ABSTRACT

Major depressive disorder (MDD) is a complex condition resulting from numerous genetic and physiologic factors. This article reviews the neurochemical mechanisms underlying MDD, summarizes recent genetic findings, and examines the efficacy of various treatments. The norepinephrine (NE) and serotonin (5-HT) pathways affect several areas of the nervous system that are disrupted in MDD, and agents that increase levels of either NE (NE reuptake inhibitors [NRIs]) or 5-HT (selective serotonin reuptake inhibitors [SSRIs]) are known to be effective in alleviating MDD symptoms. The dual-action hypothesis suggests that drugs affecting both neurotransmitters simultaneously (serotonin norepinephrine reuptake inhibitors [SNRIs]) may have a greater therapeutic effect in some patients than either NRIs or SSRIs alone. Literature shows that this hypothesis is valid, but the magnitude of the effect is smaller than might be predicted, possibly because of genetic heterogeneity among patients or differences in selectivity among the various SNRIs, and because modulation of 5-HT and NE activity does not entirely explain the pathophysiology of MDD. Until it is possible to select patients who are more likely to respond to specific classes of drugs based on certain genes or biomarkers, data suggest that dual-acting antidepressants are slightly more effective than those that are selective for a single neurotransmitter in the treatment of patients with MDD.

INTRODUCTION

In the past 50 years, there has been an exponential increase in research aiming to elucidate the neurochemical mechanisms responsible for major depressive disorder (MDD). Many plausible hypotheses have been proposed but subsequently found lacking. Much early work investigated the possible causal roles for abnormalities of the brain serotonin (5-HT) and/or norepinephrine (NE) pathways, largely driven by the marked therapeutic success of 5-HT and NE reuptake inhibitors in the treatment of MDD. However, incremental progress in the neurosciences and clinical investigation along with the rapid development of methods for genetic research has led to a set of more complex causal hypotheses. For example, research suggests that MDD is what geneticists define as a “complex” disease, where illness results from the summation of numerous genetic and environmental
factors, each of which have small effects and result in illness only when their combined effects surpass a certain threshold. If true, then biochemical and genetic causes of MDD may differ markedly among patients, similar to how genetic and physiologic underpinnings of hypertension or diabetes differ among patients. This concept may explain the sometimes inconsistent results in research studies investigating specific biochemical abnormalities in MDD and the outcome of studies testing specific treatments for MDD. The shift to conceptualizing MDD as a complex disorder has also resulted in the current movement to identify more homogeneous subgroups of patients with MDD or endophenotypes. Finally, if there is great variability in the underlying biochemistry and genetics among patients with MDD, then it may be expected that when studying a large group of people, medications with a broader pharmacologic profile should demonstrate a broader efficacy profile.

Although research suggests various causes for MDD, the opposite finding can be applied for how antidepressants function. Most or all drugs currently approved by the United States Food and Drug Administration for MDD treatment directly or indirectly increase the synaptic availability of 5-HT and/or NE. The observation that only ~33% of patients achieve remission with currently available antidepressants suggests that modulating 5-HT and NE neurotransmission is not sufficient to resolve MDD for all patients or to fully explain MDD pathophysiology; treatments based on different mechanisms merit further investigation. Nevertheless, agents that increase the availability of NE (norepinephrine reuptake inhibitors [NRIs], 5-HT (selective serotonin reuptake inhibitors [SSRIs]), or both neurotransmitters (serotonin norepinephrine reuptake inhibitors [SNRIs]) can alleviate MDD symptoms. The NE and 5-HT pathways are both involved in nervous system functions that are disrupted in MDD, including mood (limbic areas and frontal cortex); emotion and anxiety (limbic areas); attention and cognition (prefrontal cortex); appetite, sex drive, sleep, and pleasure (hypothalamus and brainstem); and somatic symptoms (limbic areas and spinal cord). Therefore, the possibility that antidepressants whose effects involve both 5-HT and NE pathways may have a qualitatively different or quantitatively greater therapeutic effect is the essence of the dual-action hypothesis. This article reviews basic science and human research on the neurobiology of antidepressants relevant to the dual-action hypothesis of antidepressant action.

