sciendo Acta Marisiensis - Seria Medica 2023;69(4):244-251 DOI: 10.2478/amma-2023-0042

REVIEW

Psychotherapy, pharmacotherapy, and their combination in the treatment of major depressive disorder: How well are we making use of available therapies?

Ingrid Karina Nădășan, Gabriel Hancu*

Department of Pharmaceutical and Therapeutic Chemistry, George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures, Targu Mures, Romania

Major depressive disorder stands as a profound challenge in the realm of psychiatric illnesses disrupting the well-being and daily existence of affected individuals. This heterogeneous condition continues to baffle researchers due to the elusive nature of its full neurological mechanisms. This review delves into the complex landscape of major depressive disorder, exploring the diverse therapeutic avenues available, from the nuanced realms of psychotherapy to the pharmacological and non-pharmacological approaches that have been the focus of extensive research. In the relentless pursuit of relief for those afflicted, substantial efforts and resources are tirelessly channeled into the exploration of novel antidepressants and the refinement of existing therapeutic protocols. This review juxtaposes the efficiencies of existing treatments, unraveling their comparative effectiveness, and shedding light on their respective strengths and limitations. Even so, the question remains, how well are we managing the treatment of major depressive disorder, and which is the best option not only to treat this condition but also to reach full remission. Consequently, we have compiled findings on treatment selections and how efficient they are in relation to each other. The more we understand how to treat depression effectively the more we can improve the quality of life of individuals affected by this disorder. By comprehensively evaluating the diverse modalities, this review aims to guide clinicians and researchers toward evidence-based decisions, facilitating the formulation of individualized and targeted treatment protocols.

Keywords: depression, antidepressants, psychotherapy, pharmacotherapy, combined therapy

Received 19 July 2023 / Accepted 11 October 2023

Introduction

Depression is a common and serious mood disorder, affecting around 5% of adults globally according to the World Health Organization (WHO); however, the actual number of people suffering from depression is higher than estimates due to underdiagnosis. Depression can impact people of all ages, genders, and backgrounds, affecting their quality of life and daily functioning, their work and social life. Moreover, WHO reported that the COVID-19 pandemic has led to a 25% increase in depression and anxiety worldwide, with young people and women being the most affected [1].

The global burden of depression is extremely high, both from a social and economic point of view; according to WHO's statistics on disability-adjusted life years (DALYs), depression is one of the leading causes of disability worldwide [1]. Depression has a major impact on public health due to its high prevalence, debilitating effects, and associated costs. The economic burden of depression is also significant due to healthcare costs, lost productivity, and disability [2]. The stigma surrounding depression also has a big impact on society, since many individuals do not seek out help due to their cultural background, religious beliefs, life circumstances, etc., remaining undiagnosed and untreated [3]. Furthermore, many individuals often get the wrong diagnostics, inappropriate treatments, or have no financial means of procuring a treatment [4]. This leads to a rising prevalence of untreated depression, resulting in a significant loss of lives globally. Approximately 700000 of people suffering major depressive disorder (MDD) die by suicide worldwide every year, making this the fourth leading cause of death among individuals aged 15 to 29 [5].

Depression is characterized by intense sadness, hopelessness, loss of interest in once enjoyable activities, lack of motivation, low energy, difficulty concentrating and making decisions, as well as ruminating on past mistakes, regrets, and fears. Physical symptoms like appetite and sleep changes, unexplained physical pain, and chronic fatigue can also accompany depression. In severe cases, depression may lead to thoughts of death and suicide [6].

Depression has a heterogeneous nature; therefore, a standardized classification hasn't been formulated yet. There are different systems used to classify depression, usually based on symptomatology, duration, or presumed etiology. According to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), depressive disorders include mood dysregulation, MDD, dysthymia (persistent depressive disorder), medication-induced depression, and premenstrual dysphoric disorder [6].

On the other hand, the International Classification of Diseases, 10th revision (ICD-10) categorizes depression based on the severity of symptoms, ranging from mild, moderate to severe, with or without psychotic symptoms. Other types of depressive disorders defined by the ICD-10 are atypical depression, recurrent depressive disorder, and persistent affective disorder [6].

* Correspondence to: Gabriel Hancu
E-mail: gabriel.hancu@umfst.ro

Aside from the typical symptomatology, MDD can also be associated with symptoms specific to other affective disorders, such as anxiety, bipolar disorder, or psychosis [7].

It is crucial to differentiate and accurately specify various types of depression to be able to establish effective treatment guidelines. However, current classifications are incomplete due to limited knowledge about the exact underlying mechanisms and causes of depression. Advancements in neuropsychology and genetic research offer hope for a deeper understanding of this condition and the potential for improved treatment protocols and strategies to be developed [8].

Depression can have multiple causative factors, and it is often difficult to pinpoint a single cause. In general, behind a depressive episode lies an environmental stress factor of an affective nature, e.g., losing a loved one, financial instability, problems in interpersonal relationships, or serious illnesses. However, most of the time, this approach is not sufficient to explain how a depressive episode triggers itself. One explanatory paradigm for depression is the diagnosis-stress model, a theory that links genetic predisposition with external environmental factors that can trigger or precipitate depressive episodes. This can lead to chronic depression when additional stressors keep occurring [9]. Another detailed model is the biopsychosocial (BPS) model, which emphasizes the ties between biological, psychological, and environmental factors in triggering depression. Genetic factors, maladaptive cognition, and external stressors contribute to the development and persistence of depression. Therefore, understanding the psychological aspect of depression is essential for effective treatment management [10].

