Published in final edited form as:

Curr Opin Chem Biol. 2009 June ; 13(3): 291–302. doi:10.1016/j.cbpa.2009.04.617.

Emerging targets for antidepressant therapies

Jeffrey J Rakofsky¹, Paul E Holtzheimer², and Charles B Nemeroff²

¹ Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, 2004 Ridgewood Dr, Suite 218, Atlanta, GA 30322, United States

² Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, 101 Woodruff Circle NE, Suite 4000, Atlanta, GA 30322, United States

Abstract

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 CRF₁ 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).

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

© 2009 Elsevier Ltd. All rights reserved.

Corresponding author: Rakofsky, Jeffrey J (jrakofs@emory.edu), Holtzheimer, Paul E (pholtzh@emory.edu) and Nemeroff, Charles B (cnemero@emory.edu).

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 Corcept; 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).

JJR has no financial relationships or other potential conflicts of interest to disclose.

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 neuro-modulation. 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]. Mono-therapy 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 hypothalamohypophyseal 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 anti-depressant potential of direct modulation of CRF neuro-transmission.

Two main CRF receptor subtypes, CRF₁ and CRF₂, exist in the central nervous system (CNS). CRF₁ 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 CRF₁ blockade [61]. CRF₂ receptors are not widely distributed throughout the CNS and overlap only slightly with the distribution of CRF₁ receptors. CRF binds more avidly to CRF₁ receptors than to CRF₂ receptors; urocortin is the preferred endogenous ligand for CRF₂ receptors. Heightened anxiety-like behaviors in animals have been connected to the decreased activity of CRF₂ receptors [61].

Several CRF₁ 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 CRF₁ 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 CRF₁ 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 CRF₁ 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. Ketaconazole, aminoglutethimide, 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-NH₂) 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 HAM-D 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 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 anti-depressant 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.

Acknowledgements

The authors were supported by the NIH/National Institute of Mental Health (MH 58922, MH 42088, MH 69056, and MH 77083; MH 77869), and NARSAD.

PEH is supported by grants from the Dana Foundation, NARSAD, National Institute of Mental Health (K23 MH-077869), National Institutes of Health Loan Repayment Program, Stanley Medical Research Institute, and Woodruff Foundation. He is currently a consultant to Advanced Neuromodulation Systems (a division of St. Jude Medical), and has previously consulted to Tetragenex, Inc. and AstraZeneca, Inc.

References

1. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005; 62(6):593–602. [PubMed: 15939837]
2. Murray, CJL.; Lopez, AD. *The Global Burden of Disease*. Harvard University Press; Boston: 1996.
3. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, Norquist G, Howland RH, Lebowitz B, McGrath PJ, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry*. 2006; 163(1):28–40. [PubMed: 16390886]
4. Rush AJ, Trivedi MH, Wisniewski SR, Stewart JW, Nierenberg AA, Thase ME, Ritz L, Biggs MM, Warden D, Luther JF, et al. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *N Engl J Med*. 2006; 354(12):1231–1242. [PubMed: 16554525]
5. Arroll B, Macgillivray S, Ogston S, Reid I, Sullivan F, Williams B. Efficacy and tolerability of tricyclic antidepressants and SSRIs compared with placebo for treatment of depression in primary care: a meta-analysis. *Ann Fam Med*. 2005; 3(5):449–456. [PubMed: 16189062]
6. Dunlop BW, Nemeroff CB. The role of dopamine in the pathophysiology of depression. *Arch Gen Psychiatry*. 2007; 64(3):327–337. [PubMed: 17339521]
7. Liang Y, Shaw AM, Boules M, Briody S, Robinson J, Oliveros A, Blazar E, Williams K, Zhang Y, Carlier PR, et al. Antidepressant-like pharmacological profile of a novel triple reuptake inhibitor, (1S,2S)-3-(methylamino)-2-(naphthalen-2-yl)-1-phenylpropan-1-ol (PRC200-SS). *J Pharmacol Exp Ther*. 2008; 327(2):573–583. [PubMed: 18689611]
8. Skolnick P, Popik P, Janowsky A, Beer B, Lippa AS. Antidepressant-like actions of DOV 21,947: a “triple” reuptake inhibitor. *Eur J Pharmacol*. 2003; 461(2–3):99–104. [PubMed: 12586204]
9. Skolnick P, Popik P, Janowsky A, Beer B, Lippa AS. “Broad spectrum” antidepressants: is more better for the treatment of depression? *Life Sci*. 2003; 73(25):3175–3179. [PubMed: 14561522]
10. Aluisio L, Lord B, Barbier AJ, Fraser IC, Wilson SJ, Boggs J, Dvorak LK, Letavic MA, Maryanoff BE, Carruthers NI, et al. In-vitro and in-vivo characterization of JNJ-7925476, a novel triple monoamine uptake inhibitor. *Eur J Pharmacol*. 2008; 587(1–3):141–146. [PubMed: 18499098]
11. Bannwart LM, Carter DS, Cai HY, Choy JC, Greenhouse R, Jaime-Figueroa S, Iyer PS, Lin CJ, Lee EK, Lucas MC, et al. Novel 3,3-disubstituted pyrrolidines as selective triple serotonin/norepinephrine/dopamine reuptake inhibitors. *Bioorg Med Chem Lett*. 2008; 18(23):6062–6066. [PubMed: 18954985]
12. Beer B, Stark J, Krieter P, Czobor P, Beer G, Lippa A, Skolnick P. DOV 216,303, a “triple” reuptake inhibitor: safety, tolerability, and pharmacokinetic profile. *J Clin Pharmacol*. 2004; 44(12):1360–1367. [PubMed: 15545306]

