subanaesthetic doses of esketamine preferentially bind to NMDA receptors on GABA-secreting inhibitory neurons. This results in the disinhibition of pyramidal cells, leading to increased glutamate release and higher extracellular glutamate concentrations. The resultant excitatory effect on neurons activates AMPA receptors, and combined with NMDA receptor blockade, promotes neurotropic effects such as the release of BDNF and activation of downstream trophic signalling cascades. Another hypothesis posits that esketamine directly inhibits extra-synaptic NMDA receptors containing GluN2B subunits on pyramidal neurons. This GluN2B-dependent mechanism involves Eukaryotic elongation factor 2 (eEF2) dephosphorylation, increased BDNF translation, and activation of homeostatic mammalian target of rapamycin (mTOR) synaptic plasticity (72).

Although esketamine also acts on other neuronal receptors, evidence indicates that the anaesthetic, antidepressant, and acute psychological effects of esketamine are mediated primarily by its non-competitive antagonism of NMDA receptors. Given that its upstream effects depend on the specific neurons it targets, esketamine should be regarded as a glutamatergic modulator rather than merely a glutamatergic antagonist (72).

7.1.2 Pharmacokinetics, Metabolism and Adverse Effects

Bioavailability of ketamine, and thus esketamine, depend on the mode of administration. Intravenous (IV) administration of ketamine offers the most predictable dosing with 100% bioavailability. In contrast, intranasal (IN) esketamine shows a bioavailability ranging from 8% to 45%. When administered intranasally, esketamine is rapidly absorbed through the richly vascularized nasal cavity, achieving peak plasma concentration within 10-14 minutes (70). The terminal half-life of esketamine is approximately 11.1 hours, while its active metabolite, noresketamine, has a half-life of about 7.5 hours (73). Unlike other routes, IN esketamine bypasses extensive hepatic first-pass metabolism and has a plasma protein binding rate of 27%, allowing it to be widely distributed throughout well-perfused tissues in the body. Esketamine undergoes rapid and extensive metabolism in the liver, primarily through the CYP enzymes CYP2B6 and CYP3A4, via N-demethylation to its active metabolite (70).

Adverse effects of esketamine treatment for depression are generally mild to moderate in severity and typically manifest during or immediately after treatment, with symptoms resolving within the same day. The most common side effects, similar to those observed with ketamine, include headache, dizziness, dissociation, blurred vision, transient hypertension, and anxiety (70).

7.1.3 Use in Specific Populations

Esketamine is not recommended during pregnancy and for women of childbearing potential who are not using contraception. Data on the use of esketamine in pregnant women is limited or non-existent, and animal studies have shown that ketamine induces neurotoxicity in developing fetuses, suggesting that a similar risk with esketamine cannot be ruled out. Additionally, it is unknown whether esketamine is excreted in breast milk; however, animal data have shown ketamine excretion in milk, indicating a potential risk to a breastfeeding child. Furthermore, the safety and efficacy of esketamine in paediatric patients aged 17 and under have not been established (74).

7.1.4 Clinical Trials

Janssen R&D initiated a developmental program that included phase II and phase III clinical trials to evaluate the efficacy and safety of esketamine in patients with TRD and those at imminent risk of suicide (71).

A randomized double-blind phase II study (SYNAPSE) demonstrated the rapid and significant efficacy of IN esketamine administered twice weekly compared to placebo in patients with TRD who were continuing their current oral antidepressant treatment. The response rates were 38%, 36%, and 50% for esketamine doses of 28 mg, 56 mg, and 84 mg, respectively, compared to 10% in the placebo group. Improvements in the mean Montgomery-Asberg Depression Rating Scale (MADRS) ratings persisted over the 8-week follow-up period, and adverse events were transient (71).

IN esketamine also proved effective in reducing suicidal ideation in patients at imminent risk of suicide. In the randomized double-blind phase II study (PeRSEVERe), esketamine treatment led to a rapid and significant improvement compared to placebo in the MADRS suicidal thoughts item score (71).

Following the promising results of phase II studies, IN esketamine advanced to phase III development, with the efficacy studies named the TRANSFORM studies. In these studies, patients began or continued a new oral antidepressant. TRANSFORM-1 evaluated short-term treatment with a fixed dose of IN esketamine versus placebo, both added to an oral antidepressant in adults with TRD. The primary efficacy endpoint, a change in the MADRS total score, was not significant (71).

TRANSFORM-2 assessed the short-term treatment of a flexible dose of intranasal esketamine versus placebo, both added to an oral antidepressant in adults with TRD. The primary efficacy endpoint showed a significant improvement in depressive symptoms for esketamine compared to placebo (71).

TRANSFORM-3 focused on the short-term treatment of a flexible dose of intranasal esketamine versus placebo, both added to an oral antidepressant in elderly patients with TRD. The primary efficacy endpoint did not show a significant difference for esketamine compared to placebo (71).

SUSTAIN-1, a long-term randomized withdrawal study, evaluated the efficacy of an individually selected dose of IN esketamine for relapse prevention in adult patients with TRD. The study reported relapse rates of 26.7% in the esketamine group versus 45.3% in the placebo group, with esketamine-treated patients having a 51% reduced risk of relapse during the maintenance phase (71).

7.2 Ketamine Assisted Psychotherapy (KAP)

Research on ketamine for treating mental health problems began in the 1970s, initially as an adjunct to psychotherapy. Over the last few decades, it has been investigated and used clinically *off-label*, demonstrating efficacy in TRD. Due to its long history of use and wide availability, the cost of ketamine is significantly low (72).

A protocol for the medical use of ketamine emerged, involving IV administration. In this protocol, ketamine is infused at a rate of 0.5 mg/kg over 40 minutes. This approach allows ketamine to provide a break from the ordinary state of mind, offering relief from negativity and facilitating an openness to expansive thoughts and self-awareness. These effects significantly enhance the patient's ability to participate in meaningful psychotherapy both during and after the administration (75).

