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Emerging targets for antidepressant therapies

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Despite adequate antidepressant monotherapy, the majority of depressed patients do not achieve remission. Even optimal and aggressive therapy leads to a substantial number of patients who show minimal and often only transient improvement. In order to address this substantial problem of treatment-resistant depression, a number of novel targets for antidepressant therapy have emerged as a consequence of major advances in the neurobiology of depression. Three major approaches to uncover novel therapeutic interventions are: first, optimizing the modulation of monoaminergic neurotransmission; second, developing medications that act upon neurotransmitter systems other than monoaminergic circuits; and third, using focal brain stimulation to directly modulate neuronal activity. We review the most recent data on novel therapeutic compounds and their antidepressant potential. These include triple monoamine reuptake inhibitors, atypical antipsychotic augmentation, and dopamine receptor agonists. Compounds affecting extra-monoamine neurotransmitter systems include CRF_1 receptor antagonists, glucocorticoid receptor antagonists, substance P receptor antagonists, NMDA receptor antagonists, nemifitide, omega-3 fatty acids, and melatonin receptor agonists. Focal brain stimulation therapies include vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS), magnetic seizure therapy (MST), transcranial direct current stimulation (tDCS), and deep brain stimulation (DBS).

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Introduction

Depression is prevalent and disabling [1,2]. Despite adequate care with currently available treatments, up to 70% of depressed patients have residual symptoms [3], and, even with more aggressive therapies, 20% or more may show only a limited response [4]. Rather than being the exception, recurrent episodes are the rule, and there are few evidence-based approaches to help clinicians maintain a patient's antidepressant response. Persistent depression is associated with an increase in substance and alcohol abuse, an increased risk for suicide and for cardiovascular disease. Thus, improved treatments for depression are urgently needed.

Various forms of psychotherapy, pharmacotherapy, and electroconvulsive therapy (ECT) are currently the most commonly used antidepressant treatments. Serendipitous discoveries and/or a limited understanding of the neurobiology of depression which largely focused on the monoaminergic neurotransmitter systems led to the development of many of these treatments. As knowledge of the neuroscience of depression advances, a number of novel targets for antidepressant treatment are being uncovered and actively investigated. Generally, these treatments fall into three major categories: first, medications that optimize the modulation of monoaminergic neurotransmitters; second, medications that target nonmonoamine neurotransmitter and neuromodulatory systems; and third, devices that produce focal electrical brain stimulation targeting brain regions implicated in the pathophysiology of depression. In this review, we discuss these treatments and highlight those that hold the most promise.

Optimizing monoaminergic modulation

The major monoamines include serotonin (5HT), norepinephrine (NE), and dopamine (DA). Several randomized, double-blind, placebo-controlled trials demonstrate that medications that modulate monoaminergic neurotransmission possess antidepressant efficacy [5]. Such medications include selective serotonin reuptake inhibitors (SSRIs), 5HT and NE dual-reuptake inhibitors (SNRIs), tricyclic/tetracyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and a number of atypical antidepressants (e.g. mirtazapine, trazodone, nefazodone, and bupropion). Mechanisms of action for the TCA, SSRI, and SNRI medications include inhibition of the reuptake of NE and/or 5HT into the presynaptic terminal. MAOIs inhibit monoamine oxidase, the enzyme which degrades 5HT, NE, and DA in the presynaptic terminal. Mirtazapine, nefazodone, trazodone, and several atypical antipsychotic drugs block or stimulate one or more presynaptic and/or postsynaptic monoamine neurotransmitter receptors.

Following the success of these agents in treating many depressed patients, interest and research have focused on

novel approaches to optimize monoaminergic neuromodulation. Considerable effort has been targeted to DA circuits based on a growing database implicating DA dysfunction in the pathophysiology of depression [6]. Novel treatments in this category include triple reuptake inhibitors, atypical antipsychotic augmentation, and DA receptor agonists.