13. Rascol O, Poewe W, Lees A, Arstin M, Salin L, Juhel N, Waldhauser L, Schindler T. Tesofensine (NS 2330), a monoamine reuptake inhibitor, in patients with advanced Parkinson disease and motor fluctuations: the ADVANS study. *Arch Neurol*. 2008; 65(5):577–583. [PubMed: 18474731]
14. Meltzer HY. The mechanism of action of novel antipsychotic drugs. *Schizophr Bull*. 1991; 17(2): 263–287. [PubMed: 1679253]
15. Meyer JM. A retrospective comparison of weight, lipid, and glucose changes between risperidone- and olanzapine-treated inpatients: metabolic outcomes after 1 year. *J Clin Psychiatry*. 2002; 63(5): 425–433. [PubMed: 12019668]
16. Bystritsky A, Ackerman DL, Rosen RM, Vapnik T, Gorbis E, Maidment KM, Saxena S. Augmentation of serotonin reuptake inhibitors in refractory obsessive-compulsive disorder using adjunctive olanzapine: a placebo-controlled trial. *J Clin Psychiatry*. 2004; 65(4):565–568. [PubMed: 15119922]
17. Connor KM, Payne VM, Gadde KM, Zhang W, Davidson JR. The use of aripiprazole in obsessive-compulsive disorder: preliminary observations in 8 patients. *J Clin Psychiatry*. 2005; 66(1):49–51. [PubMed: 15669888]
18. Bogan AM, Koran LM, Chuong HW, Vapnik T, Bystritsky A. Quetiapine augmentation in obsessive-compulsive disorder resistant to serotonin reuptake inhibitors: an open-label study. *J Clin Psychiatry*. 2005; 66(1):73–79. [PubMed: 15669891]
19. Hamner MB, Deitsch SE, Brodrick PS, Ulmer HG, Lorberbaum JP. Quetiapine treatment in patients with posttraumatic stress disorder: an open trial of adjunctive therapy. *J Clin Psychopharmacol*. 2003; 23(1):15–20. [PubMed: 12544370]
20. Bartzokis G, Lu PH, Turner J, Mintz J, Saunders CS. Adjunctive risperidone in the treatment of chronic combat-related posttraumatic stress disorder. *Biol Psychiatry*. 2005; 57(5):474–479. [PubMed: 15737661]
21. Stein MB, Kline NA, Matloff JL. Adjunctive olanzapine for SSRI-resistant combat-related PTSD: a double-blind, placebo-controlled study. *Am J Psychiatry*. 2002; 159(10):1777–1779. [PubMed: 12359687]
22. Pollack MH, Simon NM, Zalta AK, Worthington JJ, Hoge EA, Mick E, Kinrys G, Oppenheimer J. Olanzapine augmentation of fluoxetine for refractory generalized anxiety disorder: a placebo controlled study. *Biol Psychiatry*. 2006; 59(3):211–215. [PubMed: 16139813]
23. Brawman-Mintzer O, Knapp RG, Nietert PJ. Adjunctive risperidone in generalized anxiety disorder: a double-blind, placebo-controlled study. *J Clin Psychiatry*. 2005; 66(10):1321–1325. [PubMed: 16259547]
24. Katzman MA, Vermani M, Jacobs L, Marcus M, Kong B, Lessard S, Galarraga W, Struzik L, Gendron A. Quetiapine as an adjunctive pharmacotherapy for the treatment of non-remitting generalized anxiety disorder: a flexible-dose, open-label pilot trial. *J Anxiety Disord*. 2008; 22(8): 1480–1486. [PubMed: 18455360]
25. Ostroff RB, Nelson JC. Risperidone augmentation of selective serotonin reuptake inhibitors in major depression. *J Clin Psychiatry*. 1999; 60(4):256–259. [PubMed: 10221288]
26. Hellerstein DJ, Batchelder S, Hyler S, Arnaout B, Corpuz V, Coram L, Weiss G. Aripiprazole as an adjunctive treatment for refractory unipolar depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008; 32(3):744–750. [PubMed: 18164528]
27. Sokolski KN. Adjunctive aripiprazole for bupropion-resistant major depression. *Ann Pharmacother*. 2008; 42(7):1124–1129. [PubMed: 18492784]
28. Dannlowski U, Baune BT, Bockermann I, Domschke K, Evers S, Arolt V, Hetzel G, Rothermundt M. Adjunctive antidepressant treatment with quetiapine in agitated depression: positive effects on symptom reduction, psychopathology and remission rates. *Hum Psychopharmacol*. 2008; 23(7): 587–593. [PubMed: 18663773]
29. Olver JS, Ignatiadis S, Maruff P, Burrows GD, Norman TR. Quetiapine augmentation in depressed patients with partial response to antidepressants. *Hum Psychopharmacol*. 2008; 23(8):653–660. [PubMed: 18816504]
30. Takahashi H, Kamata M, Yoshida K, Higuchi H, Ishigooka J. Augmentation with olanzapine in TCA-refractory depression with melancholic features: a consecutive case series. *Hum Psychopharmacol*. 2008; 23(3):217–220. [PubMed: 18172909]

31. Thase ME. What role do atypical antipsychotic drugs have in treatment-resistant depression? *J Clin Psychiatry*. 2002; 63(2):95–103. [PubMed: 11874227]
32. Worthington JJ 3rd, Kinrys G, Wygant LE, Pollack MH. Aripiprazole as an augmentor of selective serotonin reuptake inhibitors in depression and anxiety disorder patients. *Int Clin Psychopharmacol*. 2005; 20(1):9–11. [PubMed: 15602109]
33. Papakostas GI, Petersen TJ, Nierenberg AA, Murakami JL, Alpert JE, Rosenbaum JF, Fava M. Ziprasidone augmentation of selective serotonin reuptake inhibitors (SSRIs) for SSRI-resistant major depressive disorder. *J Clin Psychiatry*. 2004; 65(2):217–221. [PubMed: 15003076]
34. Hirose S, Ashby CR Jr. An open pilot study combining risperidone and a selective serotonin reuptake inhibitor as initial antidepressant therapy. *J Clin Psychiatry*. 2002; 63(8):733–736. [PubMed: 12197455]
35. Yoshimura R, Umene-Nakano W, Ueda N, Ikenouchi-Sugita A, Hori H, Nakamura J. Addition of risperidone to sertraline improves sertraline-resistant refractory depression without influencing plasma concentrations of sertraline and desmethylsertraline. *Hum Psychopharmacol*. 2008; 23(8):707–713. [PubMed: 18803170]
36. Marcus RN, McQuade RD, Carson WH, Hennicken D, Fava M, Simon JS, Trivedi MH, Thase ME, Berman RM. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol*. 2008; 28(2):156–165. [PubMed: 18344725]
37. Berman RM, Marcus RN, Swanink R, McQuade RD, Carson WH, Corey-Lisle PK, Khan A. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2007; 68(6):843–853. [PubMed: 17592907]
38. Keitner GI, Garlow SJ, Ryan CE, Ninan PT, Solomon DA, Nemeroff CB, Keller MB. A randomized, placebo-controlled trial of risperidone augmentation for patients with difficult-to-treat unipolar, non-psychotic major depression. *J Psychiatr Res*. 2009; 43(3):205–214. [PubMed: 18586273]
39. Mahmoud RA, Pandina GJ, Turkoz I, Kosik-Gonzalez C, Canuso CM, Kujawa MJ, Gharabawi-Garibaldi GM. Risperidone for treatment-refractory major depressive disorder: a randomized trial. *Ann Intern Med*. 2007; 147(9):593–602. [PubMed: 17975181]
40. Reeves H, Batra S, May RS, Zhang R, Dahl DC, Li X. Efficacy of risperidone augmentation to antidepressants in the management of suicidality in major depressive disorder: a randomized, double-blind, placebo-controlled pilot study. *J Clin Psychiatry*. 2008; 69(8):1228–1336. [PubMed: 18681749]
41. Chaput Y, Magnan A, Gendron A. The co-administration of quetiapine or placebo to cognitive-behavior therapy in treatment refractory depression: a preliminary trial. *BMC Psychiatry*. 2008; 8:73. [PubMed: 18752690]
42. Baune BT, Caliskan S, Todder D. Effects of adjunctive antidepressant therapy with quetiapine on clinical outcome, quality of sleep and daytime motor activity in patients with treatment-resistant depression. *Hum Psychopharmacol*. 2007; 22(1):1–9. [PubMed: 17191266]
43. McIntyre A, Gendron A. Quetiapine adjunct to selective serotonin reuptake inhibitors or venlafaxine in patients with major depression, comorbid anxiety, and residual depressive symptoms: a randomized, placebo-controlled pilot study. *Depress Anxiety*. 2007; 24(7):487–494. [PubMed: 17177199]
44. Konstantinidis A, Hrubos W, Nimberger G, Windhager E, Lehofer M, Aschauer H, Kasper S. Quetiapine in combination with citalopram in patients with unipolar psychotic depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007; 31(1):242–247. [PubMed: 16962224]
45. Doree JP, Des Rosiers J, Lew V, Gendron A, Elie R, Stip E, Tourjman SV. Quetiapine augmentation of treatment-resistant depression: a comparison with lithium. *Curr Med Res Opin*. 2007; 23(2):333–341. [PubMed: 17288688]
46. Garakani A, Martinez JM, Marcus S, Weaver J, Rickels K, Fava M, Hirschowitz J. A randomized, double-blind, and placebo-controlled trial of quetiapine augmentation of fluoxetine in major depressive disorder. *Int Clin Psychopharmacol*. 2008; 23(5):269–275. [PubMed: 18703936]

