Mechanism of Action of Antidepressant Medications

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The psychopharmacology of depression is a field that has evolved rapidly in just under 5 decades. Early antidepressant medications—tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs)—were discovered through astute clinical observations. These first-generation medications were effective because they enhanced serotonergic or noradrenergic mechanisms or both. Unfortunately, the TCAs also blocked histaminic, cholinergic, and α_1-adrenergic receptor sites, and this action brought about unwanted side effects such as weight gain, dry mouth, constipation, drowsiness, and dizziness. MAOIs can interact with tyramine to cause potentially lethal hypertension and present potentially dangerous interactions with a number of medications and over-the-counter drugs. The newest generation of antidepressants, including the single-receptor selective serotonin reuptake inhibitors (SSRIs) and multiple-receptor antidepressants venlafaxine, mirtazapine, bupropion, trazodone, and nefazodone, target one or more specific brain receptor sites without, in most cases, activating unwanted sites such as histamine and acetylcholine. This paper discusses the new antidepressants, particularly with regard to mechanism of action, and looks at future developments in the treatment of depression.
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In just under 5 decades, the psychopharmacology of depression has evolved from medications discovered through serendipitous clinical observations to drugs designed to target a single receptor site to ones that target multiple sites that have been found to be associated with depression. The first antidepressants were identified through a process comprising serendipitous observations followed by minor structural modifications to produce structural analogues (e.g., secondary and tertiary amine tricyclic antidepressants). Most of these agents acted at several sites in the brain, each of which might or might not affect depression. In most cases, the mechanism of action was unknown. The next generation of antidepressants (the selective serotonin reuptake inhibitors, or SSRIs) was rationally designed to act on one specific neurotransmitter, i.e., serotonin. The newest generation of psychotropic medications (e.g., venlafaxine, mirtazapine) was tailored to act at several specific receptor sites that are implicated in depression. Table 1[1] shows the presence and extent of antidepressant action on each receptor site. This paper recounts the brief history of antidepressant medications, with particular emphasis on mechanism of action.

The history of the psychopharmacology of depression is only several decades old. Seymour S. Kety and others noted the role of norepinephrine in depression in the mid-1950s, and Schildkraut[2] first proposed the catecholamine hypothesis in 1965. The hypothesis suggested that at least some depression could be traced to lowered norepinephrine levels at important adrenergic receptor sites located in the brain; higher-than-normal levels were suggested to cause manic behavior. Clinical observations were consistent with the catecholamine hypothesis. Medications with sedative or depressive effects in humans—reserpine and tetrabenazine—depleted catecholamines in the brain. Amphetamine, a stimulant, released norepinephrine into the brain. Monoamine oxidase inhibitors (MAOIs) increased catecholamine levels in the brain; the TCA imipramine inhibited the cellular uptake and inactivation of serotonin and norepinephrine. Soon, Lapin and Oxenkrug,[3] among others, proposed that abnormally low levels of serotonin at certain brain receptor sites were related to depression; abnormally high levels were related to mania. Working separately, Kuhn[4] in Switzerland and Lehmann and Kline[5] in the United States reported 2 classes of drugs—TCAs and MAOIs—effective in treating depression. These drugs affect both norepinephrine and serotonin receptors in the brain.

TCAs interact with a number of other receptor sites, including histamine, acetylcholine, and epinephrine, and also have substantial atropine-like effects, including dry mouth, dizziness, blurred vision, constipation, sedation, and orthostatic hypotension, which can cause falls. Cardiovascular effects are common, often restricting treatment at sufficient dosages. Death from TCA overdose generally has a cardiovascular etiology secondary to the quinidine-like effect. In overdose, TCAs slow intraventricular conduction, which causes complete heart block or

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Table 1. Effects of Single-Receptor and Multiple-Receptor Newer Antidepressants on CNS Neurotransmitters*

Antidepressant	Serotonin	Norepinephrine	Dopamine
Single-receptor			
Fluoxetine	++++	0	0
Paroxetine	++++	0	0
Sertraline	++++	0	0/+
Multiple-receptor			
Bupropion	+	+	++[a,b]
Mirtazapine	+++[c]	++[a]	0
Nefazodone	+++[d]	+	0
Trazodone	++[d]	0	0
Venlafaxine	++++	++	0/+

