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Novel Targets for Antidepressant Therapies

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Abstract

Most depressed patients fail to achieve remission despite adequate antidepressant monotherapy, and a substantial minority show minimal improvement despite optimal and aggressive therapy. However, major advances have taken place in elucidating the neurobiology of depression, and several novel targets for antidepressant therapy have emerged. Three primary approaches are currently being taken: 1) optimizing the pharmacologic modulation of monoaminergic neurotransmission, 2) developing medications that target neurotransmitter systems other than the monoamines, and 3) directly modulating neuronal activity via focal brain stimulation. We review novel therapeutic targets for developing improved antidepressant therapies, including triple monoamine reuptake inhibitors, atypical antipsychotic augmentation, dopamine receptor agonists, corticotropin-releasing factor-1 receptor antagonists, glucocorticoid receptor antagonists, substance P receptor antagonists, *N*-methyl-D-aspartate receptor antagonists, nemifitide, omega-3 fatty acids, and melatonin receptor agonists. Developments in therapeutic focal brain stimulation include vagus nerve stimulation, transcranial magnetic stimulation, magnetic seizure therapy, transcranial direct current stimulation, and deep brain stimulation.

Introduction

Depression is a highly prevalent and disabling condition. Available treatments lead to symptomatic improvement in most patients, although antidepressant effects typically are not fully realized for several weeks. Up to 70% of depressed patients have residual symptoms despite adequate treatment, and 20% or more may show limited response even with the most aggressive therapies. Additionally, recurrent episodes are the rule rather than the exception,

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and few evidence-based approaches to maintaining an antidepressant response are available. Thus, improved antidepressant treatments are clearly needed.

Currently available and commonly used antidepressant treatments include various forms of psychotherapy, pharmacotherapy, and electroconvulsive therapy (ECT). Vagus nerve stimulation (VNS) recently was approved by the US Food and Drug Administration (FDA) for the adjunctive treatment of medication-refractory depression, although the Centers for Medicare and Medicaid Services and most other third party payers largely have refused to reimburse providers for this treatment. Most of these treatments were developed based on serendipitous discoveries and/or a limited understanding of the neurobiology of depression that focused almost exclusively on the monoaminergic neurotransmitter systems. As our understanding of the neuroscience of depression has advanced, several novel targets for antidepressant treatment have been identified and are under active investigation. Generally, these treatments fall into three major categories: 1) medications aimed at optimizing modulation of monoaminergic neurotransmitters, 2) medications targeting other neurotransmitter and neuromodulatory systems beyond the monoamines, and 3) focal electrical brain stimulation techniques. In this review, we survey these developing treatments and highlight those that appear to hold the most promise.

Optimizing Monoaminergic Modulation

Medications that modulate monoaminergic neurotransmitter function by one mechanism or another can possess antidepressant efficacy, as demonstrated in multiple randomized, double-blind, controlled trials. Such medications include the tricyclic/tetracyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin (5-HT) reuptake inhibitors (SSRIs), 5-HT and norepinephrine (NE) dual-reuptake inhibitors (SNRIs), and several atypical antidepressants (eg, nefazodone, bupropion, and mirtazapine). Mechanisms of action for these medications primarily include the following: 1) inhibiting reuptake of NE and/or 5-HT into the presynaptic terminal from the synapse (TCAs, SSRIs, and SNRIs); 2) inhibiting monoamine oxidase, the enzyme that degrades 5-HT, NE, and dopamine (DA) in the presynaptic terminal (MAOIs); or 3) blocking or stimulating presynaptic and/or postsynaptic monoamine neurotransmitter receptors (mirtazapine, nefazodone, trazodone, and several atypical antipsychotics).

Given these agents' success in treating many patients with depression, increasing interest and research has focused on novel ways of optimizing monoaminergic neuromodulation. In particular, efforts have targeted DA circuits based on a burgeoning database supporting a critical role for DA dysfunction in the pathophysiology of depression [1•]. Emerging treatments in this category include triple reuptake inhibitors, atypical antipsychotic augmentation, and DA receptor agonists.