47. Jensen NH, Rodriguiz RM, Caron MG, Wetsel WC, Rothman RB, Roth BL. N-desalkylquetiapine, a potent norepinephrine reuptake inhibitor and partial 5HT_{1A} agonist, as a putative mediator of quetiapine's antidepressant activity. *Neuropsychopharmacology*. 2008; 33(10):2303–2312. [PubMed: 18059438]
48. Shelton RC, Tollefson GD, Tohen M, Stahl S, Gannon KS, Jacobs TG, Buras WR, Bymaster FP, Zhang W, Spencer KA, et al. A novel augmentation strategy for treating resistant major depression. *Am J Psychiatry*. 2001; 158(1):131–134. [PubMed: 11136647]
49. De la Fuente JM. Case report: excellent response to long-term higher dose single olanzapine in a case of recurrent brief depression. *Pharmacopsychiatry*. 2008; 41(4):156–158. [PubMed: 18651345]
50. Corya SA, Williamson D, Sanger TM, Briggs SD, Case M, Tollefson G. A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, fluoxetine, and venlafaxine in treatment-resistant depression. *Depress Anxiety*. 2006; 23(6):364–372. [PubMed: 16710853]
51. Calabrese JR, Keck PE Jr, Macfadden W, Minkwitz M, Ketter TA, Weisler RH, Cutler AJ, McCoy R, Wilson E, Mullen J. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. *Am J Psychiatry*. 2005; 162(7):1351–1360. [PubMed: 15994719]
52. Thase ME, Macfadden W, Weisler RH, Chang W, Paulsson B, Khan A, Calabrese JR. Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). *J Clin Psychopharmacol*. 2006; 26(6):600–609. [PubMed: 17110817]
53. Zarate CA Jr, Payne JL, Singh J, Quiroz JA, Luckenbaugh DA, Denicoff KD, Charney DS, Manji HK. Pramipexole for bipolar II depression: a placebo-controlled proof of concept study. *Biol Psychiatry*. 2004; 56(1):54–60. [PubMed: 15219473]
54. Goldberg JF, Burdick KE, Endick CJ. Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression. *Am J Psychiatry*. 2004; 161(3):564–566. [PubMed: 14992985]
55. Cassano P, Lattanzi L, Soldani F, Navari S, Battistini G, Gemignani A, Cassano GB. Pramipexole in treatment-resistant depression: an extended follow-up. *Depress Anxiety*. 2004; 20(3):131–138. [PubMed: 15549689]
56. Lattanzi L, Dell'Osso L, Cassano P, Pini S, Rucci P, Houck PR, Gemignani A, Battistini G, Bassi A, Abelli M, et al. Pramipexole in treatment-resistant depression: a 16-week naturalistic study. *Bipolar Disord*. 2002; 4(5):307–314. [PubMed: 12479663]
57. Cassano P, Lattanzi L, Fava M, Navari S, Battistini G, Abelli M, Cassano GB. Ropinirole in treatment-resistant depression: a 16-week pilot study. *Can J Psychiatry*. 2005; 50(6):357–360. [PubMed: 15999953]
58. Arborelius L, Owens MJ, Plotsky PM, Nemeroff CB. The role of corticotropin-releasing factor in depression and anxiety disorders. *J Endocrinol*. 1999; 160(1):1–12. [PubMed: 9854171]
59. Veith RC, Lewis N, Langohr JI, Murburg MM, Ashleigh EA, Castillo S, Peskind ER, Pascualy M, Bissette G, Nemeroff CB, et al. Effect of desipramine on cerebrospinal fluid concentrations of corticotropin-releasing factor in human subjects. *Psychiatry Res*. 1993; 46(1):1–8. [PubMed: 8464952]
60. Nemeroff CB, Bissette G, Akil H, Fink M. Neuropeptide concentrations in the cerebrospinal fluid of depressed patients treated with electroconvulsive therapy. Corticotrophin-releasing factor, beta-endorphin and somatostatin. *Br J Psychiatry*. 1991; 158:59–63. [PubMed: 1673078]
61. Gutman, D.; Owens, M.-J.; Nemeroff, CB. Corticotropin-releasing factor receptor and glucocorticoid receptor antagonists: new approaches to antidepressant treatment.. In: JA, Den Boer; GJ, ter Host, editors. *Current and Future Developments in Psychopharmacology*. Benecke, N.I.; Amsterdam: 2005. p. 133–158.
62. Zobel AW, Nickel T, Kunzel HE, Ackl N, Sonntag A, Ising M, Holsboer F. Effects of the high-affinity corticotropin-releasing hormone receptor 1 antagonist R121919 in major depression: the first 20 patients treated. *J Psychiatr Res*. 2000; 34(3):171–181. [PubMed: 10867111]
63. Binneman B, Feltner D, Kolluri S, Shi Y, Qiu R, Stiger T. A 6-week randomized, placebo-controlled trial of CP-316,311 (a selective CRH1 antagonist) in the treatment of major depression. *Am J Psychiatry*. 2008; 165(5):617–620. [PubMed: 18413705]