*Data from reference 1. Symbols: ++++ = high, +++ = moderate, ++ = low, + = very low, 0 = none.
[a]a_2 presynaptic antagonist.
[b]Acutely, increases; chronically, stabilizes.
[c]5-HT_2 and 5-HT_3 antagonist.
[d]5-HT_2 antagonist.

ventricular reentry arrhythmias. TCAs can also be seizurogenic in overdose, and patients who experience seizures may have sometimes life-threatening broadening of the QRS duration or hypotension.[6] DeToledo et al.[7] suggested that clomipramine in combination with valproic acid can lead to increased levels of clomipramine and subsequent seizures in patients predisposed to these events. The increased side effect burden of the TCAs can lead to reduced tolerability in patients, especially when the drugs are administered over the long term. Brodkin et al.[8] looked at 35 adults with DSM-IV diagnoses of pervasive developmental disorders treated with clomipramine. They found 13 patients with clinically significant adverse effects, including 3 patients with seizures. Despite these drawbacks, TCAs were still widely prescribed through the 1970s and 1980s. Olfson and Klerman,[9] analyzing data from 3 National Ambulatory Medical Care Surveys, found that, in the 3 years studied (1980, 1985, and 1989), TCAs were the type of antidepressant most often prescribed by office-based psychiatrists, and they continue to be used commonly today. Many European psychiatrists still believe that the TCAs, and particularly the tertiary amines—such as clomipramine and amitriptyline, which have substantial effects on both norepinephrine and serotonin—are the most potent antidepressants.

MAOIs, which also interact with several receptor sites, have their own set of problems. Because MAOIs can interact with tyramine, causing potentially lethal hypertension, patients taking them must adhere to a diet that restricts or eliminates tyramine-containing foods. This is less critical for reversible MAOIs (RIMAs) such as moclobemide. MAOIs also present interaction problems with a number of drugs, including other MAOIs, TCAs, and SSRIs. Other problematic side effects of the MAOIs include hypotension, weight gain, and sexual dysfunction. Nevertheless, there are a number of patients with depressive disorders who respond better to MAOIs than to any other class of drugs. Gardner et al.[10] reviewed literature on dietary restrictions during MAOI treatment and also conducted tyramine assays. They proposed that dietary restrictions be limited and asserted that MAOIs are effective alternatives when patients do not respond to TCAs, particularly for atypical depression, dysthymia, and bipolar depression.

SINGLE-RECEPTOR ANTIDEPRESSANTS

Selective Serotonin Reuptake Inhibitors

On the basis of the hypothesis that alterations in receptor sensitivity may play a role in both the mechanism of action of antidepressant drugs and the pathophysiology of the depressive disorders, researchers in Scandinavia began to search for an agent that would act only at serotonin receptors. Zimelidine was the first such compound to be clinically tested and made available.[11] However, because of significant neurotoxicity and immunogenicity, the compound was withdrawn from the worldwide market. Nonetheless, clinical trials and clinical experience demonstrated that this was an effective antidepressant. Even though zimelidine was withdrawn from the worldwide market, the result of this methodical research led to a new generation of antidepressants, the SSRIs, which have since become the most widely utilized class of antidepressants on an international basis. These agents, which include fluoxetine, paroxetine, sertraline, fluvoxamine, and citalopram, combine the effectiveness of their older counterparts with a much-improved side effect profile.

