The Future of Psychopharmacology of Depression

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There are clear limitations to the currently approved pharmacotherapies of depression, including the fact that they are all essentially monoamine-based, have modest efficacy and a relatively slow onset of efficacy, and suffer from significant tolerability issues, particularly in the long term, including sexual dysfunction, weight gain, and cognitive impairments. This article reviews some of the most promising novel mechanisms that are not represented in compounds currently approved for depression in either the United States or Europe and that may represent the future of the psychopharmacologic treatment of depression, potentially addressing some of the efficacy and tolerability issues of antidepressants on the market. These potential antidepressant treatments include the multimodal serotonergic agents, the triple uptake inhibitors, the neurokinin-based novel therapies, the glutamatergic treatments, the nicotinic receptor–based treatments, the neurogenesis-based treatments, and antiglucocorticoid therapies. Some of these mechanisms appear to be more advanced in terms of drug development than others, but they all contribute to the global effort to develop more effective and better tolerated treatments for major depressive disorder.

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It has been more than 20 years since the last major revolution in antidepressant pharmacotherapy, the introduction of selective serotonin reuptake inhibitors (SSRIs). The SSRIs seemed to promise efficacy comparable to that of the antidepressants already on the market, namely, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), without the problematic side effects and drug interactions of those drug classes. Similar hopes were attached to their derivative compounds, the serotonin-norepinephrine reuptake inhibitors (SNRIs) and norepinephrine reuptake inhibitors (NERIs), and to other new antidepressants developed since then, such as bupropion and mirtazapine. Indeed, these new antidepressants have proven to be more tolerable and acceptable than TCAs and MAOIs: SSRIs accounted for more than half of all antidepressant prescriptions in 2006,[1] and, following their introduction, adult use of antidepressants nearly tripled from 1988–1994 to 1999–2004.[2] In the recent Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, a large "real-world" study of depression treatment, approximately half of all patients became symptom-free with one of the first 2 treatment strategies in the study.[3,4]

All the same, these newer medications represent only a limited advance beyond their predecessors. One major reason is that all existing pharmacotherapies of depression are essentially monoamine-based. While the effects of monoamine-based antidepressants may go well beyond the initial changes in monoamine system function and may lead to broader brain circuitry changes,[5] so far they have all been limited by relatively modest efficacy overall[6] and significant tolerability issues, particularly in the long term.[7]

The therapeutic efficacy limitations of these monoamine-based antidepressants include the following concerns: (1) relatively modest remission rates[8]; (2) relatively slow onset of efficacy and delayed time to remission, so that, of ultimate remitters, as many as half will not remit until 6 to 12 weeks of ongoing antidepressant therapy[9]; and (3) lower effectiveness for certain depressive symptoms such as sleep disturbances and fatigue than for others.[10]

The tolerability limitations of currently available antidepressant therapies are also of great significance. Among them are the following: (1) elevated rates of sexual dysfunction,[11] with the possible exceptions of bupropion,[12] vilazodone,[13] and agomelatine[14]; (2) modest yet troublesome rates of weight gain during long-term antidepressant treatment,[15] once again with the exception perhaps of bupropion,[16] NERIs such as reboxetine,[17] and agomelatine[18]; (3) relatively high rates of insomnia and/or daytime sleepiness[19–21]; (4) treatment-emergent anxiety and nervousness[21]; and (5) relatively high rates of cognitive, memory, and attentional difficulties during long-term antidepressant treatment.[22]

This article will review some of the most promising novel mechanisms that are not represented in compounds currently approved for depression in either the United States or Europe and that may represent the future of the psychopharmacologic treatment of depression, potentially addressing some of the efficacy and tolerability issues of antidepressants on the market.