Ketamine Assisted Psychotherapy (KAP) leverages the neurobiological effects of ketamine while incorporating psychological support. This approach has been used in various psychiatric services within Portugal's national health system since 2021 (72).

At sub-anesthetic doses, ketamine exhibits subjective dissociative effects, such as the sensation of disconnecting from the body and alterations in time perception. Ketamine induces modifications akin to classical psychedelics during its administration, thus it is widely regarded as an atypical psychedelic (72).

Given that ketamine induces an altered state, which inherently renders an individual vulnerable, akin to any mind-altering encounter, it necessitates careful consideration of both set and setting (72,75). It should only be administered in a hospital setting, within a properly prepared space. The administration of a psychedelic drug with psychological support typically involves preparatory sessions, drug dosing sessions with

psychological support, and integration sessions focused on processing the psychedelic experience. These sessions last a total of two and a half hours, with the most significant changes in mental state lasting for one hour (72).

7.3 Gepirone

Gepirone, an analog of the anti-anxiety medication buspirone, is an oral selective serotonin 5HT1A receptor agonist. Both gepirone and buspirone belong to the azapirone class and act as 5HT1A receptor agonists, with gepirone being a more potent agonist (15). Fabre-Kramer Pharmaceuticals, Inc. formulated gepirone hydrochloride extended-release (ER) for once-daily administration to treat psychiatric disorders (76). In September 2023, the FDA approved gepirone for treating MDD in adults, but there is no information available about its submission to the EMA (15).

7.3.1 Mechanism of action

The antidepressant effect of gepirone is thought to be related to its modulation of serotonergic activity in the CNS through selective agonist activity at 5HT1A receptors. The pharmacological activity of gepirone is attributed to the parent drug and its major metabolites, 3'-OH-gepirone and 1-pyrimidinylpiperazine (1-PP) (77). The 1-PP metabolite, a presynaptic alpha-2 adrenoreceptor antagonist did not exhibit antidepressant-like characteristics in pre-clinical tests. However, the 3'-OH gepirone metabolite has significant affinity for 5-HT1A receptors, enhancing 5-HT neurotransmission. Initially, gepirone reduces the firing of 5-HT neurons, but repeated exposure desensitizes 5-HT1A autoreceptors, gradually increasing 5-HT release and neuronal 5-HT activity (78).

7.3.2 Pharmacokinetics, Metabolism and Adverse Effects

The pharmacokinetics of gepirone after oral administration are linear and dose-proportional over an 18.2-72.6 mg dose range. Steady-state plasma concentration is typically achieved within two to four days of daily dosing (77).

Food significantly affects the maximal plasma concentration (Cmax) of gepirone ER and, to a lesser extent, its total exposure (AUC). The systemic exposure of gepirone ER and its major metabolites is higher under fed conditions compared to fasted conditions;

the extent of this effect depends on the fat content of the meal. Under fasting conditions, the Cmax of gepirone ER is achieved within 6 hours (Tmax), whereas after a high-fat meal, Tmax is reduced to 3 hours (77).

The absolute bioavailability of gepirone ER is 14%-17%. In vitro, gepirone ER is 72% bound to human plasma proteins, while its metabolites 1-PP and 3'-OH-gepirone are 42% and 59% plasma protein-bound, respectively. Gepirone ER is extensively metabolized, primarily by CYP3A4, with a mean terminal half-life of approximately 5 hours. It is excreted in both urine and feces. The presence of hepatic or renal impairment affects the apparent clearance of gepirone ER (77).

The most commonly reported adverse effects were dizziness, nausea, insomnia, abdominal pain and dyspepsia (77). Gepirone is contraindicated in individuals with congenital long QT syndrome and in patients with a prolonged QTc interval, as it can extend this interval. It is also contraindicated in patients with severe hepatic impairment and those receiving strong CYP3A4 inhibitors due to the risk of increased gepirone plasma concentrations. Clinical trials have shown that gepirone ER treatment is not associated with sexual dysfunction or weight gain, which are common adverse events with SSRIs (76).

7.3.3 Use in Specific Populations

Animal reproduction studies have shown that gepirone adversely affects embryo/fetal and postnatal development. Neonates exposed to other serotonergic antidepressants in the third trimester have experienced complications requiring prolonged hospitalization, respiratory support, and tube feeding (77).

Currently, there is no data on the presence of gepirone in human milk, its effects on breastfed infants, or its impact on milk production. However, since gepirone is present in rat milk, it is likely to be present in human milk as well. The safety and effectiveness of gepirone for treating MDD in paediatric patients have not been established (77).

7.3.4 Clinical Trials

The efficacy of gepirone for treating MDD was assessed in two eight-week, randomized, double-blind, placebo-controlled, flexible-dose studies involving adults diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for MDD. The primary efficacy measure in both studies was the change from baseline in the Hamilton Depression Rating Scale (HAMD-17) total score at week 8. Results showed that patients in the EXXUA group, the commercial brand name for gepirone, experienced a statistically significantly greater improvement on the primary endpoint compared to those in the placebo groups (77).

Gepirone's journey to FDA approval was notably protracted. Initially submitted by Organon in 2001, gepirone showed promising results in reducing HAMD-17 scores, however the FDA required two large positive trials. A second submission in 2003, including a relapse prevention trial, was also rejected. Fabre-Kramer, who reacquired gepirone in 2005, conducted another trial with similar results, but a 2007 application was again denied due to concerns over several negative studies. An appeal led to a 2015 Psychopharmacologic Drugs Advisory Committee (PDAC) hearing, which ruled against the drug. Surprisingly, the FDA overturned this in 2016, eventually approving gepirone after a resubmission in 2022 (79).