SSRIs are now prescribed widely in this country and in many others. Pincus et al.[12] tracked the prescriptions written for psychotropic medications in the United States from 1988 to 1994. Of the patients who were treated for depression, 60% were prescribed antidepressants—34% SSRIs and 26% non-SSRIs and the older generic antidepressants. The SSRI class of drugs has a wide range of clinical application in the full spectrum of depressive disorders and in many other psychiatric disorders, including but not limited to obsessive-compulsive disorder,[13] panic disorder,[14] social phobia,[15,16] eating disorders,[17,18] and premenstrual dysphoric disorders.[19] SSRIs are well tolerated, with safety in overdose and low seizurogenicity. These properties have been confirmed by acute and long-term maintenance studies. Even though SSRIs cost more than the older generic antidepressants, pharmacoeconomic studies have consistently demonstrated their indirect and direct cost-effectiveness in terms of use of medical facilities and regained productivity.[20]

However, some investigators have suggested that the SSRIs tend to lose efficacy over time. In a review of the literature on clinical trials of antidepressants, Byrne and Rothschild[21] found that depressive symptoms returned during maintenance treatment in 9% to 57% of patients, most of whom were treated with SSRIs. Fava et al.[22] reported that 26 among 77 patients taking a 20 mg/day main-

tenance dose of fluoxetine under double-blind conditions lost efficacy.

Selective Norepinephrine Reuptake Inhibitors

A number of projects to develop a specific norepinephrine reuptake inhibitor have failed, mostly because of cardiovascular side effects. Reboxetine (still being tested in the United States but in use in Great Britain) appears to be effective and well tolerated.[23]

MULTIPLE-RECEPTOR ANTIDEPRESSANTS

Venlafaxine and Venlafaxine XR

With the evolution of antidepressants that target specific single receptors have come antidepressant medications designed to interact with more than one receptor site. Venlafaxine, mirtazapine, trazodone, and nefazodone, for example, affect both serotonin and norepinephrine receptors. Serotonin-norepinephrine reuptake inhibitors (SNRIs) are a new class of antidepressant, of which venlafaxine is currently the only member. This new class acts on both serotonin and norepinephrine, but it does not interact with histaminic and cholinergic-adrenergic receptors and thus avoids troublesome adverse events such as dry mouth, hypotension, and sedation. Venlafaxine also interacts very weakly with dopamine receptors, an action that may have clinical applicability at very high doses. It can be titrated to relatively high doses to enhance response when clinically indicated. There is a dose response with this drug, and at higher doses, the adrenergic effects of the drug are increased.

A number of studies indicate the potential therapeutic superiority of venlafaxine over SSRIs. Dierick et al.[24] conducted an 8-week double-blind comparison of outpatients with major depression taking fluoxetine (N = 151) or venlafaxine (N = 153). Seventy-two percent of patients taking venlafaxine or 60% of patients taking fluoxetine registered a meaningful clinical response, defined as at least a 50% decrease from baseline to endpoint (6 weeks) in the total Hamilton Rating Scale for Depression (HAM-D) scores.

Clerc et al.[25] conducted a double-blind randomized trial of venlafaxine and fluoxetine in severely depressed inpatients. In this 6-week study, venlafaxine-treated patients received 200 mg/day and fluoxetine-treated patients received 40 mg/day. Efficacy was rated using the Clinical Global Impressions scale (CGI), the Montgomery-Asberg Depression Rating Scale (MADRS), and the HAM-D. The researchers found differences favoring venlafaxine at most time points. The CGI scores followed a similar pattern, with significant differences seen at week 4. The MADRS and HAM-D improvements of 50% or greater from baseline to endpoint were considered meaningful clinical response. Venlafaxine-treated subjects responded at a significantly higher rate than did the fluoxetine-treated subjects (MADRS: 76% vs. 47%, $p = .024$; HAM-D: 76% vs. 41%, $p = .006$; CGI-Improvement: 76% vs. 47%) for the first 4 weeks of the study. Fewer venlafaxine-treated patients (18%) than fluoxetine-treated patients (37%) withdrew from the study for any reason. The researchers concluded that venlafaxine was more effective than fluoxetine in the treatment of severely depressed hospitalized patients.

Guelfi et al.[26] performed a randomized, double-blind, parallel-group study of 93 patients hospitalized with severe depression who were randomly assigned to treatment with venlafaxine (N = 46) or placebo (N = 47) for 4 weeks. Efficacy was measured with the HAM-D, the MADRS, and the CGI. At day 4, the MADRS score had decreased a mean ± SD of 3.3 ± 4.6 points in the venlafaxine-treated patients and 1.0 ± 4.9 points in the placebo-treated patients ($p = .026$). At week 1, the HAM-D score had decreased 5.7 ± 6.2 in the venlafaxine group and 3.1 ± 6.8 in the placebo group ($p = .043$). Response, defined as a 50% decrease in MADRS scores, occurred at a rate of 65% for the venlafaxine group and 28% for the placebo group at endpoint ($p \leq .001$). All of these results acheived statistical signifigance for venlafaxine versus placebo and support early onset of action.