64. Ising M, Zimmermann US, Kunzel HE, Uhr M, Foster AC, Learned-Coughlin SM, Holsboer F, Grigoriadis DE. High-affinity CRF1 receptor antagonist NBI-34041: preclinical and clinical data suggest safety and efficacy in attenuating elevated stress response. *Neuropsychopharmacology*. 2007; 32(9):1941–1949. [PubMed: 17287823]
65. Wolkowitz OM, Reus VI. Treatment of depression with antiglucocorticoid drugs. *Psychosom Med*. 1999; 61(5):698–711. [PubMed: 10511017]
66. Murphy BE, Filipini D, Ghadirian AM. Possible use of glucocorticoid receptor antagonists in the treatment of major depression: preliminary results using RU 486. *J Psychiatry Neurosci*. 1993; 18(5):209–213. [PubMed: 8297920]
67. Belanoff JK, Flores BH, Kalezhan M, Sund B, Schatzberg AF. Rapid reversal of psychotic depression using mifepristone. *J Clin Psychopharmacol*. 2001; 21(5):516–521. [PubMed: 11593077]
68. Belanoff JK, Rothschild AJ, Cassidy F, DeBattista C, Baulieu EE, Schold C, Schatzberg AF. An open label trial of C-1073 (mifepristone) for psychotic major depression. *Biol Psychiatry*. 2002; 52(5):386–392. [PubMed: 12242054]
69. Ku YH, Tan L, Li LS, Ding X. Role of corticotropin-releasing factor and substance P in pressor responses of nuclei controlling emotion and stress. *Peptides*. 1998; 19(4):677–682. [PubMed: 9622022]
70. Bittencourt JC, Benoit R, Sawchenko PE. Distribution and origins of substance P-immunoreactive projections to the paraventricular and supraoptic nuclei: partial overlap with ascending catecholaminergic projections. *J Chem Neuroanat*. 1991; 4(1):63–78. [PubMed: 1707281]
71. Pelletier G, Steinbusch HW, Verhofstad AA. Immunoreactive substance P and serotonin present in the same dense-core vesicles. *Nature*. 1981; 293(5827):71–72. [PubMed: 6167867]
72. Culman J, Unger T. Central tachykinins: mediators of defence reaction and stress reactions. *Can J Physiol Pharmacol*. 1995; 73(7):885–891. [PubMed: 8846426]
73. Helke CJ, Krause JE, Mantyh PW, Couture R, Bannon MJ. Diversity in mammalian tachykinin peptidergic neurons: multiple peptides, receptors, and regulatory mechanisms. *FASEB J*. 1990; 4(6):1606–1615. [PubMed: 1969374]
74. Kramer MS, Cutler N, Feighner J, Shrivastava R, Carman J, Sramek JJ, Reines SA, Liu G, Snavely D, Wyatt-Knowles E, et al. Distinct mechanism for antidepressant activity by blockade of central substance P receptors. *Science*. 1998; 281(5383):1640–1645. [PubMed: 9733503]
75. Culman J, Klee S, Ohlendorf C, Unger T. Effect of tachykinin receptor inhibition in the brain on cardiovascular and behavioral responses to stress. *J Pharmacol Exp Ther*. 1997; 280(1):238–246. [PubMed: 8996202]
76. Geraciotti TD Jr, Carpenter LL, Owens MJ, Baker DG, Ekhtor NN, Horn PS, Strawn JR, Sanacora G, Kinkead B, Price LH, et al. Elevated cerebrospinal fluid substance p concentrations in posttraumatic stress disorder and major depression. *Am J Psychiatry*. 2006; 163(4):637–643. [PubMed: 16585438]
77. Bondy B, Baghai TC, Minov C, Schule C, Schwarz MJ, Zwanzger P, Rupprecht R, Moller HJ. Substance P serum levels are increased in major depression: preliminary results. *Biol Psychiatry*. 2003; 53(6):538–542. [PubMed: 12644359]
78. Keller M, Montgomery S, Ball W, Morrison M, Snavely D, Liu G, Hargreaves R, Hietala J, Lines C, Beebe K, et al. Lack of efficacy of the substance p (neurokinin1 receptor) antagonist aprepitant in the treatment of major depressive disorder. *Biol Psychiatry*. 2006; 59(3):216–223. [PubMed: 16248986]
79. Kramer MS, Winokur A, Kelsey J, Preskorn SH, Rothschild AJ, Snavely D, Ghosh K, Ball WA, Reines SA, Munjack D, et al. Demonstration of the efficacy and safety of a novel substance P (NK1) receptor antagonist in major depression. *Neuropsychopharmacology*. 2004; 29(2):385–392. [PubMed: 14666114]
80. Herpfer I, Lieb K. Substance: P receptor antagonists in psychiatry: rationale for development and therapeutic potential. *CNS Drugs*. 2005; 19(4):275–293. [PubMed: 15813642]
81. Furmark T, Appel L, Michelgard A, Wahlstedt K, Ahs F, Zancan S, Jacobsson E, Flyckt K, Groh M, Bergstrom M, et al. Cerebral blood flow changes after treatment of social phobia with the