The current treatments that are available can be classified as pharmacotherapy, psychotherapy, and other forms of non-pharmacological interventions such as electroconvulsive therapy. Although, according to studies, these treatment options can be quite efficient to some degree, they are still not good enough, therefore depression usually has a poor prognosis. Currently, precision medicine is being adopted into guidelines more and more, seeing as individuals respond differently to each treatment, they need a more personalized approach to choosing treatment options, all of which should be based on their symptoms and responses to different therapies [11].

Another shift in the management of depression has been recognizing the importance of preventive mental health care and providing it where needed, especially in countries that have less access to preventive care [12].

There is also an increasing need to develop novel antidepressants in hopes of finding one that would possess better efficacy, a faster onset of effect, be safer and more tolerable for patients, and reduce the relapse of depressive episodes [8].

This review aims to explore the utilization of psychotherapy, pharmacotherapy, and their combination in treating MDD, examining the current research on the effectiveness of these treatments individually and together, along with their advantages and disadvantages. This review also addresses barriers to treatment utilization, patient preferences, and offers recommendations for enhancing the use of these therapies in the treatment of MDD.

The molecular neurobiology of depression

The monoamine hypothesis is a well-known theory of depression, suggesting that a deficiency in monoamine neurotransmitters like serotonin (5-HT), norepinephrine (NE), and dopamine (DA) are responsible for causing depression.

Initially, MDD was believed to stem from dysregulations in the brain's monoamine systems, a so-called „chemical imbalance." The theory surfaced after research on the antihypertensive drug reserpine showed that it affected 5-HT and NE metabolisms, causing depression-like symptoms in patients without prior MDD symptomatology. The discovery of tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) further supported this hypothesis by demonstrating their efficacy in relieving depression symptoms. More supporting evidence is that long-term use of antidepressants targeting the monoamine system leads to the desensitization and down-regulation of post-synaptic receptors, which explains the delayed therapeutic action of these substances. However, despite molecular evidence, around 30% of patients don't respond to these agents, which further emphasizes the importance of studying the underlying mechanisms of depression [13].

Since then, different studies have concluded that there is more than just a chemical imbalance involved in the development of depression. A more recent hypothesis suggests that the changes in the neurobiological processes occurring in MDD are closely tied to stress and the way the brain structures and functions are modified because of acute or chronic stress present in the patient's life [14, 15].

It is known that stress is a major contributing factor to MDD. Elevated levels of the stress hormone cortisol can damage and shrink neurons in brain structures containing glucocorticoid receptors, such as the hippocampus, which is often associated with mood disorders. These changes can further disrupt the functioning of the hypothalamic-pituitary-adrenal (HPA) axis, amygdala, and prefrontal cortex, all of which are implicated in MDD development [16].

Evidence suggests that high levels of stress also decrease the expression of brain-derived neurotrophic factor (BDNF) in the brain, causing neuronal atrophy. Therefore, the neurotrophic hypothesis became one of the major theories that explains the mechanism of MDD, the model suggesting that environmental stress factors and an increased genetic vulnerability to stress elevate glucocorticoid levels in the central nervous system (CNS), especially cortisol, therefore altering neural plasticity and causing the down-regulation of a series of growth factors in the brain, such as BDNF, neurotrophin-3 (NT-3) and neurotrophin-4 (NT-4) [17-19]. There is evidence that suggests recurring MDD

has a progressive nature and causes further neuronal atrophy, volumetric reductions, and decreased cell resistance in the limbic system [20, 21] (Figure 1).

Inflammation is also linked to the mechanism of depression; studies have shown increased levels of inflammatory markers in the blood and cerebrospinal fluid of individuals with depression. Inflammatory cytokines can affect neurotransmitter signaling and contribute to the development of depressive symptoms. For example, cytokines can decrease the availability of 5-HT and can increase the activity of the kynurenine pathway, a metabolic pathway that produces neurotoxic compounds that contribute to the development of depression. Inflammation also affects neuroplasticity, impeding the brain's ability to respond to environmental stimuli. Additionally, inflammatory cytokines can alter the structure and function of neurons, which may contribute to the development of depressive symptoms [22-24].

Depression can be hereditary, studies found that certain genes have been linked to an increased susceptibility to depression [25]. Recent research has also focused on the role of epigenetic changes, such as DNA methylation and histone modifications, that alter gene expression without changing the underlying DNA sequence; methylation can switch off genes involved in mood regulation and stress responses, leading to an increased risk for depression [26]. Epigenetic changes were identified in genes involved in stress signaling, neurotransmitter regulation, and neuroplasticity. There is evidence to support the idea that early life stress may have a long-lasting impact on the regulation of the epigenome, raising the risk of depression in later life, as evidenced by higher DNA methylation in stress-related genes among children who experienced early life stress, such as abuse or neglect [27].

Psychotherapy of depression

Conversational psychotherapies are the most efficacious in treating depression; options include cognitive-behavioral therapy (CBT), problem-solving therapy (PST), interpersonal therapy (IPT), psychodynamic therapy (PDT) and behavioral activation therapy (BAT).