Triple reuptake inhibitors

Triple reuptake inhibitors include agents designed to block synaptic reuptake of all three monoamines (5-HT, NE, and DA). Several candidates have shown antidepressant-like effects in animal studies. One compound (DOV 216303; DOV Pharmaceutical, Somerset, NJ) was found to be safe and tolerable during short-term use in an open-label, phase 1 study

[2]. Another agent, tesofensine (NS 2330; Boehringer Ingelheim, Ingelheim, Germany), has shown modest preliminary efficacy and safety in treating motor symptoms associated with advanced Parkinson's disease [3], but no clinical data for treating depression are available. Two major concerns in the development of DA reuptake inhibitors are drug abuse liability and autonomic side effects.

Atypical antipsychotic augmentation

Compared with older, high-potency "typical" antipsychotics (eg, haloperidol, perphenazine) that blocked DA D₂ receptor at occupancy rates of 90% or more, atypical antipsychotics (clozapine, olanzapine, risperidone, paliperidone, quetiapine, ziprasidone, and aripiprazole) exhibit occupancy rates at D₂ receptors of 70% or less. They also possess increased affinity for several 5-HT receptors and possibly glutamate receptors; aripiprazole also functions as a partial agonist at the D₂ receptor. Antidepressant effects seen with these agents therefore may be related to DA function modulation and other potential mechanisms. Drugs in this class generally are associated with fewer extrapyramidal side effects than typical antipsychotics, but some of these have been associated with a unique and challenging set of side effects, including weight gain, glucose intolerance, and serum lipid abnormalities. Certain drugs in this class have been shown to be effective in augmenting SSRIs in certain anxiety disorders, such as obsessive-compulsive disorder [4] and post-traumatic stress disorder [5].

Early open-label studies and retrospective case reviews suggested that atypical antipsychotics may augment the action of standard antidepressant medications, even in the absence of psychotic features in the depressive episode [6]. Aripiprazole has demonstrated antidepressant efficacy as an augmentation treatment in patients not responding to standard antidepressant medications in two large, randomized, placebo-controlled trials [7,8]; in November 2007, the FDA approved aripiprazole for this indication. An olanzapine–fluoxetine combination is FDA approved for treating bipolar depression [9]. Quetiapine monotherapy appears to be safe and efficacious in treating bipolar depression [10,11], which led to FDA approval for this indication in 2006. Considerable evidence now indicates that quetiapine is effective for treating major depressive disorder alone or in combination with standard antidepressant medications [12–15]. These effects of quetiapine are likely due in part to its potency as an NE reuptake inhibitor. Risperidone was effective as an adjunct in SSRI nonresponders in two randomized, double-blind, placebo-controlled trials [16,17].

Dopamine agonists

Pramipexole and ropinirole are DA D₂ and D₃ receptor agonists. Two placebo-controlled trials have helped to confirm that pramipexole is safe, tolerable, and efficacious for bipolar depression [18,19]. An open-label study with long-term follow-up suggested that pramipexole also may be effective in treatment-resistant unipolar depression [20,21]. Another open-label study suggested similar benefits for ropinirole [22]. Further investigation of these agents is under way.

