Major depressive disorder: Validated treatments and future challenges

Rabie Karrouri, Zakaria Hammani, Roukaya Benjelloun, Yassine Otheman

ORCID number: Rabie Karrouri 0000-0002-7859-4481; Zakaria Hammani 0000-0003-4693-4178; Roukaya Benjelloun 0000-0002-0211-3776; Yassine Otheman 0000-0003-1056-454X.

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Abstract
Depression is a prevalent psychiatric disorder that often leads to poor quality of life and impaired functioning. Treatment during the acute phase of a major depressive episode aims to help the patient reach a remission state and eventually return to their baseline level of functioning. Pharmacotherapy, especially selective serotonin reuptake inhibitors antidepressants, remains the most frequent option for treating depression during the acute phase, while other promising pharmacological options are still competing for the attention of practitioners. Depression-focused psychotherapy is the second most common option for helping patients overcome the acute phase, maintain remission, and prevent relapses. Electroconvulsive therapy is the most effective somatic therapy for depression in some specific situations; meanwhile, other methods have limits, and their specific indications are still being studied. Combining medications, psychotherapy, and somatic therapies remains the most effective way to manage resistant forms of depression.

Key Words: Depression; Treatment; Antidepressants; Psychotherapy; Cognitive-behavioral therapy; Somatic therapies; Electroconvulsive therapy

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INTRODUCTION

Depression is a common psychiatric disorder and a major contributor to the global burden of diseases. According to the World Health Organization, depression is the second-leading cause of disability in the world and is projected to rank first by 2030 [1]. Depression is also associated with high rates of suicidal behavior and mortality [2].

Treatments administered during the acute phase of a major depressive episode aim to help the patient reach a remission state and eventually return to their baseline level of functioning [3]. Acute-phase treatment options include pharmacotherapy, depression-focused psychotherapy, combinations of medications and psychotherapy, and somatic therapies such as electroconvulsive therapy (ECT). Nevertheless, managing the acute phase of depression is only the first step in a long therapy process that aims to maintain remission and prevent relapses. In this article, we discuss various treatment options implemented by clinicians, highlighting the role that each option plays in actual psychiatric practice.

PHARMACOTHERAPY

While selective serotonin reuptake inhibitors (SSRIs) remain the gold-standard treatment for depression, new antidepressants are always being developed and tested. The ultimate goal is to discover a molecule that exhibits quick effectiveness with as few side effects as possible.

Daniel Bovet studied the structure of histamine (the causative agent in allergic responses) to find an antagonist, which was finally synthesized in 1937 [4]. Since then, many researchers have studied the link between the structures and activities of different antihistaminic agents, contributing to the discovery of almost all antidepressants [5].

In the following subsections, we list the main classes of antidepressants in chronological order of apparition, highlighting the most widely used molecules in daily psychiatric practice.

Monoamine oxidase inhibitors

Iproniazid was the first drug defined as an antidepressant; it was later classified as a monoamine oxidase inhibitor (MAOI) [6,7]. Several other MAOIs have been introduced since 1957 [8]. Due to their irreversible inhibition of monoamine oxidase, MAOIs have numerous side effects, such as hepatotoxicity and hypertensive crises, that can lead to lethal intracranial hemorrhages. Consequently, MAOIs have become less commonly used over time [9].

Trials have demonstrated that MAOIs’ efficacy is comparable to that of tricyclic antidepressants (TCAs) [10,11]. However, considering MAOIs’ drug interactions, dietary restrictions, and potentially dangerous side effects, they are now almost exclusively prescribed for patients who have not responded to several other pharmacotherapies, including TCAs [9]. Furthermore, MAOIs have demonstrated specific efficacy in treating depression with atypical features, such as reactive moods, reverse neuro-vegetative symptoms, and sensitivity to rejection [12].

MAOIs are also a potential therapeutic option when ECT is contraindicated [13]. MAOIs’ effectiveness is still unclear for treating depression in patients who are resistant to multiple sequential trials with SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) [14]. Nevertheless, psychiatrists’ use of MAOIs has declined over the years [15,16]. The use of MAOIs is generally restricted to patients...
who do not respond to other treatments.