CBT is an empirically supported therapy, characterized by a structured, strategic, time-limited, and well-planned approach. Therapists collaborate with patients to explore the cognitive patterns and connections between thoughts, emotions, and behaviors that contribute to depression. The aim is to help patients understand and recognize these cognitive processes, and help them change negative thinking patterns, unhealthy behaviors, and develop coping mechanisms to alleviate depression symptoms [28].

PST focuses on identifying and solving problems that arise from stressful life events; its aim is to develop better strategies for dealing with external environmental stress factors and encourage taking the right decisions during stressful life events. The final goal is achieving a state of psychological well-being. This type of psychotherapy can be very useful for patients with specific or complex problems underlying their condition [29].

IPT is most effective for individuals whose depression symptoms are primarily related to social and interpersonal difficulties. This psychotherapy approach aims to reduce depressive symptoms by improving social functioning, communication skills, and interpersonal relationships. It is a well-structured therapy with a set number of sessions, where the therapist identifies social stress factors, sets goals, and develops strategies to overcome them. IPT provides patients with a more positive outlook on their social life [30].

During PDT, therapists assist patients in examining and comprehending unconscious feelings and thoughts that might be causing depression. PDT can be effective in treating depression, particularly in individuals with a history of trauma or other psychological issues. Typically, PDT involves exploring childhood experiences, relationship patterns, and emotions [31].

BAT is used to encourage patients to perform activities that make them feel good or give them a sense of success, even if they initially don't consider enjoying them. BAT typically involves setting goals, identifying pleasurable activities, and developing a plan to increase engagement in these activities. Therefore, BAT is effective in treating

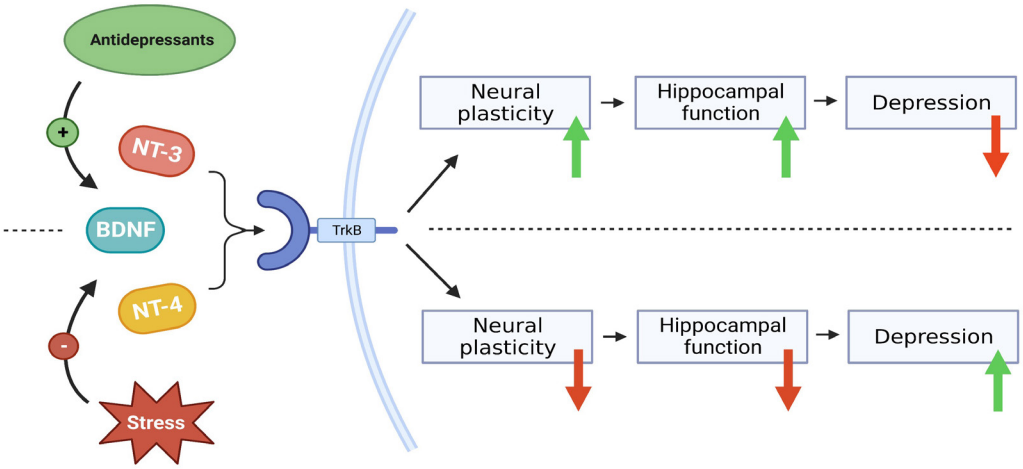

Figure 1. The neurotrophic hypothesis of depression

depression, particularly in individuals who have difficulty with motivation or activity levels [32].

The best approach when choosing the type of psychotherapy depends on the individual's unique circumstances, seeing as in a meta-analysis from 2021 by Cuijpers P it was found that all major forms of psychotherapy are effective, with minimal differences between them, therefore an individual's preferences, needs and availability play a significant role in selecting the appropriate therapy [12].

Pharmacotherapy of depression

Currently, there is a wide range of antidepressants available, each with their own set of mechanisms, therapeutic actions, and side effects. According to Stahl, antidepressants can be classified as modern antidepressants: selective serotonin reuptake inhibitors (SSRIs), serotonin partial agonist/ reuptake inhibitors (SPARIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), norepinephrine reuptake inhibitors (NRIs), norepinephrine-dopamine reuptake inhibitors (NDRIs), serotonin antagonist/ reuptake inhibitors (SARIs) and the classic antidepressants: MAOIs and TCAs [33] (Table I).

Current antidepressants primarily rely on the monoamine hypothesis, discovered over 50 years ago. The first successful antidepressant, iproniazid, was derived from the anti-tuberculosis agent isoniazid, which became the first MAOI to have major success in treating depression. Later, imipramine was approved by the FDA in 1959, becoming the prototype for tricyclic antidepressants (TCAs). Despite their effectiveness, TCAs and MAOIs have significant side effects due to their affinity to receptors outside the monoamine system. This prompted the development of newer, safer antidepressants like SSRIs, with fluoxetine being approved in 1987, this constituting the „moment zero" in the modern treatment of depression. However, even with the introduction of these medications, studies show that only 50% of individuals with depression achieve full remission, indicating the need to develop more effective treatments. It is important to recognize that antidepressant medication is not universally effective, as responses can vary greatly among individuals [36].

Blackburn states that the „Holy Grail" of antidepressants would be one that would have a vastly improved efficacy, faster onset of effect, would be safer and more tolerable for the patient without causing severe withdrawal syndrome, and one that would reduce the remission rates of depression, all whilst alleviating the harmful symptomatology [8].