Triple reuptake inhibitors

Triple reuptake inhibitors block synaptic reuptake of 5-HT, NE, and DA. Animal studies have demonstrated antidepressant-like effects for several of these compounds [7–12]. DOV 216 303, one such agent, was found to be safe and tolerable during short-term use in a Phase 1, open-label study [12]. Tesofensine (NS 2330), another compound, has shown modest preliminary safety and efficacy in treating the motor symptoms of Parkinson's Disease (PD) [13], but clinical data in treating depression are unavailable. Two double-blind, placebo-controlled trials of NS 2359, a GlaxoSmithKline compound, which included active comparators (venlafaxine and paroxetine) showed no significant antidepressant efficacy; the active comparators were more efficacious than placebo (GlaxoSmithKline, data on file). Drug abuse liability and autonomic side effects are two major concerns in the development of DA reuptake inhibitors.

Atypical antipsychotic augmentation

Atypical antipsychotics (risperidone, paliperidone, clozapine, olanzapine, quetiapine, aripiprazole, and ziprasidone) exhibit DA D2 receptor occupancy rates of less than or equal to 70%. This is in contrast to the older 'typical' antipsychotics (such as haloperidol and perphenazine) that blocked D2 receptors at occupancy rates of 90% or more. One or another of the atypical antipsychotics have a relatively high affinity for several 5HT receptors, and possibly glutamate receptors as well [14]; aripiprazole additionally functions as a partial agonist at the D2 receptor. In the treatment of psychotic disorders, these agents appear to have equivalent efficacy to the older, typical antipsychotics, but with fewer extrapyramidal side effects and lower risk of tardive dyskinesia. However, these agents have been associated with a number of worrisome side effects including lipid abnormalities, weight gain, and glucose intolerance that define the metabolic syndrome [15]. Some drugs in this class have shown efficacy in augmenting SSRI treatment of anxiety disorders, such as obsessive compulsive disorder (OCD) [16–18], post traumatic stress disorder (PTSD) [19–21] and generalized anxiety disorder [22–24].

On the basis of their unique pharmacology, these agents may exert antidepressant effects via DA function modulation as well as other mechanisms such as $5HT_{1A}$ agonism. It is well established that the atypical antipsychotics are effective in treating manic and depressive episodes with psychotic features. Initially, open-label studies and retrospective case series suggested that these medications might augment the action of antidepressant medications in the absence of psychosis [25–35]. Two, large randomized placebo-controlled trials have shown that augmentation with aripiprazole has antidepressant efficacy in patients unresponsive to standard antidepressants [36,37]; in November 2007, the FDA-approved aripiprazole for this indication. Risperidone may also be effective as an adjunct in SSRI nonresponders as demonstrated in two randomized, double-blind, placebo-controlled trials [38,39] and in one trial measuring its antisuicidal effect [40]. Evidence also indicates that quetiapine is effective in the treatment of Major Depressive Disorder (MDD), either alone or in combination with standard antidepressant medications [41–45], though one recent study did not demonstrate any such improvement [46]. Quetiapine's antidepressant effects are likely due, in part, to the NE reuptake blockade and $5HT_{1A}$ agonism properties of its metabolite, *N*-desalkylquetiapine [47]. Olanzapine added to fluoxetine demonstrated superior efficacy in the treatment of MDD when compared to olanzapine or fluoxetine monotherapy in an eight-week double-blind, placebo-controlled trial [48]. However, a single case study showed monotherapy with high-dose olanzapine to be effective in the treatment of recurrent brief depression [49].

The augmentation of antidepressants has also been effective in the treatment of bipolar depression as demonstrated by the FDA's approval of an olanzapine–fluoxetine combination to treat this condition [50]. Monotherapy with the atypical antipsychotic quetiapine was also found to be safe and efficacious in the treatment of bipolar depression [51,52], leading to an FDA approval for this indication in 2006.

Dopamine agonists

DA D2/D3 receptor agonists include pramipexole and ropinirole. Two placebo-controlled trials have confirmed that pramipexole is efficacious, safe, and tolerable in patients with bipolar depression [53,54]. Pramipexole may also be effective in treatment-resistant unipolar depression as demonstrated in an open-label study with long-term follow-up [55,56]. Ropinirole may have similar benefits in depression based on results from an open-label study [57].