The effect of gepirone ER on sexual function was explored by a clinical trial that compared this drug with fluoxetine and placebo in male patients. After eight weeks, gepirone ER demonstrated an improvement in overall sexual function compared to the placebo. Notably, even patients who did not respond to the drug's antidepressant and anxiolytic effects experienced significant enhancements in sexual function. This finding suggests that gepirone ER possesses pro-sexual activity independent of its antidepressant and anxiolytic properties (80).

A post hoc analysis investigated the effect of gepirone on women with Hypoactive Sexual Desire Disorder (HSDD) and MDD. By week two, gepirone-ER significantly reversed HSDD in women, whereas placebo and SSRIs did not. Typically, the antidepressant effects of gepirone-ER do not manifest until week four, indicating that its positive impact on HSDD may be independent of its antidepressant properties. The

reversal of HSDD was marked by both increased sexual desire and reduced distress. Additionally, gepirone-ER improved functioning in mildly depressed women compared to placebo, suggesting potential benefits for those with HSDD even in the absence of depression (81).

7.4 Zuranolone and Brexanolone

Depression with peripartum onset, commonly known as postpartum depression (PPD), is defined as a major depressive disorder episode that begins as early as the third trimester of pregnancy and extends up to 4 weeks postpartum (2).

Common symptoms of PPD include persistent sadness, anxiety, irritability, feelings of guilt, loss of interest, fatigue, difficulty bonding with the baby, persistent doubts about the ability to care for the baby, and suicidal thoughts (82).

PPD is estimated to affect 11.5% of women during pregnancy or after giving birth and is considered a public health concern due to its negative implications for the mother, offspring and family. It is also considered one of the leading direct causes of maternal mortality in the first postpartum year (83).

Prior to the FDA's approval of brexanolone in 2019, which requires inpatient administration, no pharmacological therapies were specifically approved for PPD (83). In 2023, the FDA further approved zuranolone, an orally administered medication, for the treatment of postpartum psychiatric disorders (84).

While neither brexanolone nor zuranolone is currently under review by the EMA for approval, brexanolone has been granted PRIority MEdicines (PRIME) designation, indicating its potential to address unmet medical needs (85). Additionally, zuranolone is being considered for potential use in children, as indicated by the acceptance of a modification to the agreed paediatric investigation plan (86).

7.4.1 Mechanism of action

Zuranolone and Brexanolone act as allosteric modulators of GABA-A receptors, targeting GABA neurotransmission. They are classified as "allopregnanolone agonists" (15).

Neurosteroids, synthesized from cholesterol in the brain, modulate neuronal excitability via membrane receptors without directly affecting gene expression. GABA-A receptors, ligand-gated anion channels, typically consist of α and β subunits, paired with either a γ subunit in synaptic receptors or a δ subunit in extrasynaptic receptors. Allopregnanolone, or 3α-hydroxy-5α-pregnan-20-one (ALLO), is a significant pregnancy hormone and a highly potent positive allosteric modulator of both synaptic and extrasynaptic GABA-A receptors. Dysregulation of neurosteroidogenesis has been linked to several neuropsychiatric disorders, including PPD and unipolar depression (82).

Brexanolone is an exogenous analog of allopregnanolone, a key metabolite of progesterone. During pregnancy, levels of allopregnanolone increase significantly but sharply decline after childbirth. This hormonal drop and the subsequent downregulation of GABA-A receptors are believed to trigger PPD. While the exact mechanism by which brexanolone treats PPD is not fully understood, it is thought to function as a positive allosteric modulator of GABA-A receptors (83).

Zuranolone enhances current in both the γ subunit containing synaptic receptors and the sigma subunit containing extrasynaptic receptors. Similar to brexanolone, it is thought to be related to its positive allosteric modulation of GABA-A receptors. It was designed to optimize the pharmacologic, pharmacokinetic and pharmacodynamic properties of this class of neuroactive steroid GABA modulators (84).

7.4.2 Pharmacokinetics, Metabolism and Adverse Effects

Brexanolone is administered intravenously over a 60-hour infusion. The volume of distribution is approximately 3 L/kg, indicating extensive distribution into tissues. Furthermore, its plasma protein binding exceeds 99% and is independent of plasma

concentrations. Brexanolone has a terminal half-life of about 9 hours and a plasma clearance rate of 1 L/h/kg (87).

In terms of metabolism, brexanolone is extensively processed through non-CYP pathways, including keto-reduction, glucuronidation, and sulfation. Notably, the three major metabolites are pharmacologically inactive and thus do not contribute to its efficacy. Following administration, brexanolone is eliminated approximately equally in both urine and feces (87).

The most frequently reported adverse reactions to brexanolone in clinical trials included sedation, somnolence, dry mouth, loss of consciousness, and flushing or hot flushes. The FDA has issued black box warnings for brexanolone due to risks of central nervous system depression, loss of consciousness, and the necessity for administration in a specialized care facility (87).

Zurzuvae, the brand name for Zuranolone, is a 14-day oral treatment, taken once daily in the evening with fat containing food (88). Although the absolute bioavailability has not been evaluated, it is known that the volume of distribution of zuranolone following oral administration exceeds 500L, and plasma protein binding is greater than 99.5%. Furthermore, the terminal half-life ranges from approximately 19.7 to 24.6 hours, with a mean apparent clearance of 33L/h (89).

Zuranolone undergoes extensive metabolism, with CYP3A4 identified as the primary enzyme involved. There were no circulating human metabolites greater than 10% of the total drug-related content. Similar to brexanolone, zuranolone is eliminated approximately equally through both urine and feces (89).

Adverse events reported during clinical trials were generally mild to moderate, with the most common being somnolence, dizziness, diarrhea, fatigue, and urinary tract infections (89).

