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Final dissertation

Evidence-based treatment for depression: an update

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ABSTRACT

Introduction: Depression is a common and debilitating mental disorder that affects millions of people worldwide. The current treatments for depression, such as pharmacotherapy and psychotherapy, have moderate effectiveness and there is a lot of possibility for improvement. Therefore, there is a need for developing more effective and personalized interventions that target the biological, psychological, and social factors involved in depression.

Methods: This work reviews the recent advances in the understanding of the etiopathogenesis of depression, and how the design of integrated treatment approaches that combine different modalities, could potentially change therapy of depression and quality of life of the patients. The focus was on reviewing and analyzing literature.

Results and conclusion: There is a significant improvement in the approaches and strategies towards treating major depressive disorder in the past decade. The possible future direction of the integrated treatment of depression can offer a more comprehensive and tailored solution for addressing the complex and heterogeneous nature of this disorder. With the aim to personalize treatment approaches towards patients' needs, new parameters like severity of depression are examined in the pursuit of a more specific treatment in a stepped-care approach.

CHAPTER ONE: DEPRESSION

1.1 Depression: clinical characteristics and epidemiology

Major Depressive Disorder (MDD) is a common condition that has a severe impact on mental and social well-being and that lowers quality of life (Filatova et al., 2021). World Health Organization reported in 2008 that major depressive disorder was the third leading cause of disease burden world-wide and projected that the disease will rank first by 2030 (Figure 1.1) (World Health Organization, 2008). In practice, its detection, diagnosis, and treatment pose challenges for clinicians because of its diverse symptoms, unclear course and outcome, and inconsistent response to therapy (Malhi & Mann, 2018).

2004 Disease or injury	As % of total DALYs	Rank		Rank	As % of total DALYs	2030 Disease or injury
Lower respiratory infections	6.2	1		1	6.2	Unipolar depressive disorders
Diarrhoeal diseases	4.8	2		2	5.5	Ischaemic heart disease
Unipolar depressive disorders	4.3	3		3	4.9	Road traffic accidents
Ischaemic heart disease	4.1	4		4	4.3	Cerebrovascular disease
HIV/AIDS	3.8	5		5	3.8	COPD
Cerebrovascular disease	3.1	6		6	3.2	Lower respiratory infections
Prematurity and low birth weight	2.9	7		7	2.9	Hearing loss, adult onset
Birth asphyxia and birth trauma	2.7	8		8	2.7	Refractive errors
Road traffic accidents	2.7	9		9	2.5	HIV/AIDS
Neonatal infections and other[a]	2.7	10		10	2.3	Diabetes mellitus
COPD	2.0	13		11	1.9	Neonatal infections and other[a]
Refractive errors	1.8	14		12	1.9	Prematurity and low birth weight
Hearing loss, adult onset	1.8	15		15	1.9	Birth asphyxia and birth trauma
Diabetes mellitus	1.3	19		18	1.6	Diarrhoeal diseases

Figure 1.1 Ten leading causes of burden of disease worldwide, in 2004 (left) and 2030 (right). *Adapted from The global burden of disease, 2004 update.*

Depressed mood is characterized by hopelessness and persistent feeling of sadness, where the affected person experiences a loss of interest and is not able to derive pleasure from the once enjoyable activities (Marx et al., 2023). According to the Diagnostic and Statistical Manual of

Mental Disorders, 5th edition (DSM-5), for the MDD to be diagnosed, symptoms need to be present almost every day, during most of the day, for at least two weeks. For the MDD to be diagnosed, persistent depressed mood and/or loss of interest or pleasure (anhedonia) must be present, as well as at least five of the following symptoms:

- Weight loss or gain, persistent change in appetite
- Persistent insomnia or hypersomnia
- Persistent psychomotor retardation or agitation observable by others
- Persistent fatigue or loss of energy
- Persistent feelings of worthlessness, excessive or inappropriate guilt which can be delusional
- Persistent difficulty concentrating or making decisions
- Recurrent thoughts of death or suicide with or without a specific plan

MDD usually manifests in episodes of at least two weeks in duration which usually reoccur during lifetime (DSM-5, 2013). Symptoms disrupt various areas of functioning, such as the social, personal and work areas (DSM-5, 2013).

An estimated 3.8% of the population experience depression, including 5% of adults (4% among men and 6% among women), and 5.7% of adults older than 60 years (Global Health Data Exchange, 2023). Approximately 280 million people in the world have depression (Global Health Data Exchange, 2023). Depression is about 50% more common among women than among men (Global Health Data Exchange, 2023). Worldwide, more than 10% of pregnant women and women who have just given birth experience depression (Woody et al., 2017).

For a condition as widespread as MDD, it is also important to examine the available treatments, as well as recognize the importance of prevention. A major drawback in reducing the MDD rate is that it is often undiagnosed and untreated due to variety of reasons (Wainberg et al., 2017).

Lack of resources, social stigma, and ineffective therapies are just some of the reasons that can explain the current state (Wainberg et al., 2017). Diagnosing and treating MDD is particularly difficult because the somatic symptoms and comorbid conditions of MDD are frequently encountered in actual clinical practice (Sato, 2013).

1.2 Etiopathogenesis of depression

Although the etiopathogenesis of depression is still unclear, it is most likely a consequence of an interplay between genetic, biological, environmental, and psychological factors (Cui et al., 2024). Different hypotheses have been proposed to understand the causes of MDD.

1.2.1 Neurobiological bases

Among the numerous evidence of neurobiological alterations in depression, dysfunctions in brain regions that are involved in regulating emotions seem to be a promising venue for studying the etiopathogenesis of the disorder (Drevets et al., 2008). Specifically, the prefrontal cortex, which is involved in higher cognitive functions, controls emotional responses and stress reactivity through connections to the limbic system brain regions, such as the amygdala, the hippocampus, and the nucleus accumbens (Drevets et al., 2008). These regions are connected to emotions, learning, and reward (Drevets et al., 2008). Impairments in the connectivity between the prefrontal cortex and the limbic system may lead to difficulties in mood regulation, decrease in positive and increase in negative emotions in depressed patients (Drevets et al., 2008). Effects of impaired function of the medial prefrontal cortex and related limbic structures can result in the disturbances of emotional processing, cognitive performance, neurotransmission, autonomic regulation and neuroendocrine responses that are associated with mood disorders (Drevets et al., 2008).

The anterior cingulate cortex, another brain region that is affected in depression, is located in the middle part of the prefrontal cortex (Mayberg et al., 1999). The anterior cingulate cortex participates in conflict, error detection, monitoring, and emotional regulation (Mayberg et al., 1999). It also contributes to social cognition and empathy, which are essential for keeping interpersonal relationships (Mayberg et al., 1999). Depressed patients have shown increased activity in the anterior cingulate cortex, especially when they are exposed to negative stimuli (Mayberg et al., 1999). This may show a heightened awareness of emotional distress and a reduced capacity to control negative emotions (Mayberg et al., 1999).

The hippocampus, a brain area that is essential for creating and strengthening memories, also shows changes in depression in structure and function in neuroimaging studies (Lee et al., 2012). Depressed patients have shown lower hippocampal volume and neurogenesis, which may lead to cognitive problems, such as memory loss, and emotional problems, such as anhedonia (Lee et al., 2012). Also, clinical studies have shown that repeated stress during recurrent depressive episodes may result in cumulative hippocampal injury and volume loss (Sheline et al., 1999).

Some other regions in the brain that can be correlated to depression in terms of increased or decreased volume and/or increased or decreased function, are subgenual cingulate, orbitofrontal cortex, ventral striatum, pituitary and amygdala (Aan Het Rot et al., 2009). Depression-related changes of volume and activity of brain regions are shown in Figure 1.2.

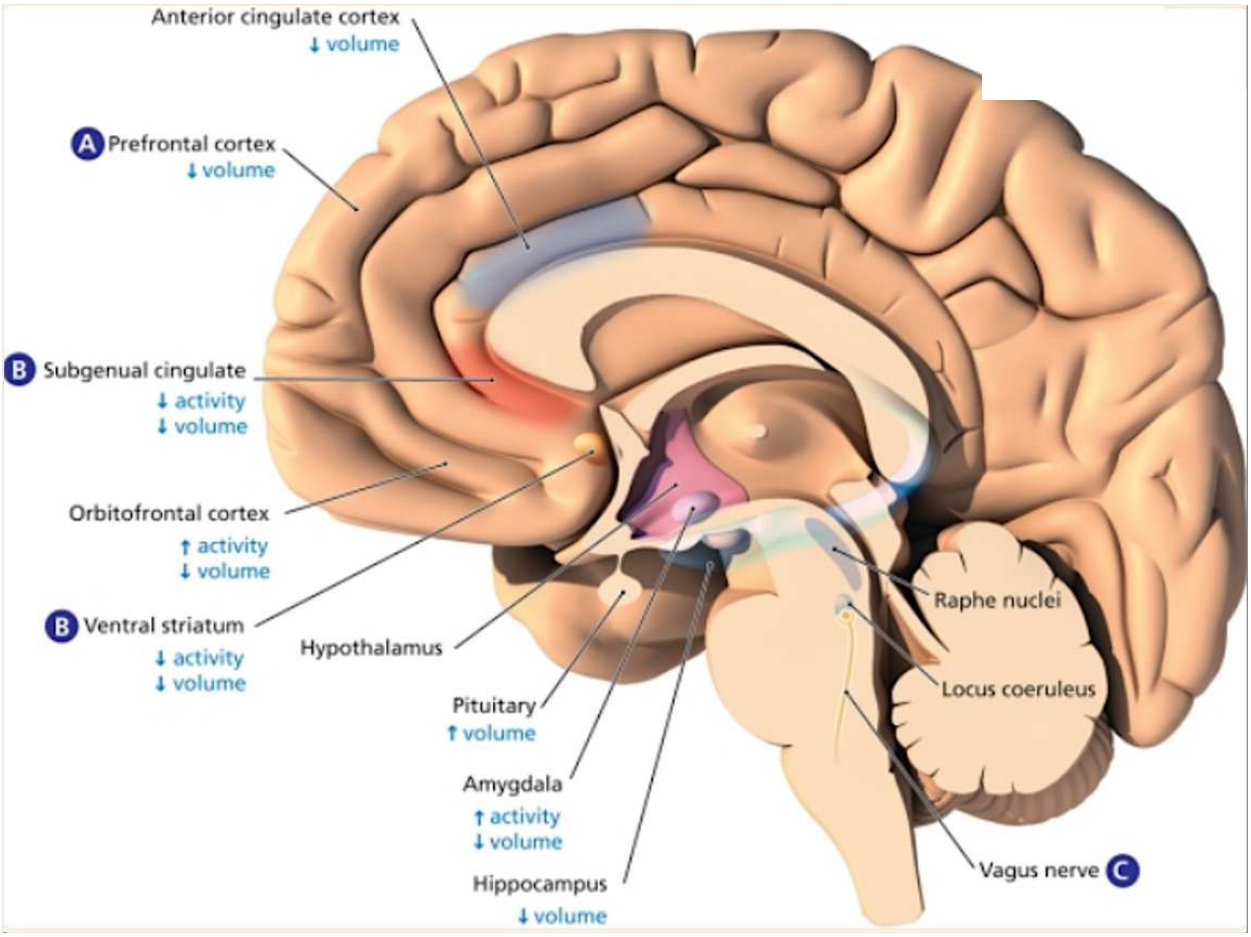

Figure 1.2 Structural and functional brain abnormalities in patients with major depressive disorder. *Adapted from Aan Het Rot et al., 2009.*