MULTIMODAL SEROTONERGIC AGENTS

These compounds are an extension of the currently available SSRIs and SNRIs. They typically include elements of inhibition of the serotonin transporter and elements that either block serotonergic receptors, such as the serotonin 5-HT_{2A} receptor, and/or act as a partial agonist of serotonergic receptors, such as the 5-HT_{1A} receptors, within the same molecule. The advantage of the additional receptor effects is supported, for example, by the fact that partial agonism of the 5-HT_{1A} receptors has been shown to help with

SSRI-induced sexual dysfunction with buspirone augmentation.[23] One example of a multimodal serotonergic agent is vilazodone, which combines the effects of an SSRI with 5-HT_{1A} receptor partial agonist activity[13]; it has shown efficacy in major depressive disorder (MDD) trials and a relatively benign sexual profile.[13] Another example is a compound under development by Lundbeck (Lu AA21004), which combines SSRI activity with 5-HT_3 receptor antagonism and 5-HT_{1A} agonism and has shown efficacy in a proof-of-concept trial by Artigas et al.[24]

TRIPLE UPTAKE INHIBITORS

The triple uptake inhibitors (TUIs) are probably considered the "low-hanging fruit" in monoamine-based drug development, as they capitalize on known pharmacologic actions. These compounds typically combine inhibition of the serotonin, norepinephrine, and dopamine transporters, with the idea that targeting the dopamine transporter will enhance overall efficacy; address anhedonia, apathy, and cognitive impairment; and minimize residual fatigue and sleepiness, as suggested by the dopamine reuptake inhibitor modafinil augmentation studies of SSRIs.[25] In addition, given the usefulness of dopaminergic compounds in treating SSRI-induced sexual dysfunction,[26,27] TUIs are expected to be associated with lesser sexual dysfunction than SSRIs and SNRIs. Another postulated advantage of the TUIs is that the synergistic effect of the triple inhibition may allow robust effects on these 3 neurotransmitters without requiring a high occupancy of the serotonin transporter, thus minimizing SSRI-related side effects.[28] The only TUI currently available, the weight loss drug sibutramine, has modest dopamine reuptake–inhibiting properties through its metabolites,[29] in addition to its SNRI activity.[30]

One of the concerns that has perhaps limited the enthusiasm for this mechanism has traditionally been the risk for abuse related to the dopamine transporter inhibition. Yet, there are clear examples in the literature to the contrary: self-administration, used as a marker of abuse liability, was not observed in rats given a TUI,[31] while an anti–alcohol abuse effect was seen in another rodent study of a TUI developed by DOV.[32]

NEUROKININ-BASED NOVEL THERAPIES (NK_1 ANTAGONISTS)

Neurokinin (NK) receptors and their endogenous ligand, substance P (SP), have been shown to be highly expressed in areas of the brain involved in the regulation of mood.[33] The NK_1 receptor is the principal central nervous system (CNS) receptor for SP in humans[34] and, for that reason, has been the target of significant drug development in depression. Due to their novel, nonmonoaminergic mechanism, NK_1 antagonists have been of great interest as monotherapy or adjunctive treatments for treatment-resistant depression (TRD). In addition, SP and its preferred NK_1 receptor have been identified within brain areas known to be involved in the regulation of stress and anxiety responses, and aversive and stressful stimuli have been shown repeatedly to change SP brain tissue content as well as NK_1 receptor binding.[35] Therefore, one of the questions concerning NK_1 antagonists is whether drug development in depression should target, in particular, anxious depression or depression with high levels of stress, or whether relapse prevention, given the role of stress in triggering relapses, would be a more appropriate role for these compounds. With respect to NK_1 antagonism, it is unclear whether a minimum level of receptor occupancy has to be achieved to obtain a consistent therapeutic effect.

Despite an initial positive study with the NK_1 antagonist aprepitant (otherwise known as MK-869 or L-754030),[36] 5 subsequent double-blind, placebo-controlled trials of aprepitant failed to show greater efficacy for aprepitant than placebo.[37] Another Merck NK_1 antagonist compound showed promise in a proof-of-concept study,[38] but the results of a subsequent double-blind study comparing 2 doses of L-759274 with paroxetine 20 mg and placebo were also interpreted as inconclusive.[39] Finally, studies involving the use of NK_2-selective receptor antagonists as monotherapy for MDD are currently underway (www.clinical trials.gov: NCT00429260, NCT00336713, NCT00415142).