Delayed onset of action common to all antidepressant medications has prompted the hypothesis that antidepressant action is mediated by neuroadaptive changes resulting from repeated administration that results in down-regulation of the β-adrenergic receptor. Unlike other antidepressants, venlafaxine has an acute onset of down-regulation of β-adrenergic receptors, which suggests a possible, as yet unproven, mechanism for early onset of action. On the basis of the results of their study, Guelfi et al. concluded that venlafaxine constitutes a rapid and effective treatment for hospitalized patients with major depression and melancholia.

Derivan et al.[27] evaluated data from 2 randomized, double-blind, placebo-controlled studies to measure the onset of action for venlafaxine in a retrospective study and found that venlafaxine-treated patients showed response by day 7. Each study employed the rapid titration of doses of venlafaxine to a mean daily dose of 200 mg/day within 7 to 8 days. Data were assessed using 3 statistical methodologies—traditional analysis of depression scale scores, pattern analysis based on timing and persistence of response, and survival analysis of sustained response. Traditional assessment observed the onset of antidepressant activity (defined as the time of the first statistically significant differences between treatment groups): all statistically significant differences between treatment groups occurring within the first 2 weeks were noted. The pattern analysis was developed by Quitkin and colleagues[28,29] to recognize distinctions between *true* or *specific* responses and *placebo* or *nonspecific* responses. In this case, a CGI-Improvement score of 1 or 2 indicated improvement, with distinctions

made between early (within 2 weeks) and delayed (after 2 weeks) responses. The survival analysis of sustained response regarded a patient as a sustained responder if a response (as defined above) was measured for at least 2 consecutive weeks and then continued for the balance of scheduled treatment. Pattern analysis revealed that, in study 1, more than half the venlafaxine-treated patients demonstrated early persistent responses as opposed to 15% of the group receiving placebo, a statistically significant ($p < .0001$) difference. In study 2, more than 30% of venlafaxine-treated patients and 4% of patients receiving placebo demonstrated early persistent responses to treatment. Survival analysis of sustained response, in study 1, disclosed that sustained responses were measured for 15% of venlafaxine-treated patients, as opposed to 1% of patients receiving placebo. By day 15, 25% of patients treated with venlafaxine and 4% of patients receiving placebo had demonstrated a sustained response. In study 2, 4% of venlafaxine-treated patients, as opposed to 1% of patients receiving placebo, registered a sustained response; 18% of venlafaxine-treated patients versus 2% of placebo-treated patients had achieved sustained responses by day 15.

Increased blood pressure is problematic in a small percentage (2%–4%) of venlafaxine-treated patients taking doses under 200 mg/day. When dosage is increased to 200 mg and above, the incidence is somewhat higher (6%–8%), and blood pressure monitoring is required by the Food and Drug Administration. On a clinical basis, the same monitoring is required of patients treated with TCAs and MAOIs. Benkert et al.[30] reported that increases in supine diastolic blood pressure of potentially clinical significance (of at least 15 mm Hg and to at least 105 mm Hg) occurred in 15% of patients taking venlafaxine and in 18% of patients taking placebo, with no significant differences between groups. (Doses of venlafaxine were rapidly escalated to 375 mg/day and decreased to 150 mg/day after 10 days.) Guelfi et al.[26] reported that 3 patients taking 150 to 375 mg/day of venlafaxine and 2 treated with a placebo recorded blood pressure increases. Postural hypotension occurred in both treatment groups, although twice as often among venlafaxine-treated patients as among those taking placebo.

