Differences in Mechanism of Action Between Current and Future Antidepressants

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Antidepressants are divided into several classes on the basis of their pharmacologic mechanisms of action, which are thought to be responsible for both their therapeutic actions and their side effect profiles. All classes currently available in the United States affect serotonin, norepinephrine, and/or dopamine neurotransmission. New agents in development also affect neurotransmission of such monoamines and include serotonin-norepinephrine reuptake inhibitors, serotonin-selective agents, selective monoamine oxidase inhibitors, and selective norepinephrine reuptake inhibitors. Treatments with entirely new mechanisms of action are also being studied, including hormone-linked treatments such as estrogen replacement therapy and the steroid antagonist mifepristone (RU-486 or C-1073); novel antagonist peptides such as corticotropin-releasing factor, neurokinins, and injectable pentapeptides; and agents that affect glutamate neurotransmission. The introduction of antidepressants with novel mechanisms of action could potentially revolutionize the treatment of depression.
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Over 2 dozen antidepressant agents are currently available. They are grouped into several different classes distinguished by their pharmacologic mechanisms of action.[1,2] The 2 classical groups include the monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs). Three categories of modern antidepressants are based on the inhibition of serotonin (5-HT), dopamine, and/or norepinephrine reuptake: selective serotonin reuptake inhibitors (SSRIs), "dual-action" serotonin-norepinephrine reuptake inhibitors (SNRIs or "dual-action agents"), and an agent that acts as an inhibitor of both norepinephrine and dopamine reuptake (NDRI), namely, bupropion. Other classes include predominant inhibitors of 5-HT_{2A} receptors and antidepressants with α_2-blocking properties. These agents have been extensively reviewed elsewhere[1,2] and will not be emphasized in this article.

In addition, several new antidepressant agents are on the horizon (Table 1). Novel approaches include modifications and improvements of currently available agents, as well as development of drugs selective for norepinephrine reuptake inhibition. Several other new drugs are being developed that have entirely novel mechanisms of action on newly investigated neurotransmitter systems and hormones. If these agents are shown to be effective and become available, they will not only afford more options with which to treat depression, but may ultimately revolutionize the approaches to both depression and its treatment. This article is written from the perspective of the U.S. market, although most agents are in fact developed for worldwide distribution.

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NEW DUAL-ACTION SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITORS

Two more dual-action SNRIs—in addition to the currently available venlafaxine/venlafaxine extended release—may soon become available. These drugs are duloxetine, now filed with the U.S. Food and Drug Administration (FDA), and milnacipran, which is currently available in Europe and Japan and undergoing testing in the United States. Like the currently available venlafaxine, they do not affect cholinergic, histaminergic, or α-adrenergic receptors, and so avoid the adverse effect profile of the TCAs.[3,4] However, they differ both from venlafaxine and from each other in terms of their selectivity for serotonin versus norepinephrine. While venlafaxine inhibits serotonin reuptake more potently than norepinephrine reuptake, both duloxetine and milnacipran inhibit norepinephrine reuptake at all doses. Thus, venlafaxine is more selective for serotonin reuptake than for norepinephrine reuptake, milnacipran is more selective for norepinephrine reuptake than for serotonin reuptake, and duloxetine is approximately balanced in reuptake blockade for both serotonin and norepinephrine (Table 2).[1,2,5,6]

Table 1. Mechanisms of Action of Drugs Recently Released or Soon to Be Released

Mechanism of Action	Drug
Serotonin and norepinephrine reuptake inhibition	Milnacipran, duloxetine
Selective serotonin reuptake inhibition	Escitalopram
5-HT$_{1A}$ partial agonist	Gepirone
5-HT$_{1D}$ antagonism	CP448187
Reversible inhibition of MAO-A	Befloxatone, teloxantrone, moclobemide, brofaromine
MAO-B inhibition	Selegiline
Selective norepinephrine reuptake inhibition	Reboxetine, atomoxetine
Estrogen replacement	Estrogen replacement therapy
Glucocorticoid receptor antagonism	Mifepristone and others
Corticotropin-releasing factor antagonism	R-121919 and others
Neurokinin receptor antagonism	MK-0869 and others
Unknown mechanism	Nemifitide

Abbreviations: MAO-A = monoamine oxidase A, MAO-B = monoamine oxidase B.

