CNS SPECTRUMS

CME Review Article

Novel agents in development for the treatment of depression

This activity is sponsored by the Neuroscience Education Institute

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Statement of Need

There are competencies that clinicians need to demonstrate in order to have a successful role in improving outcomes for patients with major depression who do not adequately respond to currently available treatments:

- Recognize neural circuits and molecular targets that may be implicated in depression
- Update knowledge on the development of novel antidepressant treatment strategies, including adjunctive agents, to address inadequate response

To help address these professional practice gaps and improve outcomes for patients with depression, quality improvement efforts need to provide education regarding (1) neurobiological substrates and circuits implicated in depression, and (2) the status of research and development of antidepressants with novel mechanisms of action.

Learning objectives

After completing this activity, participants should be better able to:

- Explain the neurobiological rationale for potential antidepressants with novel mechanisms of action
- Describe the mechanisms of action for novel antidepressants that are currently in development

Date of Release/Expiration

Released: December 2013
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Disclosure Statements

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CME REVIEW ARTICLE

Novel agents in development for the treatment of depression

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There are several investigational drugs in development for the treatment of depression. Some of the novel antidepressants in development target monoaminergic neurotransmission in accordance with the "monoamine hypothesis of depression." However, the current conceptualization of antidepressant actions is that it is the downstream effects on protein synthesis and neuroplasticity that account for therapeutic efficacy, rather than the immediate effects on synaptic monoamine levels. Thus, a number of novel agents in development directly target components of this "neuroplasticity hypothesis of depression," including hypothetically overactive glutamatergic neurotransmission and dysfunctional hypothalamic–pituitary–adrenal (HPA) axis functioning.

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Introduction

Virtually all antidepressants directly affect one or more of the monoamine neurotransmitter systems.[1] However, although antidepressants cause an immediate increase in monoamines, they do not have immediate therapeutic effects. In fact, clinical improvement with these agents is typically delayed by several weeks compared to the acute changes in monoamine levels.[1] This has led to the suggestion that the therapeutic effects of antidepressants may occur because the initial rise in monoamines leads to downstream changes in protein synthesis. In particular, depression may be caused by reduced synthesis of proteins involved in neurogenesis and synaptic plasticity, and antidepressant treatment may increase the synthesis of those proteins.[2–4] Indeed, research suggests that patients who show response to antidepressant treatment (both pharmacological and nonpharmacological) have concomitant increases in neuroplasticity and neurogenesis, including modulation of growth factors and intracellular signaling cascades involved in neuroplastic processes.[5] There is, specifically, evidence that brain-derived neurotrophic factor (BDNF), which is important for neuronal survival, is reduced in depression and restored by successful antidepressant treatment.[2–4] In addition, the N-methyl-d-aspartate (NMDA) antagonist ketamine, which has recently been discovered to have rapid antidepressant actions, can trigger signaling pathways that lead to an increased density of dendritic spines.[6,7] Thus, current research now supports replacement of the "monoamine hypothesis of depression" with the "neurotrophic" or "neuroplasticity" hypothesis of depression.[8]

As the conceptualization of the pathology of depression evolves, so too does the investigation into new therapeutic treatments and targets. In this article, we review agents in development or recently released for the treatment of depression, including agents that exploit the monoaminergic link to depression, as well as experimental agents with novel mechanisms of action.

Triple Reuptake Inhibitors

Triple reuptake inhibitors (TRIs), or serotonin–norepinephrine–dopamine reuptake inhibitors, are being developed based on the premise that targeting all three monoamines may provide earlier or more robust efficacy than targeting only one (ie, selective serotonin

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reuptake inhibitors) or two (ie, serotonin–norepinephrine reuptake inhibitors).[9,10] There are few agents available for depression that act on dopamine; thus, triple reuptake inhibitors may provide a therapeutic advance, especially for patients with symptoms hypothetically linked to dopamine (eg, cognitive symptoms, sexual dysfunction).[1]

Triple reuptake inhibitors that are currently in clinical trials are shown in Table 1. These agents vary with respect to their activity at each of the three monoamine transporters; in addition, some have additional pharmacological properties that may contribute to therapeutic efficacy.[11] It is not yet clear what the ideal potencies at the three transporters might be; in particular, clinical trials must identify the degree of dopamine reuptake inhibition that is sufficient to contribute to therapeutic effects without the risk of abuse potential.[9]