However, there are several limitations in developing novel antidepressants. First, animal models used to predict monoamine-based antidepressant action are not accurate enough to predict other types of antidepressant mechanisms. Second, testing antidepressant efficacies is costly and requires many patients, increasing the risk of placebo responses and trial failures. Another challenge is the financial success of monoamine-based agents, particularly SSRIs like fluoxetine, which discourages pharmaceutical investment in discovering novel antidepressants. Additionally, the incomplete understanding of depression's pathophysiology, etiology, and the interaction between environmental factors and depression-related genes hinders the development of new drug molecules [37].

Despite hindrances, the field has generally come to the same conclusion, that we must move beyond the mechanisms of action of currently available antidepressants. New directions in antidepressant drug discovery involve the identification of new potential targets, developing downstream alterations to obtain faster onsets of action and a more universal therapeutic action [38, 39].

Psychotherapy versus pharmacotherapy in depression

Since there is such a wide variety of therapies available, there are constant ongoing debates regarding the best approach when it comes to treating depression, with both sides arguing that one or the other may be superior. Table II summarizes a few clinical trials comparing both psychological treatments and antidepressant medications (ADM) (studies are listed chronologically).

There have been several meta-analyses conducted to compare the effectiveness of pharmacotherapy and psychotherapy for the treatment of depression [49-57]. Some

Table I. Antidepressant medication used in therapy [33-35]

Antidepressant class	Mechanism of action	Examples of agents
Selective serotonin reuptake inhibitors (SSRIs)	Inhibits the serotonin transporter SERT, selectively inhibiting the reuptake of 5HT	Citalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline
Serotonin partial agonist/ reuptake inhibitors (SPARIs)	Inhibits SERT and has partial agonism at the 5HT1A receptor	Vilazodone
Serotonin- norepinephrine reuptake inhibitors (SNRIs)	Inhibits SERT and the norepinephrine transporter (NET), inhibiting the reuptake of both 5HT and NE	Duloxetine, Levomilnacipran, Milnacipran, Venlafaxine, Desvenlafaxine
Norepinephrine-dopamine reuptake inhibitors (NDRIs)	Inhibits reuptake of dopamine (DA) and NE by inhibiting the dopamine transporter (DAT) and NET respectively	Bupropion
Serotonin antagonist/ reuptake inhibitors (SARIs)	Blocks 5HT2A and 5HT2C receptors and inhibits SERT	Nefazodone, Trazodone
Monoamine oxidase inhibitors (MAOIs)	Irreversibly inhibits the monoamine oxidase enzyme, inhibiting the metabolization of 5HT, NE and DA	Isocarboxazid, Phenelzine, Tranylcypromine, etc.
Tricyclic antidepressants (TCAs)	Block 5HT and NE reuptake by inhibiting their respective transporters, SERT and NET. They also block muscarinic cholinergic receptors, alpha1-adrenergic receptors, H1 histaminic receptors and voltage-sensitive sodium channels.	Imipramine, Clomipramine, Desipramine, Amitriptyline, Nortriptyline, Doxepine, etc.

Table II. Clinical trials comparing the efficiency of pharmacotherapy and psychotherapy

Author, year published	Method	Sample	Treatments that were compared	Results
Weissman MM, 1979 [40]	Randomized clinical trial	MDD, N=81	TCAs and short-term IPT, alone and in combination	The combination of both treatments was more effective than either treatment alone. TCAs and IPT alone were equally efficacious.
Keller MB, 2000 [41]	Randomized clinical trial	MDD, N=519, HRSD>20	Nefazodone and CBT	The combination of the two were more efficacious than either treatment alone, nefazodone and CBT alone are similarly efficacious, the only advantage being nefazodone having a faster onset of effect compared to psychotherapy.
de Jonghe F, 2001[42]	Randomized clinical trial	MDD, N=167, HRSD>14	ADM and short psychodynamic supportive psychotherapy	Combined treatment was found to be more efficacious as patients were significantly less likely to drop out, therefore they were more likely to recover.
DeRubeis RJ, 2005 [43]	Randomized placebo- controlled clinical trial	MDD, N=240, HRSD>20	Comparison between ADM and CT.	CT can be as effective as ADM in the initial treatment of MDD. The study emphasized that the effectiveness of psychotherapy can vary based on the therapist's experience/ expertise.
Dimidjian S, 2006 [44]	Placebo-controlled trial	MDD, N=241, BDI>20, HRSD>14	Comparison between BAT, CT, and ADM	BAT is comparable to ADM; BAT is somewhat more efficacious than CT. Highlights importance of administering treatments according to severity; less severely depressed patients showed no significant improvement from ADM compared to placebo.
Segal ZV, 2010 [45]	Randomized placebo- controlled clinical trial	MDD, N=160, HRSD>16, history of a minimum 2 depressive episodes	Comparison of the rates of relapse between MBCT and ADM	MBCT offers protection against relapse on par with that of ADM, and significantly higher than placebo. Study highlights the importance of maintaining at least one treatment in the long-term for patients displaying high remission rates.
Nakagawa A, 2017 [46]	Randomized controlled trial	Pharmacotherapy-resistant depression, N=80, ADM>8 weeks, HDRS>16	Comparative effectiveness of TAU alone and TAU associated with CBT.	The trial found that supplementing usual ADM treatment with CBT may benefit patients with pharmacotherapy-resistant depression.
Quigley L, 2019 [47]	Randomized controlled trial	MDD, N=104	Comparing the effects on cognitive change of CBT versus ADM.	Both CBT and ADM produced significant positive cognitive change and therefore improved depression symptoms.
Hemanny C, 2020 [48]	Randomized clinical trial	MDD, N=76, HRSD>15, BDI>20	Comparing effects of trial-based cognitive therapy, BAT and ADM.	The study shows evidence that trial-based cognitive therapy and BAT combined with ADM were more efficacious than ADM alone in reducing depressive symptoms.