7.4.3 Use in Specific Populations

Although there is no data on the use of brexanolone in pregnant women to assess the risk of major birth defects, miscarriage, or adverse maternal and fetal outcomes, animal studies on other GABAergic-enhancing drugs suggest that brexanolone may pose a risk to fetal health (87).

Animal reproduction studies revealed no malformations in rats or rabbits at plasma levels up to 5 and 6 times the maximum recommended human dose (MRHD). However, developmental toxicities were observed in the fetuses of rats and rabbits at 5 and ≥3 times the MRHD plasma levels, respectively. Additionally, reproductive toxicities were seen in rabbits at ≥3 times the MRHD plasma levels. These effects were absent at plasma levels of 2 times the MRHD in rats and 1.2 times the MRHD in rabbits (87).

A lactation study involving 12 women showed that brexanolone is transferred to breast milk, but the relative infant dose (RID) is low, at about 1-2% of the maternal weight-adjusted dose. Given brexanolone's low oral bioavailability in adults, infant exposure is expected to be minimal. No effects on milk production or adverse reactions in breastfed infants have been reported. Additionally, the safety and effectiveness of brexanolone in paediatric patients have not been established (87).

Available data on zuranolone use in pregnant women from the clinical development program are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal of fetal outcomes. Nonetheless, findings from animal studies indicate that zuranolone may cause fetal harm, consequently pregnant women should be advised of the potential risk to a fetus. Furthermore, oral administration of zuranolone to rats during pregnancy and lactation resulted in developmental toxicity in the offspring, including, perinatal mortality, at maternal exposures similar to that in humans at the MRHD (89).

Data from a clinical lactation study involving 14 women indicated that zuranolone is present in low levels in human milk. However, there are no data on the effects of zuranolone on a breastfed infant and limited data on its effects on milk production. Additionally, the safety and effectiveness of zuranolone in paediatric patients have not been established (89).

7.4.4 Clinical Trials

Brexanolone's efficacy and safety were evaluated through one Phase II trial (202A) and two Phase III clinical trials (202B and 202C) prior to FDA approval. All three studies included patients who were aged 18–45 years, were ≤6 months postpartum, and had either stopped lactating or were not actively breastfeeding (90).

In the 202A study, at the end of the 60-hour infusion, the mean reduction in HAM-D total score was 21 points in the brexanolone group compared to 8.8 points in the placebo group. This significant effect was maintained during the follow-up period, lasting up to 30 days. Additionally, remission rates, defined as a HAM-D total score of ≤7, were notably higher in the brexanolone group (90).

Similarly, studies 202B and 202C demonstrated higher mean reductions in HAM-D total scores for the brexanolone group, with these effects persisting throughout the follow-up period. The remission rates were consistently higher in the brexanolone group than in the placebo group. Furthermore, brexanolone was generally well tolerated, with no deaths, serious adverse effects, or discontinuations occurring in either group (90).

Across all three studies, the antidepressant effect of brexanolone was rapid. The majority of patients (51-70%) achieved remission by the end of the 60-hour infusion, and no patients experienced relapse during the follow-up period (90).

A phase III, double-blind, randomized, placebo-controlled clinical trial was conducted to evaluate the efficacy and safety of zuranolone in treating PPD. The study involved outpatient participants, specifically women aged 18 to 45 years, who were within six months postpartum, diagnosed with PPD, and had a HAMD-17 score of 26 or higher (91).

Participants were administered either a placebo or zuranolone at a dose of 30 mg once daily in the evening with food. The primary efficacy endpoint was the change from baseline in the HAMD-17 total score at day 15. Secondary efficacy endpoints included changes from baseline in HAMD-17 total scores at additional time points, including days 3, 8, 21, and 45 (91).

The study achieved its primary endpoint, showing a significantly greater reduction in the HAMD-17 total score with zuranolone compared to placebo at day 15. Specifically, the zuranolone group showed a reduction of -17.8 points, compared to -13.6 points in the placebo group. Moreover, greater reductions in HAMD-17 scores favoring zuranolone were observed at all measured time points from day 3 through day 45, extending to four weeks after treatment cessation. Overall, zuranolone was generally well-tolerated (91).

7.5 Dextromethorphan + Bupropion

Combination therapies with agents with distinct pharmacological mechanisms have gained recognition as effective alternatives to monotherapy in the treatment of acute depression. Reflecting this approach, the FDA approved Auvelity in November 2022, a novel, rapid-acting oral treatment for MDD in adults. Auvelity is an extended-release combination tablet that integrates dextromethorphan and bupropion, offering a unique therapeutic option (92). To date, there is no available information regarding when the EMA might begin its evaluation of this combination.

This combination's innovative pharmacologic properties confer several advantages over traditional antidepressants. It has demonstrated significant efficacy after just one week of treatment and presents a more favorable side-effect profile compared to other fast-acting antidepressants, such as IN esketamine. Moreover, as an oral formulation, Auvelity can be conveniently self-administered, enhancing patient compliance and accessibility (92).

7.5.1 Mechanism of action

Auvelity combines the mechanisms of action from various antidepressant classes into a single therapeutic agent. Dextromethorphan acts as an uncompetitive NMDA receptor antagonist and sigma-1 receptor agonist, a non-opioid receptor residing specifically at the endoplasmic reticulum (93), while bupropion is an inhibitor of dopamine and noradrenaline transporters. Both compounds increase noradrenaline availability by inhibiting its reuptake and functioning as alpha-4-beta-2 nicotinic (nACh) antagonists. Additionally, bupropion enhances dopamine availability by blocking its reuptake, and dextromethorphan boosts glutamate levels by acting as an NMDA receptor antagonist.

