Are All Antidepressants the Same?

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Historically, the clinician's choice of antidepressant agent has been determined largely by consideration of tolerability, given the perception that the therapeutic efficacy of the various antidepressants was broadly comparable. However, with the advent of the newer, more selective antidepressants, indications of variation in clinical efficacy have begun to emerge. The advent of the selective serotonin reuptake inhibitors has been welcomed by patients, largely owing to their superior tolerability profile compared with older antidepressants. However, severely depressed patients appear to benefit particularly from agents that include a noradrenergic mode of action, such as tricyclic antidepressants and the modern dual-action antidepressants mirtazapine, venlafaxine (at higher doses), and milnacipran. In addition, a noradrenergic component may offer superior efficacy in social functioning. The recent development of a novel, selective norepinephrine reuptake inhibitor (reboxetine) with proven efficacy in a range of depressed patients will permit the investigation of the relevance of the noradrenergic approach. Clinical observations of the effects of the newer, more selective antidepressants are important in our understanding of precise mode of action, variation in efficacy and tolerability, and comparative usefulness in clinical practice.
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Depression is a widespread, recurrent illness[1] that places significant burdens on afflicted individuals, their families,[2] and society at large. The financial burden of depression is also considerable due to days lost to work, decreased work productivity, and increased health care utilization.[3–5] There has been, over recent years, a continuing effort to improve treatments for depressive disorders, to more fully address the needs of certain groups of patients, and to reduce the side effect burden associated with treatment and thereby improve compliance. Quality-of-life issues have also become an important feature of clinical decision making in recent years and are now considered an important outcome measure in the treatment of a range of medical and psychiatric conditions.

Three neurotransmitters are regarded as key to the development and resolution of depressive disorders: norepinephrine, serotonin, and dopamine. Dysfunction in one (or more) of these systems is thought to result in the array of symptoms classed as depression. The precise nature of this dysfunction is unclear, as are the precise mechanisms involved in the resolution of depressive symptomatology brought about by antidepressant agents.

A deeper understanding of the causes of depression has allowed a targeted approach to the development of antidepressants. The early antidepressants, while effective, are often associated with significant side effect burdens owing to their effects at sites not thought to be related to their therapeutic efficacy.[6,7] For example, the potential for cardiovascular and cognitive side effects as well as dizziness and orthostatic hypotension associated with tricyclic antidepressants (TCAs) limits their use in the elderly, those with preexisting cardiac disorders, and suicidal patients (because of their toxicity in overdose).

While most patients will respond well to antidepressant therapy,[8] some literature suggests that not all antidepressants are equally effective in the treatment of all depressed patients. Clinical observations of the effects of the newer, more selective antidepressants are important in our understanding of their precise mode of action, variation in their efficacy and tolerability, and their comparative usefulness in clinical practice.

ANTIDEPRESSANT MECHANISMS OF ACTION

The majority of currently available antidepressants are thought to exert their therapeutic effects through increasing or altering the synaptic concentrations of monoamines (principally norepinephrine and serotonin). For example, TCAs inhibit reuptake of monoamines from the synaptic cleft, whereas monoamine oxidase inhibitors (MAOIs) inhibit their metabolism. TCAs have long been established as effective agents in the treatment of depressive disor-

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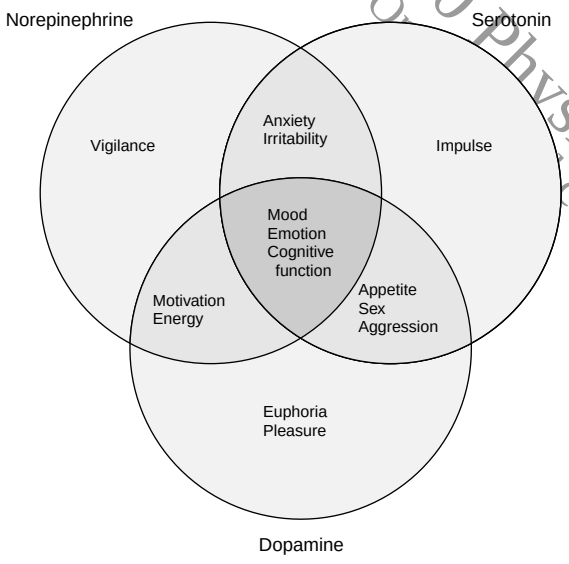
Table 1. Examples of Adverse Events Associated With Antidepressants and Their Presumed Pharmacologic Origin

