The symptoms of depression can be improved by agents that act by various mechanisms to increase synaptic concentrations of monoamines. This finding led to the adoption of the monoamine hypothesis of depression, first put forward over 30 years ago, which proposes that the underlying biological or neuroanatomical basis for depression is a deficiency of central noradrenergic and/or serotonergic systems and that targeting this neuronal lesion with an antidepressant would tend to restore normal function in depressed patients. The hypothesis has enjoyed considerable support, since it attempts to provide a pathophysiologic explanation of the actions of antidepressants. However, in its original form it is clearly inadequate, as it does not provide a complete explanation for the actions of antidepressants, and the pathophysiology of depression itself remains unknown. The hypothesis has evolved over the years to include, for example, adaptive changes in receptors to explain why there should be only a gradual clinical response to antidepressant treatment when the increase in availability of monoamines is rapid. Still, the monoamine hypothesis does not address key issues such as why antidepressants are also effective in other disorders such as panic disorder, obsessive-compulsive disorder, and bulimia, or why all drugs that enhance serotonergic or noradrenergic transmission are not necessarily effective in depression. Despite these limitations, however, it is clear that the development of the monoamine hypothesis has been of great importance in understanding depression and in the development of safe and effective pharmacologic agents for its treatment.

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Reserpine produces sedation and motor retardation in animals, symptoms that are thought to be related to depression in humans. In both humans and animals, these symptoms were reversible on cessation of reserpine treatment. Monoamine precursors can also be used to reverse reserpine-induced symptoms. Administration of the nor-epinephrine precursor dihydroxyphenylalanine (DOPA), but not the serotonin precursor 5-hydroxytryptophan, was effective at reversing reserpine-induced changes in an animal model of depression. DOPA was also observed to reverse the psychological effects induced by reserpine in humans. Taken together, such findings are supportive of a biochemical basis for depression.

Further evidence came from the serendipitous discovery that iproniazid, an antitymocobacterial agent, improved mood in tubercular patients with depression. Isoniazid and its isopropyl derivative iproniazid were developed in 1951. A year later, iproniazid was found to inhibit monoamine oxidase (MAO)—the mitochondrial enzyme that degrades free monoamines in the presynaptic nerve terminal—thus preventing the degradation of serotonin and nor-epinephrine. Subsequently, iproniazid was also found to be effective against depression in non tubercular depressed patients, and further monoamine oxidase inhibitors (MAOIs) were developed for the treatment of depression. Notably, these agents produced increased levels of norepinephrine and serotonin in the brain, which correlated with behavioral excitation. Such findings indirectly supported the hypothesis that the antidepressant effects of MAOIs were due to an increase in monoamine levels.

IMPACT ON DEVELOPMENT OF ANTIDEPRESSANTS

The development of imipramine, a tricyclic antidepressant (TCA) that did not inhibit MAO, initially cast doubt on the monoamine hypothesis. Imipramine was originally developed as an anxiolytic for use in agitated psychotic patients. It was ineffective in this regard, but had a remarkable effect on certain patients with concomitant symptoms of depression. In experimental systems it appeared to act by inhibiting the reuptake of norepinephrine and sero-tonin, peripherally and centrally. Subsequently, a number of TCAs were developed that inhibited serotonin and/or norepinephrine reuptake to varying degrees, though none is completely specific for one neurotransmitter.

Although the TCAs have been used effectively for many years in the treatment of depression, the nonspecific actions of TCAs at neurotransmitter receptor sites lead to a range of undesirable adverse effects such as drowsiness, sedation, hypotension, dry mouth, constipation, blurred vision, urinary retention, arrhythmia, and confusion. In addition, the TCAs can be fatal in overdose. The development of newer antidepressant agents has thus aimed to improve on the safety and tolerability profile of the TCAs. Therefore, reuptake inhibitors have been developed that are selective to a single monoamine system. Fluoxetine, sertraline, paroxetine, fluvoxamine, and citalopram are selective inhibitors of the serotonin reuptake transporter; nometesine (though no longer on the market) is selective for the dopaminergic system; and reboxetine represents the first selective norepinephrine reuptake inhibitor (selective NRI). Other agents, in particular venlafaxine and mirtazapine, have also been developed that enhance monoamine activity in more than one system.

While previous classes of antidepressants had been discovered serendipitously, the selective serotonin reuptake inhibitors (SSRIs) were designed from the outset. Key requirements were inhibition of serotonin (but not norepi-nephrine) reuptake and avoidance of the condensed ring structure of the TCAs, which was thought to be at least partly responsible for the affinity of TCAs for muscarinic, adrenergic, and histaminergic receptors and thus for some of their unwanted adverse effects. The SSRIs have been shown to be effective, not only in depression, but also in obsessive-compulsive, anxiety, and panic disorders. In particular, they are effective in a number of patients previously resistant to therapy. They are generally better tolerated than the TCAs, but can cause headache, nausea and vomiting, and sexual dysfunction.

Though the SSRIs are effective across a broad range of patients, their relative efficacy in severe depression is controversial. This may not be the case with the selective NRIs. For example, reboxetine, the first of these agents, has shown superior efficacy to fluoxetine in the treatment of patients with severe depression.

PROBLEMS WITH THE MONOAMINE HYPOTHESIS

There are several major issues that the monoamine hypothesis does not address. One of these is the delay in onset of the antidepressant effect common to all antidepressant drugs. Whereas SSRIs usually inhibit the serotonin transporter within hours, it takes several weeks before the antidepressant effect becomes apparent. This phenomenon is a matter of concern in clinical practice, because the adverse effects of these agents are manifest within hours or days, while their antidepressant action is delayed, causing considerable problems with compliance.

Some antidepressants act as agonists for the neurotransmitter receptors on the postsynaptic membrane. These include the atypical antidepressants buspirone and gepirone and the TCAs that bind to the 5-HT1A receptor. Short-term use of these agents results in reduced neuronal firing—as a consequence of their binding to somatodendritic receptors—which is overcome by sustained treatment. Some antidepressants bind to neurotransmitter receptors nonspecifically, particularly to the histaminergic and muscarinic receptors. As described above, the newer
antidepressants tend to have lower affinities for these receptors (by design), and this is linked to their lower incidence of adverse effects. 16,23

The original hypothesis has evolved to include our understanding of the regulation of neurotransmitter release by autoreceptors. Studies on the intracellular events that follow receptor binding are in their early stages; they will no doubt further expand our understanding of depression and the role of monoamines and their receptors in its etiology. The effects of the various classes of antidepressants on these receptors, most of which are linked to G proteins, are only beginning to be unraveled. Despite differences, they share some transduction pathways—in this regard there is emerging evidence of an interaction or “cross-talk” between neurotransmitter systems at the intracellular level, such that binding at one type of receptor influences events at another (Figure 1). 24

**SUMMARY**

In conclusion, the original hypothesis of enhanced central monoamine activity has led to the development of many safe and effective antidepressant agents. At the dawn of the new millennium, however, it is clear that the original hypothesis is inadequate in the light of the scientific and clinical evidence.

**REFERENCES**


**Drug names:** buspirone (BuSpar), citalopram (Celexa, Cipramil, and others), fluoxetine (Prozac, Fluclit), fluvoxamine (Luvox, Faverin, and others), isoniazid (Rifamate and others), mirtazapine (Remeron, Zispin, and others), paroxetine (Paxil, Seroxat, and others), reboxetine (Vesta, Edronax, and others), sertraline (Zoloft, Lustral), 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.