ADM – antidepressive medication; BAT - behavioral activation therapy; BDI - Beck Depression Inventory; CBT - cognitive–behavioral therapy; CT – cognitive therapy; IPT - interpersonal Psychotherapy; HRSD - Hamilton rating scale for depression; MBCT - Mindfulness-based cognitive therapy; MDD – Major depressive disorder; TAU – treatment as usual; TCA – tricyclic antidepressant.

studies showed that most types of psychotherapy have comparable if not equal effects to pharmacotherapy, however, most of the results are dependent on the severity of the depressive symptoms and in the case of psychotherapy, the expertise of the therapist plays a major role in the outcome of the treatment.

Most importantly, several studies demonstrated that the combination of both treatments is more efficacious than either treatment option administered on their own, displaying a significantly higher reduction of depressive symptoms [40-48].

These findings have been further confirmed by various meta-analyses, which are presented in Table III (studies are listed chronologically).

As most of the meta-analysis presented above suggest, both types of therapy options are viable for treating and improving the symptomatology and quality of life of individuals suffering from MDD. Psychotherapy can provide long-term benefits and help individuals develop new coping skills; it is especially helpful in acute phases of depression and mild to moderate cases [49-57].

Antidepressants, on the other hand, can provide faster relief of symptoms and were also proven to be more efficacious than psychotherapy in severe or chronic depression.

What these findings suggest is that ultimately, the choice between psychotherapy and pharmacotherapy should depend on everyone's needs, severity of symptoms, and underlying causes, as well as take preferences and costs into consideration.

Most studies also emphasize the fact that there is still a need to further study how we manage depression, invest resources and finances into discovering novel antidepressants and further improve treatment options, since the ones we have available are still not ideal.

The high risk of relapse and the recurrent nature of depression are major problems when it comes to treating this condition. If patients do end up responding to ADM, they often require medication to be administered continuously to prevent the reoccurrence of their symptoms after ADM discontinuation. However, the issue when it comes to administering ADM chronically is that the side effects are usually not well tolerated. This is why psychotherapies, especially CBT that has been proven to have a long-lasting protective effect against recurrence, have the potential to become long-term supportive therapies, either in monotherapy for less severe forms of depression or in combination with pharmacotherapy for more severe or chronic forms of depression. The downside of psychotherapies is that their effect is highly dependent on the therapist's expertise and requires a longer time for the effects to be seen and felt by the patient, which might interfere with adherence [42,45,48].

A meta-analysis by Breedvelt JJF from 2021, concluded that psychotherapy delivered sequentially during and/or

Table III. Meta-analysis comparing the efficiency of pharmacotherapy and psychotherapy

Authors, year published	Method	Sample	Comparison	Results
Cuijpers P, 2008 [49]	Meta-analysis	30 randomized clinical trials, 3178 patients, depressive disorders (MDD, dysthymia, minor depressive disorder)	Psychological and ADM	Both treatments were effective in mild to moderate depressive disorders, SSRIs were found to be significantly more effective for MDD than psychological treatments. Pharmacological interventions may be more effective than psychological interventions in dysthymia. The study concluded that both interventions have their own merits.
Imel ZE, 2008 [50]	Meta-analysis	28 studies, 3381 patients, MDD, dysthymia, minor depression	Psychotherapy and ADM	Both psychotherapy and medication are viable treatments for MDD, with psychotherapy having the advantage of offering a prophylactic effect that medication does not provide. This study found that in the treatment of dysthymia, medication was more efficacious than psychotherapy.
Cuijpers P, 2013 [51]	Meta-analysis	67 studies, 5993 patients, MDD, dysthymia, anxiety, seasonal affective disorder, panic disorder	Psychotherapy and ADM	Both treatment options have comparable effects in most depressive and anxiety disorders. The study found that for dysthymia pharmacotherapy was more efficacious. This study highlights the importance of taking costs and patient preferences into account and investigating that aspect further.
Leichsenring F, 2016 [52]	Meta-analysis and individual studies	MDD	Efficacy of psychotherapy and ADM	Both treatments were found to be equally efficacious in short-term administration, with psychotherapy showing superiority in long-term treatment.
Karyotaki E, 2016 [53]	Meta-analysis	23 studies, 2184 participants, MDD	Combined therapy compared to either psychotherapy or antidepressant treatment alone.	Combined therapy has a superior effect on MDD than other treatments alone. Psychotherapy alone in the acute phase is as effective as combined therapy in the long-term. The study highlights the importance of patient preference when choosing the treatment option.
Kamenov K, 2017 [54]	Meta-analysis	153 studies, MDD	The effect of psychotherapy, pharmacotherapy alone and in combination on quality of life	Combined treatment has the best outcome. Psychotherapy and pharmacotherapy alone are also efficacious for quality of life.
Hofmann SG, 2017 [55]	Meta-analysis	37 studies (24 CBT, 13 SSRIs), MDD	The effect of CBT or SSRIs on quality of life	Both treatment options proved to be efficacious in improving QoL. The study highlights that each one targets a different aspect of depressive symptoms so their combination might be the most efficacious.
Kappelmann N, 2020 [56]	Meta-analysis	38 studies	Comparative effect of ADM and psychotherapy at the individual symptom level.	The study reports that there is no difference between ADM and psychotherapy at symptom levels.
Cuijpers P, 2020 [57]	Network meta-analysis	101 studies (N=11,910), moderate to severe MDD	The relative effects of psychotherapies, pharmacotherapies and their combination in treating adult depression.	Combined treatment was more effective than either psychotherapy or pharmacotherapy alone. No significant differences were found between either monotherapy options.