**TCAs**
The first TCA was discovered and released for clinical use in 1957 under the brand name Tofranil[5,17]. Since then, TCAs have remained among the most frequently prescribed drugs worldwide[9]. TCAs—such as amitriptyline, nortriptyline, protriptyline, imipramine, desipramine, doxepin, and trimipramine—are as effective as other classes of antidepressants—including SSRIs, SNRIs, and MAOIs—in treating major depression[18,19].

However, some TCAs can be more effective than SSRIs when used to treat hospitalized patients[20]. This efficacy can be explained by the superiority of TCAs over SSRIs for patients with severe major depressive disorder (MDD) symptoms who require hospitalization[21-24]. However, no differences have been detected in outpatients who are considered less severely ill[18,20]. In most cases, TCAs should generally be reserved for situations when first-line drug treatments have failed[25].

**SSRIs**
In December 1987, a series of clinical studies confirmed that an SSRI called fluoxetine was as effective as TCAs for treating depression while causing fewer adverse effects[26]. After being released onto the market, its use expanded more quickly than that of any other psychotropic in history. In 1994, it was the second-best-selling drug in the world[7].

Currently available SSRIs include fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, and escitalopram. They have elicited different tolerance rates and side effects—mostly sexual and digestive (nausea and loss of appetite), as well as irritability, anxiety, insomnia, and headaches[27]. Nevertheless, SSRIs have a good tolerability profile[28].

In most systematic reviews and meta-analyses, SSRIs have demonstrated comparable efficacy to TCAs[18,19,29], and there is no significant evidence indicating the superiority of any other class or agent over SSRIs[29-31]. Furthermore, studies show no differences in efficacy among individual SSRIs[29,31-34]. Therefore, most guidelines currently recommend SSRIs as the first-line treatment for patients with major depression[25].

**Norepinephrine reuptake inhibitors**
Other monoamine (norepinephrine, serotonin, and dopamine) neurotransmitter reuptake inhibitors called SNRIs emerged during the 1990s to protect patients against the adverse effects of SSRIs[35]. Currently available SNRIs are venlafaxine, desvenlafaxine (the principal metabolite of venlafaxine), and duloxetine. The extended-release form of venlafaxine is the most commonly used drug in this class. Clinical guidelines commonly recommend prescribing SNRI to patients who do not respond to SSRIs[25].

In individual studies, venlafaxine and duloxetine are generally considered effective as SSRIs[36]. Also, venlafaxine’s efficacy is comparable to that of TCAs[37,38].

According to some meta-analyses, reboxetine (a selective noradrenaline reuptake inhibitor) seems less efficacious than SSRIs[39]. However, these findings could be due to the relatively poor tolerance of reboxetine[40].

**Other antidepressants**
Trazodone is the oldest medication of the so-called “other antidepressants” group that is still in wide use[41,42]. It has been shown to be an effective antidepressant in placebo-controlled research. However, in contemporary practice, it is much more likely to be used in low doses as a sedative-hypnotic than as an antidepressant[41,42].

Nefazodone’s structure is analogous to that of trazodone, though it has different pharmacological properties[43]. Its efficacy and overall tolerability are comparable to those of SSRIs, as indicated by comparative trials[43]. However, its use is associated with rare (but fatal) cases of clinical idiosyncratic hepatotoxicity[44].

Bupropion’s mechanism of action remains unclear, though it is classified as a norepinephrine and dopamine reuptake inhibitor[45]. It appears to have a more activating profile than SSRIs that are modestly superior to bupropion in patients with MDD[46]. However, for individuals with low to moderate levels of anxiety, the efficacy of bupropion in treating MDD is comparable to that of SSRIs[46]. Moreover, bupropion has a better tolerability profile than SSRIs, with minimal weight gain (or even leading to weight loss)[46]. In addition, bupropion is more likely than some SSRIs to improve symptoms of fatigue and sleepiness[47].
Mirtazapine and mianserin are tetracyclic compounds believed to increase the availability of serotonin or noradrenaline (or both), at least initially. Mirtazapine’s ability to antagonize serotoninergic subtype receptors, <5-HT2A> and <5-HT2C>, could also increase noradrenaline and dopamine release in cortical regions[25]. Mirtazapine is about as effective as SSRIs[48].

