Clinical Perspective

Major depressive disorder: treatment and future perspective

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Practice Points

- Selective serotonin reuptake inhibitors are the primary medications prescribed for major depressive disorder due to their effectiveness, mild side effects and lower level of toxicity in overdose compared with other antidepressants.
- Pharmacotherapy in major depression treatment is helpful in approximately two-thirds of cases only.
- Several pharmacological strategies in treating a nonresponsive major depression are well established while others are still being explored.
- Brain stimulation methods are evolving rapidly and in many patients they succeed where pharmacotherapy failed.
- Psychiatrists should be aware of the potential of brain stimulation methods as well as possible complications.
- Electroconvulsive therapy is a first-line acute treatment for life-threatening depression.

SUMMARY Major depressive disorder is a mood disorder characterized by both severe affective and neurovegetative symptoms together. It is a common disorder seen in a quarter of consecutively admitted depressed patients and is often associated with severe symptomatology, increased suicide risk, poor acute response to antidepressants and poor acute and long-term treatment outcome. The question of the optimal duration of pharmacotherapy in order to prevent relapse and improve the long-term (i.e., 5-year) outcome is a focus of current investigation. This article will review currently recommended treatment strategies for the acute, continuation and maintenance phases of therapy. In particular, it will address the role of newer-generation antidepressants, the use of mood stabilizers and indications for electroconvulsive therapy. Other possible treatment strategies such as transcranial magnetic stimulation, vagus nerve stimulation, deep brain stimulation and glucocorticoid receptor antagonists will be discussed.

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National household probability samples of diffuse populations in the USA have found a lifetime prevalence of major depressive disorder (MDD) as high as 17.9% [1]. The initial therapeutic approach to the treatment of depression consists of medication or psychotherapy. For patients who do not respond, suitable alternatives include other classes of medications, augmentative regimens and, eventually, electroconvulsive therapy (ECT). The STAR*D trial studied a broadly representative adult outpatient sample with nonpsychotic MDD (n = 3671) and found the overall cumulative remission rate after four treatment steps to be 67% [2].

ECT is suggested as a first-line acute treatment for life-threatening depression and as a second-line treatment for patients with MDD who do not respond or only partially respond to antidepressant drugs [3]. A meta-analysis, which included 15 studies, found ECT to be superior to pharmacotherapy in the acute treatment of major depression [4]. The UK ECT Review Group found ECT to be an effective short-term treatment for depression, and concluded that it was probably more effective than drug therapy [5].

The variability in response to antidepressive treatments mostly derives from the heterogeneity of depression. Multiple mechanisms whose nature have yet to be fully discovered lead to depression, creating a need for novel antidepressant treatments with different mechanisms of action.

The aim of this article is to summarize effective treatments for MDD, and also envision future treatment possibilities.

The literature reviewed was gathered through a PubMed® search using the following keywords: major depression treatment, psychotherapy, cognitive behavioral therapy (CBT), pharmacotherapy, antidepressants, brain stimulation, ECT, transcranial magnetic stimulation (TMS), vagus nerve stimulation and deep brain stimulation.

Treatment possibilities

■ Pharmacotherapy

Pharmacologic interventions remain the predominant treatment for major depression in patients. Response rates have varied from 35 to 72%, while remission rates have varied from 28 to 44% [6]. Researchers and clinicians have demonstrated that the effectiveness of antidepressants is minimal in patients with mild-to-moderate depression but significant in those with a severe disorder [7].

Selective serotonin reuptake inhibitors (SSRIs) are the primary medications prescribed due to their effectiveness, mild side effects and lower level of toxicity in overdose compared with other antidepressants. A review of the evidence for antidepressant augmentation, combination and switching published in January 2011 concluded that the strength of the evidence supporting a trial of augmentation or a switch to a new agent is very similar, with remission rates between 25 and 50% in both cases [8]. Almost 50% of patients who do not respond to a first SSRI will response to a second SSRI. In clinical terms this means that the cumulative rate of responders to two SSRIs is approximately two-thirds of the patients.

Other effective pharmacologic treatments include tricyclic antidepressants, monoamine oxidase inhibitors and serotonin–norepinephrine reuptake inhibitors (SNRIs). While the efficacy of these drugs is similar to that of SSRIs, they possess different side-effect profiles [6,7].

Additional new classes of drugs with similar effects have recently been developed, including noradrenergic and serotonergic antidepressants and norepinephrine reuptake inhibitors. Lifelong treatment must be considered for patients who have had three or more episodes in their life [9].