Dextromethorphan also increases serotonin levels by acting as a serotonin reuptake inhibitor and enhancing serotonin activity in the dorsal raphe via sigma-1 agonism (94,95).

The therapeutic benefits of dextromethorphan are limited due to its rapid metabolism by CYP2D6, resulting in a half-life of only 4 hours and subtherapeutic plasma levels. Maintaining adequate levels of dextromethorphan is crucial for sustained NMDA receptor antagonism. Bupropion increases the bioavailability and half-life of dextromethorphan to 22 hours by inhibiting CYP2D6, thereby raising dextromethorphan plasma concentrations (92,96).

7.5.2 Pharmacokinetics, Metabolism and Adverse Effects

Steady-state plasma concentrations of dextromethorphan and bupropion, when administered as Auvelity, are reached within 8 days. The median Tmax for dextromethorphan is 3 hours, while for bupropion, it is 2 hours. The maximum Cmax of the hydroxybupropion metabolite is observed approximately 3 hours post-dose, with the erythrohydroxybupropion and threohydroxybupropion metabolites peaking around 4 hours post-dose. Dextromethorphan exhibits plasma protein binding of about 60-70%, while bupropion binds at approximately 84%. The mean elimination half-life is roughly 22 hours for dextromethorphan and 15 hours for bupropion. In CYP2D6 extensive metabolizers, 37-52% of the orally administered dextromethorphan dose is recovered in the urine, whereas in poor metabolizers, this increases to 45-83% (95).

The most common reported adverse reactions were dizziness, headache, diarrhea, somnolence and dry mouth (92).

7.5.3 Use in Specific Populations

Based on animal studies, Auvelity may cause fetal harm if used during pregnancy, therefore, it is not recommended for pregnant individuals. If a patient becomes pregnant while taking Auvelity, the treatment should be discontinued, and the patient should be counseled on the potential risks to the fetus (95).

Limited data from postmarketing reports on the use of bupropion in lactating patients have not established a clear link to adverse reactions in breastfed infants. However, bupropion and its metabolites are present in human milk. It is unknown whether dextromethorphan is excreted in human milk, and there is no data on its effects on breastfed infants or milk production. Due to findings of neurotoxicity in juvenile rats exposed to a combination of dextromethorphan and quinidine, breastfeeding is not recommended during treatment with Auvelity and for 5 days following the last dose (95).

The safety and effectiveness of Auvelity in paediatric patients have not been established. Since antidepressants, including bupropion, can increase the risk of suicidal thoughts and behaviours, Auvelity is not approved for use in this population (95).

7.5.4 Clinical Trials

The efficacy and safety of dextromethorphan-bupropion for treating MDD were evaluated in a Phase 2, randomized, double-blind, active-controlled trial, with bupropion as the control. The 6-week treatment phase, followed by a safety assessment at week 7, focused on changes in the MADRS total score from baseline to week 6 as the primary endpoint. Patients received either dextromethorphan-bupropion (45/105 mg) or sustained-release bupropion (105 mg) once daily for 3 days, then twice daily. By week 6, the dextromethorphan-bupropion group showed significantly greater reductions in MADRS scores, with notable improvements starting at week 2. Remission and response rates were also significantly higher in this group. The treatment was generally well-tolerated, without adverse events like abuse, weight gain, sexual dysfunction, or psychotomimetic effects (92).

The GEMINI trial, a Phase 3 double-blind, randomized controlled trial, further assessed the safety and efficacy of dextromethorphan-bupropion versus placebo over 6 weeks. Participants were randomly assigned to receive either the active treatment or placebo, with the same primary endpoint as in the Phase 2 trial. Significant reductions in MADRS scores were observed as early as week 1 and continued throughout the study. By week 6, 39.5% of the dextromethorphan-bupropion group achieved remission compared to 17.3% in the placebo group (92).

7.6 Toludesvenlafaxine

Toludesvenlafaxine is a novel chemical entity classified as a triple reuptake inhibitor (TRI), which effectively blocks the reuptake of serotonin, dopamine, and norepinephrine in the CNS. It is a prodrug of desvenlafaxine formulated as an ER oral tablet for the treatment of MDD in adults. This first-in-class medication was initially approved by the Chinese National Medical Products Administration (NMPA) in November 2022 and has been under review by the FDA since 2020 (15,97).

7.6.1 Mechanism of action

Toludesvenlafaxine inhibits the activity of transport proteins responsible for clearing dopamine, serotonin, and norepinephrine from the synaptic cleft, leading to increased levels of these neurotransmitters in the striatum following oral administration. The compound demonstrates high affinity for SERT, NET, and DAT transporters, with IC50 values of 31.4 ± 0.4 nM for serotonin, 586.7 ± 84 nM for norepinephrine, and 733.2 ± 10 nM for dopamine reuptake, respectively (98).

Elevating synaptic dopamine levels in the mesolimbic cortex can enhance the delayed onset effects of antidepressants. Furthermore, increasing dopamine levels in the hypothalamus can alleviate anhedonia, improve cognitive function, and enhance rewarding motivation and goal-directed behaviours, while also reducing sexual dysfunction commonly associated with SSRIs and SNRIs. Toludesvenlafaxine thus presents a potentially improved therapeutic profile for treating depression, with benefits such as a faster onset of action, enhanced cognitive function, and reduced anhedonia and sexual dysfunction (97).