Recently, drugs have been developed that block serotonin reuptake while affecting a variety of 5-HT receptor subtypes. The advantages of these agents (e.g., vilazodone and vortioxetine) over SSRIs are not fully clear. However, they appear to produce less sexual dysfunction and, in the specific case of vortioxetine, have particular benefits in depression-related cognitive impairment[49]. Indeed, vortioxetine is a very recent antidepressant with a multimodal mechanism that is thought to have a high affinity for serotonin transporters and 5-HT3, 5HT1A, 5HT7 receptors. Such a specific profile seems to indicate a level of efficacy to other antidepressants with a specific action on cognitive impairments[50,51].

In conclusion, no significant differences have been found between different classes of antidepressants in terms of their efficacy[52], though some drugs show some weak-to-moderate evidence indicating they are more effective than some other drugs[53]. Concerning the acceptability of these drugs, citalopram, escitalopram, fluoxetine, sertraline, and vortioxetine have been deemed more tolerable than other antidepressants, whereas amitriptyline, clomipramine, duloxetine, fluvoxamine, trazodone, and venlafaxine had the highest dropout rates[53] because of their more frequent and severe side effects. Nausea and vomiting were the most common reasons for treatment discontinuation; sexual dysfunction, sedation, priapism, and cardiotoxicity were also reported[51,41].

Ketamine and related molecules
In intravenous sub-anesthetic doses, ketamine has very quick effects on resistant unipolar (and, possibly, bipolar) depression and acute suicidal ideation[54,55]. The antidepressant effect of ketamine can persist for several days but eventually wanes. A few reports are have cited oral and intranasal formulations of ketamine for treatment-resistant depression[56,57], but there is still no data about the potential link between the onset of action and the route of administration.

Common adverse effects of ketamine include dizziness, neurotoxicity, cognitive dysfunction, blurred vision, psychosis, dissociation, urological dysfunction, restlessness, headache, nausea, vomiting, and cardiovascular symptoms[58]. Such adverse effects tend to be brief in acute, low-dose treatments[36], whereas prolonged exposure may predispose patients to neurotoxicity and drug dependence[56]. Lastly, since ketamine is associated with a higher risk of drug abuse and addiction, it cannot be recommended in daily clinical practice[59,60].

Ketamine is not a miracle drug, and many important factors still need to be defined, such as the most effective dose and the optimal administration route[61,62]. The current lack of guidelines about the therapeutic monitoring of ketamine treatment for depression further complicates the expanding use of this treatment[56]. Even though ketamine might never reach the market, it has stimulated research in the neurobiology of depression, including studies on potential fast and long-lasting antidepressants.

Ketamine has an active metabolite (hydroxynorketamine) that can produce rapid and sustained glutamatergic stimulation. It also seems to be free of many of the safety problems associated with ketamine and, thus, should be studied.

Research on the S-enantiomer of ketamine (S-ketamine, or esketamine, especially intranasal) could also be valuable, as it has a 3 to 4 times greater affinity than ketamine for the N-methyl-D-aspartate (NMDA) receptor[40]. It was approved by the United States Food and Drug Administration in March 2019 for treatment-resistant depression. However, current knowledge about the effects of prolonged esketamine therapy is still preliminary. In addition, regarding the potential risk of abuse, esketamine use must be carefully monitored[63-65].

Other glutamate receptor modulators have been evaluated in small studies as monotherapy agents or as adjuncts to other antidepressants. Examples include noncompetitive NMDA receptor antagonists (mementine, dextromethorphan/quinidine, dextromethorphan/bupropion, and lanicemine), NR2B subunit-specific NMDA receptor antagonists (traxoprodil), NMDA receptor glycine site partial agonists (D-cycloserine, rapastinel), and metabotropic glutamate receptor antagonists (basimiglurant, dedogurant)[66-68] (Table 1).