Pharmacotherapy for MDD seems to be effective, but its use is limited owing to several age-related factors. Especially in the elderly, multiple medications can result in an increased morbidity, disability and mortality owing to physical comorbid diseases. The frequent use of medication could cause the patient to be particularly prone to the side effects of antidepressants [10]. Pharmacokinetic change, particularly reduced hepatic metabolism and reduced renal clearance, could result in higher plasma concentrations and prolonged elimination half-lives. These pharmacokinetic changes are often magnified by the presence of comorbid medical conditions [11].

Antidepressant medications may adversely affect other disorders associated with age, such as cardiac arrhythmias, hypotension, postural instability, prostatic hypertrophy, constipation, impaired vision and cognitive impairment [11].

According to the American Psychiatric Association's practice guidelines for the treatment of MDD, an antidepressant medication

is recommended as the initial treatment choice for patients with mild-to-moderate MDD [12]. A SSRI, a SNRI, mirtazapine or bupropion could also be an optimal treatment [12].

Pharmacotherapy algorithm

According to practice guidelines, in the case of nonresponse patients may be changed to an antidepressant from the same pharmacological class (e.g., from one SSRI to another SSRI) or to one from a different class [12]. For patients who have not responded to trials of SSRIs, the trial of a SNRI may be helpful [12]. Antidepressant medications can be augmented with another nonmonoamine oxidase inhibitor antidepressant, generally from a different pharmacological class, or a nonantidepressant medication such as lithium, thyroid hormone supplements or second-generation antipsychotics (SGAs) [12]. Additional strategies whose efficacy has not been as strongly demonstrated include augmentation using anticonvulsant agents, ω-3 fatty acids, folic acid or psychostimulant medications such as modafinil [12].

Papakostas suggests that clinicians have four broad pharmacologic strategies to treat nonresponders [13]:

- Increasing the dose of the antidepressant;
- Switching to a different antidepressant;
- Augmenting the treatment regimen with other agents rather than antidepressants;
- Combining the original antidepressant with another antidepressant.

Switching antidepressants, especially to the newer agents including SSRIs, bupropion, mirtazapine and venlafaxine, has been demonstrated to be an effective strategy [13]. Following the first-line failure of a SSRI, clinicians suggest switching to another option within the class or to a SNRI; however, switching from a SSRI to bupropion or mirtazapine may potentially offer greater benefits [8].

Lithium augmentation is currently the best-supported augmentation therapy for the treatment of MDD. Bauer *et al.* published a review of lithium augmentation strategies for the treatment of depressive episodes. They found that more than 30 open-label studies and ten placebo-controlled double-blind trials have demonstrated the substantial efficacy of lithium augmentation in the acute treatment of depressive episodes. One placebo-controlled trial in the continuation treatment phase showed that responders to acute-phase lithium augmentation should be maintained on the lithium–antidepressant combination for at least 12 months to prevent early relapses [14].

Bauer *et al.* concluded that augmentation of antidepressants with lithium is currently the best-evidenced augmentation therapy for the treatment of depressed patients who do not respond to antidepressants [14].

Another method of augmentation is the addition of atypical antipsychotics to the therapeutic regimen of patients with unipolar MDD who do not respond adequately to treatment. This strategy has become a common intervention recently [15]. Komossa *et al.* evaluated the effects of SGA drugs (alone or in augmentation) compared with placebos or antidepressants for people with MDD or dysthymia. They explored 28 published trials with 8487 participants covering five SGAs: amisulpride, aripiprazole, olanzapine, quetiapine and risperidone. Komossa *et al.* reached the conclusion that all augmentation drugs showed some beneficial effects compared with placebos [16].

Connolly and Thase published about augmentation strategies for lithium, thyroid hormone, pindolol, psychostimulants and SGAs [8]. Tri-iodothyronine augmentation seems to have the best benefit:risk ratio for augmentation [8]. Quetiapine and aripiprazole augmentation were also found to be effective; however, neither the cost–effectiveness of these drugs nor the longer-term benefit/side-effect profiles of these strategies has been explored yet [8].

Future treatments

Potential antidepressant treatments include multimodal serotonergic agents, triple-uptake inhibitors, neurokinin-based novel therapies, glutamatergic treatments, nicotinic receptor-based treatments, neurogenesis-based treatments and antiglucocorticoid therapies [17]. These preliminary treatments are advanced in terms of drug development and all contribute to the global effort to develop more effective and better-tolerated treatments for MDD [17].