1.2.2 Monoamine hypothesis

Imbalances of the neurotransmitters norepinephrine, serotonin, and dopamine are linked to depression (Jesulola et al., 2018). Norepinephrine travels from the brain stem to most brain areas and affects the prefrontal cortex, working memory, behavior, attention and emotional memory (Jesulola et al., 2018). Serotonin reaches all brain areas and is a multifunctional neurotransmitter in the brain (Jesulola et al., 2018). Dopamine influences reward and motivation functions, working memory and attention (Jesulola et al., 2018).

These three systems are thought to have a role in influencing many depressive symptoms, such as low mood, alertness, motivation, fatigue and psychomotor changes (Jesulola et al., 2018).

Changes in serotonin levels are related to behavioral and bodily functions (e.g., appetite, sleep, sex, pain, temperature and rhythm) that change in depression, where lower serotonin levels have been found in depressed brains compared to non-depressed brains (Jesulola et al., 2018). Dopamine abnormalities negatively influence motivation and concentration, whereas dopamine transmission may improve cognitive outcomes like decision making and motivation (Jesulola et al., 2018). Also, low norepinephrine levels (along with serotonin and dopamine) affect many depressive symptoms including sex, appetite, concentration and motivation (Jesulola et al., 2018).

Many brain functions rely on different neurotransmitters that act on the pre-and post-synaptic membranes of many neurons in the brain, and studies suggest that some neurotransmitters are involved in depression onset (Jesulola et al., 2018). The *monoamine hypothesis* suggests that reduced levels of the main monoamine neurotransmitters (serotonin, norepinephrine, and dopamine) lead to less neurotransmission, which may cause depression (Barchas & Altemus, 1999). The lack of monoamines in depression could also happen because of lower protein transporter functions and problems in the neurotransmitter receptor function (Jesulola et al., 2018). Low serotonin levels can hamper mechanisms preventing the recovery from depression but do not seem to lower mood in all vulnerable individuals (Cowen & Browning, 2015). Knowledge about the mechanism of action of neurotransmitters led to the development of drugs, known as antidepressants, which alter the level of neurotransmitters (Taylor et al., 2005). Antidepressants will be discussed in pharmacotherapy of depression in Chapter 2 of this study.

For the past few decades, the monoamine hypothesis of depression has been the dominant framework for explaining both the causes of depression and the effects of pharmacological treatments, and it has resulted in the development of several antidepressant drugs (Massart et al., 2012).

However, the current monoamine theory has serious shortcomings, and other factors, such as abnormalities in the hypothalamic–pituitary–adrenal axis, as well as neurodegenerative and inflammatory changes, may also be involved in the origin of mood disorders (Massart et al., 2012). Furthermore, new evidence has recently shown that epigenetic mechanisms such as histone modifications and DNA methylation could influence various pathways leading to depression-like behaviors in animal models (Massart et al., 2012).

Additional biological models

In hypothalamic-pituitary-adrenal (HPA) axis dysfunction hypothesis high levels of glucocorticoids play a core role in the pathogenesis of MDD, and thyroid hormone and estrogen are also involved in functions of the HPA axis (Keller et al., 2017). In some patients, stress leads to long-term elevated glucocorticoids, resulting in synaptic structural changes and remodeling, and the stress-induced hyperactivity of the HPA axis leads to negative feedback imbalance of the HPA axis (Keller et al., 2017).

The inflammatory hypothesis explains that the neuro-inflammation induced by reactive oxygen species, inflammatory cytokines and inflammasomes activation is suggested to promote the occurrence of MDD (Cui et al., 2024). The brain has weak antioxidative defenses and a high oxygen consumption rate, making it particularly susceptible to oxidative stress (Early et al., 2018). Inflammasomes in microglia can be activated by reactive oxygen species, which causes inflammatory cytokines, including TNF-α, IL-1β, and IFN-γ to be produced (Early et al., 2018).

In the genetic and epigenetic anomaly hypothesis some genes are susceptible in the patients with MDD. Over 100 gene loci, including those associated with presynaptic vesicle trafficking,

dopaminergic neurotransmission (a primary target of antipsychotics), glutamate ionotropic receptor kainate type subunit 5, and metabotropic glutamate receptor 5, and neuronal calcium signaling such as calcium voltage-gated channel subunit alpha1 E and calcium voltage-gated channel auxiliary subunit alpha2 delta1, are found to be associated with an increased risk of MDD by genome-wide association studies (Wray et al., 2018; Power et al., 2017; Huang et al., 2019). On the other hand, genetic variants are expected to have only minor effects on the overall risk of disease, and various hereditary factors combined with environmental factors such as stress are likely more essential for the development of MDD (Cohen-Woods et al., 2013).

1.2.3 Cognitive models

At the center of cognitive models of depression is the notion that individuals' thoughts, beliefs, attitudes, and interpretations, along with how they approach and remember information, have a direct influence on their risk of developing depression (Gotlib & Joormann, 2010). The emphasis is on the fact that it is not the situation the individuals find themselves in that is relevant, but that how the individual interprets the situation affects their mood, and then as a result, also their behavior (Gotlib & Joormann, 2010).

Beck's Cognitive Model is the most important cognitive model given its important influence on depression treatment (Beck, 1976). The idea is that biased interpretations and dysfunctional automatic negative thoughts get activated spontaneously in the individual with depression (Beck, 1976). Beck's cognitive triad model identifies three aspects of this thinking: negative thoughts about the self, the world, and the future (Beck, 1976). These automatic negative thoughts are characterized by feelings of worthlessness and hopelessness, which interfere with how information is being processed, leading to cognitive distortions (Beck, 1976). Automatic negative thoughts can influence memory and perception of the events and may serve as a mechanism to

maintain the depressed state (Beck, 1976). Their materialization may derive from childhood experiences, from traumatic events, or from parent neglect, abuse, or overprotection (Beck, 1976). Later in life, those schemas could be activated and form negative biases filtering information contrary to their premises (Beck, 1976). Beck defined 12 cognitive distortions (Figure 1.3) (Beck, 1979). For example, with "All-or-nothing" distortion, one could easily turn any less than favorable situation into a disaster and add more evidence to the knowledge negative thoughts are based on (Beck, 1979). Depressed individuals proved to have higher levels of cognitive distortions, and it has been shown that a causal relation exists particularly in women, where having negative cognitive styles resulted in more negative life events (Alloy et al., 2006).

Another important cognitive-behavioral model is the *Learned Helplessness Model*, which posits that depression is a result of a perceived lack of control over situation outcomes (Seligman, 1975). Depression is learned when an individual repeatedly experiences negative outcomes of events that seem unavoidable (Seligman & Maier, 1967). This causes them to learn to expect future lack of control, believing they are incapable of influencing their environment (Abramson et al., 1978). The model involves cognitive processes connected to the way individuals perceive and interpret their environment (Abramson et al., 1978). This theory presents with some limitations, as it could not explain why, when confronted with an uncontrollable event, some individuals developed depression while others did not. To address these limitations, Abramson developed the hopelessness theory, which builds upon attribution theory (Abramson et al., 1989). In this model, attribution style is important, as it relates to how people attribute a cause to their helplessness. This cause can be stable or unstable, global or specific, and internal or external (Abramson et al., 1978). Depressed individuals tend to attribute the cause of their helplessness to internal (personal), stable (unchanging), and global (affecting many areas of life) causes (Abramson et al., 1978).

All-or-Nothing Thinking	Viewing situations in a binary, as black and white view. For example, thinking that anything less than an A+ is a failure.
Overgeneralization	Generalizing a single incident into a broader truth. For example, thinking one is a bad parent if they lost a temper with a child once.
Catastrophizing	Always expecting the worst scenario to happen in any situation. For example, thinking that failing a test would mean never graduating.
Selective Abstraction	Focusing only on negative details and ignoring the broader picture. For instance, dwelling on one bad remark and ignoring all the compliments.
Disqualifying the Positive	Rejecting the positive aspects by disregarding they “don’t count.” For example, believing you passed the test because you are lucky or it was easy.
Mind Reading	Believing others are thinking negatively about you for no reason. For instance, believing a colleague thinks you’re bad at your job without them inferring that.
Fortune Telling	Strongly believing that a negative outcomes will happen. For example, believing with certainty that one’s plane will crash.
Magnification and Minimization	Exaggerating negative aspects of events and disregarding positive. For example, thinking the party is ruined because you forgot the candles.
Emotional Reasoning	Believing that current emotions are reflection of the reality. For example, believing feeling worthless means you are.
Should Statements	Believing how things should be and pressuring oneself to fulfil the expectations. For instance, "I should always be productive"
Labeling and Mislabeling	Labelling oneself or others to describe them. For example, calling yourself a "loser" and looking to justify it through experience.
Personalization	Taking responsibility for events that not under one’s control. For example, blaming yourself for your friend’s sickness worsening.