Perspectives
A purely neurotransmitter-based explanation for antidepressant drug action-especially serotonin-inhibiting drugs-is challenged by the significant percentage of patients...
Table 1 Main classes of antidepressants with their date of approval, contributions, and disadvantages

| Product                  | Date of FDA approval | Contributions                                                                 | Disadvantages                                                                 |
|--------------------------|----------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| MAOI²                    | Iproniazid 1958      | Confirmed the role of monoaminergic transmission in depression.               | Drug interactions, dietary restrictions                                      |
|                          |                      | Led to a new search methodologies to develop new antidepressants.              | Hepatotoxicity and hypertensive crises                                        |
| TC³                      | Imipramine 1959      | Efficacy in patients with more severe symptoms of MDD                        | Cardiovascular toxicity and anticholinergic side effects.                    |
|                          | Desipramine          |                                                                                 | Risk of lethal toxicity from overdoses                                         |
|                          | Nortriptyline 1992   |                                                                                 |                                                                               |
|                          | Amitriptyline 1961   |                                                                                 |                                                                               |
|                          | Clomipramine Not approved |                                                                                 |                                                                               |
|                          | First tetracyclmaprotiline |                                                                                 |                                                                               |
| SSRI¹                    | Fluoxetine 1987      | Improved tolerability                                                         | Several minor side effects (sexual dysfunction, loss of appetite, vomiting, nausea, irritability, anxiety, insomnia, and headache). Paroxetine had the highest rate of sexual dysfunction. Fluvoxamine is associated with the most overall adverse events |
|                          | Citalopram 1998      |                                                                                 |                                                                               |
|                          | Fluvoxamine 2007     |                                                                                 |                                                                               |
|                          | Paroxetine 1992      |                                                                                 |                                                                               |
|                          | Escitalopram 2002    |                                                                                 |                                                                               |
|                          | Sertraline 1999      |                                                                                 |                                                                               |
| SNRI²                    | Venlafaxine 2008     | Commonly recommended for patients who do not respond to SSRIs                 | No improvement in efficacy. Lower tolerability (highest rates of nausea, vomiting, and sexual dysfunction) |
|                          | Duloxetine 2004      |                                                                                 |                                                                               |
|                          | Reboxetine Not approved |                                                                                 |                                                                               |
| Other antidepressants    | Trazodone 1981       | Comparable efficacy to SSRIs                                                  | High rate of somnolence                                                       |
|                          | Nefazodone 2003      |                                                                                 | Rare but fatal hepatotoxicity                                                  |
|                          | Bupropion 2003       | A better tolerability profile (minimal weight gain or even weight loss). Likely to improve symptoms of fatigue and sleepiness | May increase risk for seizures (low evidence)                                 |
|                          | Vortioxetine 2013    | Efficacy in elderly patients. Supposed cognitive-enhancing properties. Safety profile is similar to SSRIs | The most commonly reported adverse effect was nausea                          |
|                          | Vilazodone 2011      | Less sexual dysfunction (low evidence). Safety profile is similar to SSRIs     | The most commonly reported adverse effects were diarrhea and nausea           |
|                          | Mirtazapine 1997     | Comparable efficacy to SSRIs. Low risk of sexual dysfunction                   | Weight gain                                                                   |
| Ketamine and related drugs | Ketamine Not approved | Rapid effects on resistant depression and acute suicidal ideation             | Short antidepressant effect. Possible neurotoxicity and drug dependence        |
|                          | Esketamine 2019      | Treatment-resistant depression. Greater affinity for NMDA receptor than ketamine | Potential risk of abuse. Lack of hindsight                                     |

¹United States Food and Drug Administration.  
²Monoamine oxidase inhibitors.  
³Tricyclic antidepressant.  
⁴Selective serotonin reuptake inhibitors.
who never achieve full remission[6] and the delayed clinical onset, which varies from two to four weeks. Moreover, studies show an acute increase in monoamines in the synaptic cleft immediately following treatment[69], even when the depletion of tryptophan (serotonin’s precursor) does not induce depressive-like behavior in healthy humans[70,71].

This finding shows that research on the pharmacological options for treating depression must go beyond monoaminergic neurotransmission systems. Research on the development of new antidepressants should explore several mechanisms of action on several types of receptors: Antagonism, inhibition of the reuptake of neurotransmitters, and modulators of glutamate receptors, as well as interactions with α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic, brain-derived neurotrophic factor, tyrosine kinase B receptor (the mechanistic target of rapamycin), and glycogen synthase kinase-3[72].