Psychotherapy

CBT is currently the most studied and efficiently used psychotherapy option. CBT aims to solve problems concerning dysfunctional

emotions, behaviors and cognitions through a goal-oriented, systematic procedure focused on the present. The cooperation and understanding required lead CBT to produce beneficial effects more efficiently in patients, leading to higher levels of rational thoughts, less hopelessness, fewer negative thoughts and fewer cognitive distortions. CBT is particularly effective in preventing relapse [18].

Other variants of psychotherapy were shown to be effective to some extent as well, such as interpersonal therapy [19], behavioral therapy [20] and psychodynamic psychotherapy used as an aid for adherence to pharmacotherapy [21].

■ Brain stimulation

Electroconvulsive therapy

ECT involves the passage of a brief electrical current through the brain to induce a generalized CNS seizure under general anesthesia and muscle relaxation. Although a favorable response to ECT can occur quickly, the clinical benefits typically require multiple treatments administered over a period of several weeks.

ECT can be conducted traditionally, with either bilaterally or unilaterally placed electrodes, or by a newer method of bifrontal (BF) stimulation. A meta-analysis of randomized controlled trials comparing the efficacy and side effects of BF ECT with those of bitemporal or right unilateral BF ECT in depression found that BF ECT might have modest short-term benefits for specific memory domains [22].

Patients respond more rapidly to bilateral ECT whereas unilateral ECT causes, at least in the first couple of weeks, less cognitive impairment. Recent advances in ECT have further lessened memory impairment. ECT is often used as a maintenance treatment in order to sustain the response to ECT. Indications for ECT treatment include response failure to several antidepressants, intolerability of antidepressant side effects and psychotic depression resistant to pharmacotherapy. ECT is generally well tolerated by patients [9].

van der Wurff *et al.* conducted a review of 121 studies concluding that ECT in elderly patients is generally safe [10], although a number of serious complications possibly related to ECT have been described.

ECT is the treatment of choice in older patients with severe depression [9]. In a prospective, multisite study at four hospitals, the treatment outcomes of adult (59 years of age and younger), young-old (60–74 years of age) and old-old (75 years of age and older) patients treated with ECT for MDD were compared. A total of 268 patients with primary unipolar major depression and scores of at least 20 on the 24-item Hamilton Depression Rating Scale were treated with suprathreshold right unilateral or bilateral ECT. Tew *et al.* concluded that, despite a higher level of physical illness and cognitive impairment, the oldest patients with severe major depression showed tolerance levels for ECT similar to those of younger patients and responded well to the treatment [23]. In a study of 253 patients in acute phase of major depression, bilateral ECT was given to three age groups (≥65, 46–64 and ≤45 years of age). Investigators concluded that the patient's age positively influenced the response to treatment [24].

Bosboom and Deijen investigated the interaction between ECT, depression and neuropsychological outcomes related to age [25]. ECT has been shown to be effective in the treatment of depression. Improvement in depression was mainly associated with improvement in cognitive domains such as memory, information processing and executive function. The short-term cognitive improvement was greater in older patients but in the long term there were no differences. Current findings show a positive relationship between improvement in cognitive functioning and improvement of depression in elderly patients treated with ECT [25].

Ultra-brief pulse wave ECT is a novel treatment that shows advantages over existing treatments for depression. Patients treated with the method have less memory loss and confusion than those treated with longer-duration ECT [26].

Magnetic seizure therapy

Magnetic seizure therapy (MST) has recently been introduced as a safer alternative to ECT. Although both MST and ECT induce seizures through brain stimulation, the electric field induced by MST is more focal and limited than that induced by ECT. MST allows for greater control over the site and extent of stimulation than can be achieved with ECT. A study of ten hospitalized MDD patients referred for ECT demonstrated MST's superiority over ECT due to its shorter duration, lower ictal EEG amplitude and lower postictal suppression. Patients had fewer subjective side effects and recovered

orientation more quickly with MST than ECT. MST was also superior to ECT on measures of attention, retrograde amnesia and category fluency. Magnetic seizure induction in patients with depression is feasible and appears to have a superior acute side-effect profile to that of ECT [27].

Vagus nerve stimulation

Vagus nerve stimulation (VNS) therapy is administered through an implanted pulse generator that delivers programmed electrical pulses through an implanted lead to the left vagus nerve [28].

The vagus nerve exerts a direct influence on areas of the brain associated with the regulation of mood and increases the level of biogenic amines. Several studies confirmed increased activity of the fronto-orbital and prefrontal cortex, hypothalamus and cingulum, as well as changed concentration of serotonin and noradrenalin in the CNS and cerebrospinal fluid [29,30].