Figure 1.3 Cognitive distortions defined by Beck (1979).

In addition, the *Rumination Theory* proposes that the duration of depressive symptoms is directly influenced by the way people respond to these symptoms. Rumination is a process in which people reflect on the causes, consequences, emotional states and meanings of their negative emotional experiences in isolation (Nolen-Hoeksema, 1991). By engaging in rumination, the individual is prevented from problem-solving and engaging in actions that would potentially assist them in leaving the depressive mood (Nolen-Hoeksema, 1991). This is in line with findings that individuals with ruminative response styles endured significantly longer episodes of depressed mood (Nolen-Hoeksema, 1991).

Another model related to rumination is the *Self-Regulatory Executive Function Model* which focuses on top-down control and maintenance of the disorder and depends on the individual's thinking style and strategies (Wells, 2000). It relies on metacognition, particularly on flawed knowledge about interpreting one's own thinking and emotional states (Wells, 2009). The style called Cognitive Attentional Syndrome consists of worry, rumination, and maintains the individual in a mode of constant threat monitoring (Wells, 2009). The model posits that the individual begins by using rumination as a coping strategy to analytically think about the negative state they are experiencing in order to find a solution (Wells, 2009). The consequence of thinking positively about rumination and utilizing it to address problems results in the negative consequences of rumination and negative ideas, which in combination with negative beliefs about the uncontrollability and harmfulness of thoughts and emotions can lead to the development of a disorder (Wells, 2009).

1.2.4 Social and environmental factors

Socioeconomic status has a great impact on individuals' quality of life in general. The greater the extent of social inequalities, the more they represent a risk factor (Nutakor et al., 2023). Living in poverty is associated with a set of challenges that negatively influence mental health (e.g. financial stress, lack of resources), and it is also important to acknowledge the bidirectional relationship that exists between mental health and socioeconomic status (Knifton & Inglis, 2020). Having mental disorders can potentially lead to having a lower income and unemployment, which could in turn result in poverty, and in potentially developing a mental disorder (World Health Organization, 2014). Unemployment is not merely correlated to distress but can represent the cause

of its development. Unemployment can cause financial hardship, loss of social identity and routine, which can result in development of depression (Paul & Moser, 2009).

Family dynamics influence the development of depression both for children and adults (Beardslee et al., 1998). During development, parents assume a crucial role in the development of their children (Beardslee et al., 1998). Childhood experiences are shaped both by environmental and genetic factors, and the effects extend beyond childhood (Beardslee et al., 1998). If the parents experience mental health issues, the children are at a greater risk for their development (Beardslee et al., 1998). It was observed that a child with a mentally ill parent has a 40% chance of experiencing an episode of major depression by the time they are 20 years old (Beardslee et al., 1998). Even if not qualifying for depression, issues with attachment, functioning, increased guilt, and interpersonal relations were reported (Beardslee et al., 1998).

Dysfunctional marriages can result in higher levels of distress in both men and women (Whisman, 2007). Marital distress was found to be associated with major depressive disorder, and that association increased in magnitude with increasing age (Whisman, 2007). Exposure to violence can contribute to depression development through both chronic stress and trauma. Also, exposure to violence between parents and physical punishment are two predictors for partner violence (Ehrensaft et al., 2003). The probability of injury of a partner is the direct effect of childhood physical abuse (Ehrensaft et al., 2003). If the individual has been abused or neglected during childhood, a significant risk for the development of depression later in life exists for both men and women, even decades after the occurrence of adverse childhood experiences (Chapman et al., 2004).

Unlike continuous influences like family dynamics and socioeconomic status, certain life events can contribute to depression as well. For instance, losing a loved one can represent a trigger

for a type of depression called bereavement-related depression (Kendler et al., 2008). Compared to individuals with depression related to other stressful life events, those with bereavement-related depression are more likely to be female and slightly older, have significantly lower levels of neuroticism and are less likely to seek treatment (Kendler et al., 2008). They also tend to experience loss of interest and tiredness more frequently and experience the feeling of guilt less frequently (Kendler et al., 2008).

Quality of individuals' surroundings, like high-density urban environments proved also to be stressful and have been linked to higher rates of psychiatric disorders (Peen et al., 2010). Another environmental factor is the quality of the neighborhood. Depression levels were shown to be lower in the neighborhoods where people knew each other, and higher when in a neighborhood people endured exposure to neighborhood violence (Aneshensel & Sucoff, 1996).

CHAPTER TWO: EVIDENCE-BASED TREATMENTS FOR DEPRESSION

Treating MDD is still a significant challenge. Evidence-based treatments for depression are pharmacotherapy, psychological interventions, and neuroscience-based interventions. In this Chapter, effectiveness, mechanism of action and integrated approach of these treatment options will be described.

2.1 Towards an integrated treatment of depression

Currently, depression treatment guidelines universally recommend a combination of pharmacotherapy and psychological treatment over single-treatment approaches for certain individuals (Table 1) (Dunlop, 2016). A combined therapy might improve the chances of remission, expedite the remission process, and encourage commitment to the treatment plan (Dunlop, 2016). In terms of maintenance, advantages may involve a decreased chance of depression relapse and improvement in overall well-being (Dunlop, 2016). A meta-analysis conducted by Cuijpers and colleagues suggests that combining drug treatments and psychological therapy offers a modest advantage over the use of either approach independently (Cuijpers et al., 2015).

Organization	**Source**	**Summary of Guideline Recommendations**
American Psychiatric Association	American Psychiatric Association, 2010	A Combination treatment is recommended for patients with severe major depressive disorder, and it may be used for patients with mild to moderate depression severity and psychosocial or interpersonal problems, a personality disorder, or intrapsychic conflict. Psychotherapy and antidepressant medication may be used as an initial treatment for patients with moderate to severe major depressive disorder. In addition, combining psychotherapy and medication may be a useful initial treatment even in milder cases for patients with psychosocial or interpersonal problems, intrapsychic conflict, or co-occurring axis II disorder.
British Association for Psychopharmacology	Cleare et al., 2015	A combination of psychological treatment and antidepressant medication may be superior to psychotherapy alone when treating moderate-to-severe major depressive disorder. Combination treatment is more effective than antidepressant treatment alone, most likely

		on the basis of greater effects among patients with at least moderate depression severity.
Canadian Network for Mood and Anxiety Treatments	Parikh et al., 2009	A combination treatment is superior to either modality alone, with the greatest support for use in special populations, such as elderly patients or women. Sequential addition of cognitive-behavioral therapy (CBT) or interpersonal therapy (IPT) for patients with partial response to antidepressant medication should be considered. Discontinuing an antidepressant with crossover to CBT, mindfulness-based cognitive therapy, or IPT provides relapse prevention that is generally comparable with that achieved with maintenance antidepressant medication.
National Institute for Health and Clinical Excellence	National Institute for Health and Clinical Excellence, 2009	A combination of pharmacotherapy and high-intensity psychotherapy (IPT, CBT) should be provided for patients with moderate-to-severe depression.
Department of Veterans Affairs and Department of Defense	Management of MDD Working Group, 2009	A combination treatment of antidepressant medication and psychotherapy should be used for moderate-to-severe major depressive disorder or as a potential strategy for treating patients who have had partial or nonresponse to monotherapy. Chronic patients can be considered for combination treatment regardless of severity level.
World Federation of Societies for Biological Psychiatry	Bauer et al., 2015	Psychotherapy is recommended in combination with antidepressants for patients with moderate to severe depression and for patients who have had only partial response to antidepressant medications or who have had problems with adherence to antidepressant medications.

Table 1 Evidence-Based Applications of Combination Psychotherapy and Pharmacotherapy for Depression. *Adapted from Dunlop, 2016.*

In the context of depression treatment, a model that has been shown to be efficient in the treatment of depression is the Stepped Care Model applied by the National Health System of the UK (Firth et al., 2015). This model entails a structured approach to treating depression that matches the intensity of treatment to the severity of the patient's symptoms (Firth et al., 2015). The key principles of the model are efficiency, cost-effectiveness, and patient-centered care, ensuring that patients receive the most appropriate treatment at the right time (Firth et al., 2015; National Institute for Health and Care Excellence, 2009).

Steps 1 and 2 include the management of low-intensity clinical manifestations (Rivero-Santana et al., 2021). Step 1 involves the identification, assessment, psychoeducation and active surveillance (Rivero-Santana et al., 2021). Step 2 targets ongoing subclinical symptoms or mild to moderate depression with low-intensity psychosocial strategies such as guided self-help, digital CBT, structured group exercise, medications, and recommendations for additional assessment and therapy (Rivero-Santana et al., 2021). Steps 3 and 4 involve the management of high-intensity clinical manifestations (Rivero-Santana et al., 2021). Step 3 includes the treatment of individuals experiencing moderate to severe depression, offering more intensive treatments like various forms of psychotherapy, (CBT, IPT, behavioral activation, couple's therapy, or short-term psychodynamic therapy if others are declined), combined approaches (medication alongside CBT or IPT), collaborative care, and renewed evaluation suggestions (Rivero-Santana et al., 2021). Step 4 is designed for individuals with severe depression posing an immediate danger to life or exhibiting extreme self-neglect (Rivero-Santana et al., 2021). This includes high-intensity psychological treatments, electroconvulsive therapy, combined modalities, crisis intervention, extensive multiprofessional care, and hospital admission (Rivero-Santana et al., 2021). Adoption of the Stepped Care Model may lead to a more logical treatment protocol for depression, potentially curbing overall costs and minimizing the incidence of side effects associated with the excessive use of antidepressants (Rivero-Santana et al., 2021).

Present findings indicate that the Stepped Care Model tends to surpass traditional non-sequential treatment for individuals with moderate to severe symptoms (Rivero-Santana et al., 2021). In essence, the Stepped Care Model could be a promising method to enhance healthcare quality provided to patients suffering from depression (Rivero-Santana et al., 2021).