Novel Pharmacologic Targets: Beyond Monoamines

Corticotropin-releasing factor-1 receptor antagonists

Increased activity of the hypothalamic-pituitary-adrenal (HPA) axis characterizes the human endocrine stress response. After a stressful stimulus, the neuropeptide corticotropin-releasing factor (CRF) is released into the hypothalamo-hypophyseal portal circulation and stimulates secretion of adrenocorticotropin from the anterior pituitary. Adrenocorticotropin acts on the adrenal cortex to stimulate glucocorticoid production and release cortisol (in humans). Physical or emotional stress can precipitate or exacerbate depression in vulnerable individuals, and a growing database supports a role for the HPA axis—and specifically CRF—in this process. Depressed patients exhibit increased HPA axis activity and elevated cerebrospinal fluid CRF concentrations, increased paraventricular nucleus CRF mRNA expression, and more CRF-containing neurons compared with nondepressed controls. Antidepressant treatment (with the TCA desipramine) has been associated with reduced cerebrospinal fluid CRF concentrations in healthy volunteers, and depressed patients have shown similar changes after treatment with fluoxetine and ECT. These data (see [23] for a comprehensive review) suggest that reduced CRF activity may play a role in the mechanism of action for multiple divergent antidepressant treatments, thereby supporting investigation of direct modulation of CRF neurotransmission as an antidepressant treatment strategy.

Two main CRF receptor subtypes have been identified in the central nervous system: CRF₁ and CRF₂. CRF₁ receptors have a widespread distribution and strongly bind CRF. Blockade of CRF₁ receptors is associated with reduced anxiety-like behavior in animal models [23]. CRF₂ receptors are less widely distributed throughout the central nervous system and have limited overlap with CRF₁ receptors. CRF binds CRF₂ receptors less strongly than CRF₁ receptors; the preferred endogenous ligand for CRF₂ receptors apparently is urocortin. Decreased activity of CRF₂ receptors has been linked with heightened anxiety-like behaviors in animals [23].

Several CRF₁ receptor antagonists exhibit anxiolytic- and antidepressant-like effects in animal models [23]. R121919 (Janssen Pharmaceutica, Beerse, Belgium) was the first agent to be tested in depressed patients and showed encouraging antidepressant effects [24]. Unfortunately, potential liver toxicity with this agent led to discontinuation of its development. Another CRF₁ receptor antagonist (CP-316311; Pfizer, Groton, CT) failed to show significant antidepressant effects in a placebo- and sertraline-controlled trial [25]; whether the dose tested was sufficient to block central nervous system CRF₁ receptors remains unclear. A third agent (NBI-34041; Neurocrine Biosciences, San Diego, CA) has shown the ability to attenuate the endocrine stress response in healthy humans but has not been tested in depressed patients [26]. Three placebo-controlled trials with various CRF₁ receptor antagonists in major depressive disorder are now completed or under way.

Inhibition of glucocorticoid function

Inhibition of adrenocortisol activity—through decreased synthesis or receptor blockade—may have antidepressant effects. Agents that interfere with cortisol synthesis (eg,

ketaconazole, aminoglutethimide, and metyrapone) have shown some antidepressant efficacy, but adverse effects have limited their development. The glucocorticoid 2 receptor antagonist mifepristone (also known as RU486 [Roussel Uclaf, Romainville, France]) has shown antidepressant efficacy in an early case series of patients with severe, chronic depression [27]. Two follow-up studies (one placebo-controlled and one open-label) suggested that mifepristone was safe and efficacious in treating severe, psychotic depression, with notable effects seen within 1 week [28,29]. However, these benefits were primarily in psychotic—as opposed to depressive—symptoms, suggesting that this agent may have a more specific role in treating psychotic depression. A minimal plasma concentration may be necessary to produce this compound's therapeutic effects.

Substance P (neurokinin-1) antagonists

Neurokinins are neuropeptides involved in nociception and a myriad of other physiologic processes. Neurokinin receptors have extensive central nervous system distribution, and the most abundant and widely distributed receptor subtype is neurokinin-1 (NK-1). Substance P is the best-studied neurokinin, with localization in the amygdala, hypothalamus, periaqueductal gray matter, locus ceruleus, and parabrachial nucleus, as well as colocalization with 5-HT and NE neurons. Increases in substance P are associated with a behavioral and physiologic stress response in animals [30] that is attenuated by administration of an NK-1 antagonist [31]. Elevated cerebrospinal fluid substance P concentrations have been reported in depressed patients and patients with post-traumatic stress disorder after exposure to a stressful stimulus [32]; decreased levels have been associated with an antidepressant response [33].