NEUROBIOLOGICAL UNDERPINNINGS OF THE DUAL-ACTION CONCEPT

The brain’s emotion and cognition circuits play a central role in mediating the symptoms that define mood disorders. The relevant areas and circuits comprise the structures historically referred to as the limbic system, although it is now believed that the original concept of the limbic system as emotion circuits separate and distinct from cognition circuits was not complete—these circuits are now believed to significantly overlap and interact with each other. The emotion and cognition circuits most relevant to mood disorders predominantly comprise local circuits within and along hierarchical circuits between specific regions of the brain, including the prefrontal cortex, cingulate gyrus, amygdala, hippocampus, insula, ventral striatum, thalamus. Mood disorders most likely result from dysfunction of either the neurons that comprise these emotion and cognition circuits or the neurochemical systems that modulate their function. Regardless of circuit malfunction cause, it is important to remember that these brain structures and circuits are the most likely proximal mediators of the alterations in emotions, cognitions, and behaviors that define mood disorders. Although other neurochemical mediators (eg, glutamate, γ-aminobutyric acid) play an equal or greater role in the firing of these circuits, the role of 5-HT and NE systems in modulating emotion has attracted the interest of researchers in part because they are almost exclusively organized as large systems of single-source divergent neurons able to simultaneously coordinate neural activity across many parts of the brain, particularly limbic and cognition circuits. In addition, the unique organizational structure of the 5-HT and NE systems is ideally suited for modulating emotion, attention, cognition, and certain aspects of sensory perception.

The NE neurons in the central nervous system originate from several distinct nuclei in the brainstem and project rostrally to almost all areas of the mid- and forebrain, dorsally to the cerebellum, and caudally to the lumbar segments of the spinal cord. Approximately 50% of all central nervous system NE cell bodies originate from the locus coeruleus (LC) in the dorsal pons, which is acutely sensitive to novel stimuli and activated by a variety of stressful and aversive conditions. The LC influences arousal and is involved in the process of using working memory to regulate behavior and attention and shifting attention. NE projections to the amygdala are thought to play an important role in the acquisition of new memories, especially those that are emotionally arousing, while NE projections to the thalamus and spinal cord are important in the modulation of both central and peripheral nervous system aspects of pain and pain perception. The 5-HT system is the largest cohesive neurotransmitter system in the brain, and 5-HT neurons innervate all areas of the brain. There are two major subdivisions: the ascending and the descending arms. The descending arm projects to the spinal cord and is involved in pain perception. Limbic brain regions (hippocampus, amygdala, and temporal lobes) and areas involved in sensory transmission and pain (thalamus) are heavily innervated by the ascending arm, while motor areas of the frontal cortex receive much lower levels of innervation. The 5-HT-containing neurons terminate in both classical syn-
aptic connections and nonsynaptic terminals, such that some 5-HT release may be independent of cell firing, accounting for some of the discrepancies between measures of 5-HT levels and changes in firing rate of 5-HT neurons after stress. Preclinical studies in laboratory animals demonstrate that altering the function of the 5-HT system alters many of the behaviors and somatic functions that form the core symptoms of MDD, including appetite, sleep, sexual function, pain sensitivity, body temperature, and circadian rhythms.

Although the NE and 5-HT systems have overlapping projections, major differences in the physiologic function and regulation of these systems exist, and this has implications for how they differentially modulate behavior. In some target brain areas, such as the frontal cortex, NE decreases spontaneous neuronal activity while augmenting activity evoked by afferent stimulation, increasing the “signal/noise” ratio. In contrast, 5-HT neurons fire similar to a pacemaker, with no change in firing rate in response to novelty. For example, if a freely moving cat is exposed to an environmental stressor (eg, pain), the firing rate of 5-HT neurons does not change, while, in contrast, the rate of firing of NE neurons increases. However, physical activity, and more specifically, repetitive motor activity (eg, grooming behaviors) markedly increases the firing rate of 5-HT neurons.

Additionally, there are significant differences in the physical structure of NE and 5-HT neurons and the timing of their maturation during development. There are two distinct types of 5-HT nerve terminals. Nerve fibers from the dorsal raphe have a fine morphology with small granular varicosities and respond more to drugs that stimulate 5-HT receptors, while fibers from the median raphe are coarse with large spherical varicosities and have a lower response to drugs that stimulate 5-HT receptors. The LC neurons demonstrate >4 distinct cell types. The NE neurons mature later in development than 5-HT neurons, and aging produces a loss of ~30% to 40% of NE neurons, whereas 5-HT neurons are less changed.