Novel pharmacological targets: beyond monoamines

Corticotropin-releasing factor (CRF)-1 receptor antagonists

Increased activity of the hypothalamic–pituitary–adrenal (HPA) axis is a major component of the mammalian endocrine stress response. Following a stressful encounter, the neuropeptide CRF is secreted into the hypothalamo-hypophysial portal circulation where it acts to stimulate the release of adrenocorticotropin (ACTH) from the anterior pituitary. ACTH stimulates glucocorticoid production and

release from the adrenal cortex. Stress (physical or emotional) can precipitate or worsen depression in vulnerable individuals. A burgeoning database links HPA axis activity and more specifically CRF to this process. Compared to nondepressed controls, depressed or depressed suicidal patients show increased HPA axis activity and elevated cerebrospinal fluid (CSF) CRF concentrations, increased paraventricular nucleus (PVN) CRF mRNA expression, and a larger number of CRF-expressing neurons in the PVN [58]. In healthy volunteers, desipramine reduces CSF CRF concentrations [59], and in depressed patients fluoxetine and ECT have shown similar effects [60]. These data suggest that antidepressant treatments with different mechanisms of action may ultimately reduce CRF activity as part of their mechanism of action. Consequently, research is focusing closely on the antidepressant potential of direct modulation of CRF neurotransmission.

Two main CRF receptor subtypes, CRF_1 and CRF_2, exist in the central nervous system (CNS). CRF_1 receptors are distributed widely throughout the CNS including many brain regions implicated in the neurobiology of various mood and anxiety disorders. Animal models demonstrate reduced anxiety-like behavior associated with CRF_1 blockade [61]. CRF_2 receptors are not widely distributed throughout the CNS and overlap only slightly with the distribution of CRF_1 receptors. CRF binds more avidly to CRF_1 receptors than to CRF_2 receptors; urocortin is the preferred endogenous ligand for CRF_2 receptors. Heightened anxiety-like behaviors in animals have been connected to the decreased activity of CRF_2 receptors [61].

Several CRF_1 receptor antagonists possess anxiolytic-like and antidepressant-like effects in animal models [61]. R121919 showed encouraging antidepressant effects in humans but its development was discontinued as a result of potential liver toxicity [62]. CP-316 311, another CRF_1 receptor antagonist, did not show significant antidepressant effects in a placebo-controlled and sertraline-controlled trial [63]; however, it is unclear whether the dose tested was sufficient to block CNS CRF_1 receptors effectively. NBI-34041, a third agent, has not yet been tested in depressed patients but in healthy humans has shown an ability to attenuate the endocrine stress response [64]. Results from three separate placebo-controlled trials testing CRF_1 receptor antagonists in depression will be available soon and will clarify the safety and efficacy of these agents.

Inhibition of glucocorticoid function

Decreased synthesis or receptor blockade of adrenal glucocorticoids may have antidepressant effects. Ketaconozale, aminogluthemide, and metyrapone are agents that interfere with cortisol synthesis. All of these have shown some antidepressant potential, but adverse events have limited their development [65]. Mifepristone, also known as RU486, is a glucocorticoid 2 receptor antagonist that showed antidepressant efficacy in an early case series of patients with severe, chronic depression [66]. Two additional studies in patients with severe, psychotic depression (one open-label and one placebo-controlled) both found mifepristone to be safe and efficacious, with therapeutic effects seen within one week [67,68]. Because these benefits were primarily in psychotic symptoms and not in depressive symptoms, this agent may be more appropriate for treating psychotic depression.