Beside stepped approach, there is also the stratified approach, which aims to identify individuals who will have the most clinical benefit or least harm from specific treatments (Hingorani et al., 2013). Recent studies have indicated that stratified care has potential to improve the effectiveness of psychological care for depression (Delgadillo et al., 2016; Delgadillo et al., 2017; Lorenzo-Luaces et al., 2017; Saunders et al., 2016). A growing literature in the field of depression suggests that treatment outcomes could be improved through personalized treatment selection (Cohen, 2018). A recent clinical study examined the stratified care and the stepped approach, comparing the extent of improvement of patients' score in the 9-item Patient Health Questionnaire (Delgadillo et al., 2022). The 9-item Patient Health Questionnaire measures depression severity, with a focus on symptom frequency in the past 2 weeks (Kroenke et al., 2001). Findings in the study showed that stratified approach is better than stepped approach, regarding improvement in the 9-item Patient Health Questionnaire (Delgadillo et al., 2022).

2.2 Pharmacotherapy

Pharmacological treatment of depression can help reduce the duration and severity of depressive symptoms, improve mood and functioning, and prevent relapse. It addresses the underlying biological factors involved in depression, such as imbalances in neurotransmitters, hormones, and inflammation (American Psychiatric Association, 2019).

Selective serotonin reuptake inhibitors (SSRIs) are currently the first-line agents for the treatment of depression (Sangkuhl et al., 2009). Some of the most used SSRIs are Sertraline, Fluvoxamine, Fluoxetine, Paroxetine, Citalopram, Escitalopram (Sheffler et al., 2023). SSRIs block reuptake and prolong serotonergic neurotransmission (Santarelli et al., 2003). SSRIs are generally better tolerated than other antidepressants, but common side effects may include nausea, vomiting,

insomnia, drowsiness, headache, decreased sex drive, and agitation (Chu & Wadhva, 2023). Also, there are some of the less common adverse effects of SSRIs reported in literature, for example, extrapyramidal symptoms (EPS), serotonin syndrome, QT prolongation, rash, birth defects, hyponatremia, and cataracts (Edinoff et al., 2021). In systematic reviews and meta-analyses, SSRIs have demonstrated comparable efficacy to Tricyclic Antidepressants (MacGillivray et al., 2003; Barbui et al., 2004; Montgomery, 2001). Current data does not demonstrate a clear advantage of any class of medication over SSRIs (Montgomery, 2001; Gartlehner et L., 2008; Kennedy et al., 2006). Additionally, research indicates that there is no significant variation in effectiveness among different SSRIs (Montgomery, 2001; Gartlehner et L., 2008; Kennedy et al., 2006; Garnock-Jones, 2010; Edwards, 1999; Bauer et al., 2007).

Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs) block serotonin and norepinephrine reuptake in the synaptic cleft, increasing postsynaptic receptors' stimulation (Sheffler et al., 2023). SNRIs differ in their affinity, namely how strongly they bind to serotonin and norepinephrine transporters. Some of the most used SSRIs are Venlafaxine, Desvenlafaxine, Duloxetine, Milnacipran, Levomilnacipran (Sheffler et al., 2023). Unlike the others, Milnacipran and Levomilnacipran are more targeted towards norepinephrine reuptake compared to serotonin reuptake (Lambert et al., 2002; Asnis et al., 2015). Some of the most common side effects include anxiety, insomnia, and restlessness, and possible sexual dysfunction and headaches (Santarsieri & Schwartz, 2015). Compared with the SSRI class, the SNRI class tends to induce more nausea, insomnia, dry mouth, and in rare cases elevated blood pressure (Santarsieri & Schwartz, 2015). In individual studies, venlafaxine and duloxetine are generally considered effective as SSRIs (Thase et al., 2007). Also, venlafaxine’s efficacy is comparable with Tricyclic antidepressants (Bauer et al., 2009; Cipriani et al., 2009).

Atypical antidepressants have various mechanisms of action. *Bupropion*, for example, works by inhibiting the reuptake of dopamine and norepinephrine at the synaptic cleft (Horstet et al., 1998). Some of the most common side effects are headache, agitation, insomnia, loss of appetite, weight loss, sweating, but on the other hand there is no sexual dysfunction or weight gain (Santarsieri & Schwartz, 2015). Studies showed that bupropion is not effective as SSRI for patients with major depressive disorder with high levels of anxiety (Papakostas et al., 2008). Indeed, there was no statistically significant difference in effectiveness between bupropion and the SSRIs among patients with major depressive disorder with moderate/low levels of anxiety (Papakostas et al., 2008). *Agomelatine* works as an agonist at melatonin receptors MT1 and MT2. It also blocks postsynaptic serotonin 5-HT2C receptors, which boosts dopamine and norepinephrine release (Hickie et al., 2004). The findings of meta-analysis highlight the antidepressant effect of *agomelatine* at par with other antidepressants (Maddukuri et al., 2021). *Mirtazapine* works by blocking alpha-2 adrenergic receptors on the cell bodies and nerve terminals, promoting the release of norepinephrine into the synapse cleft (Harmer et al., 2017). Furthermore, mirtazapine antagonizes the serotonin receptor, which has been shown to increase norepinephrine and dopamine in the brain cortical regions of the brain (Harmer et al., 2017). Most common side effects are sedation, increased appetite, weight gain, although there is reduced nausea and sexual dysfunction compared with SSRI/SNRI. (Santarsieri & Schwartz, 2015). Meta analysis suggests that mirtazapine and the SSRIs differ with respect to their side-effect profile but not their overall efficacy in the treatment of MDD (Papakostas et al., 2008).

Serotonin modulators such as *Vilazodone* and *Vortioxetine* inhibit the presynaptic reuptake of serotonin. It is also a partial agonist at the postsynaptic serotonin 5-HT1A receptor (Wang et

al., 2016). Efficacy of *Vilazodone* is proved across several clinical trial in comparison with placebo, but there is a need for more data (Wang et al., 2016). Some of the side effects are nausea, diarrhea, insomnia, but on the other hand *vilazodone* have better safety profile than most atypical antidepressants with lower risk of sexual dysfunction or weight gain (Santarsieri & Schwartz, 2015). Efficacy of *Vortioxetine* is comparable with other antidepressants and safety profile is similar to SSRIs (Pae et al., 2015; Santarsieri & Schwartz, 2015). *Trazodone* acts upon postsynaptic serotonin 5-HT2A and 5-HT2C receptors and weakly inhibits presynaptic serotonin reuptake (Horst, 1998). Some of the side effects are sedation, nausea, priapism, but there is lower risk of weight gain and sexual dysfunction in comparison with other antodepressants (Santarsieri & Schwartz, 2015). *Nefazodone* antagonizes postsynaptic serotonin 5-HT2A receptors and inhibits presynaptic serotonin and norepinephrine reuptake; these actions enhanced activation of serotonin 5-HT1A receptors (Horst, 1998). *Nefazodone* has fallen out of use due to fear of hepatotoxicity (Santarsieri & Schwartz, 2015). Results of meta-analysis suggest that the 5HT2-receptor antagonists trazodone and nefazodone and the SSRIs do not differ with respect to their overall efficacy and tolerability in the treatment of MDD (Papakostas et al., 2007).

Tricyclic Antidepressants **(**TCAs**)**, inhibits the reuptake of norepinephrine and serotonin at the presynaptic neuronal membrane (Gilman, 2007). Some of the most used TCAs are Amitriptyline, Clomipramine, Doxepin, Imipramine, Trimipramine, Desipramine, Nortriptyline, Protriptyline, Maprotiline, Amoxapine (Sheffler et al., 2023). Some of the most common side effects are weight gain, sedation, dry mouth, nausea, blurred vision, constipation, tachycardia (Santarsieri & Schwartz, 2015). *Tricyclic antidepressants* are as successful as SSRIs, SNRIs, and MAOIs in managing major depression (MacGillivray et al., 2003; Barbui et al., 2004). However, TCAs may prove to be more effective than SSRIs for treating severe cases of major depressive disorder (MDD) in

hospitalized patients (Anderson, 1998). In recent meta-analysis is showed that TCAs had similar efficacy to SSRIs, but also TCAs were associated with more dropouts and lesser tolerability (Undurraga & Baldessarini, 2017). These data are in a correlation with clinical selection of SSRIs over TCAs as a first choice in the treatment of acute major depression (Undurraga & Baldessarini, 2017).

Monoamine Oxidase Inhibitors (MAOIs) inhibit the monoamine oxidase enzyme responsible for catabolizing serotonin, norepinephrine, and dopamine. MAOIs were the first antidepressants discovered and they are not recognized as the first-line treatment for depression because of the adverse effects and drug-drug interactions (Fiedorowicz et al., 2004). Due to the irreversible inhibition of monoamine oxidase by these drugs, there are several side effects including hepatotoxicity, nephrotoxicity, and hypertensive crises, which may result in fatal intracranial hemorrhages (López-Muñoz et al., 2007). Due to significant considerations regarding drug interactions, especially with serotonin and norepinephrine agents, dietary limitations, and possible severe adverse effects, MAOIs are currently mainly prescribed for patients who have not been receptive to multiple drug treatments (López-Muñoz et al., 2007). They are often considered as an alternative therapeutic approach when electroconvulsive therapy is not recommended or in managing depression that exhibits non-classical symptoms (Henkel et al., 2006). The new generation of these drugs (e.g. Moclobemide) is instead made up of compounds capable of reversibly inhibiting MAOIs and have a greater selectivity, which makes them easier to use (Finberg & Gillman, 2011).