However, other researchers have failed to find significant increases in blood pressure in studies of venlafaxine. Gründer et al.[31] compared the effects on blood pressure of patients taking venlafaxine with those of patients taking imipramine. Patients taking venlafaxine had their doses rapidly titrated to 375 mg/day, then reduced to 150 mg/day at day 28. Both the group treated with imipramine and the group treated with venlafaxine sustained systolic blood pressure reductions of 5% (imipramine: 4 mm Hg; venlafaxine: 7 mm Hg) after 14 days. Dierick et al.[24] reported no clinically significant changes in heart rate or blood pressure in either 153 patients treated with 75 to 150 mg/day of venlafaxine or 161 patients taking 40 mg/day of fluoxetine in an 8-week, double-blind comparison. Mahapatra and Hackett[32] conducted a randomized, double-blind study comparing venlafaxine with dothiepin, a TCA used widely in the United Kingdom. Seventeen percent of patients taking dothiepin experienced standing systolic blood pressure changes, as opposed to 2% of venlafaxine-treated patients. Electrocardiogram (ECG) interval changes with either clinical significance or potentially clinical significance were found more often in the dothiepin-treated than in the venlafaxine-treated group. This author,[33] in a survey of MEDLINE literature covering 15 years, found clinically significant increases in blood pressure (increase in diastolic blood pressure of ≥ 15 mm Hg and to ≥ 105 mg Hg from baseline) in 5.5% of patients taking more than 200 mg/day of venlafaxine. There was a lower incidence of clinically significant blood pressure increases in patients taking less than 200 mg/day of venlafaxine.

Augustin et al.,[34] in a survey of venlafaxine clinical trials, also found the frequency of hypertension in patients to be dose dependent. Hypertension (defined as treatment-emergent diastolic blood pressure > 90 mm Hg and diastolic blood pressure > 10 mm Hg above baseline for 3 consecutive visits) occurred at a rate of 1.1% in patients taking 75 mg/day (a rate equal to that in patients taking placebo). In patients taking 225 mg/day, the rate of hypertension was 2.2%; in patients taking 375 mg/day, it was 4.5%. The authors noted the limited number of venlafaxine-treated patients reporting sustained hypertension.

Drug-drug interactions affect the potential usefulness of any medication. Most psychotropic drugs, including antidepressants, are metabolized by cytochrome P450 (CYP) isoenzymes. Most antidepressants competitively inhibit the isoenzymes CYP1A2, CYP2D6, CYP3A3/4 (the joint designation of 2 very similar isoenzymes, CYP3A3 and CYP3A4), CYP2C8/9, and CYP2C19, among others. CYP2D6 plays a role in the metabolism of desipramine, nortriptyline, clomipramine, risperidone, some β-blockers, paroxetine, fluoxetine, and phenothiazine antipsychotics. Several SSRIs inhibit CYP2D6. CYP3A3/4 metabolizes sertraline, among other agents. Drug-drug interactions can occur when inhibition of the CYP system causes additive or synergistic drug effects. For example, when a lipophilic β-blocker and a CYP2D6-inhibitor SSRI are used together, the resulting increased concentrations of the β-blocker may cause bradycardia. Ereshefsky[35] has commented that venlafaxine has a favorable drug interaction profile, noting that it does not substantially inhibit the activity of isoenzymes CYP2C9, CYP2D6, CYP1A2, or CYP3A3/4.

Because venlafaxine tends to have fewer problems related to drug interactions than older antidepressants, it is ideal for administration to geriatric patients taking multiple medications for comorbid medical disorders. Khan et

al.[36] conducted an open-label clinical study evaluating patient acceptance and safety of venlafaxine in depressed geriatric patients. Fifty-eight patients were recruited for the study, and 24 completed the full 12 months of the study. Most of those who failed to complete the study withdrew because of treatment-emergent study events; no particular adverse event occurred more often than another. The most common adverse events were headache, nausea, dry mouth, and sweating. Only 1 patient had an adverse event judged definitely drug related. Two patients presented with elevated blood pressure that was deemed probably drug related. Adverse conditions in these 3 patients resolved with no medical consequences after they had withdrawn from the study.