Several NK-1 receptor antagonists possess antidepressant-like effects in preclinical studies. An initial placebo-controlled trial with aprepitant (MK-869; Merck & Co., Whitehouse Station, NJ) reported antidepressant efficacy for this compound [31], but later studies failed to confirm this [34]. Two other compounds (L-759274; Merck & Co., Whitehouse Station, NJ and CP-122721; Pfizer, Groton, CT) have revealed antidepressant effects in pilot studies [35,36], although confirmatory findings have not yet been reported. Another agent (GR-205171; Eli Lilly and Company, Indianapolis, IN) has shown preliminary efficacy in treating social phobia [37] and has demonstrated antidepressant-like effects in an animal model [38].

Glutamatergic modulation

Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system. Subtypes of glutamate receptors include ionotropic (*N*-methyl-D-aspartate [NMDA], AMPA, and kainate receptors) and metabotropic (g-protein coupled receptors). Excitatory glutamatergic neurotransmission has been hypothesized to be involved in the pathophysiology of depression [39], and ionotropic receptor antagonists may attenuate stress-induced atrophy in hippocampal neurons in animals [40].

NMDA receptor antagonists may have antidepressant properties. Amantadine, a nonselective NMDA receptor antagonist, has been shown to enhance the antidepressant-like effects of medications in animals [41]. Furthermore, amantadine augmentation has

demonstrated preliminary efficacy in medication-resistant depression [42]. Selective NMDA receptor antagonists also have demonstrated antidepressant-like effects in animals [43]. Ketamine, an NMDA receptor antagonist, has shown acute (within hours) antidepressant efficacy in a case report [44] and one randomized, placebo-controlled trial [45], although effects were transient, with relapse occurring within several days. A single case report of a severe, treatment-resistant depressed patient noted acute antidepressant efficacy from a single infusion of ketamine that lasted for approximately 1 month; a second ketamine infusion resulted in an attenuated antidepressant response, with relapse within 1 week [46]. In contrast, memantine (an NMDA antagonist) has not shown efficacy in treating depression [47].

Riluzole, an agent approved for treating amyotrophic lateral sclerosis, has been posited to act by inhibiting glutamate release. In open-label pilot studies in bipolar depression [48,49] and treatment-resistant depression (TRD) [50], riluzole has demonstrated anti-depressant effects.

Nemifitide

Nemifitide is a novel analogue of melanocyte-inhibiting factor, a small peptide (Pro-Leu-Gly-NH₂) present in the central nervous system. Nemifitide is currently administered via subcutaneous injection. Its potential mechanism of action in depression is unknown, although melanocyte-inhibiting factor was associated with acute antidepressant effects in an early study [51]. A recent placebo-controlled study failed to show a significant antidepressant effect for either of two doses of Nemifitide; however, a post hoc responder analysis showed that the higher dose of Nemifitide was associated with a greater response rate in patients with more severe depression [52]. An open-label study in patients with chronic TRD found that 9 of 25 had an antidepressant response (based on primary or secondary measures) that persisted for at least 2 weeks after treatment. These patients were enrolled in a maintenance phase, and the mean duration of maintained response was 2 months.

Omega-3 fatty acids

Populations with a high rate of seafood consumption (high in omega-3 fatty acids) may have a lower incidence of depression and other mood disorders [53]. Furthermore, patients with mood disorders appear to have lower omega-3 fatty acid levels compared with healthy controls [53]. Several studies have found statistically significant antidepressant effects for the omega-3 fatty acid ethyl-eicosapentaenoate (EPA) [54]. One placebo-controlled study in patients with bipolar disorder suggested that omega-3 fatty acids led to longer remission of all mood episodes over 4 months [55], although the study was not designed with a specific focus on depression. Other placebo-controlled studies have found no antidepressant effects for omega-3 fatty acids, including EPA [56]. A recent meta-analysis found that omega-3 fatty acids had statistically significant antidepressant effects, although this report also noted that publication bias and significant heterogeneity between studies limited this finding's clinical significance [57•]. Omega-3 fatty acids may have a role in treating perinatal depression [58], but results are mixed [59].

