Triple

Current PSYCHIATRY

reuptake inhibitors

What to expect from 'mega-antidepressants'

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Rapid onset of action could make serotonin-norepinephrine-dopamine reuptake blockers a clinically useful option for patients with depression

The first triple reuptake inhibitors are at least several years from approval, but this novel antidepressant class represents an intriguing strategy for treating depression. Several pharmaceutical companies are developing these compounds—with at least one in phase-III clinical trials.

Adding a dopamine reuptake component to serotonin and norepinephrine reuptake blockade could result in an antidepressant with a more rapid onset of action, greater efficacy, and fewer side effects. This article updates what is known about triple reuptake inhibitors and suggests their potential role among first-line antidepressants and in treating patients who have not responded adequately to existing agents.

ROLE OF MONOAMINES IN DEPRESSION

Remission—the absence of depression signs and symptoms—is the optimum goal in treating depression. Patients who do not meet this goal are more likely to relapse and to relapse more rapidly than those whose symptoms are treated to remission. Incomplete response rates and delayed onset of action limit the efficacy of available antidepressants (*Box, page 32*).[1-6]

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Box

Incomplete response, 'therapeutic lag' can limit antidepressants' efficacy

Antidepressant response. An estimated 60% to 70% of depressed patients respond to antidepressants, but only 20% to 40% achieve remission; 15% of depressed patients do not respond to any available antidepressants.[1,2]

Delayed onset of action with most antidepressants means that depression does not improve noticeably for at least 1 week and typically 3 weeks or more.[3,4] Many patients remain greatly impaired during this "therapeutic lag" and can perceive that the medication isn't helping them with signs and symptoms such as:

- persistent sad mood
- decreased interest in pleasurable activities (anhedonia)
- changes in body weight or appetite
- changes in sleep patterns
- difficulty thinking or concentrating
- feelings of worthlessness or guilt
- low energy, fatigue, or increased agitation
- recurrent thoughts of death or suicide
- poor self-esteem.

Newer antidepressants such as selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, and dual serotonin/norepinephrine reuptake inhibitors generally are better tolerated and easier to use than tricyclics and monoamine oxidase inhibitors. Even the newer antidepressants can cause side effects such as weight gain and sexual dysfunction, however, and might not be more efficacious than older antidepressants.[5,6]

Monoamine hypothesis. Although the precise pathophysiology of depression is unclear, dysfunction of monoamine neurotransmission has been a central hypothesis in depression research for decades. This hypothesis is based in part on observations that antidepressants alter monoamine neurotransmission via acute pharmacologic effects at the synapse.

Three major mechanisms account for the acute actions of antidepressants on monoamines:

- inhibition of monoamine oxidase, the enzyme that degrades serotonin, norepinephrine, and dopamine
- blockade of neurotransmitter reuptake by binding to transporters
- antagonism of presynaptic neurotransmitter receptors, resulting in an increase in neurotransmitter release.[4]

Most antidepressants act by increasing the synaptic availability of serotonin (such as fluoxetine and paroxetine); norepinephrine (such as reboxetine); norepinephrine and serotonin (such as duloxetine and venlafaxine); or norepinephrine, serotonin, and dopamine (such as phenelzine). Although controversial, some clinical data suggest that antidepressants that elevate synaptic levels of both norepinephrine and serotonin have greater efficacy and higher remission rates than antidepressants that are selective for norepinephrine or serotonin.[7]

Monoamine oxidase inhibitors (MAOIs)—the only available antidepressants known to elevate synaptic levels of norepinephrine, serotonin, and dopamine—are recommended for use in appropriately selected, treatment-resistant patients.[8] Meta-analysis of clinical trial data suggests that MAOIs such as phenelzine are particularly effective in outpatients with atypical depression features.[9] Even so, the clinical usefulness of MAOIs is limited by their potential for serious drug-drug interactions.

Other mechanisms. Because the synaptic actions of available antidepressants on monoamine neurotransmission occur within hours of administration, the several-week delay in onset of therapeutic action suggests that monoamine dysfunction might not be solely responsible for depression's

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pathophysiology. Recent investigations suggest that chronic antidepressant use could cause alterations in gene expression, neuronal plasticity, and downstream signaling pathways that underlie the therapeutic effect.[10]

Even so, medications that target serotonin, norepinephrine, and dopamine remain mainstays of depression pharmacotherapy.