SSRIs were the first cohort of designer antidepressants that selectively bound to and blocked the 5-HT transporter. Several NE selective drugs were also developed (eg, atomoxetine, reboxetine); however, clinical trials of atomoxetine failed to demonstrate antidepressant benefits, and results of reboxetine clinical studies showed only modest benefits. Therefore, neither drug is currently FDA-approved as an antidepressant. Subsequently, monoamine selective “dual-action” drugs, which potently block both 5-HT and NE reuptake (eg, venlafaxine, duloxetine, and milnacipran), were developed and found to be effective. All current SSRIs and SNRIs bind selectively to the 5-HT and/or NE transporters, with low or minimal affinities for other receptors and transporters (eg, muscarinic, histamine, adrenergic, dopamine [D], opiate, and γ-aminobutyric acid). For example, venlafaxine exhibited no significant affinity for muscarinic, cholinergic; α1-, α2-, and β-adrenergic; histamine (H1); 5-HT1A; 5-HT2; D2; or opiate receptor binding sites. Duloxetine also inhibited 5-HT and NE uptake but was a weak inhibitor of D uptake in rat brain synaptosomes, and it exhibited a lack of affinity for muscarinic acetylcholine; H1; α1-, α2-, and β-adrenergic subtypes of 5-HT1A (A,B,C, and D), 5-HT2, D2, and opiate receptors. Milnacipran inhibited 5-HT and noradrenaline uptake in rat brain tissue and showed no affinity for α1-, α2-, β-adrenergic; D2; serotonergic (5-HT1A or 5-HT2); muscarinic; H3; or benzodiazepine receptors. The recently FDA-approved drug desvenlafaxine also demonstrated selective inhibitory activity of 5-HT and NE neurotransmitter uptake; no significant affinity to 96 targets, including receptors, transporters, enzymes, and channels; and no significant affinity besides 5-HT and NE monoamine transporters.

There may be important differences and similarities in the pharmacologic properties of SSRIs and SNRIs. For example, the SSRI sertraline shows high affinity for the D transporter, suggesting that, at higher doses, D reuptake blockade may occur in some patients. Similarly, data suggest that paroxetine may have sufficiently high affinity for the NE transporter for it to be a factor in some patients taking higher doses. Additionally, the selectivity ratios for 5-HT and NE transporter binding differ among the various SNRIs (Table). Desvenlafaxine exhibits a Kᵣ ratio of 1:30 as demonstrated by its inhibition of specific radioligand binding to human NE and 5-HT transporters with Kᵣ values of 2480 and 82 nM, respectively. Duloxetine shows a Kᵣ ratio of 1:9 based on its inhibition of specific radioligand binding to NE and 5-HT human transporters with Kᵣ values of 7.5 and 0.8 nM, respectively. Desvenlafaxine has a Kᵣ ratio of 1:14 as determined by its inhibition of specific radioligand binding to NE and 5-HT human transporters with Kᵣ values of 558 and 40 nM, respectively. Although milnacipran is largely regarded as a noradrenergic drug, it inhibits binding of NE and 5-HT nearly equipotently (1:2 ratio). It is important to note that the findings of such preclinical studies can vary considerably, likely as the result of the different methodologies.

ANTIDEPRESSANT EFFICACY OF SELECTIVELY INCREASING BRAIN SEROTONIN AND/OR NOREPINEPHRINE

The most compelling evidence for the role of 5-HT and NE in antidepressant effects is that medications designed to selectively increase one or both of these neurotransmitters are effective in treating MDD. To date, the same cannot be said for any other pharmacologic property. The first antidepressants (tricyclic antidepressants [TCAs] and monoamine oxidase inhibitors [MAOIs]) possess a plethora of pharmacologic effects, but newer antidepressants were specifically designed to have a much narrower profile. These drugs did not share any of the adrenergic, histaminergic, or cholinergic receptor antagonist properties of TCAs but retained the monoamine reuptake inhibition.
employed to evaluate reuptake inhibition. Further, uncertainty exists about the exact relationship between in vitro binding affinity and the magnitude of inhibition achieved in vivo and even more so, how that relates to clinical effects. However, the ratio of 5-HT and NE reuptake inhibition could lead to differences in effects on central and peripheral targets. For example, venlafaxine appears to affect 5-HT and NE uptake inhibition sequentially over its dose range such that, at both low and high doses, platelet 5-HT uptake is inhibited, whereas the pressor effect to tyramine is less blunted at low versus high doses of the SNRI. Duloxetine, with a relatively more balanced NE:5-HT ratio, was found to affect functional consequences of reuptake inhibition, such as decreased whole blood 5-HT levels, increased sympathetic tone, and decreased whole body NE turnover in studies of healthy volunteers.