Table 2. Selectivity of Serotonin Versus Norepinephrine Reuptake for Serotonin-Norepinephrine Reuptake Inhibitors[a]

Neurotransmitter Reuptake	SNRI
5-HT > NE	Venlafaxine
NE > 5-HT	Milnacipran
5-HT approximately equal to NE	Duloxetine

[a]Data from Bymaster et al.[5] and Bel and Artigas.[6]
Abbreviations: NE = norepinephrine, SNRI = serotonin-norepinephrine reuptake inhibitor, 5-HT = serotonin.

Duloxetine is a once-daily agent and appears to be effective in depression,[7,8] with the prototypical superior depression remission rates over SSRIs found generally for SNRIs as a class. In addition, it appears to have promising efficacy in reducing the painful physical symptoms associated with depression, which may account for some of its enhanced remission rates compared with SSRIs. It is also undergoing testing in various pain-related syndromes including fibromyalgia. So far, the side effect profile of duloxetine shows limited hypertension, withdrawal symptoms after discontinuation, and urinary retention, which is characteristic of other agents in the SNRI class. Thus, duloxetine promises to be a very tolerable form of SNRI therapy.

Milnacipran is administered twice daily and appears to be effective in depression. It is currently in testing in the United States for fibromyalgia and functional somatic syndromes. It does appear to have the superior efficacy for depression remission over SSRIs that is characteristic of the class of SNRIs and little or no associated hypertension, although some urinary retention has been observed, particularly in elderly men.[9]

NEW SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Escitalopram, or S-citalopram, is the isolated active enantiomer of the SSRI citalopram.[10] Escitalopram is more selective for serotonin than racemic citalopram, with negligible affinity for histaminic, adrenergic, and muscarinic receptors and virtually no inhibition of the P450 system.[10–13] It is also more potent than citalopram, with uptake inhibition for serotonin of 2.5 nmol/L versus 9.6 nmol/L for citalopram.[10] The inactive enantiomer, called R-citalopram, is thought to be responsible for some of the behavioral and sexual side effects of citalopram and for the histamine-1 receptor binding and CYP2D6 inhibition of citalopram, so, theoretically, escitalopram will have an improved side effect profile compared with citalopram.[10] Clinical data have shown that there are lower rates of adverse effects for escitalopram than for citalopram, as well as lower rates of discontinuation due to side effects. Preclinical data also suggest that escitalopram has more than twice the potency of racemic citalopram in studies of behavioral efficacy, indicating perhaps that the presence of R-citalopram in the racemic mixture may interfere in the ability of the active S-enantiomer to bind to the serotonin transporter. Clinical data to date support this possibility, as the antidepressant efficacy of 10 mg of escitalopram seems comparable to that of 40 mg of the racemate.[14,15]

Escitalopram has demonstrated efficacy for depression, as well as preliminary demonstration of efficacy for various anxiety disorders, including generalized anxiety disorder,[16] panic disorder,[17] and social anxiety disorder.[18] Escitalopram has been approved by the FDA for the treatment of major depressive disorder.