- neurokinin-1 antagonist GR205171, citalopram, or placebo. *Biol Psychiatry*. 2005; 58(2):132–142. [PubMed: 16038684]
82. Chenu F, Guiard BP, Bourin M, Gardier AM. Antidepressant-like activity of selective serotonin reuptake inhibitors combined with a NK1 receptor antagonist in the mouse forced swimming test. *Behav Brain Res*. 2006; 172(2):256–263. [PubMed: 16806519]
83. Paul IA, Skolnick P. Glutamate and depression: clinical and preclinical studies. *Ann N Y Acad Sci*. 2003; 1003:250–272. [PubMed: 14684451]
84. Zarate CA Jr, Du J, Quiroz J, Gray NA, Denicoff KD, Singh J, Charney DS, Manji HK. Regulation of cellular plasticity cascades in the pathophysiology and treatment of mood disorders: role of the glutamatergic system. *Ann N Y Acad Sci*. 2003; 1003:273–291. [PubMed: 14684452]
85. McEwen BS. Stress and hippocampal plasticity. *Annu Rev Neurosci*. 1999; 22:105–122. [PubMed: 10202533]
86. Sapolsky RM. The possibility of neurotoxicity in the hippocampus in major depression: a primer on neuron death. *Biol Psychiatry*. 2000; 48(8):755–765. [PubMed: 11063972]
87. Rogoz Z, Skuza G, Maj J, Danyś W. Synergistic effect of uncompetitive NMDA receptor antagonists and antidepressant drugs in the forced swimming test in rats. *Neuropharmacology*. 2002; 42(8):1024–1030. [PubMed: 12128003]
88. Rogoz Z, Skuza G, Kusmider M, Wojcikowski J, Kot M, Daniel WA. Synergistic effect of imipramine and amantadine in the forced swimming test in rats. *Behavioral and pharmacokinetic studies*. *Pol J Pharmacol*. 2004; 56(2):179–185. [PubMed: 15156068]
89. Stryjer R, Strous RD, Shaked G, Bar F, Feldman B, Kotler M, Polak L, Rosenzweig S, Weizman A. Amantadine as augmentation therapy in the management of treatment-resistant depression. *Int Clin Psychopharmacol*. 2003; 18(2):93–96. [PubMed: 12598820]
90. Palucha A, Branski P, Szewczyk B, Wieronska JM, Klak K, Pilc A. Potential antidepressant-like effect of MTEP, a potent and highly selective mGluR5 antagonist. *Pharmacol Biochem Behav*. 2005; 81(4):901–906. [PubMed: 16040106]
91. Pilc A, Kłodzinska A, Branski P, Nowak G, Palucha A, Szewczyk B, Tatarczyńska E, Chojnacka-Wojcik E, Wieronska JM. Multiple MPEP administrations evoke anxiolytic- and antidepressant-like effects in rats. *Neuropharmacology*. 2002; 43(2):181–187. [PubMed: 12213272]
92. Ostroff R, Gonzales M, Sanacora G. Antidepressant effect of ketamine during ECT. *Am J Psychiatry*. 2005; 162(7):1385–1386. [PubMed: 15994728]
93. Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, Charney DS, Manji HK. A randomized trial of an *N*-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry*. 2006; 63(8):856–864. [PubMed: 16894061]
94. Liebrecht M, Stohler R, Borgeat A. Repeated intravenous ketamine therapy in a patient with treatment-resistant major depression. *World J Biol Psychiatry*. 2007; 1–4. [Epub ahead of print].
95. Phelps LE, Brutsche N, Moral JR, Luckenbaugh DA, Manji HK, Zarate CA Jr. Family history of alcohol dependence and initial antidepressant response to an *N*-methyl-D-aspartate antagonist. *Biol Psychiatry*. 2009; 65(2):181–184. [PubMed: 18996507]
96. Zarate CA Jr, Singh JB, Quiroz JA, De Jesus G, Denicoff KK, Luckenbaugh DA, Manji HK, Charney DS. A double-blind, placebo-controlled study of memantine in the treatment of major depression. *Am J Psychiatry*. 2006; 163(1):153–155. [PubMed: 16390905]
97. Muhonen LH, Lonnqvist J, Juva K, Alho H. Double-blind, randomized comparison of memantine and escitalopram for the treatment of major depressive disorder comorbid with alcohol dependence. *J Clin Psychiatry*. 2008; 69(3):392–399. [PubMed: 18348597]
98. Sanacora G, Kendell SF, Levin Y, Simen AA, Fenton LR, Coric V, Krystal JH. Preliminary evidence of riluzole efficacy in antidepressant-treated patients with residual depressive symptoms. *Biol Psychiatry*. 2007; 61(6):822–825. [PubMed: 17141740]
99. Zarate CA Jr, Payne JL, Quiroz J, Sporn J, Denicoff KK, Luckenbaugh D, Charney DS, Manji HK. An open-label trial of riluzole in patients with treatment-resistant major depression. *Am J Psychiatry*. 2004; 161(1):171–174. [PubMed: 14702270]
100. Zarate CA Jr, Quiroz JA, Singh JB, Denicoff KD, De Jesus G, Luckenbaugh DA, Charney DS, Manji HK. An open-label trial of the glutamate-modulating agent riluzole in combination with

lithium for the treatment of bipolar depression. *Biol Psychiatry*. 2005; 57(4):430–432. [PubMed: 15705360]

101. Levy MI, DeNigris Y, Davis KL. Rapid antidepressant activity of melanocyte-inhibiting factor: a clinical trial. *Biol Psychiatry*. 1982; 17(2):259–263. [PubMed: 6122475]
102. Feighner JP, Sverdlov L, Hlavka J, Nicolau G, Cartwright K, Freed JS. Clinical effect of nemifitide, a novel pentapeptide antidepressant, in the treatment of severely depressed refractory patients. *Int Clin Psychopharmacol*. 2008; 23(1):29–35. [PubMed: 18090505]
103. Montgomery SA, Feighner JP, Sverdlov L, Shrivastava RK, Cunningham LA, Kiev A, Hlavka J, Tonelli G. Efficacy and safety of 30 mg/d and 45 mg/d nemifitide compared to placebo in major depressive disorder. *Int J Neuropsychopharmacol*. 2006; 9(5):517–528. [PubMed: 16259645]
104. Parker G, Gibson NA, Brotchie H, Heruc G, Rees AM, Hadzi-Pavlovic D. Omega-3 fatty acids and mood disorders. *Am J Psychiatry*. 2006; 163(6):969–978. [PubMed: 16741195]
105. Hakkarainen R, Partonen T, Haukka J, Virtamo J, Albanes D, Lonnqvist J. Is low dietary intake of omega-3 fatty acids associated with depression? *Am J Psychiatry*. 2004; 161(3):567–569. [PubMed: 14992986]
106. Mischoulon D, Best-Popescu C, Laposata M, Merens W, Murakami JL, Wu SL, Papakostas GI, Dording CM, Sonawalla SB, Nierenberg AA, et al. A double-blind dose-finding pilot study of docosahexaenoic acid (DHA) for major depressive disorder. *Eur Neuropsychopharmacol*. 2008; 18(9):639–645. [PubMed: 18539007]
107. Peet M. Eicosapentaenoic acid in the treatment of schizophrenia and depression: rationale and preliminary double-blind clinical trial results. *Prostaglandins Leukot Essent Fatty Acids*. 2003; 69(6):477–485. [PubMed: 14623502]
108. Osher Y, Bersudsky Y, Belmaker RH. Omega-3 eicosapentaenoic acid in bipolar depression: report of a small open-label study. *J Clin Psychiatry*. 2005; 66(6):726–729. [PubMed: 15960565]
109. Nemets B, Stahl Z, Belmaker RH. Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. *Am J Psychiatry*. 2002; 159(3):477–479. [PubMed: 11870016]
110. Su KP, Huang SY, Chiu CC, Shen WW. Omega-3 fatty acids in major depressive disorder. A preliminary double-blind, placebo-controlled trial. *Eur Neuropsychopharmacol*. 2003; 13(4):267–271. [PubMed: 12888186]
111. Su KP, Huang SY, Chiu TH, Huang KC, Huang CL, Chang HC, Pariante CM. Omega-3 fatty acids for major depressive disorder during pregnancy: results from a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2008; 69(4):644–651. [PubMed: 18370571]
112. Rees AM, Austin MP, Parker GB. Omega-3 fatty acids as a treatment for perinatal depression: randomized double-blind placebo-controlled trial. *Aust N Z J Psychiatry*. 2008; 42(3):199–205. [PubMed: 18247194]
113. da Silva TM, Munhoz RP, Alvarez C, Naliwaiko K, Kiss A, Andreatini R, Ferraz AC. Depression in Parkinson's disease: a double-blind, randomized, placebo-controlled pilot study of omega-3 fatty-acid supplementation. *J Affect Disord*. 2008; 111(2–3):351–359. [PubMed: 18485485]
114. Lin PY, Su KP. A meta-analytic review of double-blind, placebo-controlled trials of antidepressant efficacy of omega-3 fatty acids. *J Clin Psychiatry*. 2007; 68(7):1056–1061. [PubMed: 17685742]
115. Stoll AL, Severus WE, Freeman MP, Rueter S, Zboyan HA, Diamond E, Cress KK, Marangell LB. Omega 3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial. *Arch Gen Psychiatry*. 1999; 56(5):407–412. [PubMed: 10232294]
116. Silvers KM, Woolley CC, Hamilton FC, Watts PM, Watson RA. Randomised double-blind placebo-controlled trial of fish oil in the treatment of depression. *Prostaglandins Leukot Essent Fatty Acids*. 2005; 72(3):211–218. [PubMed: 15664306]
117. Rogers PJ, Appleton KM, Kessler D, Peters TJ, Gunnell D, Hayward RC, Heatherley SV, Christian LM, McNaughton SA, Ness AR. No effect of n-3 long-chain polyunsaturated fatty acid (EPA and DHA) supplementation on depressed mood and cognitive function: a randomised controlled trial. *Br J Nutr*. 2008; 99(2):421–431. [PubMed: 17956647]
118. Keck PE Jr, Mintz J, McElroy SL, Freeman MP, Suppes T, Frye MA, Altshuler LL, Kupka R, Nolen WA, Leverich GS, et al. Double-blind, randomized, placebo-controlled trials of ethyl-