Table legend: ADM – antidepressive medication; CBT - cognitive–behavioral therapy; MDD – Major depressive disorder; SSRI – selective serotonin reuptake inhibitor

after tapering antidepressant medications proved to be an effective preventive method for the relapse of depression instead of administering antidepressants in the long-term management of recurring depression [58].

Enhanced care, focusing on accessibility and personalization, aims to improve depression treatment outcomes and enhance patients' quality of life. This approach encompasses physical, psychological, and social aspects, tailoring therapies based on individual needs, symptoms, and causes. It combines psychotherapy, medication, and supportive interventions, including lifestyle changes.

Crucially, enhanced care involves collaborative efforts among healthcare providers, including general physicians, psychiatrists, therapists, and specialists. Continuity of care, through regular check-ups and monitoring, is emphasized to prevent relapse and maintain well-being post-treatment [59, 60].

The way forwards in lowering the prevalence of depression should consist of improving the quality of treatments available, implementing collaborative care and personalized treatments, providing as early as possible interventions, implementing psychological treatments to lower the risk of recurrence, and raising social awareness to counter most of the causative factors of depression [61].

Conclusion

Depression, is a widespread psychiatric disorder, treated through psychotherapy and pharmacotherapy. Both approaches have their strengths and weaknesses, and the most effective treatment will depend on the individual's unique circumstances and needs.

Psychotherapy, conducted with a therapist, explores underlying causes of depression, and equips individuals with coping skills; sometimes it's as effective as medication, offering long-lasting benefits, although it may take longer to see significant improvement of symptomatology.

Pharmacotherapy, involving the use antidepressants, alters brain chemistry, providing relief. Combining these methods, tailored to individual needs, maximizes effectiveness. Treatment choice depends on personal circumstances. The effectiveness of antidepressants can vary widely depending on the individual, and it may take several weeks or even months to see significant improvement of symptomatology. Overall, antidepressants are moderately effective for the treatment of depression, with response rates ranging from 30-50%, depending on the medication and the individual.

Both psychotherapy and medication are effective treatments for depression, with a combination often being the

most successful. Medication can address severe symptoms, but it may not tackle underlying causes, where psychotherapy is valuable. Improving depression outcomes is vital, considering the millions affected globally. While progress has been made, ensuring accessible help for everyone remains a challenge, necessitating ongoing efforts in research and treatment accessibility.

The choice between psychotherapy and medication for depression hinges on individual preferences, symptom severity, and other factors. Despite the challenges posed by the growing prevalence of depression, there is hope. Efforts are being made to prioritize patient needs, shift paradigms, enhance clinical trials, refine diagnostic criteria, emphasize prevention, reduce social stigma, extend professional care to underserved areas, improve treatment guidelines, and explore novel approaches to depression treatment. Optimal handling of depression as a public health concern necessitates ongoing research, advocacy, and continuous support tailored to individual needs.

Conflict of interest

The authors declare no conflict of interest.

Author contributions:

IKN (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Validation; Visualization; Writing – original draft) GH (Conceptualization; Formal analysis; Investigation; Methodology; Supervision; Writing – review & editing)