SELECTIVE NOREPINEPHRINE REUPTAKE INHIBITORS

Bupropion is the only nontricyclic antidepressant currently on the market in the United States that has no direct actions on the serotonin system.[1,19,20] Rather, it acts via inhibition of norepinephrine and dopamine reuptake and is consequently classified as an NDRI. However, 2 new agents, one of which recently became available and one of which may soon become available, do not directly affect serotonin. These agents, atomoxetine and reboxetine, are selective norepinephrine reuptake inhibitors (NRIs).[21,22] Noradrenergic agents may treat a different symptom profile than serotonergic agents. While deficiency in serotonin may be associated with anxiety symptoms, food craving, and bulimia, deficiency in norepinephrine may be associated with cognitive impairment, psychomotor retardation, and fatigue.[1] In fact, reboxetine and atomoxetine are not currently being developed to treat depression; rather, reboxetine is being developed to treat neuropathic pain and atomoxetine has been developed to treat attention-deficit/hyperactivity disorder. Although reboxetine is available in Europe and other countries as an antidepressant, it is not likely to come to the United States for the treatment of depression. It also has an active enantiomer that may replace racemic reboxetine in clinical development where there is potentially some continuing testing for this agent in the treatment of neuropathic pain. Atomoxetine, as a selective NRI, should theoretically be an effective antidepressant. Even if not developed commercially for depression, it may have utility either as monotherapy or in combination with other agents for the treatment of depression.

Noradrenergic agents also have different side effects than drugs affecting the serotonin system. While selective serotonergic agents have minimal effects on acetylcholine, noradrenergic agents may inhibit release of acetylcholine and thus cause such side effects as constipation, dry mouth, and urinary retention.[1]

NEW NOVEL SEROTONIN AGONIST AND ANTAGONIST

Other agents undergoing development include a controlled-release formulation of the 5-HT_{1A} partial agonist gepirone. This agent is structurally and mechanistically related to buspirone and should have a different tolerability profile compared with SSRIs, particularly less sexual dysfunction. Another novel 5-HT agent in testing is a 5-HT_{1D} antagonist. Serotonin-1D receptors are presynaptic autoreceptors, so when these receptors are blocked, serotonin release is disinhibited, or "turned on."[1] Interestingly, this receptor is also antagonized as one of the numerous pharmacologic actions of a currently available atypical antipsychotic, ziprasidone, which may contribute to its efficacy in affective disorders.[23]

NEW MONOAMINE OXIDASE INHIBITORS

Newer MAOIs only target either monoamine oxidase A (MAO-A) or monoamine oxidase B (MAO-B) and thus are selective either to serotonin and norepinephrine or to dopamine alone.[2,24] Reversible inhibitors of MAO-A (RIMAs) do not affect MAO-B and thus do not increase dopamine levels.[1,19] They are also reversible and can be displaced from the enzyme, allowing it to function once again. At low to moderate doses, these agents do not require the dietary restrictions of classical MAOIs, and so compliance may be more likely. RIMAs that have been developed or are undergoing development include befloxatone, teloxantrone, moclobemide, and brofaromine. At this time, it is unclear if these agents will become available in the United States.

One agent that has been filed with the FDA for the treatment of depression is the MAO-B–specific inhibitor, selegiline.[19] This drug is administered as a transdermal patch and appears to be both effective and tolerated. Like the RIMAs, transdermal selegiline does not require dietary restrictions.[24]

HORMONE-LINKED TREATMENT

While several of the new drugs discussed so far have mechanisms of action different from current drugs, they all still share the common feature of acting directly on 1 or more monoamine systems. Mechanisms of action that extend beyond the monoamine systems are now being explored and may prove to be valuable additions to the treatment of depression. Specifically, this may include targeting the receptor superfamily known as "nuclear-ligand–activated transcription factors."[25,26] This receptor superfamily includes steroid hormone receptors such as those for estrogen and glucocorticoids.

Evidence is beginning to accumulate to suggest that estrogen replacement therapy can be effective in treating depressive symptoms during the perimenopausal and the postpartum periods.[27–33] Estrogen acts on genes via estrogen-response elements to activate the production of growth factors, enzymes, brain-derived neurotrophic factors, and receptors that facilitate neurotransmission.[1] These include monoamine receptors and, in particular, serotonin receptors. It has been demonstrated in animal studies that loss of estrogen leads to reduced serotonergic functioning and that estrogen replacement enhances serotonergic functioning.[34] The apparent ability of estrogen to affect the actions of neurotransmitters suggests that it may be able to produce antidepressant effects.[25,26,35] Early studies were not well controlled and generated mixed results regarding the efficacy of estrogen replacement therapy in treating depression.[35] However, recent controlled studies have shown sublingual and transdermal 17β-estradiol to be effective in treating severe premenstrual syndrome, postpartum depression, and depression during perimenopause.[27–33,36–38] In addition, estrogen replacement therapy may be effective as an adjunct to SSRIs in treatment-refractory depression.[39,40]