Glutamate is an excitatory neurotransmitter that binds to N-methyl-D-aspartate (NMD) and consequently, *NMD Antagonists* are useful in the treatment of depression (Singh et al., 2016). *Esketamine*, the derivate of ketamine, is a non-selective (they do not target a specific *NMD* receptor agonist subtype), non-competitive *NMD* receptor antagonists and it is indicated in treatment-re-

sistant depression (Singh et al., 2016). The anti-suicidal effect of esketamine represents a key reason to explore its properties since managing suicidal behavior in patients with MDD is difficult with the use of previous generations of antidepressants (Vasiliu, 2023). The most reported side effects were nausea, dissociation, dizziness, and headache (Fedgchin et al., 2019). *Dextromethorphan* works by blocking *NMD* receptors agonists and activating opioid σ receptors in the brain (Iosifescu et al., 2022). *Bupropion*, as discussed above, works by inhibiting the uptake of dopamine and norepinephrine (Tabuteau, 2022). The fixed drug combination (physically in one tablet) of *Dextromethorphan-Bupropion* has a rapid effect of approximately one week in patients with MDD (Iosifescu et al., 2022; Tabuteau, 2022). Some of the most common side effects are dizziness, nausea, dry mouth, decreased appetite, and anxiety (McCarthy et al., 2023). The current lack of guidelines about the therapeutic monitoring of ketamine treatment for depression further complicates the expanding use of this treatment (Swiatek et al., 2016).

In 2018, a comprehensive network meta-analysis was released in *The Lancet*, examining the efficacy and tolerability of 21 antidepressant medications for major depressive disorder based on data from over 100,000 patients (Cipriani et al., 2018). In terms of efficacy, all antidepressants were more effective than placebo (Figure 2.1) (Cipriani et al., 2018). For acceptability, only atypical antidepressant (agomelatine) and SSRI (fluoxetine) were associated with fewer dropouts than placebo, whereas TCA (clomipramine) was worse than placebo (Figure 2.2) (Cipriani et al., 2018). In head-to-head studies, atypical antidepressants (mirtazapine, agomelatine), serotonin modulator (vortioxetine), TCA (amitriptyline), SSRIs (escitalopram, paroxetine) and SNRI (venlafaxine) were more effective than other antidepressants, whereas SSRIs (fluoxetine, fluvoxamine) and SNRI (reboxetine), and were the least effective drugs (Cipriani et al., 2018). For acceptability, atypical antidepressant (agomelatine), SSRIs (citalopram, escitalopram, fluoxetine, sertraline) and

serotonin modulator (vortioxetine) were more tolerable than other antidepressants, whereas TCAs (amitriptyline, clomipramine), SNRIs (reboxetine, venlafaxine, duloxetine) and SSRI (fluvoxamine) had the highest dropout rates (Cipriani et al., 2018). This meta-analysis included a large amount of unpublished data, which is associated with less favorable effect sizes for antidepressants (Cipriani et al., 2018). Another limitation is that the long-term efficacy of the pharmacotherapy and the effect on the maintenance phase of depression are not reviewed in this meta-analysis (Cipriani et al., 2018).

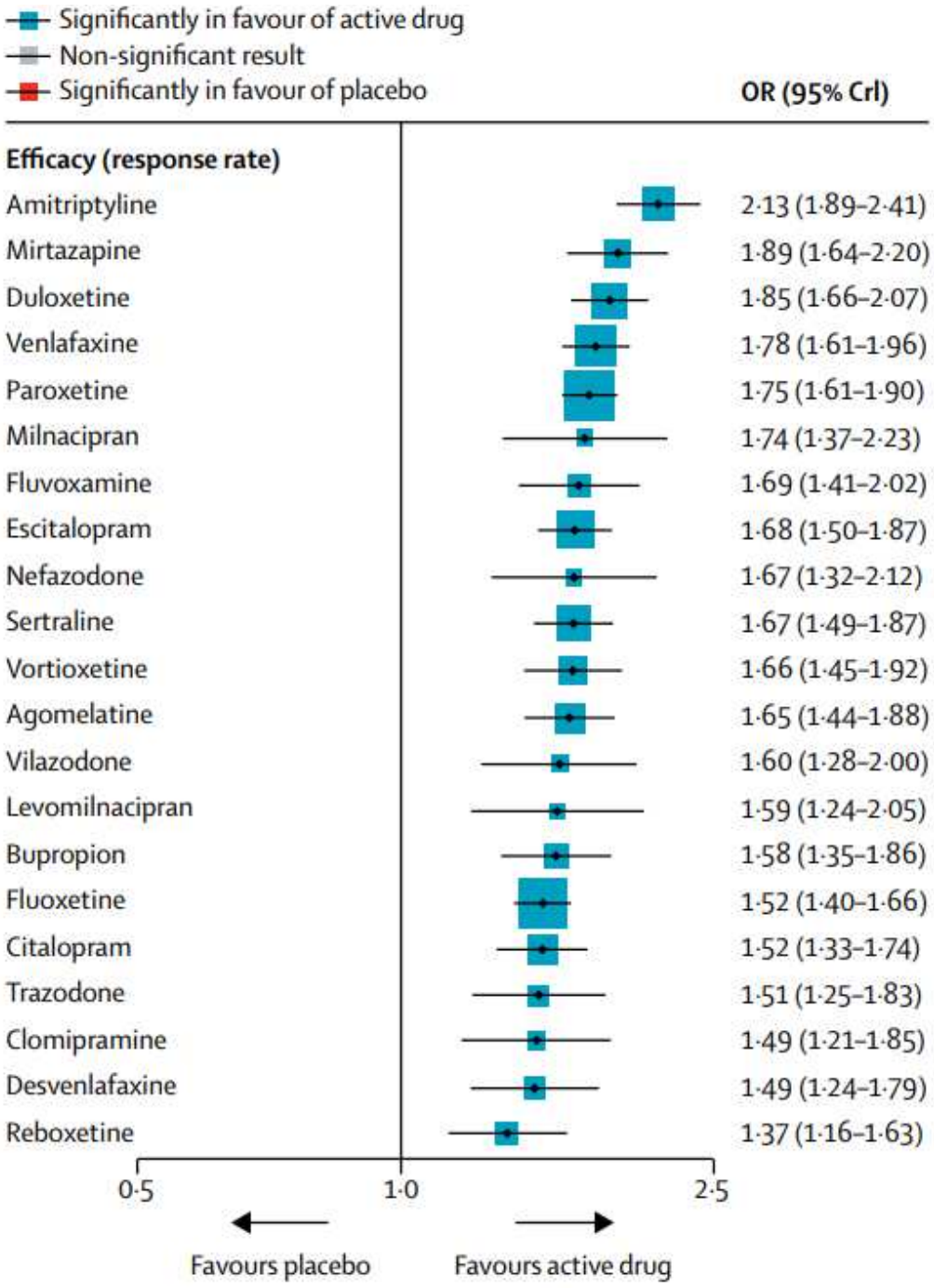

Figure 2.1 Forest plot of network meta-analysis of all trials for efficacy. Antidepressants were compared with placebo, which was the reference compound. OR=odds ratio. CrI=credible interval. *Adapted from Cipriani, 2018.*

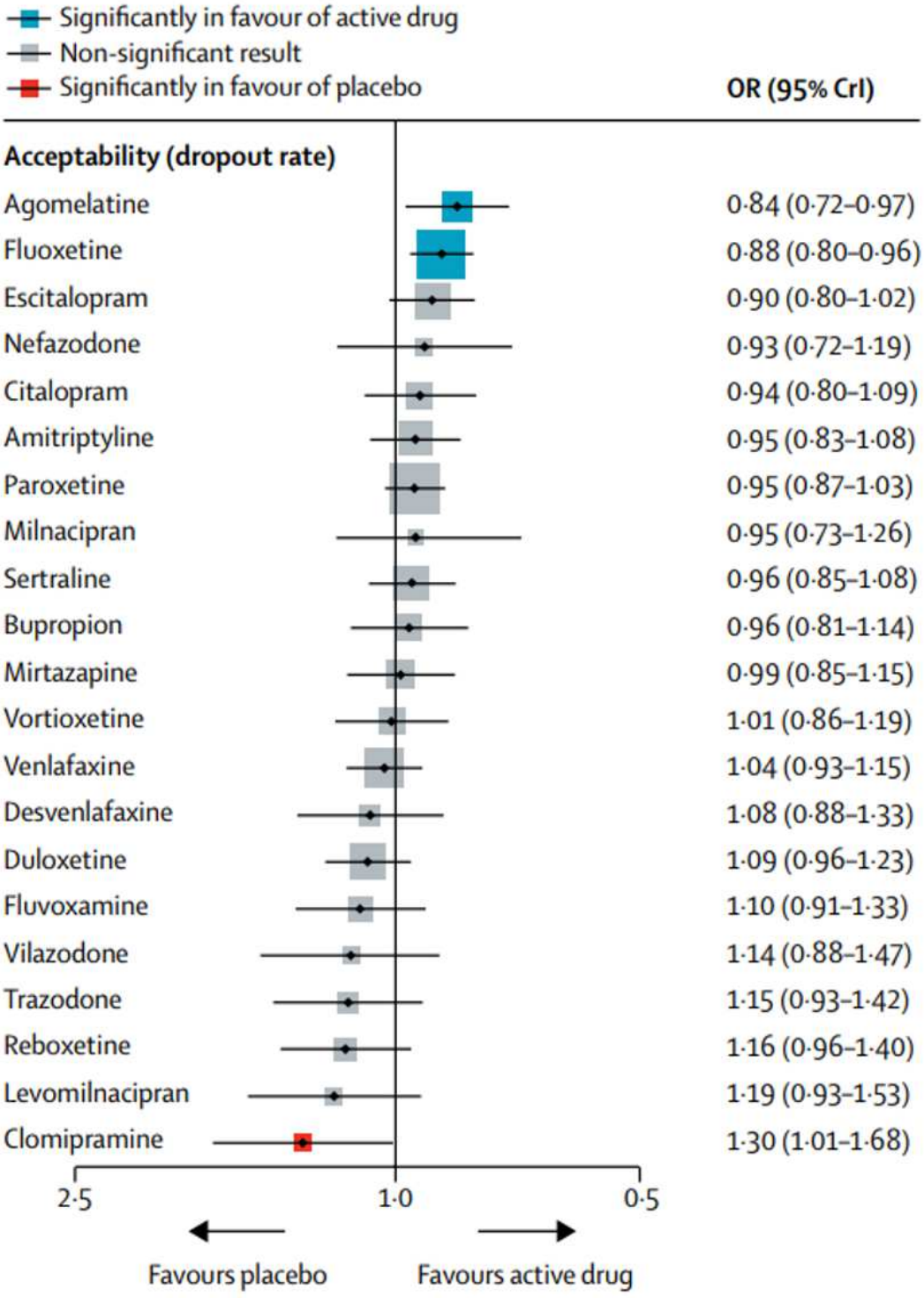

Figure 2.2 Forest plot of network meta-analysis of all trials for acceptability. Antidepressants were compared with placebo, which was the reference compound. OR=odds ratio. CrI=credible interval. *Adapted from Cipriani, 2018.*

2.3 Psychological interventions

Whether combined with pharmacotherapy or provided independently, psychological interventions represent a cornerstone in the treatment of depression. According to the stepped care approach from the National Institute for Health and Care Excellence, psychotherapy is indicated in Step 2 for mild cases of depression, even without pharmacotherapy (NICE, 2022). In a study conducted by Cuijpers and colleagues, psychotherapy for depression proved to be effective compared to control conditions, however it is important to mention that more than half of the patients did not respond to therapy, and only about one-third remitted (Cuijpers et al., 2021). This highlights the need for the development of more effective treatments (Cuijpers et al., 2021).