7.6.2 Pharmacokinetics, Metabolism and Adverse Effects

Toludesvenlafaxine is a prodrug that rapidly converts to its primary metabolite, O-desvenlafaxine (ODV), through hydrolysis by ubiquitous esterases i*n vivo*. Pharmacokinetic studies in Wistar rats demonstrated that following an intragastric administration of 8 mg/kg of toludesvenlafaxine, a minimal amount (0.55 ng/ml) of the parent compound was detectable in the blood serum 15 minutes post-dosing and remained at low levels throughout the study. In contrast, its major metabolite, ODV, was present at significantly higher levels (90.89 ng/g tissue) in the blood 15 minutes

post-dosing, peaking at 1 hour and substantially decreasing 12 hours post-dosing. These findings suggest that after absorption, toludesvenlafaxine is rapidly metabolized and redistributed to the brain, particularly the hypothalamus, where ODV concentrations are notably high. The recorded Tmax was 0.48 ± 0.23 hours with a Cmax of 101.23 ± 30.99 ng/ml. Prolonged administration of toludesvenlafaxine over 91 days led to a dose-dependent reduction in serum prolactin levels and an increase in serum testosterone, indicating a low risk of sexual dysfunction and potential improvement in sexual function in patients with depression (97).

The pharmacokinetics of toludesvenlafaxine ER tablets are dose-proportional within the 20 to 200 mg/day range, and dietary intake does not significantly affect its pharmacokinetics. Common adverse reactions include nausea, vomiting, diarrhea, dizziness, and elevated levels of total bilirubin or alanine aminotransferase (99).

7.6.3 Use in Specific Populations

A study evaluated the effects of toludesvenlafaxine at doses of 30 mg/kg, 100 mg/kg, and 300 mg/kg on pregnancy rates in gravid rats and the reproductive function of Sprague Dawley (SD) rats. No significant abnormalities in sperm motility or morphology were observed in any toludesvenlafaxine-treated groups. However, there was a dose-dependent increase in sperm concentration and count across the treated groups (100).

Regarding pregnancy outcomes, a reduction in the number of implantation sites was noted in female rats treated with 300 mg/kg of toludesvenlafaxine, as well as in untreated females. This reduction was linked to fewer viable fetuses, a higher pre-implantation loss rate, and an increase in both total pregnancy losses and overall loss rate. These results suggest that toludesvenlafaxine at a dose of 300 mg/kg may interfere with processes such as sperm-egg fusion, gamete and zygote formation, and implantation. However, no significant changes were observed in fetal resorption or fetal death rates in gravid rats treated with toludesvenlafaxine, indicating that toludesvenlafaxine does not appear to affect embryo development (100).

7.6.4 Clinical Trials

In a phase 2, multicenter, randomized, double-blind, placebo-controlled, dose-finding trial, the efficacy and safety of orally administered toludesvenlafaxine ER were evaluated in 260 patients with MDD. Participants received fixed doses of toludesvenlafaxine (40 mg/day, 80 mg/day, 120 mg/day, or 160 mg/day) or placebo for 6 weeks. The primary outcome was the change in the total HAMD-17 score from baseline to week 6. At the trial's conclusion, all groups receiving toludesvenlafaxine showed significant improvement compared to placebo, and the drug was generally well tolerated (99).

Additionally, a phase 3 trial conducted in China enrolled 558 adults with MDD to further assess toludesvenlafaxine's efficacy and tolerability. Patients were treated with either 80 mg or 160 mg of toludesvenlafaxine, or placebo, over 8 weeks. This trial demonstrated significant improvement in both primary and secondary outcomes for patients receiving the active drug compared to placebo. Notably, MADRS scores decreased significantly at week 8 compared to both baseline and placebo in the 80 mg and 160 mg groups. Secondary endpoints, including the total HAMD-17 score, also showed significant improvement versus placebo by the end of week 8. Most adverse events reported were mild to moderate in severity (99).

7.7 Psilocybin

To date, more than 180 species of mushrooms containing psilocybin have been identified. These mushrooms have played a role in various cultures across every inhabited continent for at least 7,000 years (101).

Psilocybin was first isolated in 1959 from the *Psilocybe mexicana* species, and the following year, the Swiss pharmaceutical company Sandoz, which was already marketing LSD for psychiatric conditions, introduced a 2 mg psilocybin tablet named Indocybin® as an adjunct to psychotherapy (101).

However, psilocybin was later classified as a controlled substance, leading to its prohibition. In 2004, research into its therapeutic potential resumed, particularly for treating psychological suffering related to cancer. Today, psilocybin is the most

extensively studied psychedelic substance in clinical settings and has been designated a "breakthrough therapy" by the FDA for treating MDD (101). The EMA is actively involved in the regulatory landscape of psychedelic substances, including psilocybin. While psilocybin is currently illegal for recreational use in the EU, the EMA is taking steps to explore its potential therapeutic applications (102).

7.7.1 Mechanism of action

Psilocybin is a substituted indolealkylamine that belongs to the group of hallucinogenic tryptamines (103). Like most classic psychedelics, psilocybin acts as a non-selective serotonin agonist, with its psychoactive effects primarily linked to the agonism of the 5-HT2A receptor subtype. Psilocin, the active metabolite of psilocybin, binds most strongly to the 5-HT2A receptor and, to a lesser extent, to the 5-HT1A receptor, while exhibiting relatively lower affinity for other serotonin receptors. Although the exact mechanism of psilocybin is not fully understood, its psychological effects are largely attributed to its interaction with the 5-HT2A receptor, as studies have shown that the 5-HT2A receptor antagonist ketanserin can reverse psilocybin-induced effects (104).

Psilocybin induces dose-dependent changes in consciousness that typically last between 3 and 6 hours. Low doses may cause drowsiness, while moderate doses lead to an altered state of consciousness, and higher doses trigger intense psychedelic experiences. The effects of psilocybin include changes in sensory perception, visual distortions or hallucinations, and synesthesia. It can also affect attention, leading to slower reaction times, and alter thought processes, sometimes causing feelings of derealization and depersonalization. Additionally, psilocybin tends to enhance positive mood states and increase emotional empathy (101).