Pilot studies of VNS for depression have shown modest response rates. However, the effect appears to have a gradual onset, with a lack of favorable response in the short term [31]. A European open-label study of VNS in 74 patients with MDD demonstrated that, after 3 months of VNS, 37% reached remission. Response rates increased to 53% after 1 year of VNS, and remission rates reached 33% [32]. In another study, 18 out of 59 patients with depression had a response to 12 weeks of VNS therapy plus medication [33]. A third study of 11 patients demonstrated response and remission rates of 55 and 27%, respectively, after 1 year of VNS therapy [34]. The response rate was 40% over a period of at least 1 year of VNS treatment for MDD [34].

A meta-analysis of VNS conducted in 2011 concluded that it cannot be ruled out that the positive results observed in the uncontrolled studies might have been mainly due to a placebo effect [35].

A systematic review including 18 add-on studies from 2000 to 2007 found that in the majority of open studies, VNS was associated with a significant improvement of the depressive symptoms [36]. An acute-phase trial comparing adjunctive VNS with sham treatments in 235 outpatients with nonpsychotic MDD (n = 210) or nonpsychotic, depressed phase, bipolar disorder (n = 25) found that the 10-week response rates were 15.2% for the active (n = 112) and 10.0% for the sham treatment (n = 110) groups. Response rates in the 30-item Inventory of Depressive Symptomatology – Self Report were 17.0% (active treatment) and 7.3% (sham treatment; p = 0.032; last observation carried forward) [37]. Long-term VNS was generally well tolerated in patients with nonpsychotic MDD [38].

Shuchman found frequent side effects were laryngeal hoarseness, coughing, dyspnea and, rarely, vocal cord paralysis or infection [33]. Corcoran *et al.* reported several serious adverse events including suicide at 9 months following implantation and vocal cord palsies of mixed duration up to 6 months [34].

Transcranial magnetic stimulation

Loo and Mitchell reviewed seven meta-analyses of sham-controlled studies of repetitive TMS (rTMS) for major depression. Only one meta-analysis failed to demonstrate efficacy of rTMS, while five others found clear evidence of efficacy [39]. Most studies of rTMS involve treatment of major depression. They demonstrated the efficacy of high-frequency treatment over the left prefrontal cortex for major depression [40–52].

Studies comparing long courses of high-frequency rTMS with ECT show comparable effectiveness in certain patient populations [39,40,53]. Grunhaus *et al.* demonstrated in two different studies the effectiveness of rTMS in nonpsychotic patients with major depression. ECT and rTMS obtained similar success rates [49,50].

In a recently published study by Eranti *et al.*, 46 patients with major depression randomly received ECT or a 15-day course of rTMS on the left dorsolateral prefrontal cortex. After the last session, the ECT outcome was far better than TMS; however, at a time point of 6 months post-treatment results were comparable [54].

rTMS in the treatment of major depression with 301 medication-free patients concluded that TMS was effective in treating major depression with fewer side effects [55]. Overall, rTMS trials have moved in the direction of administering longer-duration protocols with higher intensities [56–58].

A sham-controlled randomized trial enrolling 860 patients was recently completed. The odds of attaining remission were found to be 4.2-times greater with rTMS than with the

sham treatment. The investigators concluded that daily left prefrontal rTMS as a monotherapy produced statistically significant and clinically meaningful antidepressant therapeutic effects [59]. In October 2008, Neuronetics (PA, USA) received the US FDA's first approval for a TMS for the pharmacological treatment of nonresponder MDD patients.

Deep TMS

Although TMS treatment for depression has improved over the past few years [60], TMS does not yet yield desirable results.

Repetitive and slow TMS techniques enable direct stimulation of superficial cortical areas to a maximum depth of approximately 1 cm [61,62]. However, reward-related brain sites involved in MDD mechanism, such as the ventral prefrontal cortex, ventral striatum and ventral tegmental area, are out of reach of standard TMS coils (such as the figure-8 coil) [63].

The development of the H-coil, a novel coil allowing direct stimulation of deeper brain regions by significantly reducing the magnetic field decay rate, comes at the expense of reduced focus [64]. This relatively new tool was shown to be safe [65,66] and effective in the treatment of treatment-resistant depression [67–69].