Identifying the cellular targets of rapid-acting agents like ketamine could help practitioners develop more effective antidepressant molecules by revealing other receptors involved in gamma-aminobutyric acid regulation and glutamate transmission[73].

**PSYCHOTHERAPY**

Psychotherapeutic interventions are widely used to treat and prevent most psychiatric disorders. Such interventions are common in cases of depression, psychosocial difficulties, interpersonal problems, and intra-psychic conflicts. The specific psychotherapy approach chosen for any given case depends on the patient’s preference, as well as on the clinician’s background and availability[74]. Psychotherapy for patients with depression strengthens the therapeutic alliance and enables the patient to monitor their mood, improve their functioning, understand their symptoms better, and master the practical tools they need to cope with stressful events[75]. The following subsections briefly describe psychotherapeutic interventions that have been designed specifically for patients with depression.

**Overview of psychotherapy in depression**

Depression-focused psychotherapy is typically considered the initial treatment method for mild to moderate MDD. Based on significant clinical evidence, two specific psychotherapeutic methods are recommended: Cognitive-behavioral therapy (CBT) and interpersonal therapy (IPT). Supportive therapy (ST) and psychoeducational intervention (PEI) have also been recommended, though the evidence supporting these methods is not as strong. In more cases of severe depression, ST and PEI are used only to augment pharmacological treatments.

After remission, CBT, PEI, and mindfulness-based cognitive therapy (MBCT) are proposed to maintain and prevent depression. However, when psychotherapy has been effective during the initial phases of a depressive episode, it should be continued to maintain remission and prevent relapses while reducing the frequency of sessions [25,75,76].

Specific and intensive psychotherapeutic support is recommended for patients with chronic depression because of high rates of comorbidity with personality disorders, early trauma, and attachment deficits. The European Psychiatric Association recommends using the Cognitive Behavioral Analysis System of Psychotherapy (CBASP) for treating chronic depression and utilizing specific approaches suited to each patient’s preferences[77]. All these therapeutic options are summarized in Figure 1.

**Structured psychotherapies**

**Cognitive and behavioral therapies**: Based on robust evidence, CBT is one of the most well-documented and validated psychotherapeutic methods available. Interventional strategies are based on modifying dysfunctional behaviors and cognitions[77]. CBT targets depressed patients’ irrational beliefs and distorted cognitions that perpetuate depressive symptoms by challenging and reversing them[3]. Thus, CBT is a well-known effective treatment method for MDD[78] and has been recommended in most
Figure 1 Overview of psychotherapy in different clinical situations of depression. MDD: Major depressive disorder; CBT: Cognitive-behavioral therapy; IPT: Interpersonal therapy; ST: Supportive therapy; PEI: Psycho-educational intervention; MBCT: Mindfulness based cognitive therapy; SIPS: Specific and intensive psychotherapeutic support; CBASP: Cognitive Behavioral Analysis System of Psychotherapy.

guidelines as a first-line treatment[79-81].

However, the effectiveness of CBT depends on patient’s capacity to observe and change their own beliefs and behaviors. Some simple techniques were developed to overcome this issue, especially in primary care management. Behavioral activation is one such technique, consisting of integrating pleasant activities into daily life to increase the number and intensity of the positive interactions that the patient has with their environment[82,83].

Acceptance and commitment therapy is another form of CBT. This type of therapy, which is based on functional contextualism, can help patients accept and adjusting to persistent problems. It appears to be effective in reducing depressive symptoms and preventing relapses[77,84].

Another form of CBT is computerized CBT (CCBT), implemented via a computer with a CD-ROM, DVD, or online CCBT, allowing patients to benefit from this therapy under conditions of reduced mobility, remoteness, confinement, or quarantine[79].

CCBT and guided bibliotherapy based on CBT could be considered for self-motivated patients with mild to moderate major depression or as a complementary treatment to pharmacotherapy[25]. CBT is also recommended for patients with resistant depression in combination with antidepressants[85].