GLUTAMATE-BASED TREATMENTS

Glycine and glutamate serve as primary excitatory neurotransmitters in the CNS, where they participate in many functions through activation of several ionotropic receptors, including the *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA), and kainate receptors as well as the type I, II, and III metabotropic glutamate receptors.[40] It has been hypothesized that NMDA receptor antagonists may possess neuroprotective properties and, as a result, antidepressant effects.[41] Reports of rapid and sustained antidepressant effects following injections of the NMDA antagonist ketamine have generated significant interest in the field of depression, as has the announcement that another NMDA receptor antagonist targeting the NR2B subtype, traxoprodil (CP 101 606), has antidepressant effects in patients unresponsive to an SSRI.[42] Further interest in the development of new glutamatergic antidepressants has been spurred by a positive double-blind augmentation study of the NMDA antagonist and dopaminergic drug amantadine in depressed imipramine nonresponders[43] and by the robust improvement reported in an open trial in TRD of riluzole, an agent shown to inhibit the release of glutamic acid as well as noncompetitively inhibit the NMDA receptors.[44] More recently, however, a double-blind, placebo-controlled trial involving the use of the NMDA receptor antagonist memantine for the treatment of MDD did not reveal greater reduction in depressive symptom severity among patients receiving memantine than those receiving placebo.[45]

A major limitation in testing and potential development of NMDA antagonists as antidepressants is that some of these

agents may possess hallucinogenic properties and may even induce psychotic-like symptoms in subjects with or without a history of psychosis.[46,47]

Unlike NMDA antagonists such as amantadine, the potential role of AMPA, kainate, or metabotropic glutamate receptor antagonists in alleviating CNS diseases is not as well studied, although there is considerable interest in these compounds as well. Given the beneficial effects of glutamatergic agents such as memantine on cognition,[48] these agents are considered to be potentially effective in the treatment of cognitive dysfunction in depression or in the treatment of MDD presenting with prominent cognitive dysfunction.

NICOTINIC RECEPTOR–BASED TREATMENTS

The nicotinic receptor is an ionotropic receptor consisting of 5 subunits.[49] In the human CNS, 11 different subunits have been identified (α2–9, β2–4), with most nicotinic receptors consisting of a combination of α and β subunits.[49] The most abundant and widespread nicotinic receptors in the mammalian CNS are the α4β2, α3β4, α3β2, and α7 (ie, consisting of 5 α7 subunits).[50]

There is some evidence to suggest a potential role for nicotinic receptor antagonists in depression, since several antidepressants such as the tricyclic antidepressant imipramine also possess nicotinic receptor antagonist effects.[51] Recent findings have shown TC-5214, the *S*-(+)-enantiomer of mecamylamine, a noncompetitive nicotinic receptor antagonist (α4β2, α4β2, and α7), to be active in animal models of depression[52] and to be more effective than placebo in augmenting SSRIs in TRD in a phase 2b trial.[53]

In addition, it appears that the various nicotinic-receptor subtypes may be involved in different functions including memory, cognition, and behavioral reinforcement/addiction. For example, the α4β2[54] receptors have been reported to play a key role in acetylcholine-mediated dopamine release in areas involved in behavioral reinforcement and addiction, including the striatum, ventral tegmental area, and nucleus accumbens,[55] while the α7 receptors have been linked to cognitive functions, including learning and memory, in preclinical studies.[56] Therefore, developing specific nicotinic receptor ligands, such as α7 receptor agonists and α4β2 partial agonists, may offer opportunities to develop novel treatments for depression as well as treatments to target cognitive dysfunction and inattention in depression.