Substance P (NK-1) antagonists

Neurokinins are neuropeptides involved in nociception and many other physiologic processes. Neurokinin receptors are extensively distributed in the CNS, and the most widely distributed receptor subtype is NK-1. Substance P binds to NK-1 receptors that are located in high density in the hypothalamus, periaqueductal gray matter, amygdala, locus ceruleus, and parabrachial nucleus [69]. Substance P-containing neurons contain 5HT and share projection targets with NE neurons [70,71]. A behavioral and physiologic stress response in animals has been associated with increases in substance P [72,73] and attenuated by the administration of an NK-1 antagonist [74,75]. After exposure to a stressful stimulus, patients with MDD or PTSD exhibit elevated CSF substance P concentrations [76]; decreased serum levels have been associated with an antidepressant response [77].

Preclinical studies show that various NK-1 receptor antagonists possess antidepressant-like effects and several have been tested in humans. Aprepitant (MK-869) showed antidepressant efficacy in an initial placebo-controlled trial [74], but subsequent controlled studies failed to confirm this finding [78]. L-759274 and CP-122721 demonstrated antidepressant effects in pilot studies [79,80], though replication has not been reported for either. GR-205171 has shown preliminary efficacy in social phobia [81] and antidepressant-like effects in an animal model [82].

Glutamatergic modulation

The major excitatory amino acid neurotransmitter in the human CNS is glutamate. It binds two main receptor subtypes: ionotropic (NMDA, AMPA, and kainate receptors) and metabotropic (g-protein coupled receptors). Several studies suggest that excitatory glutamatergic neurotransmission may play a role in the pathophysiology of depression [83,84], and that stress-induced atrophy of hippocampal neurons in rodents may be attenuated by ionotropic glutamate receptor antagonists [85,86]. Glutamate receptor antagonists have been postulated to possess antidepressant properties.

A nonselective NMDA receptor antagonist, amantadine, may augment the effects of antidepressants in animals [87,88] and in patients with treatment-resistant depression (TRD) [89]. Selective NMDA receptor antagonists

have also revealed antidepressant-like effects in animals [90,91]. A case report [92] and one randomized placebo-controlled trial [93] revealed that ketamine, an NMDA receptor antagonist, delivered via intravenous infusion, results in antidepressant efficacy within hours. However, effects were transient and relapse occurred within several days. A second case report detailed acute antidepressant efficacy from a single infusion of ketamine in a single patient with severe, TRD. This effect lasted for approximately one month; a second ketamine infusion resulted in a moderate antidepressant response with relapse within one week [94]. Another case report in a patient with MDD and metastatic prostate cancer showed the same pattern: an initial, transient positive result followed by a more transient response after the second infusion. A small, open-label study reported a significantly greater response to ketamine infusion in depressed patients with a family history of alcohol dependence as compared to those without such a history [95]. This suggests that a family history of alcoholism may have a mediating/moderating influence on the efficacy of NMDA antagonists in the treatment of depression. An orally administered NMDA antagonist, memantine, failed to show antidepressant effects in a double-blind, placebo-controlled trial [96]. However, it did exhibit antidepressant effects similar to those of escitalopram in a double-blind study of patients with comorbid MDD and alcohol dependence [97].

Riluzole may inhibit glutamate release and is approved for the treatment of amyotrophic lateral sclerosis. It has also demonstrated antidepressant effects in open-label pilot studies in both TRD [98] and bipolar depression [99,100].

Nemifitide

Melanocyte-inhibiting factor, a small peptide (Pro-Leu-Gly-NH_2) located in the CNS was associated with acute antidepressant effects in an early study [101]. Nemifitide is a novel analog of melanocyte-inhibiting factor and is administered via subcutaneous injection. In a recent open-label study of nemifitide for chronic, refractory depression, 11 of 25 patients had a response (based on primary or secondary depression measures) that lasted for at least two weeks after treatment. Those patients who had a sustained response were enrolled in a maintenance phase, and maintained their response for a mean duration of two months [102]. A placebo-controlled study that used two different doses of nemifitide failed to show a significant antidepressant effect; however, a *post hoc* responder analysis showed that patients with more severe depression had a better response rate to the higher dose of the drug [103].