Schema therapy is another CBT-derived therapy that can be used in patients who have failed classical CBT, like patients with personality disorder comorbidity. Schema therapy is about as effective as CBT for treating depression[86]. In adolescent patients with depression, CBT is also a recommended option with plenty of evidence from multiple trials. Meanwhile, it remains the first-line treatment in children despite mixed findings across trials[87]. CBT is also a promising option for elderly depressed patients, though substantial evidence is still lacking because of the limited data on the subject[88].

IPT: The goal of IPT is to identify the triggers of depressive symptoms or episodes. These triggers may include losses, social isolation, or difficulties in social interactions. The role of the intervention is to facilitate mourning (in the case of bereavement), help the patient recognize their own affect, and resolve social interaction dysfunction by building their social skills and social supports[89]. IPT, like CBT, is a first-line treatment for mild to moderate major depressive episodes in adults; it is also a well-established intervention for adolescents with depression[25].
Problem-solving therapy: The problem-solving therapy (PST) approach combines cognitive and interpersonal elements, focusing on negative assessments of situations and problem-solving strategies. PST has been used in different clinical situations, like preventing depression among the elderly and treating patients with mild depressive symptoms, especially in primary care. Despite its small effect sizes, PST is comparable to other psychotherapeutic methods used to treat depression[88,90].

Marital and family therapy: Marital and family therapy (MFT) is effective in treating some aspects of depression. Family therapy has also been used to treat severe forms of depression associated with medications and hospitalization[91]. Marital and family problems can make people more vulnerable to depression, and MFT addresses these issues[92]. Marital therapy includes both members of the couple, as depression is considered in an interpersonal context in such cases. Some of the goals of this therapy are to facilitate communication and resolve different types of marital conflict. Family therapy uses similar principles as other forms of therapy while involving all family members and considering depression within the context of pathological family dynamics[93].

ST: Although ST is not as well-structured or well-evaluated as CBT or IPT, it is still commonly used to support depressed patients. In addition to sympathetic listening and expressing concern for the patient’s problems, ST requires emotionally attuned listening, empathic paraphrasing, explaining the nature of the patient’s suffering, and reassuring and encouraging them. These practices allow the patient to ventilate and accept their feelings, increase their self-esteem, and enhance their adaptive coping skills[94].

Psychodynamic therapy: Psychodynamic therapy encompasses a range of brief to long-term psychological interventions derived from psychoanalytic theories. This type of therapy focuses on intrapsychic conflicts related to shame, repressed impulses, problems in early childhood with one’s emotional caretakers that lead to low self-esteem and poor emotional self-regulation[93,95]. Psychodynamic therapy’s efficacy in the acute phase of MDD is well-established compared to other forms of psychotherapy.

Group therapy: The application of group therapy (GT) to MDD remains limited. Some data support the efficacy of specific types of GT inspired by CBT and IPT[96-98]. Group CBT for patients with subthreshold depression is an effective post-depressive-symptomatology treatment but not during the follow-up period[99]. Supportive GT and group CBT reduce depressive symptoms[96], especially in patients with common comorbid conditions[100]. However, studies are still lacking in this domain.

MBCT: MBCT is a relatively recent technique that combines elements of CBT with mindfulness-based stress reduction[101]. Studies have shown that eight weeks of MBCT treatment during remission reduces relapse. Thus, it is a potential alternative to reduce, or even stop, antidepressant treatment without increasing the risk of depressive recurrence, especially for patients at a high risk of relapse (i.e., patients with more than two previous episodes and patients who have experienced childhood abuse or trauma)[102].

Other psycho-interventions

Psycho-education: This type of intervention educates depressed patients and (with their permission) family members involved in the patient’s life about depression symptoms and management. This education should be provided in a language that the patient understands. Issues such as misperceptions about medication, treatment duration, the risk of relapse, and prodromes of depression should be addressed. Moreover, patients should be encouraged to maintain healthy lifestyles and enhance their social skills to prevent depression and boost their overall mental health. Many studies have highlighted the role of psycho-education in improving the clinical course, treatment adherence, and psychosocial functioning in patients with depression[103].