The main obstacle in the drug development of pronicotinergic-based treatments for depression is the abuse liability associated with nicotinic receptor agonism, which is thought to be secondary to nicotinic receptor–mediated dopamine release in mesolimbic brain areas associated with reward processing.[57]

NEUROGENESIS-BASED TREATMENTS

There is now good evidence for neuroplasticity impairments, in particular in adult neurogenesis and gliogenesis, that are caused by stress and that may contribute to mood disorders. Furthermore, studies show that a number of antidepressant therapies appear to increase neurogenesis.[58] These findings have contributed to the idea that novel antidepressant medication development could utilize adult neurogenesis and gliogenesis as preclinical cellular markers for predicting the antidepressant properties of novel compounds.[58] A recent positive, placebo-controlled, proof-of-concept trial of a combination therapy of buspirone plus melatonin, identified through a neurogenesis-based platform,[59] certainly supports the idea that this approach might identify novel non–monoamine-based antidepressant therapies.

ANTIGLUCOCORTICOID THERAPIES

Basic and clinical studies provide some evidence for elevated secretion of the hypothalamic neuropeptides corticotropin-releasing hormone (CRH) and vasopressin in depression and anxiety, with CRH predominantly acting through CRH_1 receptors to produce a number of anxiety- and depression-like symptoms. These findings suggest that CRH_1 receptors may be potential drug targets.[60] A recent report[60] summarized the results from clinical studies of 2 CRH_1 receptor antagonists: in the first study, originally designed as a safety and tolerability trial in MDD, the CRH_1 receptor antagonist NBI-30775/R121919 had a clinical profile comparable to that of the antidepressant paroxetine. In the second study, which investigated the effect of another CRH_1 receptor antagonist, NBI-34041, on stress hormone secretion in response to a psychosocial stressor, the administration of this compound reduced the stress-elicited secretion of cortisol. These preliminary studies do suggest that CRH_1 receptor antagonists and other types of antiglucocorticoid therapies may represent promising novel therapeutics in the psychopharmacology of depression.

OTHER POTENTIAL DIRECTIONS

Further expansions of the current armamentarium of drug treatments of depression will depend on the discovery of new pathways and targets for antidepressant treatment, but fortunately several other lines of psychiatric research hold promise for making these discoveries. For example, by identifying genes and gene products that are linked to increased vulnerability to mood disorders, psychiatric genetics could potentially unearth new mechanisms involved in the pathophysiology of depression. Similarly, neuroimaging studies are offering a new way of looking at the pathways involved in depression, while proteomics and neurohormonal research may lead to the discovery of other potential treatment targets. It is also likely that the use of biomarkers for treatment response may be coupled with the treatment development process so that treatments can be targeted for specific populations based on neurobiological characteristics. These approaches, combined with advances in

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nonmedication treatments ranging from the development of variants of behavioral therapies to the greater interest in somatic treatments such as transcranial magnetic stimulation, make evident the great potential for improving on the successes of the most recent generation of antidepressants.

SUMMARY

There are clear limitations to the currently approved pharmacotherapies of depression, including the fact that they are all essentially monoamine-based, have modest efficacy and a relatively slow onset of efficacy, and suffer from significant tolerability issues, particularly in the long term, including sexual dysfunction, weight gain, and cognitive impairments. A number of promising novel mechanisms, which are not represented in compounds currently approved for depression in either the United States or Europe, may represent the future in the psychopharmacologic treatment of depression; the hope is that they will address some of the efficacy and tolerability issues of currently available antidepressants. These potential antidepressant treatments include the multimodal serotonergic agents, the triple uptake inhibitors, the neurokinin-based novel therapies, the glutamatergic treatments, the nicotinic receptor–based treatments, the neurogenesis-based treatments, and anti-glucocorticoid therapies. In addition, other lines of research such as psychiatric genetics and neuroimaging could point the way toward other potential new drug mechanisms. Some of these mechanisms appear to be more advanced in terms of drug development than others, but they all contribute to the global effort to develop more effective and better tolerated treatments for MDD.

Drug names: amantadine (Symmetrel and others), aprepitant (Emend), bupropion (Wellbutrin, Aplenzin, and others), buspirone (BuSpar and others), imipramine (Tofranil and others), memantine (Namenda), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), sibutramine (Meridia).

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