Multimodal Agents

It may be that combining different modes of action could enhance efficacy for some patients with depression. Thus, agents that target not just transporter inhibition but also actions at G-protein receptors [eg, serotonin (5HT) 1A receptors] and/or ion-channel receptors [eg, 5HT3 receptors, N-methyl-d-aspartate (NMDA) receptors] are under investigation. One such agent, vortioxetine, has just been approved by the U.S. Food and Drug Administration (FDA). Vortioxetine combines actions at all three modes, with a total of five pharmacological actions: inhibition of the serotonin transporter, actions at G protein receptors (5HT1A and 5HT1B partial agonism and 5HT7 antagonism), and actions at ion channels (5HT3 antagonism).[12,13] Through these various actions, vortioxetine seems to increase the release of five different neurotransmitters: the three monoamines serotonin, norepinephrine, and dopamine, as well as acetylcholine and histamine.[12,14] Theoretically, enhancing neurotransmission, not just of multiple monoamines but also other neurotransmitters as well, could likewise enhance therapeutic efficacy compared to agents with fewer modes of action and effects on fewer neurotransmitters (Table 2).

TABLE 1. Triple reuptake inhibitors in development as antidepressants

Triple reuptake inhibitor	Clinical trial phase
Amitifadine	Phase III
GSK 372475	Phase II
BMS 820836	Phase II
SEP 225289	Phase II
Lu AA24530*	Phase II

*This agent also has actions at 5HT2C, 5HT3, 5HT2A, and alpha 1A receptors.

Glutamatergic Targets

The discovery of rapid antidepressant effects following subanesthetic infusions of the NMDA receptor antagonist ketamine is perhaps the most dramatic development in depression research in years.[15,16] Unfortunately, the effects of ketamine infusions are short-lived; however, the discovery has opened avenues of research into other glutamatergic approaches to the treatment of depression.

Ketamine acts as an open channel inhibitor of NMDA receptors, which leads to downstream glutamate release.[1] This stimulates two other types of glutamate receptors: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and metabotropic glutamate receptors.[1] It is not yet known if ketamine's antidepressant effects are due directly to its NMDA antagonism or to its downstream stimulation of AMPA receptors. One hypothesis is that activation of AMPA receptors leads to activation of the ERK/AKT signal transduction cascade, which in turn triggers the mammalian target of the rapamycin (mTOR) pathway.[17,18] This causes the expression

TABLE 2. Multimodal actions of vortioxetine[1,12–14]

Mode of action	Pharmacological action	Neurotransmitters affected	Theoretical clinical effects
Transporter inhibition	Serotonin reuptake inhibition	Serotonin	Antidepressant Anxiolytic
G-protein receptor actions	5HT1A partial agonism	Serotonin	Anxiolytic
		Dopamine	Boost antidepressant action Reduce sexual dysfunction?
	5HT1B/D partial agonism	Serotonin	Boost antidepressant action?
	5HT7 antagonism	Serotonin	Antidepressant
		Glutamate?	Pro-cognitive
Ion channel receptor actions	5HT3 antagonism	Serotonin	Antidepressant?
		Acetylcholine?	Pro-cognitive?
		Norepinephrine?	
		Glutamate?	

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TABLE 3. Glutamatergic targets

Mechanism	Agent	Clinical trial phase
Inhibits glutamate release by interfering with sodium channels	Lamotrigine	Phase IV
Inhibits glutamate release	Riluzole	Phase II
Weak NMDA antagonist	Memantine	Phase III
NMDA antagonist	Ketamine	Phase IV
Potent sigma 1 receptor antagonist, uncompetitive NMDA antagonist	Dextromethorphan	Phase IV
NR2B selective NMDA antagonist	Traxoprodil (CP101,606)	Phase II
NR2B selective NMDA antagonist	AZD6765	Phase II
NR2B selective NMDA antagonist	EVT101/103	Phase II
NR2B selective NMDA antagonist	Radiprodil (RGH 896)	Phase II
NR2B selective NMDA antagonist	MK 0657	Phase II

of synaptic proteins and leads to an increased density of dendritic spines, which has been seen with ketamine administration in animals.[6,7] Hypothetically, this increase in dendritic spines causes the rapid antidepressant effect.