Physical exercise: Most guidelines for treating depression, including the National Institute for Health and Care Excellence, the American Psychiatric Association, and the Royal Australian and New Zealand College of Psychiatrists, recommend that depressed patients perform regular physical activity to alleviate symptoms and prevent relapses[104]. Exercise also promotes improvements in one’s quality of life in general[105]. However, exercise is considered an adjunct to other anti-depressive treatments[25].
Although psychotherapy is effective for treating depression and improving patients’ quality of life, its direct actions against depressive symptoms are not fully understood [106]. Identifying factors (e.g., interpersonal variables) linked to treatment responses can help therapists choose the right therapeutic strategy for each patient and guide research to modify existing therapies and develop new ones[107].

Since depression is a primary care problematic, simplifying psychotherapy procedures will increase the use of psychological interventions for depression, especially in general practice. Brief forms (six to eight sessions) of CBT and PST have already shown their effectiveness for treating depression[108]. Nevertheless, simpler solutions must be made available to practitioners to help them manage and prevent depression.

**SOMATIC TREATMENTS**

In many situations, depression can also be managed via somatic treatments. ECT is the most well-known treatment for resistant depression, and solid evidence supports its effectiveness and safety. In recent decades, various innovative techniques have been proposed, such as repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), vagus nerve stimulation (VNS), deep brain stimulation (DBS), and magnetic seizure therapy, with varying efficiency levels[109].

**ECT**

ECT is arguably the most effective treatment modality in psychiatry, and its superiority over pharmacotherapy for major unipolar depression is widely supported [110]. ECT reduces the number of hospital readmissions and lightens the burden of depression, leading to a better quality of life[111,112].

Moreover, ECT is considered safe[113]. Advances in anesthesia and ECT techniques have decreased complications related to ECT while also improving cognitive outcomes and patient satisfaction. However, the stigma surrounding ECT limits its use. Most misconceptions date back to early ECT techniques (when it was performed without muscle relaxants or anesthesia). Nevertheless, some people still consider ECT as the last option for treating depression, even though most studies indicate that ECT is more beneficial in patients with fewer pharmacological treatments[114-116].

ECT is typically recommended for patients with severe and psychotic depression, a high risk of suicide, or Parkinson’s disease, as well as pregnant patients[117-119]. The maintenance ECT also appears to prevent relapses[120]. The current practice of ECT continues to improve as protocols become more advanced, mainly owing to bioinformatics, and as more research is carried out in this domain[121-125].

**rTMS**

This method, which is a type of biological stimulation that affects brain metabolism and neuronal electrical activity, has been widely used in research on depression[126]. Recent literature shows a significant difference between rTMS and fictitious stimulation regarding its improvements in depressive symptoms[127]. Preliminary research has revealed synergistic (e.g., rTMS/quetiapine) and antagonizing (e.g., rTMS/cannabinoid receptor (CB1) antagonist) interactions between neuro-modulation and pharmacotherapy[128]. Treatments combining rTMS and antidepressants are significantly more effective than placebo conditions, with mild side effects and good acceptability[129]. Although these results are encouraging, they remain inconsistent due to differences in rTMS treatment frequencies, parameters, and stimulation sites [129]. Therefore, clinical trials with large sample sizes are needed to specify which factors promote favorable therapeutic responses. Also, additional preclinical research should investigate the synergistic effects of other pharmacological molecules and guide integrated approaches (rTMS plus pharmacotherapy).

**tDCS**

This technique delivers weak currents to the brain via electrodes placed on the scalp [130]. It is easy to use, safe, and tolerable[131]. The tDCS technique significantly outperforms the simulator in terms of the rate of response and remission[132]. However, its effect remains lower than that of antidepressants[133] and rTMS[134]. It can be used as a complementary intervention or as monotherapy to reduce depressive symptoms in unipolar or bipolar depression patients[135]. The antidepressant effects of tDCS may involve long-term neuroplastic changes that continue to occur even after
the acute phase of treatment, which explains its delayed efficacy[135].