References

1. World Health Organization. Depression and other common mental disorders: Global Health Estimates. 2017. Available at: https://apps.who.int/iris/handle/10665/254610
2. Greenberg PE, Fournier A-A, Sisitsky T, Simes M, Berman R, Koenigsberg SH, et al. The economic burden of adults with major depressive disorder in the United States (2010 and 2018). PharmacoEconomics. 2021;39(6):653-665.
3. Patel V, Saxena S, Lund C, Thornicroft G, Baingana F, Bolton P, et al. The Lancet Commission on Global Mental Health and Sustainable Development. Lancet. 2018;392(10157):1553–1598.
4. Thornicroft G, Chatterji S, Evans-Lacko S, Gruber M, Sampson N, Aguilar-Gaxiola S, et al. Undertreatment of people with major depressive disorder in 21 countries. BJPsych. 2017;210(2):119-124.
5. World Health Organization. Suicide. 2021. Available at: https://www.who.int/news-room/fact-sheets/detail/suicide
6. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 2013.
7. Paykel ES. Basic concepts of depression. Dialogues Clin Neurosci. 2008;10(3):279–289.
8. Blackburn TP. Depressive disorders: Treatment failures and poor prognosis over the last 50 years. Pharmacol Res Perspect. 2019;7(3).
9. Penner-Goeke S, Binder EB. Epigenetics and depression. Dialogues Clin Neurosci. 2019;21(4):397-405
10. Garcia-Toro M, Aguirre I. Biopsychosocial model in Depression revisited. Med Hypotheses. 2007;68(3): 683–691.
11. Cohen ZD, DeRubeis RJ. Treatment selection in depression. Annu Rev Clin Psychol. 2018;14(1):209-236.
12. Cuijpers P, Quero S, Noma H, Ciharova M, Miguel C, Karyotaki E, et al. Psychotherapies for depression: A network meta-analysis covering efficacy, acceptability and long-term outcomes of all main treatment types. World Psychiatry. 2021;20(2):283-293.
13. Al-Harbi KS. Treatment-resistant depression: Therapeutic trends, challenges, and Future Directions. Patient Prefer Adherence. 2012;6:369-388.
14. aan het Rot M, Mathew SJ, Charney DS. Neurobiological mechanisms in major depressive disorder. CMAJ. 2009;180(3):305–313.
15. Harmer CJ, Duman RS, Cowen PJ. How do antidepressants work? New Perspectives for Refining Future Treatment Approaches. Lancet Psychiatry. 2017;4(5):409–418.
16. Maletic V, Robinson M, Oakes T, Iyengar S, Ball SG, Russell J. Neurobiology of depression: An integrated view of key findings. Int J Clin Pract. 2007;61(12):2030–2040.
17. Boku S, Nakagawa S, Toda H, Hishimoto A. Neural basis of major depressive disorder: Beyond monoamine hypothesis. PCN. 2017;72(1):3–12.
18. Villas Boas GR, Boerngen de Lacerda R, Paes MM, Gubert P, Almeida WL, Rescia VC, et al. Molecular aspects of depression: A review from neurobiology to treatment. Eur J Pharmacol. 2019;851:99–121.
19. Castrén E, Monteggia LM. Brain-derived neurotrophic factor signaling in depression and antidepressant action. Biol Psychiatry. 2021;90(2):128–136.
20. Cole J, Costafreda SG, McGuffin P, Fu CHY. Hippocampal atrophy in first episode depression: A meta-analysis of Magnetic Resonance Imaging Studies. J Affect Disord. 2011;134(1–3):483–487.
21. Lang UE, Borgwardt S. Molecular mechanisms of depression: Perspectives on New Treatment Strategies. Cell Physiol Biochem. 2013;31(6):761–777.
22. Su KP. Inflammation in psychopathology of depression: Clinical, biological, and therapeutic implications. BioMedicine. 2012;2(2):68–74.
23. Makhija K, Karunakaran S. The role of inflammatory cytokines on the aetiopathogenesis of depression. Aust N Z J Psychiatry. 2013;47(9):828–839.
24. Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: A social signal transduction theory of depression. Psychol Bull. 2014;140(3):774–815.
25. McGuffin P, Katz R, Bebbington P. Hazard, heredity and depression. A family study. J. Psychiatr. Res. 1987; 21: 365-375.
26. Peña CJ, Nestler EJ. Progress in epigenetics of depression. Prog Mol Biol Transl Sci. 2018;157:41–66.
27. Park C, Rosenblat JD, Brietzke E, Pan Z, Lee Y, Cao B, et al. Stress, epigenetics and depression: A systematic review. Neurosci Biobehav Rev. 2019;102:139–152.
28. Fenn K, Byrne M. The key principles of cognitive behavioural therapy. InnovAiT. 2013;6(9):579–585.
29. D'Zurilla TJ, Nezu AM, Problem-solving therapy, in Dobson KS (ed): Handbook of Cognitive-behavioral Therapies, Guilford Press, NY, 2010, 197–225.
30. Markowitz JC, Weissman MM. Interpersonal psychotherapy: principles and applications. World Psychiatry. 2004;3(3):136-139.
31. Summers RF, Barber JP. Psychodynamic therapy: A guide to evidence-based practice. Guilford Press, NY, 2010.
32. Dimidjian S, Hollon SD, Dobson KS, Schmaling KB, Kohlenberg RJ, Addis ME, et al. Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the acute treatment of adults with major depression. J Consult Clin Psychol. 2006;74(4):658–670.
33. Stahl SM, Grady MM, Muntner N. Stahl's essential psychopharmacology: Neuroscientific basis and practical applications, Cambridge University Press, Cambridge, UK, 2021.
34. Hillhouse TM, Porter JH. A brief history of the development of antidepressant drugs: From monoamines to glutamate. Exp Clin Psychopharmacol. 2015;23(1):1–21.
35. Lopez-Munoz F, Alamo C. Monoaminergic neurotransmission: The history of the discovery of antidepressants from 1950s until today. Curr Pharm Des. 2009;15(14):1563–1586.
36. Berton O, Nestler EJ. New approaches to antidepressant drug discovery: Beyond monoamines. Nat Rev Neurosci. 2006;7(2):137–151.
37. Harmer CJ, Duman RS, Cowen PJ. How do antidepressants work? New Perspectives for Refining Future Treatment Approaches. Lancet Psychiatry. 2017;4(5):409–418.
38. Wang Q, Dwivedi Y. Advances in novel molecular targets for antidepressants. Prog Neuropsychopharmacol Biol Psychiatry. 2021;104:110041.
39. Jarończyk M, Walory J. Novel molecular targets of antidepressants. Molecules. 2022;27(2):533.
40. Weissman MM, Prusoff BA, Dimascio A, Neu C, Goklaney M, Klerman GL. The efficacy of drugs and psychotherapy in the treatment of acute depressive episodes. Am J Psychiatry. 1979;136(4B):555-558.
41. Keller MB, McCullough JP, Klein DN, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. N Engl J Med.