Another approach to measuring the effects of antidepressants on brain monoamines is to use microdialysis. Studies in living animals with implanted microdialysis probes show that antidepressants generally increase monoamine levels in various brain regions within minutes of peripheral administration. SSRIs tend to selectively increase 5-HT, while NRIs tend to selectively increase both NE and D. SNRs increase the concentration of 5-HT and NE in central nervous system areas within 30–60 minutes of administration. For example, administration of venlafaxine 3–30 mg/kg subcutaneous led to a dose-dependent increase in extracellular NE in the rat frontal cortex with an increase over preinjection levels of 403% at the 30 mg/kg dose. In contrast, desvenlafaxine 10 and 30 mg/kg treatment led to a 96% (P=.0221) and 118% (P=.0034) increase above baseline, respectively, in rat hypothalamic extracellular NE concentrations in the hypothalamus.

One interesting aspect of microdialysis data is that levels of 5-HT are generally lower after acute dosing compared with much higher levels found after chronic administration. This phenomenon is thought to be due to an initial reduction in firing rate of 5-HT neurons via stimulation of 5-HT1A receptors that desensitize over time. The NE release after chronic administration of NRI and SNRIs tends to change less over time, although blocking feedback inhibition of neuronal firing with α2-adrenergic receptor antagonists will markedly increase NE release in the presence of the reuptake inhibitor.

**5-HT OR NE DEPLETION REVERSES CLINICAL ANTIDEPRESSANT RESPONSES**

While “downstream” changes in neuroplasticity may be the final changes mediating antidepressant efficacy, neurotransmitter depletion studies in humans suggest that the initial effects on NE and 5-HT may be necessary for the therapeutic effects of many current drugs. Selective depletion of 5-HT causes a rapid MDD relapse in depressed patients having had therapeutic responses to and maintained on serotonergic antidepressants. The relapse is qualitatively similar to before treatment MDD and correlates with the time course of monoamine depletion, and patients improve rapidly as monoamine content returns to baseline levels. Although similar results have been demonstrated with NE depletion in responders to noradrenergic antidepressants, it is important to note that similar studies have not yet been conducted with SNRI antidepressants.

Depletion studies suggest that the 5-HT and NE effects of antidepressants may be independent of each other. For example, depleting 5-HT causes a rapid MDD return in depressed patients who have responded to fluoxetine, fluvoxamine, MAOIs, and imipramine but not in those who have responded to desipramine, nortriptyline, or bupropion. Depleting NE and D causes a rapid MDD return in those depressed patients who have improved on desipramine and mazindol but not on fluoxetine. The selectivity seen in neurotransmitter depletion studies argues against a single monoamine as being responsible for the therapeutic actions of antidepressants. Noteworthy in these studies, symptoms of MDD appeared within ~5–24 hours after depletion; furthermore, patients recovered rapidly (within 48 hours) after testing was concluded. Neither 5-HT nor NE depletion resulted in MDD symptoms in nondepressed volunteers. In a randomized, double-blind, crossover trial, Shansis and colleagues examined the effect of tryptophan on mood, memory, attention, and induced anxiety in 12 healthy male volunteers. None of these parameters was affected by 5-HT depletion. Likewise, NE depletion in eight healthy volunteers failed to provoke symptoms of depression. Additionally, patients who were experiencing an MDD episode did not experience worsened symptoms with 5-HT or NE depletion.