Omega-3 fatty acids

A link between omega-3 fatty acids and mood disorders is suggested by studies showing a lower incidence of depression among populations with a diet rich in omega-3 fatty acids [104,105]. Additionally, lower levels of omega-3 fatty acids have been reported in mood disorder patients compared to healthy controls [104]. Supporting this link further, several studies using ethyl-eicosapentanoate (EPA) and docosahexanoic acid (DHA), have shown the antidepressant potential of these compounds [106–110]. Omega-3 fatty acids may be useful in patients with perinatal depression as well [111], though results are mixed [112]. In patients with comorbid PD and MDD, a double-blind, randomized, placebo-controlled study showed that adding omega-3 fatty acids with and without antidepressants, resulted in statistically significant improvements in depressive symptoms [113]. A recent meta-analysis of omega-3 fatty acid studies found statistically significant antidepressant effects, but the clinical significance was limited secondary to publication bias and significant heterogeneity between studies [114]. In patients with bipolar disorder, a placebo-controlled study suggested that omega-3 fatty acids resulted in a longer remission of all mood episodes [115], though the study did not specifically focus on depressive phases.

A small number of placebo-controlled studies have failed to show antidepressant effects for omega-3 fatty acids [116–119]. One recent double-blind, placebo-controlled study of EPA/DHA in middle-aged women with depressive symptoms and psychological distress found no benefit [120]. Stratification analyses revealed that EPA/DHA was more efficacious than placebo among those patients not suffering a full major depressive episode but with no efficacy for those patients with MDD [120].

Melatonin

Circadian rhythm abnormalities, such as sleep and appetite disturbances, are important elements of the depressive syndrome. Melatonin clearly influences circadian activity and may therefore play a role in the pathophysiology of depression and other mood disorders [121]. Melatonin treatment has been associated with sleep improvements in some depressed patients but not with concomitant improvements in mood [122]. Another study showed melatonin to be efficacious in the treatment of seasonal affective disorder [123]. Agomelatine, a melatonin receptors 1 and 2 agonist (but also a $5HT_{2C}$ receptor antagonist), demonstrated antidepressant effects in an open label [124] and two placebo-controlled trials [125,126] and has been approved now in some European countries. A double-blind study comparing agomelatine and venlafaxine XR among patients with major depressive disorder revealed equivalently high rates of remission and less sexual side effects in the agomelatine group [127]. An open-label study suggests this drug may also have efficacy in bipolar depression [128].

Focal brain stimulation

Widely considered as the most effective acute treatment for depression [129], electroconvulsive therapy (ECT) is

unfortunately associated with cardiopulmonary complications, postictal confusion, transient memory disturbance, and longer term cognitive disturbance that limit its use in many patients [130,131]. Moreover, ECT is associated with a high relapse rate, with 50% or more patients experiencing a return of symptoms despite maintenance medication or continuation ECT [132,133]. In an effort to match or at least approach the acute efficacy of ECT — but to improve on its safety, tolerability, and long-term effectiveness — alternative forms of brain stimulation have been investigated. Research on these novel treatments has been supported and advanced by an improved understanding of the neural networks underlying normal and abnormal mood regulation based on a number of resting state and functional imaging studies [134].

Vagus nerve stimulation

Vagus nerve stimulation (VNS) is a treatment that consists of stimulating the vagus nerve intermittently (e.g. 30 s on every 5 min) via an electrode connected to both the vagus nerve and a programmable, implanted pulse generator (IPG). VNS surgery is relatively benign; however, side effects from stimulation include coughing, hoarseness, or dysphagia. VNS is FDA-approved for medication-resistant epilepsy (since 1997) and more recently the long-term adjunctive treatment for recurrent or chronic depression not responding to four or more medications [135]. However, the Center for Medicare and Medicaid Services and most other third party payers do not provide reimbursement for VNS surgery for depression.