Deep brain stimulation

Deep brain stimulation (DBS) involves creating a small burr hole in the skull and passing a fine wire into selected brain regions. This wire can be excited at its terminal end by a pacemaker-like device connected subdermally and implanted in the chest wall. When the DBS is implanted, the wire provides high-frequency stimulation and temporarily stops brain function in the region. DBS involves the delivery of an electrical current to the brain parenchyma through implanted electrodes. One of the main advantages of the technique is that most of its side effects are reversible and can be managed by adjusting stimulation parameters (e.g., reducing the amplitude of the delivered current). The target most extensively employed in recent DBS treatment of depression is the subcallosal cingulate gyrus. Additional proposed DBS targets for the surgical treatment of depression are the inferior thalamic peduncle [70] and the nucleus accumbens [71]. Clinical ratings improved in three patients in whom DBS electrodes were implanted in the nucleus accumbens [71].

Mayberg *et al.* reported sustained remission of depression in four of six patients treated with DBS implementation to the subgenual cingulate [72].

The same research group reported 3 years later on the results of these six patients and an additional 14 patients with extended follow-up (20 patients altogether). At 1 month postsurgery, 35% of patients met criteria for response, with 10% of patients in remission. At 6 months postsurgery, 60% of patients responded and 35% met criteria for remission, benefits that were largely maintained at 12 months. DBS therapy was associated with specific changes in metabolic activity localized to the cortical and limbic circuits implicated in the pathogenesis of depression. The number of serious adverse effects was small, with no patients experiencing permanent deficits [73].

An extended follow-up of 20 patients with treatment-resistant depression who received DBS to the subcallosal cingulate gyrus (Brodmann area 25) found that the average response rates 1, 2 and 3 years after DBS implantation were 62.5, 46.2 and 75%, respectively. At the last follow-up visit (range: 3–6 years), the average response rate was 64.3%. The conclusion was that DBS remains a safe and effective treatment for treatment-resistant depression [74].

Bewernick *et al.* studied ten patients suffering from treatment-resistant depression who did not respond to pharmacotherapy, psychotherapy or ECT. Patients were implanted with bilateral DBS electrodes in the nucleus accumbens. At 12 months after the initiation of DBS treatment, five patients had reached 50% reductions of the Hamilton Depression Rating Scale [75].

Malone *et al.* treated 15 patients with chronic, severe, highly refractory depression with DBS of the ventral capsule/ventral striatum. Responder rates were 40% at 6 months and 53.3% at last follow-up (longer than 4 years). Remission rates were 20% at 6 months and 40% at last follow-up (longer than 4 years) [76].

Blomstedt *et al.* conducted a review of the literature on DBS in the treatment of MDD. They reported positive results obtained from DBS targeted at the nucleus accumbens, internal capsule/ventral striatum and subcallosal cingulate gyrus [77].

Hauptman *et al.* conducted a comprehensive literature review and found the subgenual cingulate cortex, inferior thalamic peduncle and nucleus accumbens to be safe and effective targets of DBS in the treatment of MDD [78].

Transcranial direct current stimulation

Transcranial direct current stimulation (tDCS) involves the application of low currents to the scalp via cathodal and anodal electrodes and has been shown to affect a range of motor, somatosensory, visual, affective and cognitive functions [79]. A randomized double-blind clinical trial of tDCS given to the left dorsolateral prefrontal cortex was found to be effective in reducing depression [80]. In a double-blind placebo-controlled study, 22 patients with MDD were randomly assigned to a crossover protocol to compare tDCS with placebo stimulation as an add-on to medication. There was no significant difference in depression after 2 weeks of real compared with 2 weeks of sham tDCS [81].

Conclusion & future perspective

The primary conclusion of this review is that practicing physicians should not limit treatment options to medications and psychological therapies; they must be aware of brain stimulation methods as well, especially since some of these methods are already approved by the FDA.

The authors believe that the first step in decreasing depression worldwide must be preventative intervention. Early diagnosis and education of physicians, patients and their families could improve the avoidance of both new-onset depression and relapse in patients. Psycho-educational prevention programs such as the 'Coping with Depression' course have been shown to be effective [82]. In addition, new classes of antidepressants are being introduced that are more effective or have fewer side effects than the older medications. CBT, a psychological intervention, has also proven to be effective in the prevention of relapse. New variations of ECT such as ultra-brief pulse wave ECT and BF ECT have purported advantages over conventional ECT; however, these techniques have yet to be proven. Another novel alternative to ECT, MST, has been found to have a superior side-effect profile to that of ECT. DBS and VNS have been shown to be promising brain stimulation methods for treating depression but will probably be the last line of treatment owing to their invasiveness. rTMS is a brain method that has been well established as an effective treatment for depression. Deep rTMS is a novel TMS method with preliminary success, the effectiveness of which is yet to be clarified. tDCS is a rather old brain stimulation method that is being studied again with some preliminary success.

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