Melatonin

Circadian rhythm abnormalities (eg, sleep disturbance) are common in depression, suggesting a role for melatonin in the pathophysiology of mood disorders. Melatonin can be efficacious in treating seasonal affective disorder [60] and has been associated with improvement of sleep abnormalities (but not mood) in depressed patients [61]. Agomelatine is a melatonin receptor 1 and 2 agonist and a 5-HT_{2C} receptor antagonist that exhibited antidepressant effects in an early open study [62] and two placebo-controlled studies [63,64]; open-label data in bipolar depression also suggest efficacy [65].

Focal Brain Stimulation

ECT is widely considered the most effective acute treatment for depression. However, ECT is also associated with an unfavorable side effect profile, including postictal confusion, transient memory disturbance, longer-term cognitive disturbance, and cardiopulmonary complications. Also, even when it results in remission, ECT is associated with a high relapse rate after the end of treatment, with 50% or more of patients experiencing relapse despite maintenance medication or continuation ECT [66]. The clear acute efficacy of ECT tempered by side effects and high relapse rate has led to pursuit of other brain stimulation techniques that may be useful in patients with medication-refractory depression.

Vagus nerve stimulation

VNS is FDA approved for the adjunctive treatment of medication-resistant epilepsy [67] and chronic or recurrent TRD. VNS treatment is comprised of surgery to connect an electrode to the patient's left vagus nerve and implant a programmable pulse generator subcutaneously in the patient's chest wall. Stimulation is typically delivered intermittently (eg, 30 seconds on, alternating with 5 minutes off) but chronically. The surgery is relatively benign, and possible side effects of stimulation include hoarseness, coughing, and difficulty swallowing during the on phase of the on/off cycle.

Two open-label studies suggested an acute benefit for VNS in patients with TRD [68], with higher response rates associated with longer duration of treatment (up to 2 years) [69]. A sham-controlled study of VNS for TRD failed to show statistically significant antidepressant effects after 10 weeks of treatment [70], although response rates increased after 1 year of open-label treatment combined with treatment as usual (TAU) [71]. The antidepressant response to VNS plus TAU over 1 year was statistically significantly greater than the response seen with TAU alone [72]. Also, the maintenance of response with VNS plus TAU [73] appears to be greater than that seen with TAU alone [74], although this has not been studied in a randomized, controlled fashion.

Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) uses an electromagnetic coil held against the scalp to induce a rapidly changing magnetic field that passes through to the cortex and depolarizes cortical neurons. Different physiologic effects are seen with single-pulse TMS versus repetitive TMS (rTMS)—in which a series of pulses are typically delivered very rapidly over a few seconds—and with low-frequency (< 1 Hz) versus high-frequency (> 5 Hz)

rTMS. *Dose* is generally defined in relative terms, often in relation to the individual patient's motor threshold (ie, the minimal intensity needed to generate activity in a defined muscle group over about half of a series of trials). rTMS parameters can vary widely, although the parameters used in studies of depression have been fairly consistent (with some important differences).

Multiple open and controlled studies (all with relatively small sample sizes) have investigated rTMS in depressed patients with a history of treatment resistance. Meta-analyses generally have agreed that high-frequency rTMS delivered at or above motor threshold over the left dorsolateral prefrontal cortex (DLPFC) for 10 or more sessions has statistically significant antidepressant effects [75]. Fewer studies have demonstrated statistically significant antidepressant effects for low-frequency rTMS applied to the right DLPFC [76,77], but again, this approach's clinical significance has not been established. A review of these earlier studies suggested that many of these may have actually used suboptimal rTMS in rather highly treatment-resistant patients [78]. In support of this, studies using more aggressive parameters (eg, intensity 110% motor threshold for 15 sessions) in less severely resistant patients generally have shown higher response rates [78,79].