Two open-label studies suggested an acute benefit for VNS in TRD patients [136] with longer duration of treatment associated with higher response rates [137–139]. After one year of receiving VNS open-label combined with treatment-as-usual (TAU), response rates increased [140]. A *post hoc* analysis of a two-year open-label study with VNS showed that bipolar I and II TRD patients had acute, one-year and two-year outcomes that were similar to those of patients with unipolar TRD [141]. A sham-controlled study of VNS for TRD did not demonstrate significant antidepressant effects after a 10-week treatment course [142].

VNS plus TAU over one year was more effective as compared with TAU alone. Twenty-seven percent of TRD patients in the VNS plus TAU group were responders based on HAMD scores compared to 13% of those in the TAU alone group [143]. The same is true with regard to the maintenance of response over an additional year with close to 65–77% of patients in the VNS plus TAU group maintaining their response [144] as compared to 38% of patients receiving TAU alone [145]. Interpretation of these results is limited by the lack of randomization, absence of a placebo-controlled group, and differences in samples when comparing the data from the VNS plus TAU maintenance of response study with data from the two-year naturalistic TAU study.

Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is achieved by placing a device with an electromagnetic coil against the scalp and inducing a rapidly changing magnetic field that depolarizes cortical neurons. Multiple trials have investigated TMS in TRD patients and have yielded mixed but generally positive results. TMS parameters can vary among studies which may explain some of the variance in outcome. The quantity of pulses (single versus repetitive TMS [rTMS]), their frequency (low versus high) and different 'dose' levels influence the physiologic effects. In studies for depression, these parameters have been fairly consistent with the differences noted in the following discussion.

Meta-analyses of rTMS studies in TRD patients have generally found that high-frequency rTMS over the left dorsolateral prefrontal cortex (DLPFC) at adequate doses for a minimum of 10 sessions has statistically significant antidepressant effects [146–149]. More recent randomized, sham-controlled, adjuvant studies of rTMS over the left DLPFC have resulted in mixed findings [150,151]. Low-frequency rTMS over the right DLPFC has also revealed statistically significant antidepressant effects [152–155]. According to one randomized study, low-frequency and high-frequency rTMS were found to be equally effective in the treatment of depression [156]. The right parietal lobe may be a less viable target for rTMS in view of the finding that a two-week, double-blind, randomized trial of rTMS delivered at 2 Hz in this location was no more effective in treating depression than sham TMS [157]. A double-blind, randomized, sham-controlled study using ultrahigh-frequency (50 Hz) rTMS in patients with MDD, showed safety but no antidepressant efficacy. However, this study included patients with relatively mild to moderate depression severity and little treatment resistance and was limited to two weeks [158]. Many of the earlier rTMS studies may have used suboptimal doses in highly treatment-resistant patients [159,160]. Studies using more aggressive parameters (such as intensity $\geq$110% motor threshold for 15 or more sessions) in less severely resistant patients have shown larger response rates [153,161].

A large, multisite, sham-controlled study of high-frequency left DLPFC rTMS in patients with at least one antidepressant treatment failure in the current episode just barely failed to show a statistically significant advantage for active rTMS with respect to the primary outcome variable (change on the Montgomery-Asberg Depression Rating Scale by week four) [162]. However, after four and six weeks, active rTMS resulted in statistically significantly greater response rates, with 18% (versus 11% of sham patients) at week four and 24%

(versus 12% of sham patients) at week six meeting response criteria. Nevertheless, the active rTMS patients showed a statistically higher remission rate only at week six (14% versus 6%). Overall, rTMS was safe and well tolerated. An open-label extension of this study showed that after another six weeks of active rTMS in those who did not respond to the acute trial, 26% showed a response, and 11% were in remission [163]. This suggests that a longer course of treatment with rTMS may be more effective. A recently published subanalysis of this data shows that active rTMS patients who failed only one antidepressant trial during the current episode improved significantly more than those who failed two to four adequate trials [164]. The NIMH is currently funding a second multisite, sham-controlled study using similar stimulation parameters.

The antidepressant benefits of rTMS in medication free, TRD patients may be sustained for a mean of nearly five months. After each repeated course of treatment over a four-year period, one-half of these patients may continue to experience a clinically significant effect [165]. A case report of a patient with bipolar depression with rapid cycling and a case series of patients with late life depression both suggest modest benefits of adjuvant rTMS in these populations as well [166,167].