2000;342(20):1462-1470.
42. de Jonghe F, Kool S, van Aalst G, Dekker J, Peen J. Combining psychotherapy and antidepressants in the treatment of depression. J Affect Disord. 2001;64(2-3):217-229.
43. DeRubeis RJ, Hollon SD, Amsterdam JD, et al. Cognitive therapy vs medications in the treatment of moderate to severe depression. Arch Gen Psychiatry. 2005;62(4):409-416.
44. Dimidjian S, Hollon SD, Dobson KS, et al. Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the acute treatment of adults with major depression. J Consult Clin Psychol. 2006;74(4):658-670.
45. Segal ZV, Bieling P, Young T, et al. Antidepressant monotherapy vs sequential pharmacotherapy and mindfulness-based cognitive therapy, or placebo, for relapse prophylaxis in recurrent depression. Arch Gen Psychiatry. 2010;67(12):1256-1264.
46. Nakagawa A, Mitsuda D, Sado M, et al. Effectiveness of Supplementary Cognitive-Behavioral Therapy for Pharmacotherapy-Resistant Depression: A Randomized Controlled Trial. J Clin Psychiatry. 2017;78(8):1126-1135.
47. Quigley L, Dozois DJA, Bagby RM, Lobo DSS, Ravindran L, Quilty LC. Cognitive change in cognitive-behavioural therapy v. pharmacotherapy for adult depression: a longitudinal mediation analysis. Psychol Med. 2019;49(15):2626-2634.
48. Hemanny C, Carvalho C, Maia N, et al. Efficacy of trial-based cognitive therapy, behavioral activation and treatment as usual in the treatment of major depressive disorder: preliminary findings from a randomized clinical trial. CNS Spectr. 2020;25(4):535-544.
49. Cuijpers P, van Straten A, Andersson G, van Oppen P. Psychotherapy for depression in adults: a meta-analysis of comparative outcome studies. J Consult Clin Psychol. 2008;76(6):909-922.
50. Imel ZE, Malterer MB, McKay KM, Wampold BE. A meta-analysis of psychotherapy and medication in unipolar depression and dysthymia. J Affect Disord. 2008;110(3):197-206.
51. Cuijpers P, Berking M, Andersson G, Quigley L, Kleiboer A, Dobson KS. A meta-analysis of cognitive-behavioural therapy for adult depression, alone and in comparison with other treatments. Can J Psychiatry. 2013;58(7):376-385.
52. Leichsenring F, Steinert C, Hoyer J. Psychotherapy Versus Pharmacotherapy of Depression: What's the Evidence?. Z Psychosom Med Psychother. 2016;62(2):190-195.
53. Karyotaki E, Smit Y, Holdt Henningsen K, et al. Combining pharmacotherapy and psychotherapy or monotherapy for major depression? A meta-analysis on the long-term effects. J Affect Disord. 2016;194:144-152.
54. Kamenov K, Twomey C, Cabello M, Prina AM, Ayuso-Mateos JL. The efficacy of psychotherapy, pharmacotherapy and their combination on functioning and quality of life in depression: a meta-analysis. Psychol Med. 2017;47(3):414-425.
55. Hofmann SG, Curtiss J, Carpenter JK, Kind S. Effect of treatments for depression on quality of life: a meta-analysis. Cogn Behav Ther. 2017;46(4):265-286.
56. Kappelmann N, Rein M, Fietz J, et al. Psychotherapy or medication for depression? Using individual symptom meta-analyses to derive a Symptom-Oriented Therapy (SOrT) metric for a personalised psychiatry. BMC Med. 2020;18(1):170.
57. Cuijpers P, Noma H, Karyotaki E, Vinkers CH, Cipriani A, Furukawa TA. A network meta-analysis of the effects of psychotherapies, pharmacotherapies and their combination in the treatment of adult depression. World Psychiatry. 2020;19(1):92-107.
58. Breedvelt JJF, Warren FC, Segal Z, Kuyken W, Bockting CL. Continuation of Antidepressants vs Sequential Psychological Interventions to Prevent Relapse in Depression: An Individual Participant Data Meta-analysis. JAMA Psychiatry. 2021;78(8):868-875.
59. Gilbody S, Bower P, Fletcher J, Richards D, Sutton AJ. Collaborative care for depression: a cumulative meta-analysis and review of longer-term outcomes. Arch Intern Med. 2006;166(21):2314-2321.
60. Katon W, Guico-Pabia CJ. Improving quality of depression care using organized systems of care: a review of the literature. Prim Care Companion CNS Disord. 2011;13(1):PCC.10r01019blu.
61. Ormel J, Kessler RC, Schoevers R. Depression: more treatment but no drop in prevalence: how effective is treatment? And can we do better?. Curr Opin Psychiatry. 2019;32(4):348-354.