2.3.1 Cognitive-behavioral therapy

Cognitive-behavioral therapy focuses on patients' negative thought patterns, namely their dysfunctional thoughts, core beliefs, and information processing biases (Beck et al., 1979). Core beliefs develop in early childhood and lead to the development of dysfunctional assumptions, which can be then activated after a critical life event where the automatic negative thoughts and symptoms of depression develop (Beck et al., 1979).

In order to change what they feel, patients are encouraged to change the maladaptive ways of thinking and behaving by acquiring and using different techniques (Johnco et al., 2024). A process called cognitive restructuring aims to identify and bring negative thought patterns into patients' awareness before focused is placed on changing them (Beck et al., 1979). The premise is that negative thought patterns are based on cognitive distortions, and cognitive restructuring focuses on providing more functional and realistic thoughts to challenge and replace those biases (Beck et al., 1979). It relies on the notion that these negative thoughts play a crucial role in the

development and maintenance of the depressive state, and that by providing the patient with the necessary skills, the patient would be set in a direction of challenging those automatic thoughts, providing alternatives and over time managing to engage themselves in rewarding activities more (Beck et al., 1979). Psychoeducation is important for providing a framework for the patient's better understanding of the state they are experiencing and the process they are set to go through (National Institute for Health and Care Excellence, 2009). Typical session structure of CBT is given in the Figure 2.3 (Gautam et al., 2020).

Serial number	Component	Time (min)
1	Beginning of the session	
	Mood check	5–10
	Agenda setting	
	Reviewing homework	
2	Discussion of agenda items/problems	35–40
	Description of occurrence of specific problem	
	Elicitation and confirmation of elements of the cognitive model	
	Collaborative discussion regarding how to approach a problem	
	Rationale for the introduction of intervention	
	Assessment of the efficacy of intervention	
	Summary by patient	
	Collaborative action plan in writing	
	Planning and discussing a homework and how to approach it	
3	Feedback to the therapist	1–2

Figure 2.3 Session structure of cognitive-behavioral therapy. *Adapted from Gautam, 2020.*

Problem-solving is a CBT module during which patients are trained to identify a problem, a potential solution and strategies needed to transition from the former to the latter (Sakata et al., 2021). It is suggested that the patient's poor problem-solving ability to cope with minor and major stressful events represents a vulnerability factor for depression (Nezu et al., 1998). While the aim of the module is to improve patients' problem-solving capabilities, it also examines how the patient

approaches problems in life, the expectations, assumptions, and beliefs concerning them (Nezu et al., 1989). It promotes strategies like adoption of positive problem orientation, problem recognizing and generating wide range of possible solutions, decision making and outcome monitoring (Nezu et al., 1998). Another technique included in the CBT training is behavioral activation (Nezu et al., 1989). It relies on the notion that because of the depressive state, patients tend to avoid activities that they once enjoyed (Nezu et al., 1989). Therefore, the idea is to encourage patients to immerse themselves in the activities that are likely to result in the feeling of pleasure, and to reduce the frequency of aversive events (Nezu et al., 1998).

Compared to control conditions, behavioral activation therapy, problem-solving therapy, and cognitive restructuring proved to be effective and acceptable in the treatment of adult depression, with also no significant differences between them (Cuijpers et al., 2021; Ciharova et al., 2021). Among all the interventions being compared, behavioral activation therapy achieved the highest value for response and the standardized mean difference (Figure 2.4), which represents the effect size (Cuijpers et al., 2021). This suggests that in terms of the impact it had on the outcomes, it was more effective at producing positive changes or reducing symptoms compared to the other therapies being evaluated. The same study showed also that behavioral activation and problem-solving therapies ranked highest for remission (Figure 2.4). Cognitive-behavioral therapy, behavioral activation, and problem-solving all had significant effects at one-year follow-up compared to care-as-usual (Cuijpers et al., 2021). Cognitive-behavioral therapy proved to be more effective compared to control conditions and similarly effective to pharmacotherapy in treating depression (Hofmann et al., 2012). It was shown that CBT combined with antidepressant medication was more effective than CBT alone (Lepping et al., 2017).

	Response	SMD	Remission	Acceptability
Cognitive behavioural therapy	64.0	72.8	75.1	48.4
Behavioural activation therapy	85.2	82.1	86.3	39.1
Problem-solving therapy	62.9	67.2	83.5	40.8
"Third wave" therapies	66.5	75.7	76.3	51.1
Interpersonal psychotherapy	64.6	52.0	62.3	62.1
Psychodynamic therapy	52.8	49.2	46.3	10.0
Non-directive supportive counseling	26.6	30.8	30.5	42.3
Life-review therapy	93.1	87.1	46.5	72.5
Care-as-usual	12.0	14.5	10.7	71.8
Waiting list	0.0	1.10	0.2	97.2
Pill placebo	22.3	17.4	32.2	14.6

Figure 2.4 Ranking of psychotherapies and control conditions according to the "surface under the cumulative ranking" for response, standardized mean difference, remission and acceptability. *Adapted from Cuijpers, 2021.*

2.3.2 Behavioral activation therapy

Behavioral activation therapy is a component of CBT, but after it demonstrated high clinical efficacy, it also became a stand-alone treatment (Spates et al., 2006). Behavioral activation therapy is based on the behavioral model proposed by Lewinsohn in 1971 (Lewinsohn & Shaffer, 1971) and updated in 1974 (Lewinsohn, 1974). Lewinsohn defined response-contingent positive reinforcement as positive or pleasurable outcomes of an individual's behaviors in their environment, and as such they determine the likelihood of those behaviors being repeated. The behavioral model proposed by Lewinsohn posits that low levels of response-contingent positive reinforcement

represent a critical predictor of clinical depression. The levels of response-contingent positive reinforcement depend on the number of events that are rewarding to the individual, their availability in the individual's environment, and the individual's instrumental behavior (Lewinsohn, 1974).

Behavioral activation aims to identify and encourage the individual's involvement in activities and situations that provide positive reinforcement and that align with the individual's long-term objectives (Lejuez et al., 2011). In the initial stage, it is important to identify patients' behavior, their positive and negative reinforcements in the context of their daily lives (Lejuez et al., 2011). Then, the reinforcements for depressed behavior are discussed and there is an effort to establish an agreement for them to be eliminated or reduced (Lejuez et al., 2011). Increasing positive reinforcement is negotiated in a manner of a homework and accountability and the objectives are set with constant progress monitoring (Lejuez et al., 2011).

Another important aspect that is considered are the patterns of avoidance and withdrawal (Dimidjian et al., 2006). For the patient to avoid potential short-term distress, they tend to engage in avoidance, like social situations, daily routines (Dimidjian et al., 2006). This behavior then results in long-term negative consequences, such as decreasing the opportunities for potentially positive reinforcement in their life context and developing new negative reinforcement (Dimidjian et al., 2006). This intervention aims to break this cycle by introducing strategies like self-monitoring, scheduling daily activities aimed at eliciting positive outcomes, rating the level of pleasure obtained from those activities, challenging current behaviors and suggesting alternatives, redirecting attention away from the ruminative thoughts towards the immediate context (Dimidjian et al., 2006).

Research of the behavioral activation effectiveness over the span of three decades proved that this intervention is a successful treatment for depression, achieving outcomes comparable to those of the currently recommended psychological interventions (Mazzucchelli et al., 2009).

2.3.3 Interpersonal therapy

Interpersonal therapy emphasizes the interpersonal and social factors as key contributors to the depressive state (Klerman et al., 1996). It aims to examine patients' relationships and patients' social adjustment in their current context (Klerman et al., 1996). Although problems in interpersonal relations are not sufficient for the development of depression, they are usually present in the depressed patients' interpersonal relations (Klerman et al., 1996).

The patient and therapist together define the focus of the treatment, the *interpersonal problem* (Markowitz & Weissman, 2004). Current state of patients' relationships, their capacity for intimacy in their relationships, and their default social responses are closely examined with a special focus on the current state of patients' relationships (Markowitz & Weissman, 2004). The *interpersonal problem* falls into one of four categories. If the patient recently experienced a death of someone close, they belong to the *complicated bereavement* category (Markowitz & Weissman, 2004). If they recently lived through an important life change, they belong to the *role transition* category (Markowitz & Weissman, 2004). If they are experiencing issues with a significant other, their problem falls into the *role dispute* category (Markowitz & Weissman, 2004). If the patient's life situation cannot be matched with any of these three categories, the focus is placed on *interpersonal deficits,* while the focus is placed on the reduction of social isolation (Markowitz & Weissman, 2004). The therapist and the patient analyze together the patient's social situations and provide alterative interpersonal options in case of adverse social situations, or the therapist encourages

any positive encounter the patient might have (Markowitz & Weissman, 2004). The patient and the therapist collaborate to understand the effects of the recent social events and their impact on the patient's mood (Markowitz & Weissman, 2004). The patient is encouraged to examine alternative responses to the events that caused them to suffer, challenge their social responses, and as a result, develop their interpersonal skills (Markowitz & Weissman, 2004). Interpersonal therapy proved to be significantly more effective than non-directive supportive counseling (Cuijpers et al., 2021) (Figure 2.4), an intervention that involves the therapist offering empathetic support allowing clients to explore their thoughts and feelings and find their own solutions without direct guidance (Rogers, 1951). Interpersonal therapy also proved to be more effective in improving social functioning compared with control conditions (CBT, treatment-as-usual, no treatment) (Bian et al., 2023). It has been recommended as a first-line treatment for acute mild to moderate depression, as a maintenance therapy together with medications, or as a relapse prevention method after remission of depression (Warnick et al., 2021).