Magnetic seizure therapy

Magnetic seizure therapy (MST) involves using an rTMS device to create a generalized seizure with antidepressant effects similar or equivalent to high-dose right unilateral ECT. Unlike ECT, however, it has fewer cognitive side effects [168–170]. Larger, controlled studies are currently underway. A case report of successful treatment with MST in a bipolar I depressed patient suggests efficacy and limited side effects in this population as well [171].

Transcranial direct current stimulation

Transcranial direct current stimulation (tDCS) is another noninvasive technique that uses two scalp electrodes to deliver an electrical current strong enough to modulate cortical cell firing. However, it does not usually result in direct depolarization. LDLPFC tDCS demonstrated greater antidepressant efficacy compared to occipital tDCS (active control) and sham tDCS in a single double-blind, randomized, controlled study [172]. Although these findings are only preliminary, they warrant further investigation.

Deep brain stimulation

Deep brain stimulation (DBS) is an established treatment for patients with dystonia, essential tremor, or severe, medication-refractory PD. It is produced by a subclavian subcutaneous pulse generator that connects to neurosurgically implanted electrodes that stimulate a focused region in the brain. The pulse generator can be programmed by using an external wand. The advantages of DBS over older interventions, such as ablative lesion surgery, are that it can be completely removed, placed in a different region, and parameters can be adjusted for greater efficacy with fewer side effects.

An antidepressant response for DBS was demonstrated in an open-label, proof-of-concept study of six patients with severe, TRD. In this study, four patients improved significantly after six months of bilateral DBS targeting the subgenual cingulate white matter [173]. An extension of this study included 20 patients followed for 12 months: 60% demonstrated an antidepressant response after 6 months of DBS and 55% at 12 months [174]. No notable adverse events were associated with this intervention. Currently, a multisite pivotal trial is underway to confirm the antidepressant efficacy of DBS at this particular neuroanatomic location.

Other potential DBS targets in the brain for TRD patients have been proposed. The anterior limb of the anterior internal capsule (ALIC; a target of ablative treatment in severe psychiatric disorders) is one such region [175]. DBS of this location has been associated with the improvement of depressive symptoms in patients with treatment-resistant, severe OCD [176–178]. A recent open-label DBS study in TRD patients that targeted the ventral capsule/ventral striatum region showed significant improvement in depressive symptoms in TRD patients, some of whom were followed longer than four years [179]. Other promising locations include the habenula [180], nucleus accumbens [181], and the thalamic peduncle [182].

Conclusion

Despite the efficacy of our currently available antidepressant medications and somatic therapies, residual depressive symptoms and relapse are common. This creates a challenge for the clinician as s/he seeks to completely eliminate symptoms and help patients fully recover. To reach these goals, improved treatment strategies are needed. Understanding the neurobiology of depression has helped researchers uncover a number of novel targets for antidepressant therapies. Compounds that reach those targets are being investigated in animal models, case reports, and small open-label studies, which so far have suggested antidepressant potential. Several pivotal trials will help clarify which of these treatments may be clinically realized. Over the next several years, the treatment of depression will likely be improved by the introduction of several of these novel interventions that no longer rely solely on monoamine reuptake inhibition.

Disclosures

CBN in the past year served on the scientific advisory boards of the American Foundation for Suicide Prevention (AFSP); AstraZeneca; NARSAD; Quintiles; Forest; and PharmaNeuroboost. He holds stock/equity in Cor-

cept; Revaax; NovaDel Pharma; CeNeRx, and Pharma-Neuroboost. He is on the board of directors of the AFSP; George West Mental Health Foundation; NovaDel Pharma, and Mt. Cook Pharma. CBN holds a patent on the method and devices for transdermal delivery of lithium (US 6,375,990 B1) and the method to estimate serotonin and norepinephrine transporter occupancy after drug treatment using patient or animal serum (provisional filing April, 2001).

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