eicosapentanoate in the treatment of bipolar depression and rapid cycling bipolar disorder. *Biol Psychiatry*. 2006; 60(9):1020–1022. [PubMed: 16814257]

119. Marangell LB, Martinez JM, Zboyan HA, Kertz B, Kim HF, Puryear LJ. A double-blind, placebo-controlled study of the omega-3 fatty acid docosahexaenoic acid in the treatment of major depression. *Am J Psychiatry*. 2003; 160(5):996–998. [PubMed: 12727707]
120. Lucas M, Asselin G, Merette C, Poulin MJ, Dodin S. Ethyleicosapentaenoic acid for the treatment of psychological distress and depressive symptoms in middle-aged women: a double-blind, placebo-controlled, randomized clinical trial. *Am J Clin Nutr*. 2009; 89(2):641–651. [PubMed: 19116322]
121. Srinivasan V, Smits M, Spence W, Lowe AD, Kayumov L, Pandi-Perumal SR, Parry B, Cardinali DP. Melatonin in mood disorders. *World J Biol Psychiatry*. 2006; 7(3):138–151. [PubMed: 16861139]
122. Dolberg OT, Hirschmann S, Grunhaus L. Melatonin for the treatment of sleep disturbances in major depressive disorder. *Am J Psychiatry*. 1998; 155(8):1119–1121. [PubMed: 9699707]
123. Lewy AJ, Bauer VK, Cutler NL, Sack RL. Melatonin treatment of winter depression: a pilot study. *Psychiatry Res*. 1998; 77(1):57–61. [PubMed: 10710176]
124. Loo H, Hale A, D'Haenen H. Determination of the dose of agomelatine, a melatoninergic agonist and selective 5HT (2C) antagonist, in the treatment of major depressive disorder: a placebo-controlled dose range study. *Int Clin Psychopharmacol*. 2002; 17(5):239–247. [PubMed: 12177586]
125. Kennedy SH, Emsley R. Placebo-controlled trial of agomelatine in the treatment of major depressive disorder. *Eur Neuropsychopharmacol*. 2006; 16(2):93–100. [PubMed: 16249073]
126. Olie JP, Kasper S. Efficacy of agomelatine, a MT1/MT2 receptor agonist with 5HT2C antagonistic properties, in major depressive disorder. *Int J Neuropsychopharmacol*. 2007; 10(5):661–673. [PubMed: 17477888]
127. Kennedy SH, Rizvi S, Fulton K, Rasmussen J. A double-blind comparison of sexual functioning, antidepressant efficacy, and tolerability between agomelatine and venlafaxine XR. *J Clin Psychopharmacol*. 2008; 28(3):329–333. [PubMed: 18480691]
128. Calabrese JR, Guelfi JD, Perdrizet-Chevallier C. Agomelatine adjunctive therapy for acute bipolar depression: preliminary open data. *Bipolar Disord*. 2007; 9(6):628–635. [PubMed: 17845278]
129. Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. *Lancet*. 2003; 361(9360):799–808. [PubMed: 12642045]
130. Fink M. Convulsive therapy: a review of the first 55 years. *J Affect Disord*. 2001; 63(1–3):1–15. [PubMed: 11246075]
131. Sackeim HA, Ross FR, Hopkins N, Calev L, Devanand DP. Subjective side effects acutely following ECT: associations with treatment modality and clinical response. *Convuls Ther*. 1987; 3(2):100–110. [PubMed: 11940903]
132. Sackeim HA, Haskett RF, Mulsant BH, Thase ME, Mann JJ, Pettinati HM, Greenberg RM, Crowe RR, Cooper TB, Prudic J. Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. *JAMA*. 2001; 285(10):1299–1307. [PubMed: 11255384]
133. Kellner CH, Knapp RG, Petrides G, Rummans TA, Husain MM, Rasmussen K, Mueller M, Bernstein HJ, O'Connor K, Smith G, et al. Continuation electroconvulsive therapy vs pharmacotherapy for relapse prevention in major depression: a multisite study from the Consortium for Research in Electroconvulsive Therapy (CORE). *Arch Gen Psychiatry*. 2006; 63(12):1337–1344. [PubMed: 17146008]
134. Mayberg HS. Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimised treatment. *Br Med Bull*. 2003; 65:193–207. [PubMed: 12697626]
135. Ben-Menachem E. Vagus-nerve stimulation for the treatment of epilepsy. *Lancet Neurol*. 2002; 1(8):477–482. [PubMed: 12849332]
136. Sackeim HA, Rush AJ, George MS, Marangell LB, Husain MM, Nahas Z, Johnson CR, Seidman S, Giller C, Haines S, et al. Vagus nerve stimulation (VNS) for treatment-resistant depression:

efficacy, side effects, and predictors of outcome. *Neuropsychopharmacology*. 2001; 25(5):713–728. [PubMed: 11682255]