2.3.4 Mindfulness-based interventions

Mindfulness-based interventions (MBIs) are programs that emphasize the benefits of formal meditation practices in cultivating mindfulness skills and promoting mental well-being (Shapero et al., 2018). Mindfulness-based therapy (MBT) refers to integration of mindfulness practices with principles from psychotherapy (Khoury et al., 2013). Growing body of evidence suggests that mindfulness meditation can promote neuroplastic changes in the structures of the brain and functions involved in attention and emotion regulation and self-awareness (Tang et al., 2015). Most widely used MBIs are mindfulness-based stress reduction (Kabat-Zinn, 1990) and mindfulness-based cognitive therapy (Segal et al., 2013). Both last for eight weeks and are implemented in a

form of group-based therapies lead by a therapist. In this period, patients are taught mindfulness skills through various mindfulness practices, with focus on breath, thoughts, bodily sensations, sounds, and everyday activities (Gu et al., 2015). The aim is to integrate awareness in ordinary and repetitive everyday activities like eating and mindful brushing of teeth (Shapero et al., 2018).

Mindfulness-based stress reduction increases brain activity associated with present-moment experience and decreased the 'narrative network' associated with self as experienced across time. This finding is important as the 'narrative network' is connected to mind wandering, and it usually works together with present-moment experience. It is also connected to that fact that mind wondering is associated with less positive affect, as opposed to a focused state. During mindfulness-based stress reduction, the individual is trained to be more aware of what is happening in their mind from moment to moment. The idea is to gently redirect the individual's attention to what is currently most important to the individual without forcing the mind not to wander. It is important to develop non-judgmental awareness of the wandering mind, as it is the key factor of individuals' greater happiness and well-being. Mindfulness-based stress reduction is based on the notion that the individual's thoughts have a direct impact on their sense of well-being and that mindfulness is essentially a skill that, like any other, can be cultivated through practice (Kabat-Zinn, 1990).

It was shown that MBT and CBT were equivalent for treating adult depression (Sverre et al., 2023). A recent meta-analysis conducted by McCartney and colleagues indicates that mindfulness-based cognitive therapy is more effective than treatment-as-usual in preventing depression relapse over the long term and shows statistically significant benefits over both treatment-as-usual and placebo regarding the time to relapse (McCartney et al., 2020). It was also shown that compared to controls, MBIs had significantly moderate effects in reducing depression in pregnant women,

while mindfulness-based cognitive therapy had a more significant impact than mindfulness-based stress reduction on reducing depressive symptoms (Reangsing et al., 2024).

2.4 Neuroscience-based interventions

Neuroscience-based interventions for depression encompasses therapeutic approaches that incorporate findings from neuroscience. As the body of research in the domain of brain science grows, so do the possibilities for the development of new targeted interventions. Understanding neural mechanisms underlying depression can pave a path to new perspectives and initiatives for tackling depression, as well as integrating those findings into current successful treatments for depression. Some of the key neuroscience-based interventions include transcranial magnetics stimulation (TMS) and neurofeedback.

2.4.1 Neurofeedback

Neurofeedback is an intervention that enables individuals to actively regulate their own brain activity with the use of a real-time feedback of a specific neural signal involved in the disorder, with the goal of improving both neural functioning and symptoms (Gandara et al., 2020). Neurofeedback is implemented using neurofeedback setup (Figure 2.5) (Winkeler et al., 2022).

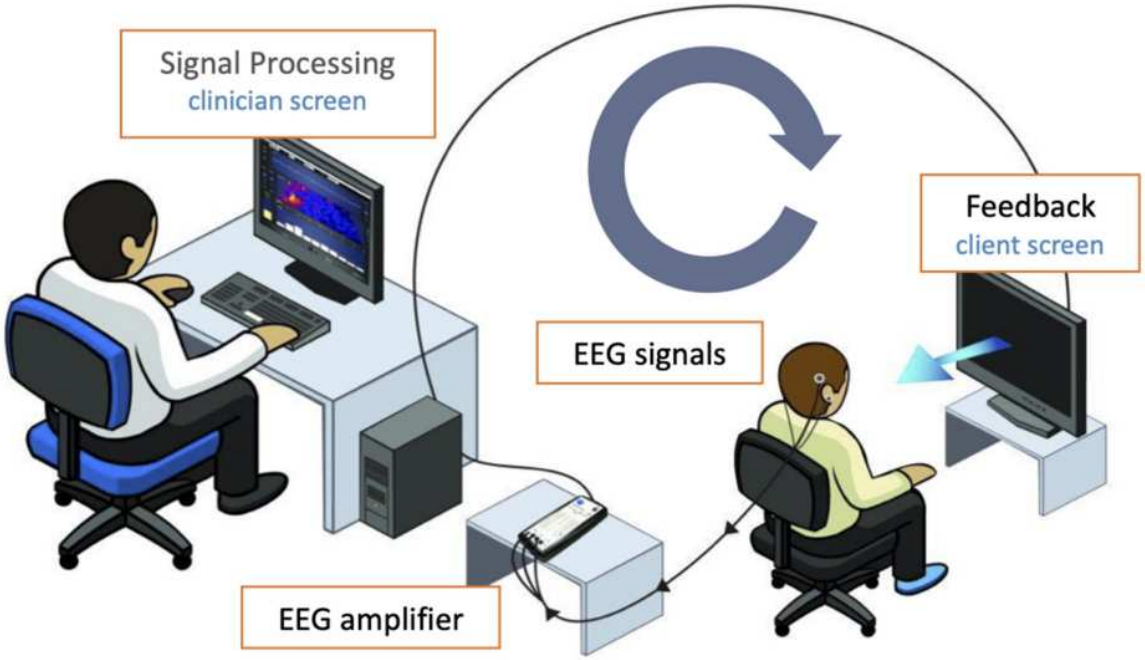

Figure 2.5 Neurofeedback setup. *Adjusted from Winkeler 2022.*

Two frequently utilized techniques in neurofeedback therapy for MDD are electroencephalogram (EEG) and functional magnetic resonance imaging (fMRI) (Thibault & Raz, 2016). Particularly, interventions using EEG typically focus on certain frequency bands, notably alpha (8–12 Hz) and theta (4–8 Hz) (Newson & Thiagarajan, 2019). One frequently used approach is the assessment and training of the frontal alpha asymmetry (FAA), which examines the relative power of the alpha band in the left and right frontal lobes (Xia et al., 2024). Numerous studies have

demonstrated a strong link between FAA and affect, indicating that FAA may be a consistent indicator of patients' affective states (Davidson et al., 1990; Davidson, 1992; Harmon-Jones & Allen, 1997; Coan & Allen, 2003; Alves et al., 2008). Frontal alpha asymmetry is defined as a relative difference in EEG alpha band power between the left and right frontal regions of the brain (Coan & Allen, 2004). It is considered that changes in EEG alpha asymmetry objectively correlate to and reflect activation of the approach and withdrawal motivational systems, namely the affective dispositions in individuals. Stimuli that provoke the withdrawal motivational system will cause a lateral shift toward relatively greater activity in the right versus left prefrontal cortex, whereas stimuli that stimulate the approach system are expected to produce a lateral shift to the left, i.e., greater activity in left versus right prefrontal cortex (Davidson, 1998). Data showed that greater left than right frontal cortical activity was associated with approach motivation, which can be either positive (e.g. enthusiasm) or negative in valence (e.g. anger) (Harmon-Jones et al., 2010). Alpha power is considered an inverse index of cortical activity. Hence, reduced alpha power in the left frontal region is considered to reflect greater left frontal activity (usually associated with approach motivation and positive affect), and reduced alpha power in the right frontal region is considered to indicate greater right frontal activity often linked to withdrawal motivation and negative affect (Coan & Allen, 2004). Consequently, the frontal alpha asymmetry is regarded as a valuable indicator for investigating emotional imbalance in depressive disorders and a cornerstone in the development of neurofeedback training.

Furthermore, studies have demonstrated that resting rostral anterior cingulate cortex activity in the theta frequency, associated with the regulation of emotions (Mulert et al., 2007; Korb et al., 2009; Schiller, 2019), band could serve as a positive predictor of treatment response across

a range of antidepressant classes in individuals with MDD (Mulert et al., 2007; Korb et al., 2009; Schiller, 2019).

fMRI-based neurofeedback employs the blood oxygen level dependent signal, which informs on the activation of certain brain areas when different tasks are performed (Xia et al., 2024). The main objective of this method is to enhance the brain activity related to the altered affective and cognitive processes in patients with MDD (Xia et al., 2024). For instance, a study has shown that fMRI-based neurofeedback can increase the neural activity in the amygdala which have demonstrated effectiveness in improving depressive symptoms. The aim was to increase amygdala activity during positive stimuli. Findings suggest that upregulation to positive stimuli led to a state where patients learned to adaptively regulate their amygdala response (Young et al., 2017). Also, it is proved the antidepressant effect of fMRI-based neurofeedback training of left dorsolateral prefrontal cortex results in a decrease of recurrent negative thoughts (Takamura et al., 2020; Yu et al., 2020).

A recent meta-analysis showed that neurofeedback is a promising intervention for reducing depressive symptoms and enhancing neurophysiological functions in individuals with MDD (Xia et al., 2024). The same meta-analysis also found no significant difference in efficacy between repetitive transcranial magnetic stimulation and transcranial direct current stimulation, and neurofeedback. The results revealed that neurofeedback outperformed both rTMS and transcranial direct current stimulation in enhancing cognitive function in MDD patients (Xia et al., 2024).