The availability of venlafaxine extended-release (XR) formulation substantially enhances tolerability and ease of administration. Rudolph and Derivan[37] reported a double-blind, placebo-controlled trial investigating the safety and efficacy of extended-release venlafaxine and fluoxetine in a population of 301 patients with major depressive disorder. Patients initially received 75 mg/day of venlafaxine XR, 20 mg/day of fluoxetine, or placebo. Venlafaxine XR doses could be raised to 150 mg/day at 2 weeks and to 225 mg/day at 4 weeks; fluoxetine could be raised to 40 mg/day and to 60 mg/day at the same intervals. Seventy-one percent of venlafaxine XR–treated patients achieved a CGI global improvement score of 1 or 2 (very much improved or much improved), while 62% of fluoxetine-treated patients and 52% of placebo-treated patients registered the same scores in these categories. Thirty-seven percent of the venlafaxine XR–treated patients, 22% of the fluoxetine-treated patients, and 18% of the placebo-treated patients achieved full remission (HAM-D total score ≤ 7). In each of these groups, the difference between rating scale scores of patients treated with venlafaxine XR and those of placebo-treated patients was statistically significant. This study provides evidence that full remission may occur more frequently in venlafaxine-treated patients than in those treated with fluoxetine.

Double-blind trials have recently demonstrated that venlafaxine XR is both clinically and statistically superior to placebo as an anxiolytic medication. In an 8-week, double-blind study,[38] 377 outpatients who met DSM-IV criteria for generalized anxiety disorder (GAD) but not for major depressive disorder were randomly assigned to take 75 mg/day, 150 mg/day, or 225 mg/day of venlafaxine XR or placebo. The primary outcome measures were the Hamilton Rating Scale for Anxiety (HAM-A) total score, the HAM-A psychic anxiety factor score, and the CGI scale. In all cases, the group taking 225 mg/day of venlafaxine XR registered statistically significant improvements over the group taking placebo. On the basis of these data, the authors suggest that venlafaxine XR is safe and effective in the treatment of GAD and may provide an important alternative to anxiolytic medications that are currently available.

Mirtazapine

Mirtazapine, a noradrenergic and specific serotonergic antidepressant, acts on both serotonin and norepinephrine through a mechanism different from reuptake or enzyme inhibition. SSRIs apparently work through a single mechanism of action. Specifically, they inhibit the neuronal uptake pump for 5-HT. The subsequent increase in 5-HT availability, as well as its duration of action, seems to be responsible for both the beneficial and adverse effects commonly associated with SSRI therapy. The down-regulation of postsynaptic 5-HT_{2A} receptors and presynaptic 5-HT_{1D} receptors appears to be responsible for the antidepressant action of this class of drugs and the adverse events frequently accompanying SSRI use, such as gastrointestinal disturbance and restlessness.

Mirtazapine blocks the serotonin receptor subtypes 5-HT_{2A}, 5-HT_{2C}, and 5-HT_3, as well as α_2-adrenergic receptors.[39,40] This blockade results in an increase of noradrenergic activity and specific serotonergic activity. This mechanism of action means that many of the side effects common to TCAs—dry mouth, drowsiness, and constipation—and SSRIs—gastrointestinal distress, insomnia, and sexual dysfunction—will be minimized. Mirtazapine does have a substantial antihistaminic effect, however, which can cause sedation—which can be used therapeutically—increased appetite, and weight gain. These side effects occur more often with mirtazapine-treated patients than with placebo-treated groups. Mirtazapine appears safe in overdose, and a half-life of 20 to 40 hours makes it suitable for once-daily bedtime dosing. The metabolism of this medication does not depend principally on the isoenzymes CYP2D6 or CYP2C19. In addition, in vitro studies indicate that mirtazapine does not inhibit the isoenzymes CYP1A2, CYP2D6, or CYP3A.