137. Nahas Z, Marangell LB, Husain MM, Rush AJ, Sackeim HA, Lisanby SH, Martinez JM, George MS. Two-year outcome of vagus nerve stimulation (VNS) for treatment of major depressive episodes. *J Clin Psychiatry*. 2005; 66(9):1097–1104. [PubMed: 16187765]
138. Marangell LB, Rush AJ, George MS, Sackeim HA, Johnson CR, Husain MM, Nahas Z, Lisanby SH. Vagus nerve stimulation (VNS) for major depressive episodes: one year outcomes. *Biol Psychiatry*. 2002; 51(4):280–287. [PubMed: 11958778]
139. Schlaepfer TE, Frick C, Zobel A, Maier W, Heuser I, Bajbouj M, O'Keane V, Corcoran C, Adolfsson R, Trimble M, et al. Vagus nerve stimulation for depression: efficacy and safety in a European study. *Psychol Med*. 2008; 38(5):651–661. [PubMed: 18177525]
140. Rush AJ, Marangell LB, Sackeim HA, George MS, Brannan SK, Davis SM, Howland R, Kling MA, Rittberg BR, Burke WJ, et al. Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. *Biol Psychiatry*. 2005; 58(5):347–354. [PubMed: 16139580]
141. Nierenberg AA, Alpert JE, Gardner-Schuster EE, Seay S, Mischoulon D. Vagus nerve stimulation: 2-year outcomes for bipolar versus unipolar treatment-resistant depression. *Biol Psychiatry*. 2008; 64(6):455–460. [PubMed: 18571625]
142. Rush AJ, Sackeim HA, Marangell LB, George MS, Brannan SK, Davis SM, Lavori P, Howland R, Kling MA, Rittberg B, et al. Effects of 12 months of vagus nerve stimulation in treatment-resistant depression: a naturalistic study. *Biol Psychiatry*. 2005; 58(5):355–363. [PubMed: 16139581]
143. George MS, Rush AJ, Marangell LB, Sackeim HA, Brannan SK, Davis SM, Howland R, Kling MA, Moreno F, Rittberg B, et al. A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. *Biol Psychiatry*. 2005; 58(5):364–373. [PubMed: 16139582]
144. Sackeim HA, Brannan SK, Rush AJ, George MS, Marangell LB, Allen J. Durability of antidepressant response to vagus nerve stimulation (VNS). *Int J Neuropsychopharmacol*. 2007; 10(6):817–826. [PubMed: 17288644]
145. Dunner DL, Rush AJ, Russell JM, Burke M, Woodard S, Wingard P, Allen J. Prospective, long-term, multicenter study of the naturalistic outcomes of patients with treatment-resistant depression. *J Clin Psychiatry*. 2006; 67(5):688–695. [PubMed: 16841617]
146. Holtzheimer PE 3rd, Russo J, Avery DH. A meta-analysis of repetitive transcranial magnetic stimulation in the treatment of depression. *Psychopharmacol Bull*. 2001; 35(4):149–169. [PubMed: 12397863]
147. Burt T, Lisanby SH, Sackeim HA. Neuropsychiatric applications of transcranial magnetic stimulation: a meta analysis. *Int J Neuropsychopharmacol*. 2002; 5(1):73–103. [PubMed: 12057034]
148. Kozel FA, George MS. Meta-analysis of left prefrontal repetitive transcranial magnetic stimulation (rTMS) to treat depression. *J Psychiatr Pract*. 2002; 8(5):270–275. [PubMed: 15985889]
149. Martin JL, Barbanoj MJ, Schlaepfer TE, Thompson E, Perez V, Kulisevsky J. Repetitive transcranial magnetic stimulation for the treatment of depression. Systematic review and meta-analysis. *Br J Psychiatry*. 2003; 182:480–491. [PubMed: 12777338]
150. Bretlau LG, Lunde M, Lindberg L, Uden M, Dissing S, Bech P. Repetitive transcranial magnetic stimulation (rTMS) in combination with escitalopram in patients with treatment-resistant major depression: a double-blind, randomised, sham-controlled trial. *Pharmacopsychiatry*. 2008; 41(2):41–47. [PubMed: 18311683]
151. Mogg A, Pluck G, Eranti SV, Landau S, Purvis R, Brown RG, Curtis V, Howard R, Philpot M, McLoughlin DM. A randomized controlled trial with 4-month follow-up of adjunctive repetitive transcranial magnetic stimulation of the left prefrontal cortex for depression. *Psychol Med*. 2008; 38(3):323–333. [PubMed: 17935639]
152. Klein E, Kreinin I, Chistyakov A, Koren D, Mecz L, Marmur S, Ben-Shachar D, Feinsod M. Therapeutic efficacy of right prefrontal slow repetitive transcranial magnetic stimulation in major

depression: a double-blind controlled study. *Arch Gen Psychiatry*. 1999; 56(4):315–320. [PubMed: 10197825]