7.7.2 Pharmacokinetics, Metabolism and Adverse Effects

Following oral administration, approximately 50% of psilocybin is absorbed, with significant amounts detectable in plasma within 20 to 40 minutes. Psilocybin is rapidly dephosphorylated into its active metabolite, psilocin, by alkaline phosphatase and nonspecific esterases in the intestinal mucosa. Maximum plasma concentrations are typically achieved after 80 to 100 minutes. The psychological effects correspond to

plasma psilocin levels of 4–6 mcg/mL, with peak effects occurring 70 to 90 minutes after oral doses of 8 to 25 mg (103,104).

Psilocybin has a shorter half-life when administered intravenously (74.1 ± 19.6 minutes) compared to oral administration (163 ± 64 minutes). Its metabolites are primarily eliminated through the kidneys (103).

The role of specific CYP enzymes in the metabolism of psilocybin remains unclear due to limited human pharmacokinetic studies. However, psilocin is glucuronidated by UDP-glucuronosyltransferases (UGTs), with UGT1A10 in the small intestine and UGT1A9 in the liver showing the highest activity in the formation of psilocin glucuronide (104).

Among psychedelics, psilocybin is often noted for its relatively favorable safety profile. In controlled settings, acute adverse effects may include headaches, nausea, vomiting, anxiety, and transient psychotic symptoms. Users might also experience derealization and depersonalization, as well as temporary increases in blood pressure and heart rate. However, these effects are generally brief and transient (101).

7.7.3 Use in Specific Populations

There are currently no human or animal studies that investigate the safety of psychedelics during the postpartum period, particularly in relation to breastfeeding (105). Psilocybin-assisted psychotherapy (PAP) may offer a potential solution to the sense of disconnection that mothers often feel from themselves and their infants in cases of PPD (105).

Although trials have yet to examine the pharmacokinetics of psilocybin and psilocin in breastmilk, psilocin's lipophilicity and low molecular weight may allow its passage into breastmilk. However, its acidic pH of 5.2 and binding affinity to human serum albumin may reduce the likelihood of significant transfer (105).

In single-dose studies, psilocybin is undetectable in urine after 24 hours, suggesting women could abstain from breastfeeding for 48 hours post-administration. By this time,

nearly all psilocybin would be cleared from the body, given its half-life of approximately three hours. Since only 4% of adverse effects from drug exposure in breastmilk occur in infants older than six months, restricting psilocybin use to after this period and advising a 48-hour breastfeeding pause could further minimize risks (105).

Psychedelic therapies hold potential for older adults facing serious medical conditions, such as post-traumatic stress disorder (PTSD), depression, prolonged grief disorder, substance use disorders, and dementia. However, research specifically addressing older adults with significant comorbidities remains limited, making it difficult to establish the safety of these treatments in this population. Further investigation is needed to better understand the safety and efficacy of psychedelics in older adults, particularly since very few have been included in clinical trials of these agents. Given the alterations in pharmacokinetics and pharmacodynamics in older individuals, along with the high prevalence of polypharmacy in this age group, ensuring drug safety is a complex challenge that requires careful consideration (106).

Many conditions targeted by psychedelic research in adults also affect children and adolescents. However, research involving minors requires strict ethical guidelines, including careful assessment of psychiatric, substance use, and trauma histories. A key concern is that these substances may cause lasting brain changes, potentially altering personality traits. While such effects have been documented in adults, their impact on the developing personalities of younger individuals remains uncertain (107).

7.7.4 Clinical Trials

Psilocybin is currently under investigation for its potential in treating mood and anxiety disorders, substance use disorders, and psychiatric symptoms associated with end-of-life care (101).

A phase II, double-blind, randomized controlled trial led by Carhart-Harris evaluated the comparative efficacy of psilocybin and escitalopram in 60 patients diagnosed with MDD over a six-week period. One cohort received two doses of 25 mg psilocybin, administered three weeks apart, alongside a daily placebo for six weeks, while the other

cohort received two 1 mg doses of psilocybin plus six weeks of daily oral escitalopram. Both groups received concurrent psychological support (108).

The trial demonstrated significant reductions in depressive symptoms across both groups, as measured by the Quick Inventory of Depressive Symptomatology - Self-Report (QIDS-SR) scale, though no statistically significant differences in overall therapeutic efficacy were observed. Nonetheless, the psilocybin group exhibited superior outcomes in key psychometric measures, including a higher response rate (70% vs. 48%) and a greater proportion achieving symptomatic remission (57% vs. 28%) (108).

A randomized, waiting list-controlled clinical trial was conducted to examine the effects of psilocybin therapy in patients with MDD. The study involved 27 participants who were randomly assigned to either an immediate treatment group or a delayed treatment group. Each participant received two psilocybin sessions, 20 mg/70 kg in the first session and 30 mg/70 kg in the second session, within a psychotherapy context.
The results indicated a significant reduction in depressive symptoms for those who received psilocybin, as measured by the Hamilton Rating Scale for Depression (HDRS-Grid). Notably, 71% of participants experienced a substantial clinical response, and 54% achieved symptomatic remission four weeks after the intervention (109).

Additionally, psilocybin demonstrated a low potential for addiction and a minimal adverse event profile, suggesting therapeutic benefits with fewer risks compared to ketamine (109).

7.7.5 Psilocybin Assisted Psychotherapy (PAP)

Although it has not yet received approval from the EMA or the FDA, the Therapeutic Goods Administration (TGA) in Australia approved psilocybin for therapeutic use in July 2023. This approval allows authorized psychiatrists to prescribe psilocybin for patients with TRD. While psilocybin is not considered a first-line treatment, it may be used alongside psychotherapy for patients who have not responded to other forms of treatment for depression (110).

To ensure safety, psilocybin administration must be supervised by authorized psychiatrists in controlled clinical settings with intensive professional support. Patients are not permitted to use psilocybin outside these supervised sessions (110).