Presumed Pharmacologic Origin	Adverse Event
Antihistaminergic	Weight gain
	Drowsiness
Anticholinergic/antimuscarinic	Constipation
	Blurred vision
	Dry mouth
	Drowsiness
α_1-Adrenergic antagonism	Dizziness
	Decreased blood pressure
	Drowsiness
5-HT_2 receptor stimulation	Agitation
	Akathisia
	Anxiety
	Panic attacks
	Insomnia
	Sexual dysfunction
5-HT_3 receptor stimulation	Nausea
	Gastrointestinal distress
	Diarrhea
	Headache

Figure 1. Proposed Roles for the 3 Key Monoamine Systems[a]



[a]Reproduced from Healy and McMonagle,[9] with permission.

ders. However, as a class they vary considerably in their precise mode of action, from the more noradrenergic agents, such as desipramine, to agents such as imipramine that inhibit the reuptake of both norepinephrine and serotonin and clomipramine, which is the most serotonin selective member of this class. Furthermore, their actions at receptor sites other than those thought to mediate their antidepressant efficacy result in a significant and clinically relevant side effect burden (Table 1).

The increased receptor specificity of more recent antidepressants does not appear to have resulted in any reduction in efficacy, but has altered or reduced the side effect burden associated with treatment (see Table 1). The selective serotonin reuptake inhibitors (SSRIs) have been shown to be effective in the short- and long-term treatment of depression and are not associated with the anticholinergic effects of TCAs. However, they have often been associated with sexual dysfunction and gastrointestinal disorders. Furthermore, their efficacy in certain patient groups, such as the severely ill, has been questioned. Other antidepressant classes appear to be variations on a theme, combining norepinephrine and serotonin specificity to varying degrees with, for example, histamine and dopamine specificity.

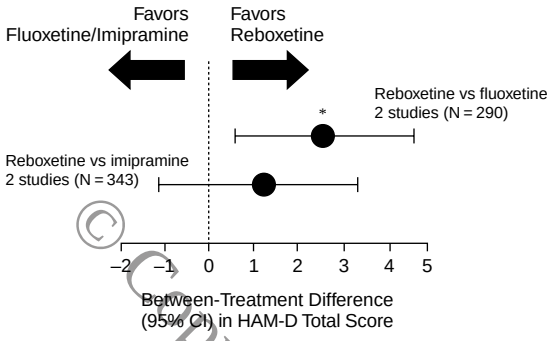
Most recently, the development of a new class of antidepressant, the selective norepinephrine reuptake inhibitor (selective NRI) reboxetine, has provided us with the first truly selective noradrenergic agent. Not only does this development open the way to examine the noradrenergic system in the etiology and treatment of depressive disorders in more detail, but clinical trials conducted with this novel antidepressant have highlighted a number of clinically relevant benefits of this class.

PHARMACOTHERAPY AND THE MONOAMINE HYPOTHESIS

There appears to be considerable overlap between the different effects of the principal monoamine systems on emotion and behavior (Figure 1). Norepinephrine is thought to enhance vigilance, motivation, and self-perception, whereas serotonin affects impulse and irritability.[9,10] With this in mind, it is perhaps not surprising that, with the advent of more selective antidepressants, clinical variation between those medications is becoming apparent.

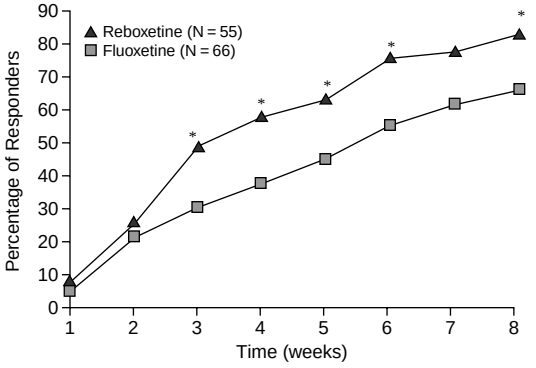
The monoamine hypothesis explains much of what is currently known about both the etiology and treatment of depressive disorders and also provides a pathophysiologic explanation for the action of antidepressants. In its simplest form, the hypothesis explains depression in terms of a neuronal lesion or deficit, for example in the synaptic concentrations of monoamines, that antidepressants seek to "normalize."[11] However, it is not clear that monoamine synaptic concentrations are in fact abnormal during depressive illness. Modern psychopharmacology believes more in receptor disturbances and other biological correlates of depression such as disturbances of the hypothalamo-pituitary-adrenal axis. Antidepressants may initiate a cascade of receptor modulations and changes in signaling processes that ultimately lead to the resolution of depressive symptoms, or may augment monoamine concentrations, creating conditions conducive to recovery from depressive disorders.[12] In this case, different but overlapping therapeutic effects would be expected between the different classes of antidepressant.[9] Key to this latter hypothesis is the fact that antidepressants, in addition to improving the core biological aspects of depression such as mood, also affect additional features of depressive disorders, such as social functioning.