The "morning-after pill," mifepristone (RU-486 or C-1073), is not only an antagonist of progesterone but also an antagonist of glucocorticoid receptors. Theoretically, mifepristone may thus be able to treat depression by blocking potentially toxic actions of cortisol on central glucocorticoid receptors, particularly in psychotic depression. This agent has therefore begun to be studied as an antidepressant.[41]

NOVEL PEPTIDES

Antagonists to the 41-amino-acid peptide corticotropin-releasing factor (CRF) are also being developed as potential treatments for depression. In animal studies, inhibiting the release of cortisol with CRF antagonists has had anxiolytic and stress-relieving effects.[1,42] This has stimulated preliminary research to test the efficacy of CRF antagonists in treating depressed patients. Several such agents are in late preclinical development, and some have begun human testing with encouraging preliminary results.[43] Several more are expected to cascade into clinical testing in the near term.

Another set of interesting peptides is the 10- to 11-amino-acid peptides known as "neurokinins" (also as "tachykinins"). Three interesting agents include substance P, neurokinin A, and neurokinin B. Their associated receptors are neurokinin-1 receptors (also called "substance P receptors" and "NK_1 receptors"), neurokinin-2 receptors, and neurokinin-3 receptors. Antagonists to all 3 neurokinin receptors have been synthesized and tested both in animals and in early human clinical trials.[44,45] Most clinical testing to date has been with the NK_1 or substance P antagonists. Although substance P has long been associated with the pain response, it now appears that it, and the other neurokinins, may play roles in emotional functioning.[44,45] In early clinical trials, antagonists to the receptors for substance P (NK_1 receptors) improved mood in depressed patients.[44,45] Thus, NK_1 antagonists, as well as antagonists to neurokinin A and neurokinin B, are being tested for their effects on mood. Other testing is being undertaken in patients with psychosis and anxiety, treatment-resistant depression, and depression associated with pain. Results to date with the substance P antagonists are variable, with some positive trials and some disappointing trials. Nevertheless, this remains a novel and interesting direction to pursue in the development of new antidepressants.

A pentapeptide of novel structure but unknown mechanism of action is INN-00835, now known as nemifitide. Administered by subcutaneous injection, this compound has provocative and early evidence of efficacy in depression and treatment-resistant depression and is undergoing extensive further testing.[46,47]

SUMMARY

Numerous new antidepressants are on the horizon, beginning with those recently approved by the FDA and extending to those that are in early clinical testing. Recent approvals include escitalopram, for depression, and atomoxetine, for attention-deficit/hyperactivity disorder. Those antidepressants most likely to be released soon include duloxetine. Other agents in late clinical development include the selegiline MAO-B transdermal patch and the 5-HT_{1A} partial agonist gepirone extended release. Novel antidepressants also in testing include various formulations of estrogen, the glucocorticoid and progesterone antagonist mifepristone, the dual-action SNRI milnacipran, the selective NRI reboxetine and its active enantiomer, and several peptides, including nemifitide and both CRF and neurokinin antagonists, especially for substance P. The potential for enhanced pharmacotherapeutics of depression appears bright as improved formulations of marketed agents that will most likely be available soon merge, in the foreseeable future, with agents that have novel mechanisms of action.

Drug names: atomoxetine (Strattera), bupropion (Wellbutrin and others), buspirone (BuSpar and others), citalopram (Celexa), escitalopram (Lexapro), mifepristone (Mifeprex), selegiline (Eldepryl and others), venlafaxine (Effexor), ziprasidone (Geodon).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, milnacipran, duloxetine, reboxetine, atomoxetine, gepirone, befloxatone, teloxantrone, moclobemide, brofaromine, selegiline, mifepristone, substance P, neurokinin A and neurokinin B, and INN-00835 (nemifitide) have not been approved by the U.S. Food and Drug Administration for treatment of major depressive disorder.

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