Table 1

Mechanisms of select antidepressants in development

Drug class/target	Proposed mechanism of action
Triple reuptake inhibitors	Block serotonin, norepinephrine, and dopamine reuptake
CRF_1 antagonists	Block receptors for corticotropin releasing factor; regulate HPA axis
NK receptor antagonists	Block substance P receptor; offer antidepressant/anxiolytic properties
Glutamate acting drugs	Block or modulate NMDA receptor
Anti-glucocorticoid agents	Block glucocorticoid receptors; modulate HPA axis feedback
cAMP signal transduction	Increases cAMP levels; may affect neuroplasticity

cAMP: Cyclic adenosine monophosphate
CRF: Corticotropin releasing factor
HPA: Hypothalamic-pituitary-adrenal (axis)
NK: Neurokinin
NMDA: *N*-methyl-D-aspartate

TRIPLE REUPTAKE INHIBITORS

Novel antidepressants that do not involve direct action on monoamines are under investigation (*Table 1*). Several compound classes—such as neurokinin and glucocorticoid receptor antagonists—are reported to be in phase-III clinical trials, with projected approval within 5 years.[11]

Even so, many strategies remain focused on directly targeting monoaminergic circuits because this mechanism of action is compelling and understandable. Among these are agents projected to reach the market by 2010[11] that simultaneously block serotonin, norepinephrine, and dopamine transporters.[6,12-15] These broad-spectrum, "triple reuptake inhibitors" are thought to have a more-rapid onset of action and greater efficacy than single or dual reuptake inhibitors.[15,16]

Triple-action rationale. Some trials have shown antidepressants that act on multiple transporters or receptors to be more effective in treating depressed patients and to have a more-rapid onset of action, compared with single-action drugs such as selective serotonin reuptake inhibitors (SSRIs).[7]

Adding dopaminergic drugs to serotonergic and/or noradrenergic antidepressants also has been shown to boost the response of patients who were treatment-resistant or partial responders.[17]

Co-administering dopamine receptor agonists such as bromocriptine, pergolide, or pramipexole (D_3 receptor-preferring) with traditional antidepressants has improved clinical symptoms in depressed patients.[13] In a retrospective chart review, Clinical Global Impressions (CGI)-Improvement Scale scores were shown to improve with adjunctive pramipexole in 6 of 12 patients with bipolar depression and 8 of 20 patients with unipolar depression.[18] Other studies have shown that bromocriptine[19] and pergolide[20] can improve refractory depression in patients receiving concurrent traditional antidepressants.

Similarly, pramipexole monotherapy has been shown to improve depressive symptoms—includ-

Table 2

Neurotransmitter uptake inhibition: Differences in transporter binding expected to broaden therapeutic options

Compound	Transporter binding affinity*		
	Serotonin	Norepinephrine	Dopamine
Investigational triple reuptake inhibitors			
PRC025	6	19	100
PRC050	6	0.4	120
DOV 21,947	99	262	213
DOV 102,677	740	1,030	222
DOV 216,303†	14	20	78
Reference antidepressants			
Paroxetine	0.13	40	490
Imipramine	1.4	37	8,500
Sertraline	0.29	420	25
Bupropion	9,100	52,000	520
Venlafaxine	9	1,060	9,300

* Affinity of each compound for binding to serotonin, norepinephrine, and dopamine transporters, as expressed by equilibrium dissociation constants (Kd) in nM.

† Data reflect inhibition of neurotransmitter reuptake.

Source: References 6,13-15

ing anhedonia—in patients with Parkinson's disease.[21,22] In a 14-week, randomized open-label trial of depressed Parkinson's patients without motor complications, pramipexole was compared with sertraline for improvement of depressive symptoms. Hamilton Depression Rating Scale (HAM-D) scores decreased in both treatment groups, but the proportion of recovered patients (defined as HAM-D ≤8) was significantly greater in the pramipexole-treated group.[21]

Dopamine agonists such as pergolide have been associated with valvular heart disease in Parkinson's patients, which may limit these agents' usefulness in depression treatment.[23]

Rank order of potency. To provide the most effective depression treatment, would a compound with equal affinity for all 3 transporters be preferable to a drug with greater affinity for 1 or 2 of the transporters compared with the third? The answer is unknown, as the optimum rank order of potency for inhibiting serotonin, norepinephrine, and dopamine transporters is not yet clear.

Having choices of agents with differing transport inhibition profiles (*Table 2*)[6,13-15] might allow

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clinicians greater treatment flexibility, however. This could be an advantage when individualizing regimens to target specific symptoms of depression or other psychiatric disorders, such as attention-deficit/hyperactivity disorder.[14]

DOPAMINE AND DEPRESSION

What can we expect of a "mega-antidepressant" that inhibits serotonin, norepinephrine, and dopamine reuptake? The answer lies in understanding dopamine's role in depression and antidepressant treatment.