Investigators are looking for other agents that can trigger the same pharmacological changes that ketamine induces, but with sustained efficacy (Table 3). One such agent is dextromethorphan, a cough medicine that acts weakly on NMDA receptors and is also a sigma 1 receptor agonist–a property that ketamine also shares.[17,19] Whether the sigma receptor properties of ketamine contribute to its antidepressant effects is not known, but selective sigma 1 agents could theoretically represent another novel avenue of research for depression treatment.[17]

Hypothalamic–Pituitary–Adrenal (HPA) Axis Targets

In depression, abnormalities of the HPA axis have long been reported, including elevated glucocorticoid levels and insensitivity of the HPA axis to feedback inhibition.[1] Some evidence suggests that HPA axis dysfunction associated with chronic stress could lead to reduced synaptic plasticity and neuronal atrophy.[20–22] The hippocampus is particularly vulnerable to stress because it has a high expression of glucocorticoid receptors, receives input from numerous stress-activated brain regions, and releases endogenous corticotropin releasing factor (CRF) in response to stress.[23] Consistent with this, animal models of severe early life stress demonstrate persistent effects on hippocampal functioning, including disrupted long-term potentiation, upregulated CRF expression, and dendritic atrophy.[24,25] In humans, brain imaging studies show that patients with depression have reduced volume of the hippocampus and prefrontal cortex.[26,27] Correspondingly, BDNF levels in the hippocampus and prefrontal cortex are low in depressed patients.[28]

Neurons from the hippocampal area normally suppress the HPA axis; thus, if stress causes hippocampal cell loss, then this in turn could contribute to over-activity of the HPA axis, creating a vicious cycle. A number of agents that target stress and the HPA axis are in clinical testing, including glucocorticoid antagonists, corticotropin-releasing factor 1 (CRF-1) antagonists, and vasopressin-1B antagonists (Table 4).

TABLE 4. HPA-axis targets

Mechanism	Agent	Clinical trial phase
Glucocorticoid antagonism	Mifepristone	Phase III
Glucocorticoid antagonism	Org 34517	Phase II
Cortisol synthesis inhibition	Metyrapone	Phase II
CRF1 antagonism	R121919	Phase II
CRF1 antagonism	BMS 562086	Phase II
CRF1 antagonism	ONO-2333Ms	Phase II
CRF1 antagonism	SSR125543	Phase II
Vasopressin 1B antagonism	SSR149415	Phase II

TABLE 5. Additional antidepressant treatment strategies in development

Mechanism	Agent	Clinical trial phase
Norepinephrine reuptake and serotonin reuptake inhibitor	Levomilnacipran	Approved July 2013
Monoamine oxidase inhibition	Curcumin	Phase IV
Tumor necrosis factor (TNF) alpha antagonist	Infliximab	Phase IV
Norepinephrine reuptake inhibition	Edivoxetine	Phase III
Unknown; derived from chicken eggs	Rellidep	Phase III
COX-2 inhibition	Cimicoxib	Phase II

Additional Treatment Strategies

Other agents in late-stage clinical development are listed in Table 5. These include traditional monoaminergic strategies, such as the recently approved levomilnacipran (active enantiomer of milnacipran) and the norepinephrine reuptake inhibitor edivoxetine, as well as novel approaches, including agents that target anti-inflammatory pathways.[11]

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Conclusion

Recent research into the pathology of depression indicates that inadequate neuroplasticity, potentially related to abnormal glutamate and/or HPA axis function, may be a key factor in the development of this disorder. Currently available antidepressants, which act on monoaminergic systems, seem to lead to downstream improvement in neuroplasticity. Investigation into new treatments for depression both extends the current emphasis on a monoaminergic link (eg, triple reuptake inhibitors) and expands the focus to include directly targeting glutamatergic neurotransmission or the HPA axis.

Disclosures

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1. Nichole is a 31-year-old patient with treatment-resistant depression. She has failed trials with various SSRIs and is having only partial response to her current treatment with the SNRI, duloxetine. You are considering switching this patient to the most recently approved antidepressant agent, levomilnacipran. Levomilnacipran has antidepressant properties due to its action as a:

   A. Triple reuptake inhibitor
   B. Glutamate antagonist
   C. Serotonin and norepinephrine reuptake inhibitor
   D. Glucocorticoid antagonist

2. The novel antidepressant metyrapone is one of the non-monoaminergic antidepressant agents currently in development. The antidepressant effects of metyrapone are due to:

   A. Antagonism of NMDA receptors
   B. Agonism of AMPA receptors
   C. Cortisol synthesis inhibition
   D. Antagonism of TNF-alpha

3. Peter is a 65-year-old patient with a long history of treatment-resistant depression. He has tried nearly every FDA-approved antidepressant treatment currently available with very little success. Various combinations of antidepressant agents have been marginally more helpful for this patient, but he is getting discouraged and asks you about some of the antidepressants that are in later stages of development. You explain that vortioxetine is an antidepressant in late-stage development and its mechanism of action includes:

   A. Serotonin reuptake inhibition
   B. 5HT1A partial agonism
   C. 5HT7 antagonism
   D. 5HT3 antagonism
   E. All of the above
   F. None of the above

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