A large, multisite, sham-controlled study of high-frequency left DLPFC rTMS in patients with a history of at least one antidepressant treatment failure in the current episode recently was completed [80]. The difference between active and sham rTMS on the primary outcome measure (change in Montgomery-Asberg Depression Rating Scale score by week 4) trended toward significance in favor of active rTMS ($P = 0.057$). After 4 and 6 weeks of treatment, active rTMS resulted in statistically significantly greater response rates, with antidepressant response to active rTMS seen in 18% of patients at week 4 (vs 11% of sham patients) and 24% at week 6 (vs 12% with sham). The remission rate was statistically greater in the active rTMS group only at week 6 (14% vs 6%). Overall, rTMS was well tolerated and safe. A second multisite, sham-controlled study (funded by the National Institute of Mental Health) is currently under way.

Magnetic seizure therapy

Magnetic seizure therapy induces a generalized seizure (similar to ECT) using an rTMS device. Magnetic seizure therapy may have antidepressant effects equivalent or at least similar to high-dose right unilateral ECT but with fewer cognitive side effects [81–83]. Larger, controlled studies are currently under way.

Transcranial direct current stimulation

Transcranial direct current stimulation (tDCS) is a noninvasive technique that uses two scalp electrodes to deliver a weak electrical current to the cortex. This current is believed to modulate the likelihood of cortical cell firing but does not typically result in direct depolarization. A single double-blind, randomized, controlled study found greater antidepressant efficacy for left DLPFC tDCS compared with occipital tDCS (active control) and sham tDCS [84]. These preliminary findings support further investigation.

Deep brain stimulation

Deep brain stimulation (DBS) uses neurosurgically implanted electrodes to stimulate a small, focused region in the brain. These electrodes are connected to a subclavian subcutaneous pulse generator that can be programmed via external wand. DBS is an established treatment for patients with severe, medication-refractory Parkinson's disease; essential tremor; or dystonia. DBS has a significant advantage over ablative lesion surgery in these patients because the DBS system can be completely removed or placed in a different location, and stimulation parameters theoretically can be adjusted to achieve greater efficacy with fewer side effects.

A proof-of-concept study of six patients with severe TRD demonstrated an antidepressant response in four patients after 6 months of open-label, bilateral DBS applied to the subgenual cingulate white matter [85]. This early study was extended to include 20 patients observed for 12 months: 60% of patients showed an antidepressant response after 6 months of DBS, and 55% of patients were responders 12 months after surgery [86•]. Chronic DBS was not associated with any notable adverse events. Further studies of DBS of this target for TRD are currently under way, including a multisite, pivotal trial.

Other targets for DBS in TRD have been proposed, including the anterior limb of the internal capsule (a previous target used for ablative treatment in severe psychiatric disorders) [87], nucleus accumbens [88], thalamic peduncle [89], and habenula [90]. DBS of the anterior limb of the internal capsule has been associated with improvement in depressive symptoms in patients with severe, treatment-resistant obsessive-compulsive disorder [91•], although data in TRD patients without obsessive-compulsive disorder are not available.

Conclusions

Currently available antidepressant medications and other somatic therapies have clear efficacy for many depressed patients. However, residual depressive symptoms and relapse are common, highlighting the need for improved treatment strategies. As the neurobiology of depression has become better understood, several novel targets for antidepressant therapies have emerged and are being actively tested in clinical populations. Data from these studies suggest promising antidepressant effects of many of these agents, and several pivotal trials are currently under way to help clarify which of these treatments may be clinically useful. Over the next few years, the treatment of depression is expected to be enhanced by the introduction of several novel interventions that represent a truly new direction in antidepressant treatment development. Coincident with these developments, it is expected that genetic and imaging techniques used to define specific endophenotypes of mood disorders will likely lead to more specialized treatment for individual patients by matching patients to treatment based on individualized pathophysiology.

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compulsive disorder severity, and 6 of 8 patients showed a decrease of at least 25%. [PubMed: 16855529]

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