Antidepressant chronic treatment has been shown to alter dopaminergic neurotransmission

Dopamine plays a part in the underlying pathophysiology of depression and in the action of antidepressant treatments—regardless of their acute mechanism—according to the literature.[24,25]

Depression pathophysiology. Mesocorticolimbic dopaminergic circuits originating in the ventral tegmental area and projecting to cortical and subcortical structures (such as the prefrontal cortex and nucleus accumbens) are important in mediating reward and incentive behavior, attention, addiction, and emotions.[26] Deficits in this pathway can contribute to depressive symptoms, particularly anhedonia.[3,4]

Alterations in dopamine pathways also appear to contribute to depression's pathophysiology. Compared with nondepressed persons, depressed and/or suicidal patients have been shown to have:

- lower levels of dopamine and its metabolite homovanillic acid[25,27-29]
- increased dopamine D_2/D_3 receptor binding[30,31] and reduced dopamine transporter activity.[31,32]

Effects of treating depression. Chronic antidepressant treatment—with pharmacotherapies, electroconvulsive therapy, and REM sleep deprivation—has been shown to:

- alter dopaminergic neurotransmission[24]
- potentiate dopamine signaling (in preclinical studies) by increasing postsynaptic mesolimbic dopamine receptor sensitivity.[13,24]

Therefore, adding dopamine reuptake blockade to serotonin and norepinephrine reuptake blockade would likely produce an effective medication that could be used as first-line antidepressant therapy.

POTENTIAL CLINICAL EFFECTS

Clinical evidence. To date, one triple reuptake inhibitor has been studied clinically and reported in the literature. This investigational compound—identified as DOV 216,303—has been found to be safe and well-tolerated when tested in small samples of normal volunteers and depressed individuals.

Healthy male volunteers were given DOV 216,303 in single doses from 5 to 150 mg or multiple doses of 50, 75, or 100 mg for 10 days. Some participants reported gastrointestinal side effects, although only at the highest doses tested.

In a multicenter comparison trial, 67 depressed patients received DOV 216,303 (50 mg bid; 36 patients) or citalopram (20 mg bid; 31

Bottom Line

By acutely blocking dopamine reuptake, triple reuptake inhibitors could have immediate effects on depression. They also might improve a broader range of symptoms than single or dual reuptake inhibitors, with less risk for sexual side effects or weight gain. Potential adverse effects from dopamine reuptake inhibition, such as dependency characteristics, warrant investigation.

Related resources

- Nutt DJ. The role of dopamine and norepinephrine in depression and antidepressant treatment. *J Clin Psychiatry* 2006;67(suppl 6):3-8.
- American College of Neuropsychopharmacology. *Neuropsychopharmacology: the fifth generation of progress.* www.acnp.org/Default.aspx?Page=5thGenerationChapters.

DRUG BRAND NAMES

Bromocriptine • Parlodel
Bupropion • Wellbutrin
Citalopram • Celexa
Duloxetine • Cymbalta
Fluoxetine • Prozac
Imipramine • Tofranil
Paroxetine • Paxil
Pergolide • Permax
Phenelzine • Nardil
Pramipexole • Mirapex
Reboxetine • Edronax
Sertraline • Zoloft
Venlafaxine • Effexor

DISCLOSURE

Dr. Shaw and Dr. Boules report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products. Dr. Richelson is a consultant to Eli Lilly and Company.

patients) for 2 weeks. After 1 week, both treatments produced comparable reductions in the primary outcome measure (HAM-D scores). Improvements also were seen in secondary measures (CGI scale and Beck Depression Inventory).[14] The authors noted that the starting citalopram dosage was higher than typically is given.

By acutely blocking dopamine reuptake, triple reuptake inhibitors could have immediate effects on dopamine-related depression symptoms such as anhedonia, rather than requiring a lead-in of chronic dosing common to other antidepressant classes.[16] A triple reuptake inhibitor also might:

- address a broader range of depression symptoms, compared with a single or dual reuptake inhibitor
- be useful for treating substance abuse if it can substitute for addictive compounds at the dopamine transporter without possessing reinforcing characteristics.

Because of dopamine transporter blockade, triple reuptake inhibitors may pose their own risks for reinforcing effects and abuse, as seen with cocaine and amphetamine. Imaging studies have shown, however, that the rate of dopamine transporter blockade—rather than the affinity of the drug for the transporter—is relevant to reinforcing effects.[33] Nonetheless, these medications will require evaluation for dependency characteristics that could limit their clinical use.

Side effects observed with SSRIs, such as sexual dysfunction and weight gain, can be related to a continuous, high occupancy of serotonin transporters. This effect might not occur with a triple reuptake inhibitor and the incidence of serotonin-associated side effects might be lower.[14]

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