Recently, neurophysiological studies have shown that the clinical effects of tDCS do not have a direct linear relationship with the dose of stimulation[136]. tDCS, as a relatively simple and portable technology, is well-suited for remote supervised treatment and assessment at home, thus facilitating long treatment durations[136].

Since the optimal clinical effects of tDCS are delayed, future clinical trials should use longer evaluation periods and aim to identify responsive patients using algorithms [137].

**VNS**

VNS is a therapeutic method that has been used for the last sixteen years to treat resistant unilateral or bipolar depression. However, despite several clinical studies attesting to its favorable benefit-risk ratio and its approval by the Food Drug Administration in 2005, it is not used very often[138].

VNS involves the implantation of a pacemaker under the collarbone that is connected to an electrode surrounding the left vagus nerve. The left vagus nerve is preferred because it exposes the patient to fewer potential adverse cardiac effects. Indeed, most cardiac afferent fibers originate from the right vagus nerve[139]. Since the turn of the century, numerous studies have demonstrated the efficacy of VNS in resistant depression[140-142].

However, only one randomized, double-blind, controlled trial comparing VNS with usual medical treatment has been conducted over a short period of 10 wk[141]. Moreover, the results of this study did not indicate that the combination of VNS with typical medical treatments was better than the typical medical treatment on its own.

However, VNS has demonstrated progressively increasing improvements in depressive symptoms, with significant positive outcomes observed after six to 12 mo; these benefits can last for up to two years[143].

More long-term studies are needed to fully determine the predictors of the correct response.

**DBS**

According to the literature, DBS of the subgenual cingulate white matter (Brodmann area = BA 25) elicited a clinical response in 60% of resistant depression patients after six months and clinical remission in 35% of patients, with benefits maintained for over 12 mo[144]. The stimulation of other targets, in particular the nucleus accumbens, to treat resistant depression has gained interest recently. Behavioral effects indicate the quick and favorable impact of stimulation on anhedonia, with significant effects on mood appearing as early as week one after treatment begins[145].

**Magnetic seizure therapy**

Magnetic seizure therapy involves inducing a therapeutic seizure by applying magnetic stimulation to the brain while the patient is under anesthesia. This technique is still being investigated as a viable alternative to ECT to treat many psychiatric disorders. Evidence supporting its effectiveness on depressive symptoms continues to grow, and it appears to induce fewer neurocognitive effects than ECT[146,147].

**Luxtherapy (phototherapy)**

The first description of reduced depression symptoms due to intense light exposure was presented in 1984[148]. Optimal improvements were obtained with bright light exposure of 2500 Lux for two hours per day, with morning exposure shown to be superior to evening exposure[149].

A review and meta-analysis[150] showed that more intense (but shorter) exposures (10000 Lux for half an hour per day or 6000 Lux for 1.5 h per day) have the same efficacy. Importantly, this treatment method is effective both for those with seasonal and non-seasonal depression. Benefits of phototherapy related to sleep deprivation and drug treatments have also been reported[151].

Neuro-modulation treatments offer a range of treatment options for patients with depression. ECT remains the most documented and effective method in this category [151]. rTMS is an interesting technique as well, as it offers a well-tolerated profile[88], while tDCS offers encouraging but varying results that depend on the study’s design and the techniques used[130].

More investigations are needed to specify which indications are the best for each method according to the clinical and biological profiles of patients. The uses of such methods are expanding, probably, with their efficiency increasing when they are tailored to the patient. Furthermore, somatic interventions for depression need to be
regularly assessed and integrated into psychiatrists’ therapeutic arsenals.

CONCLUSION

Treating depression is still a significant challenge. Finding the best option for each patient is the best way to obtaining short- and long-term effectiveness. The three principal methods available to caregivers are antidepressants, specifically structured psychotherapies, and somatic approaches. Research on depression pharmacotherapy continues to examine new molecules implicated in gamma-aminobutyric acid regulation and glutamate transmission. Also, efforts to personalize and simplify psychotherapeutic interventions are ongoing. Protocols using somatic interventions need to be studied in more depth, and their indications must be specified. ECT is the only somatic treatment with confirmed indications for certain forms of depression. Combinations of medications, psychotherapy, and somatic therapies remain the most effective ways to manage resistant forms of depression.

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