153. Fitzgerald PB, Brown TL, Marston NA, Daskalakis ZJ, De Castella A, Kulkarni J. Transcranial magnetic stimulation in the treatment of depression: a double-blind, placebo-controlled trial. *Arch Gen Psychiatry*. 2003; 60(10):1002–1008. [PubMed: 14557145]
154. Januel D, Dumortier G, Verdon CM, Stamatidis L, Saba G, Cabaret W, Benadhira R, Rocamora JF, Braha S, Kalalou K, et al. A double-blind sham controlled study of right prefrontal repetitive transcranial magnetic stimulation (rTMS), therapeutic and cognitive effect in medication free unipolar depression during 4 weeks. *Prog Neuropsychopharmacol Biol Psychiatry*. 2006; 30(1): 126–130. [PubMed: 16242826]
155. Rossini D, Lucca A, Zanardi R, Magri L, Smeraldi E. Transcranial magnetic stimulation in treatment-resistant depressed patients: a double-blind, placebo-controlled trial. *Psychiatry Res*. 2005; 137(1–2):1–10. [PubMed: 16225930]
156. Fitzgerald PB, Hoy K, Daskalakis ZJ, Kulkarni J. A randomized trial of the anti-depressant effects of low- and high-frequency transcranial magnetic stimulation in treatment-resistant depression. *Depress Anxiety*. 2009; 26(3):229–234. [PubMed: 19105212]
157. Schutter DJ, Martin Laman D, van Honk J, Vergouwen AC, Frank Koerselman G. Partial clinical response to 2 weeks of 2 Hz repetitive transcranial magnetic stimulation to the right parietal cortex in depression. *Int J Neuropsychopharmacol*. 2009; 12(5):643–650. [PubMed: 18925985]
158. Jakob F, Brakemeier EL, Schommer NC, Quante A, Merkl A, Danker-Hopfe H, Anghelescu I, Heuser I, Bajbouj M. Ultrahigh frequency repetitive transcranial magnetic stimulation in unipolar depression. *J Clin Psychopharmacol*. 2008; 28(4):474–476. [PubMed: 18626288]
159. Gershon AA, Dannon PN, Grunhaus L. Transcranial magnetic stimulation in the treatment of depression. *Am J Psychiatry*. 2003; 160(5):835–845. [PubMed: 12727683]
160. Holtzheimer PE, Avery D, Schlaepfer TE. Antidepressant effects of repetitive transcranial magnetic stimulation. *Br J Psychiatry*. 2004; 184:541–542. [PubMed: 15172952]
161. Avery DH, Holtzheimer PE 3rd, Fawaz W, Russo J, Neumaier J, Dunner DL, Haynor DR, Claypoole KH, Wajdik C, Roy-Byrne P. A controlled study of repetitive transcranial magnetic stimulation in medication-resistant major depression. *Biol Psychiatry*. 2006; 59(2):187–194. [PubMed: 16139808]
162. O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, McDonald WM, Avery D, Fitzgerald PB, Loo C, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry*. 2007; 62(11):1208–1216. [PubMed: 17573044]
163. Avery DH, Isenberg KE, Sampson SM, Janicak PG, Lisanby SH, Maixner DF, Loo C, Thase ME, Demitrack MA, George MS. Transcranial magnetic stimulation in the acute treatment of major depressive disorder: clinical response in an open-label extension trial. *J Clin Psychiatry*. 2008; 69(3):441–451. [PubMed: 18294022]
164. Lisanby SH, Husain MM, Rosenquist PB, Maixner D, Gutierrez R, Krystal A, Gilmer W, Marangell LB, Aaronson S, Daskalakis ZJ, et al. Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. *Neuropsychopharmacology*. 2009; 34(2):522–534. [PubMed: 18704101]
165. Demirtas-Tatlidede A, Mechanic-Hamilton D, Press DZ, Pearlman C, Stern WM, Thall M, Pascual-Leone A. An open-label, prospective study of repetitive transcranial magnetic stimulation (rTMS) in the long-term treatment of refractory depression: reproducibility and duration of the antidepressant effect in medication-free patients. *J Clin Psychiatry*. 2008; 69(6): 930–934. [PubMed: 18505308]
166. Dell'osso B, Carlo Altamura A. Augmentative transcranial magnetic stimulation (TMS) combined with brain navigation in drug-resistant rapid cycling bipolar depression: a case report of acute and maintenance efficacy. *World J Biol Psychiatry*. 2008:1–4. [Epub ahead of print].
167. Milev R, Abraham G, Hasey G, Cabaj JL. Repetitive transcranial magnetic stimulation for treatment of medication-resistant depression in older adults: a case series. *J ECT*. 2009; 25(1): 44–49. [PubMed: 18665102]

168. Lisanby SH, Luber B, Schlaepfer TE, Sackeim HA. Safety and feasibility of magnetic seizure therapy (MST) in major depression: randomized within-subject comparison with electroconvulsive therapy. *Neuropsychopharmacology*. 2003; 28(10):1852–1865. [PubMed: 12865903]
169. Kosel M, Frick C, Lisanby SH, Fisch HU, Schlaepfer TE. Magnetic seizure therapy improves mood in refractory major depression. *Neuropsychopharmacology*. 2003; 28(11):2045–2048. [PubMed: 12942146]
170. White PF, Amos Q, Zhang Y, Stool L, Husain MM, Thornton L, Downing M, McClintock S, Lisanby SH. Anesthetic considerations for magnetic seizure therapy: a novel therapy for severe depression. *Anesth Analg*. 2006; 103(1):76–80. table of contents. [PubMed: 16790630]
171. Kayser S, Bewernick B, Axmacher N, Schlaepfer TE. Magnetic seizure therapy of treatment-resistant depression in a patient with bipolar disorder. *J ECT*. 2008 [Epub ahead of print].
172. Boggio PS, Rigonatti SP, Ribeiro RB, Myczkowski ML, Nitsche MA, Pascual-Leone A, Fregni F. A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. *Int J Neuropsychopharmacol*. 2008; 11(2):249–254. [PubMed: 17559710]
173. Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, Schwab JM, Kennedy SH. Deep brain stimulation for treatment-resistant depression. *Neuron*. 2005; 45(5):651–660. [PubMed: 15748841]
174. Lozano AM, Mayberg HS, Giacobbe P, Hamani C, Craddock RC, Kennedy SH. Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. *Biol Psychiatry*. 2008; 64(6):461–467. [PubMed: 18639234]
175. Greenberg BD, Nahas Z, Carpenter LL. Current status of deep brain stimulation. *Primary Psychiatry*. 2005; 12:59–64.
176. Greenberg BD, Malone DA, Friehs GM, Rezai AR, Kubu CS, Malloy PF, Salloway SP, Okun MS, Goodman WK, Rasmussen SA. Three-year outcomes in deep brain stimulation for highly resistant obsessive–compulsive disorder. *Neuropsychopharmacology*. 2006; 31(11):2384–2393. [PubMed: 16855529]
177. Nuttin BJ, Gabriels L, van Kuyck K, Cosyns P. Electrical stimulation of the anterior limbs of the internal capsules in patients with severe obsessive–compulsive disorder: anecdotal reports. *Neurosurg Clin N Am*. 2003; 14(2):267–274. [PubMed: 12856493]
178. Greenberg BD, Nahas Z, Carpenter LL. Current status of deep brain stimulation. *Primary Psychiatry*. 2005; 12(10):59–64.
179. Malone DA Jr, Dougherty DD, Rezai AR, Carpenter LL, Friehs GM, Eskandar EN, Rauch SL, Rasmussen SA, Machado AG, Kubu CS, et al. Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression. *Biol Psychiatry*. 2009; 65(4):267–275. [PubMed: 18842257]
180. Sartorius A, Henn FA. Deep brain stimulation of the lateral habenula in treatment resistant major depression. *Med Hypotheses*. 2007; 69(6):1305–1308. [PubMed: 17498883]
181. Schlaepfer TE, Cohen MX, Frick C, Kosel M, Brodessaer D, Axmacher N, Joe AY, Kreft M, Lenartz D, Sturm V. Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. *Neuropsychopharmacology*. 2008; 33(2):368–377. [PubMed: 17429407]
182. Jimenez F, Velasco F, Salin-Pascual R, Hernandez JA, Velasco M, Ciales JL, Nicolini H. A patient with a resistant major depression disorder treated with deep brain stimulation in the inferior thalamic peduncle. *Neurosurgery*. 2005; 57(3):585–593. discussion 585–93. [PubMed: 16145540]