Figure 2. Subset Analyses of 4 Studies in Which Reboxetine Was Compared With Fluoxetine and Imipramine in Severely Depressed Patients[a]



[a]Adapted from Montgomery.[21] Abbreviations: CI = confidence interval, HAM-D = Hamilton Rating Scale for Depression.
*p < .05 reboxetine vs. fluoxetine.

Figure 3. Percentage of Patients With Severe Depression Who Achieved a Response (≥ 50% decrease in mean HAM-D total score) Over Time: Reboxetine (8–10 mg/day) vs. Fluoxetine (20–40 mg/day)



*p < .05 vs. fluoxetine.

The finding that certain antidepressants are effective in the treatment of psychiatric disorders other than depression offers further support that such disorders are not the result of one simple biochemical lesion. For example, the SSRIs have demonstrated efficacy in panic disorder and obsessive-compulsive disorder. With the advent of the selective NRIs, it will be possible to determine whether these agents are also effective in a range of disorders.

CLINICAL VARIATION BETWEEN ANTIDEPRESSANTS

The SSRIs have proved popular as first-line treatments for depression since their introduction in the 1980s. While their increased selectivity for the serotonergic system has not translated into increased efficacy, it does not appear to have resulted in a loss of efficacy, and numerous studies have shown that as a group, the SSRIs seem to be as effective as, for example, the TCAs. The SSRIs themselves vary somewhat in their pharmacologic profile (degree of selectivity and intensity of serotonin uptake inhibition) and clinical profile (including the precise array of adverse events with which they are associated).

Older noradrenergic agents also had wide-ranging effects on other receptors, making it difficult to examine in any detail the specific clinical effects produced by norepinephrine reuptake blockade. Nonselective NRIs, such as desipramine, have been useful as first-line treatments for depression, in patients who do not respond to SSRIs, and as adjunct therapy in severely depressed patients.[13] Reboxetine is the first truly selective NRI and was shown to be at least as effective as desipramine in a direct comparison, as measured using a range of classical rating scales.[14] Reboxetine has also been shown to be effective in both the short- and long-term treatment of depression[15]; at least as effective as desipramine, imipramine, and fluoxetine; more effective than fluoxetine in the severely ill; and more effective than fluoxetine in improving social functioning, especially in patients in remission.[15]

Severe Depression

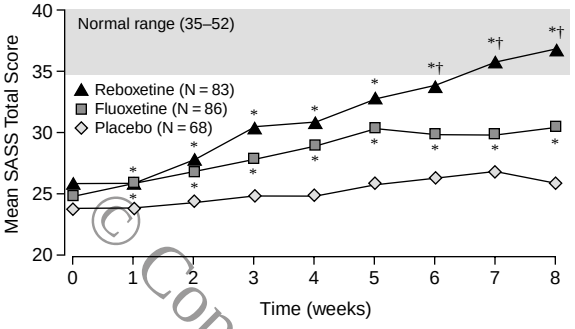
While, in general, most of the antidepressants in use today appear to be broadly comparable in their efficacy in the treatment of depressed patients, a number of questions remain. One such question is the comparative efficacy in those with severe depression, notably the efficacy of SSRIs, which has been questioned in this patient group.[16,17]

Newer antidepressants with a noradrenergic component such as mirtazapine (a noradrenergic and specific serotonergic antidepressant [NaSSA]), venlafaxine at higher doses (SNRI), milnacipran (SNRI), and now reboxetine (selective NRI) have been shown to be more effective than SSRIs in the treatment of hospitalized depressed patients and those with severe depression.[18–20] While reboxetine has been shown to be at least as effective as imipramine in this patient group (Figure 2), clear differences have been demonstrated between the selective NRI reboxetine and the SSRI fluoxetine, again in favor of the norepinephrine-selective agent[21,22] (Figures 2 and 3). This latter finding would suggest that it is not simply the addition of a noradrenergic component that results in an increased efficacy in patients with severe depression, but the noradrenergic component itself.