Bupropion

The mechanism of action of bupropion is not well understood: it increases whole body turnover of norepinephrine, and to a lesser extent blockades the reuptake of dopamine. Bupropion does not inhibit monoamine oxidase or interact with histaminic or cholinergic receptors or α_1-adrenoceptors, a fact that enhances tolerability. The drug is seizurogenic at levels slightly higher than those of typically used TCAs, but the sustained-release formulation reduces the risk of seizures. Although clinical trials have indicated the efficacy of bupropion in seriously depressed inpatient and outpatient populations, bupropion is not generally used as a broad-spectrum antidepressant.[41]

Hurt et al.[42] conducted a double-blind, placebo-controlled trial testing the efficacy of 100, 150, and 300 mg/day of bupropion in smoking cessation in 615 patients. After 7 weeks, all groups receiving bupropion improved more than the placebo-treated group, with 44 percent of the group receiving 300 mg/day of bupropion responding; at 1 year 23% of this group reported a sustained response.

Bupropion, under the trade name Zyban, is approved by the United States Food and Drug Administration for smoking cessation and is now utilized in primary care medicine.

Trazodone and Nefazodone

Trazodone and its later analogue, nefazodone, act as reuptake inhibitors for both serotonin and norepinephrine and interact with α_1-adrenoceptors. The most potent action is blockade of 5-HT_2 postsynaptic receptors. A modest antidepressant, trazodone is used mostly for its hypnotic and anxiolytic effects, particularly since the advent of SSRIs. One side effect of trazodone is priapism.

Nefazodone is a more potent antidepressant than trazodone, and it is much less likely than trazodone to cause priapism. Common side effects include sedation, impaired concentration, and lethargy. The lethargy can negate the therapeutic effect of the drug and may make long-term maintenance problematic. On the other hand, lack of antihistaminic and anticholinergic activity improves tolerability and safety. Nefazodone lacks quinidine-like activity with safety in overdose, has a low rate of seizurogenicity, and low rates of sexual dysfunction, especially when compared with SSRIs, venlafaxine, TCAs, and MAOIs.

Like trazodone, nefazodone does not interact with histaminergic or cholinergic receptors.[43] It has somewhat less affinity for the α_1-adrenergic receptor than many other antidepressants. This receptor is believed to be responsible for the sedative side effects of trazodone and may also be related to the occurrence of priapism. Nefazodone has a lower affinity for α_1-adrenergic receptors when compared with trazodone and amitriptyline.[43–45] Looking at the results of clinical trials examining the effects of nefazodone in a combined population of 593 depressed patients, Augustin et al.[34] reported no dose-dependent incidents of abnormal ejaculation or orgasm. Overall, 0.2% of the population experienced this adverse event. Blocking 5-HT_{2A} as well as inhibiting the reuptake of 5-HT, nefazodone appears to possess a dual mechanism of action on the serotonergic system. The agent produces a dose-dependent reuptake inhibition of 5-HT. Nefazodone also modestly inhibits the reuptake of norepinephrine. This inhibition is less apparent after the chronic administration of nefazodone than after acute administration. Nefazodone appears to be safe in overdose.

A recent double-blind, placebo-controlled inpatient study conducted by Feighner et al.[46] evaluated nefazodone in the treatment of 120 inpatients with marked-to-severe major depressive disorder. Fifty percent of nefazodone-treated patients responded, compared with 29% of placebo-treated patients. In this study, nefazodone was superior to placebo in the treatment of major depression, with significant ($p < .001$) clinical benefits based on HAM-D and MADRS scores noted as early as week 1 of treatment.

LINKAGE OF SEROTONIN AND NOREPINEPHRINE IN DEPRESSION

Vetulani and Sulser,[47] among others,[48] have demonstrated a link between the interaction of serotonin and norepinephrine. Norepinephrine and serotonin receptors interact anatomically and pharmacologically. Compounds that affect only serotonin have modulatory effects on both dopamine and norepinephrine. There is progressive evidence that a single amine system dysfunction is unlikely to be the pathophysiologic mechanism of depression. Both serotonergic agents and noradrenergic agents down-regulate the β-adrenoceptor. There is a specific pharmacodynamic link between serotonin and norepinephrine effects at the G-protein level. In addition, there are glucocorticoid receptors in cell bodies containing norepinephrine and serotonin. This fact demonstrates a link with glucocorticoid receptors in both serotonin and norepinephrine and may be the link between stress-induced or stress-aggravated affective episodes.