PAP follows a protocol similar to KAP. While both psilocybin and ketamine offer rapid antidepressant effects, their therapeutic impact differs significantly. Ketamine's effects typically last from a few days to two weeks, whereas the benefits of psilocybin therapy have been shown to persist for at least four weeks. Additionally, psilocybin exhibits a lower potential for addiction and has a minimal adverse event profile, suggesting it may offer therapeutic advantages with fewer associated risks compared to ketamine (109).

PAP is often perceived as more favorable by patients than widely prescribed antidepressant medications, largely due to its milder side effect profile. Another key advantage is the lasting effectiveness of psilocybin therapy after just one or a few administrations, compared to conventional antidepressants, which require daily dosing for sustained effects (109).

Recently in Portugal, the EU decided to fund a research initiative, which includes the Champalimaud Foundation (CF), focused on the application of psychedelic therapy for treatment-resistant mental disorders in palliative care settings. This is the first time the EU has supported a multicenter clinical trial for a psychedelic treatment (111).

The study, PsyPal, a randomized, controlled, multicenter trial is set to begin recruiting patients in 2025. Its aim is to investigate an innovative approach to alleviate severe psychological and existential distress in individuals with advanced-stage illnesses.
Participants will undergo three preparatory sessions, followed by two treatment sessions with either psilocybin or a placebo. PsyPal integrates psychotherapy with pharmacotherapy to meet the complex needs of these patients (111).

8 Future Perspectives

A major barrier to advancing psychiatric treatments is the high cost of drug development. Industry-sponsored trials often focus on regulatory approval, neglecting key clinical questions such as identifying optimal treatments for specific patient populations. Trials commonly exclude patients with chronicity, TRD, severe symptoms, substance use, psychosis, or bipolarity - factors prevalent in real-world practice. As a result, many patients who represent the complexity of depression are not included in antidepressant trials (112).

Models predicting individual responses to pharmacotherapy seem more promising than those for general recovery or remission (14). Exploring new antidepressant targets may lead to medications with better tolerability for specific patient subgroups. This progress requires greater diversity in clinical trials and collaboration between companies for large-scale studies, ultimately resulting in more personalized treatments (112).

Providing ineffective therapies has serious individual and societal consequences, including distress, suicide risk, productivity loss, and healthcare costs. Optimizing measurements of neurobiological and clinical depression parameters is essential to understand depression's biology and treatment resistance mechanisms. Establishing biomarker relationships with depressive disorders could greatly reduce the individual and societal burden of depression. Although there are many potential biomarkers for depression, several challenges must be overcome before they can be applied in clinical settings (68).

Additionally, further research is necessary, particularly for long-term use of psychedelics and NMDA modulators, to establish optimal dosing and frequency. So far, most advancements have focused on MDD and TRD in adults, yet a key challenge remains extending trials to older adults, children, and adolescents, especially where morbidity and treatment complexity are growing concerns. In addition, clinicians and patients worry about the misuse of novel agents like ketamine and psilocybin. Therefore, data on medicinal dosing compared to recreational use is essential. Moreover, long-term registries might help track potential risks for those using these substances, providing a clearer understanding of their safety profile (14).

Currently, five public psychiatry services in Portugal use KAP for treatment-resistant depression. To ensure ethical and safe practices for all patients undergoing KAP, these services must submit their clinical protocols to the respective institutional pharmacy and ethics committees (113).

For KAP expansion across psychiatry departments, education on psychedelics for mental health professionals is crucial. Therapists must guide patients on safety and provide information in an educational context (114).

However, many mental health professionals lack the necessary knowledge. Implementing training in medical schools or specialized programs could better equip therapists. Creating multidisciplinary supervision teams in services practicing psychedelic-assisted psychotherapy could also mitigate potential issues (114).

Regarding psilocybin, with the conclusion of Phase IIb clinical trials, the initiation of Phase III trials using psilocybin for TRD marks a significant step before submission for approval by the relevant regulatory authorities. If the results and safety profile remain acceptable, psilocybin-assisted therapy is expected to receive approval in the near future (101).

For these novel treatments - ketamine, its enantiomer, and psilocybin, to gain wider acceptance, their effectiveness must be compared to established therapies, and additional studies should focus specifically on the adverse consequences of their broader use, including special populations (115).

9 Conclusion

A wide range of antidepressants is available, but responsiveness and relapse are still a problem. While progress has been made in developing new pharmacological treatments for MDD, challenges remain, particularly regarding long-term safety, tolerability, and real-world applicability. Promising alternatives, such as gepirone, dextromethorphan-bupropion and toludesvenlafaxine, have emerged for MDD, while brexanolone and zuranolone represent important therapeutic options for PPD.

Additionally, psychedelic-assisted therapies, such as psilocybin, ketamine and more recently esketamine with its easier administration route, expand the treatment landscape, providing a new possibility for TRD with the last reflecting an evolving therapeutic landscape. These therapies have shown encouraging results, but further long-term studies are needed to ensure safety, particularly regarding neurocognitive effects. While their rapid-acting and neuroplasticity-enhancing properties introduce innovative approaches to MDD, concerns around misuse and ethical implications must be addressed through appropriate regulatory measures.

The rise of personalized medicine and biomarkers marks a significant step in depression treatment, enabling more individualized approaches that could improve patient outcomes. However, research in this area is still emerging, and further studies are necessary to validate these biomarkers in predicting treatment responses.

Future research should prioritize developing new therapeutic agents and refining existing treatments to improve safety, tolerability, and patient-centred outcomes. By advancing neuroplasticity mechanisms and rapid-onset treatments alongside personalized medicine and biomarker approaches, research efforts can offer more effective, enduring solutions for MDD, ultimately reducing the burden on individuals and society.

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