2.4.2 TMS

Interest in non-invasive brain stimulation as a therapeutic tool has increased dramatically in the last two decades (Eldaief et al., 2022). Transcranial magnetic stimulation is a method of

changing the activity level of the cortex without penetrating the skull. This is done by generating a magnetic field that can be either high- or low-intensity (Mann, 2023).

TMS was first discovered by Barker and collaborators in 1985, and it relies on the principle of electromagnetic induction of Faraday (Barker et al., 1985). In a TMS stimulator, a high-intensity, quick-changing current goes through looped windings of a plastic case (the TMS coil). The coil is on the scalp, and the current makes a fast-changing magnetic field. The magnetic field from the TMS coil passes through the scalp, skull, and dura madre without any obstacle, unless it meets materials that can carry electricity. The field gets weaker as it travels further from the source, but it does not change much until it hits the cortex (which is conductive). In this way, the magnetic field is converted into another electric field by cortical neurons that act like "pick-up coils". This causes neuronal depolarization and action potentials that then travel through a network of linked neurons by synaptic transmission (Burke et al., 2019; Camprodon et al., 2016). Transcranial magnetic stimulation can be administered using three protocols *single-pulse TMS, paired-pulse TMS* , and *Repetitive TMS* (Mann, 2023).

Repetitive TMS (rTMS) is a procedure that uses repeated TMS pulses to stimulate a specific brain region. The effects of rTMS on the brain vary depending on several factors such as frequency, intensity, duration, cortical target, number of sessions, and patient characteristics such as age, disease state, medication trial, and individual symptoms. rTMS can be high frequency (>1 Hz) or low frequency (<1 Hz). High-frequency rTMS increases cortical excitability, while low-frequency rTMS decreases it (Mann, 2023).

Based on the frontal alpha asymmetry, researchers have tried to treat patients with inhibitory (low frequency) stimulation to the right dorsolateral prefrontal cortex or excitatory (high frequency) stimulation to the left dorsolateral prefrontal cortex (George et al., 2000; Klein et al.,

1999). Also, based on fMRI depression studies, activity in limbic (anterior cingulate cortex and amygdala) and frontal cortical areas (dorsolateral prefrontal cortex) has been shown to be altered in depression during viewing or processing of emotional stimuli—mainly facial expressions (Pilmeyer et al., 2022). There is consensus that activity of limbic regions is increased, whereas in frontal regions the activity is decreased (Pilmeyer et al., 2022). Nearly a decade ago, the use of TMS was approved by the US Food and Drug Administration for treatment-resistant depression (Somani & Kar, 2019). Also, a stimulatory protocol delivering 3000 pulses per session over the right dorsolateral prefrontal cortex has been approved by the US Food and Drug Administration (Somani & Kar, 2019).

Over the course of the last two decades, there has been a significant increase in interest in the use of several forms of rTMS, various protocols, coils, and target regions (Tikka et al., 2023). While high-frequency and low-frequency stimulations are considered the conventional rTMS forms, patterned rTMS, such as theta burst stimulation (TBS), and quadri-pulse stimulation are the newer forms (Tikka et al., 2023). TBS usually involves short bursts of 50 Hz rTMS applied at a rate of 5 Hz (hence the name theta burst stimulation) (Tikka et al., 2023). TBS can be applied as either a continuous or intermittent train as shown in Figure 2.6 (Rossi et al., 2009). Several protocols, from once daily, up to even once monthly, are being investigated (Tikka et al., 2023). Further, as many as 50 TMS coil designs are being examined (Tikka et al., 2023). Moreover, apart from the conventional target sites (dorsolateral prefrontal cortex and the temporoparietal cortex), several new brain regions (cerebellum, orbitofrontal cortex, supplementary motor area, etc.) including bilateral stimulations have been chosen for studying the effects of rTMS in various mental disorders (Tikka et al., 2023).

Clinical practice shows that rTMS may have a higher chance of success when it is administered in the year of onset of an ongoing depressive episode to patients, below the age of 65 years, and in cases in which patients exhibit resistance to treatment (i.e., one or two failed pharmacological trials, with or without additional psychotherapy) (George & Post, 2011). These criteria should be considered as merely indicative as most of rTMS research in the domain of depression has been conducted in MDD patients with some form of treatment resistance (Lefaucheur et al., 2020).

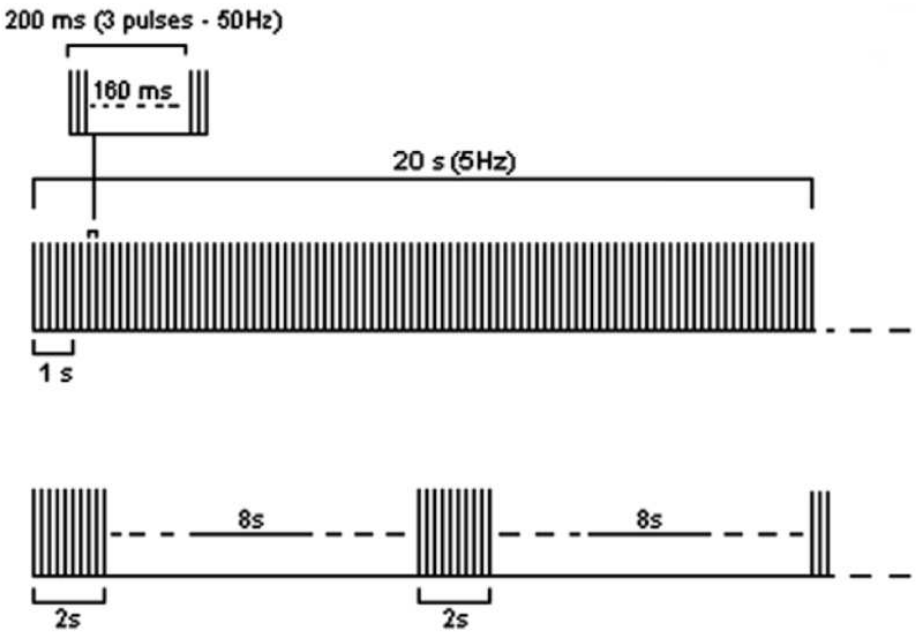

Figure 2.6 Examples of the two most common TBS protocols: continuous TBS (above) and intermittent TBS (below). *Adapted from Rossi, 2009.*

This intervention, albeit non-invasive, has several side effects. For instance, it may cause seizures, although the chance of this happening is very low, less than 0.01% per session for people who do not have epilepsy (Damar et al., 2020). For people who have epilepsy, the chance is higher, but still less than 3% per session (Damar et al., 2020). Some other possible side effects are pain in the area, usually headache or neck pain, and temporary ringing in the ears (Taylor et al., 2018).

These problems are usually mild and fade quickly. Patient adherence to treatment is a significant factor in the efficacy of rTMS, as the treatment requires multiple sessions, which can challenge patient compliance (Taylor et al., 2018; Damar et al., 2020).

2.5 Discussion and conclusion

Major depressive disorder is a multifaceted and heterogeneous condition, with causes and consequences that are not fully understood. This implies that the current theories and hypotheses cannot account for all the aspects of MDD and that more research is needed to design new evidence-based interventions and improve the already available ones. Possible causes and mechanisms of MDD were mainly reviewed from the perspective of widely accepted theories, such as the monoamine hypothesis, cognitive models, neurobiological correlates, and social and environmental factors. Theories led to the development of various treatment options and strategies. For example, the monoamine hypothesis led to the evolution of pharmacotherapy. However, a more comprehensive understanding of the pathophysiological mechanisms of MDD might greatly improve the ability to develop preventive and more effective therapeutic methods that can help reduce the suffering and the burden of MDD. This work also presented an overview of the existing treatment modalities, which include pharmacotherapy, psychological strategies, neuroscience-based treatments. The integrated approach and combination of therapies recommended in different guidelines are described. In a recent meta-analysis, it is shown that the stepped-care approach is more effective than the standard of care recommended in the guidelines and that the future of treatment should go in this direction.

The effects of combined treatment of psychotherapy and pharmacotherapy proved to be superior to administrating either one alone (Cuijpers et al., 2021). Further, the effects of only psychotherapy or pharmacotherapy were comparable in effect relative to care-as-usual or waitlist (Figure 2.4) (Cuijpers et al., 2021). Interestingly, no major differences were observed between different psychotherapy interventions. While CBT is the most widely researched intervention (Chand et al., 2023), it is interesting to observe that when examining the rates of remission, response, and effect size, behavioral activation therapy proved to be superior to CBT, problem-solving and IPT in all three (Cuijpers et al., 2021). This could be an interesting potential direction of the investigation, where there would be more of an emphasis on the patients' proactiveness in modifying their behavior in their current context. However, it is worth noting that acceptability is lower for behavioral activation therapy compared to CBT and IPT (Cuijpers et al., 2021), indicating that it could be potentially more difficult to influence patients' behavior compared to or without addressing cognitive elements. Although psychotherapy is effective compared with control conditions, a meta-analysis showed that more than half of patients receiving psychotherapy did not respond and remission rates were only reached in about one third of the patients, compared with 7%–13% in control conditions (Cuijpers et al., 2021). This data is alarming and points to a need for efficacy improvement, and consequently, a need for change and reexamination of current guidelines, as well as innovations in treatment strategies.

The insufficiency in the current understanding of depression is not due to a lack of research on the current treatments. Over the past several decades, more than 500 trials have analyzed antidepressant medications, and more than 600 have investigated psychotherapy interventions for depression. Nonetheless, fewer than 20% of medication trials and less than 30% of psychotherapy trials are considered to have a low risk of bias. The fact that the majority of trials are marked by a

high risk of bias indicates that a significant portion of research may have methodological flaws that could affect the reliability of the findings. Furthermore, the long-term effects of treatments are rarely assessed in these studies. Although an effort has been put in the research of depression treatment, with over 1000 clinical trials, many crucial questions regarding the mechanisms underlying those interventions and their effectiveness remain unanswered (Cuijpers et al., 2020).

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