Communication between serotonergic and noradrenergic receptors ameliorated by activation of protein kinase has been demonstrated repeatedly.[49,50] In theory, then, drugs that have both noradrenergic and serotonergic effects, such as venlafaxine, could potentiate the cascade of events that leads to downstream changes that may relate more directly to the core pathophysiology of depression. This could enhance the speed and quality of clinical response and may account for a more robust and earlier onset of action demonstrated specifically by venlafaxine, which has a demonstrated dual mechanism of action.[27]

Cleare et al.[51] used *d*-fenfluramine, a specific 5-HT releasing agent lacking the catecholaminergic effects of *dl*-fenfluramine, as a serotonergic neuroendocrine challenge in subjects with unipolar major depression. After cortisol and prolactin responses to 30 mg of *d*-fenfluramine were measured, the patients were randomly assigned to treatment with either a specific norepinephrine reuptake inhibitor, a TCA, or placebo. The patients treated with the norepinephrine reuptake inhibitor demonstrated a substantial increase in 5-HT–mediated cortisol responses whether or not the depression responded to treatment. The authors concluded that antidepressants selectively modifying noradrenergic function affect 5-HT function, measured by neuroendocrine testing, as well.

In a placebo-controlled procedure, Mann et al.[52] compared regional brain glucose metabolism after the serotonin-releasing drug *dl*-fenfluramine had been administered to 6 healthy inpatients and 6 drug-free inpatients with moderately severe major depression. They reported that, upon evidence of positron emission tomography (PET) scans, healthy inpatients evinced several statistically significant ($p < .01$) areas of both increased and decreased metabolism. Depressed patients did not exhibit these metabolic changes. The authors assert that the results of this study

provide visual evidence corroborating the role of impaired serotonergic transmission in depression.

Geracioti et al.[53] found no substantial differences in concentrations of the neurotransmitters tryptophan, 5-hydroxyindoleacetic acid (5-HIAA), norepinephrine, or 3-methyoxy-4-hydroxyphenylglycol (MHPG) in the cerebrospinal fluid (CSF) of 10 patients with major depression and 10 healthy controls. They did observe, however, a negative linear relationship between mean concentrations of 5-HIAA and norepinephrine in the CSF of the healthy volunteers that was absent in the CSF of the depressed patients. They report that these findings support the hypothesis that a disturbance in the relationship between serotonergic and noradrenergic systems can be found in depressive illness when no simple 5-HT or norepinephrine deficit or surplus exists.

FUTURE RESEARCH

Both serotonergic and noradrenergic agents downregulate the β-adrenoceptors. There is a specific pharmacodynamic link between 5-HT and norepinephrine effects at the G-protein level. There are glucocorticoid receptors in cell bodies that contain both serotonin and norepinephrine receptors, indicating a likely link between glucocorticoid receptors in both of these systems and perhaps a link between stress and induced or aggravated affective episodes. A cross-talk between 5-HT and norepinephrine receptors expedited by activation of a protein kinase has been repeatedly demonstrated. In theory, antidepressants—such as venlafaxine—that affect both 5-HT and norepinephrine receptors could create reactions that potentiate events leading to downstream changes relative to the core pathophysiology of depression. These changes could improve the rapidity and quality of clinical response.

The overview of the history of antidepressant medication has gone from the early discoveries of TCAs and MAOIs to drugs designed to target specific receptor sites in the brain. Increasing knowledge enables us not only to create more effective antidepressants rationally but also to understand the limitations of existing drugs.

Drug names: amitriptyline (Elavil and others), bupropion (Wellbutrin, Zyban), citalopram (Celexa), clomipramine (Anafranil), desipramine (Norpramin and others), fenfluramine (Pondimin), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Pamelor and others), paroxetine (Paxil), reserpine (Serpasi and others), risperidone (Risperdal), sertraline (Zoloft), trazodone (Desyrel and others), valproic acid (Depakene and others), venlafaxine (Effexor).

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DISCLOSURE OF OFF-LABEL USAGE

The author of this article has determined that, to the best of his clinical estimation, no investigational or off-label information about pharmaceutical agents has been presented that is outside Food and Drug Administration–approved labeling.