Social Functioning

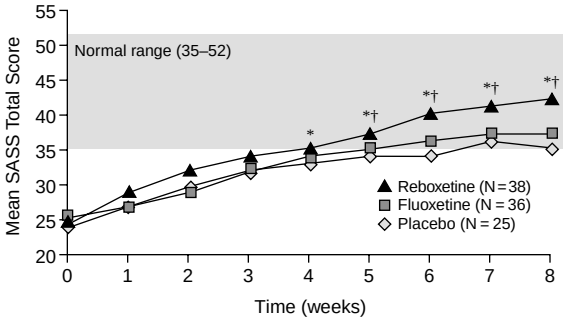
Social functioning—the ability of individuals to fulfill their social roles within their usual environment[23]—forms a key feature of quality of life. However, research in this area is complicated by poorly defined terminology and hypothetical constructs that are often used interchangeably. Comprehensive and validated rating scales are available,

Figure 4. Mean SASS Total Score in Patients Treated With Reboxetine (8–10 mg/day) vs. Fluoxetine (20–40 mg/day) or Placebo for up to 8 Weeks[a]



[a]Reproduced from Dubini et al.,[30] with permission. Abbreviation: SASS = Social Adaptation Self-Evaluation Scale.
*p < .05 vs. placebo.
†p < .05 vs. fluoxetine.

Figure 5. Mean SASS Total Score in Patients Who Achieved Symptomatic Remission Treated With Reboxetine (8–10 mg/day) vs. Fluoxetine (20–40 mg/day) or Placebo for up to 8 Weeks[a]



[a]Reproduced from Dubini et al.,[30] with permission.
*p < .05 vs. placebo.
†p < .05 vs. fluoxetine.

and a number of antidepressants have been examined in terms of efficacy in improving social functioning. Evidence is emerging of differential effects between the antidepressant classes.

A number of antidepressants have been shown to have superior efficacy in social functioning compared with placebo. Studies with the TCAs imipramine and desipramine and the MAOI phenelzine have all suggested that antidepressant therapy is more effective than placebo in relieving psychosocial impairments in those patients who respond to treatment,[24–26] while for other agents (e.g., fluoxetine) the evidence is less clear.[27]

A new rating scale, the Social Adaptation Self-Evaluation Scale (SASS),[28] has recently been developed to determine patient perception of social functioning during antidepressant therapy. This scale has been used in 2 clinical trials in which reboxetine was compared with fluoxetine and, in one study, with placebo.[29,30] In the placebo-controlled study, statistically significant differences were detected in favor of both active treatments compared with placebo[29,30] (Figure 4). In addition, patients who received reboxetine and achieved symptomatic remission experienced statistically significantly greater improvements than did those who received fluoxetine (Figure 5). This finding reflected more than a simple difference in the efficacy of the 2 drugs in the study sample, since those patients who received reboxetine and achieved symptomatic remission still fared significantly better than those who received fluoxetine and achieved symptomatic remission. Furthermore, the difference between the active treatments remained statistically significant. Thus, reboxetine appears to offer a better quality of remission in the patients' own perception of their recovery in terms of social functioning than does fluoxetine. These differences extended to individual items within the SASS scale. In the overall population, 9 items differentiated reboxetine from fluoxetine (e.g., community involvement, social attractiveness, interest in hobbies), and 14 items differentiated between the 2 treatments in patients in remission (e.g., family-seeking behavior, relationship-seeking behavior, work enjoyment).[30] Interestingly, no significant differences were detected between the active treatments when HAM-D total scores were examined.[22] These findings were replicated in the active treatment–controlled study, in which the results again favored patients who had received reboxetine.[23]

The availability of a selective noradrenergic agent, such as reboxetine, will allow us to examine in more detail the differential effects of the noradrenergic and serotonergic systems on social functioning.

CONCLUSIONS

In answer to the question initially posed, not all antidepressants are the same. Evolving evidence suggests that subtle but clinically relevant differences exist among these agents in efficacy and therapeutic profile. Improving our understanding of these differences and their relative importance to patients will serve to aid physicians in their choice of agent for the treatment of this debilitating and costly condition.

Drug names: clomipramine (Anafranil and others), desipramine (Norpramin, Pertofran, and others), fluoxetine (Prozac, Fluctin), mirtazapine (Remeron, Zispin), phenelzine (Nardil), reboxetine (Vestra, Edronax, and others), venlafaxine (Effexor, Efexor, and others).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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