**TABLE PHARMACOLOGIC CHARACTERISTICS OF THE SNRIS**

<table>
<thead>
<tr>
<th>SNRI</th>
<th>5-HT:NE Selectivity Ratio</th>
<th>Clinical Indication(s)</th>
<th>Metabolic Pathway(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desvenlafaxine</td>
<td>1:14</td>
<td>MDD</td>
<td>Conjugation</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>1:9</td>
<td>MDD, GAD, DPNP, Fibromyalgia</td>
<td>CYP 1A2, CYP 2D6</td>
</tr>
<tr>
<td>Milnacipran</td>
<td>3:1</td>
<td>MDD, Fibromyalgia</td>
<td>Conjugation</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>1:30</td>
<td>MDD, GAD, SAD, Panic disorder</td>
<td>CYP 2D6</td>
</tr>
</tbody>
</table>

SNRIs=serotonin norepinephrine reuptake inhibitors; 5-HT=serotonin; NE=norepinephrine; MDD=major depressive disorder; CYP=cytochrome P450; GAD=generalized anxiety disorder; DPNP=diabetic peripheral neuropathic pain; SAD=social anxiety disorder.

Data gleaned from monoamine depletion studies suggests that a simple deficiency of 5-HT or NE is not likely to be the sole cause of MDD. It is hypothesized that MDD is linked to dysfunction of brain areas, such as the frontal cortex, hippocampus/amygdala, and basal ganglia, known to be modulated by monoamine systems. Increased monoamines after treatment with SSRIs and NRIs may serve to partially restore neuronal function in these affected brain areas. The acute reappearance of MDD symptoms on monoamine depletion in MDD patients in remission may underscore the fragility of these neuronal networks.

DOWNSTREAM EFFECTS, INTRACELLULAR SIGNALING, AND NEURAL PLASTICITY

Because most antidepressants increase monoamine levels within hours but clinical response can take weeks, investigators have searched for the adaptive changes in various brain areas that temporally correspond with the clinical data. A chronic increase in the synaptic concentration of NE and 5-HT with antidepressants is associated with changes in β-adrenergic and 5-HT receptor density and/or sensitivity. These changes are common to most antidepressants, irrespective of whether they are NRIs, SSRIs, or SNRIs, and therefore are more likely to reflect the underpinnings of shared therapeutic or side effect profiles.

The ability of chronic antidepressant treatment to downregulate monoamine receptors appears to be associated with changes in neuronal function. This has been observed in experiments whereby chronic administration of antidepressants led to inhibition of microiontophoretically administered NE or 5-HT depression of cortical neuron firing. Again, investigators have focused on finding a single common characteristic unifying antidepressants, thereby focusing on the characteristics most likely shared across various antidepressant families rather than those that may distinguish one drug or category of drug from another.

Neural plasticity, involving changes in intracellular signal transduction pathways, gene expression, neuronal morphology, and cell survival, may play an important role in the etiology and treatment of MDD. Areas of the brain shown to be altered with MDD and stress include the hippocampus and prefrontal cortex. In the hippocampus, these changes include a decreased number and size of rodent CA3 neurons, decreased neurogenesis of rodent granule cells, and an overall decrease in hippocampal volume. Changes in the prefrontal cortex include a decrease in the number and size of neurons, decreased number of glia, and decreased volume of the subgenual prefrontal cortex.

Hippocampal volume has been shown to be reduced in patients with mood or anxiety disorders, including post-traumatic stress disorder and MDD. In a study of 30 inpatients with MDD, men with a first episode of MDD exhibited significantly smaller left gray matter hippocampal volume than that of healthy male subjects (P<.02). In addition, both male and female patients showed significantly smaller hippocampal white matter (P<.008) as well as significant left-right asymmetry versus healthy male and female subjects (P=.001). In a separate study of 38 female outpatients with recurrent MDD in remission, mean left, right, and total hippocampal gray matter was significantly smaller than that of healthy subjects (P=.005). In the MDD patient population, those patients who experienced longer durations during which MDD episodes went untreated showed a significant reduction in left (P=.0005) and right (P=.003) hippocampal volume.

Chronic treatment with antidepressants increases the proliferation and survival of new neurons in the hippocampus. Malberg and colleagues showed that chronic antidepressant treatment significantly increases the number of dividing cells in the dentate gyrus and hilus of the hippocampus. Two-week treatment with fluoxetine increased pyramidal cell dendritic spine formation in the hippocampal CA3 field, suggestive of hippocampal remodeling. Behaviorally, in rats exposed to inescapable stress associated with decreased cell proliferation of the hippocampus, this could be reversed by fluoxetine treatment. In addition, X-ray irradiation of hippocampal regions of the mouse brain (which prevents neurogenesis) blocked the behavioral and neurogenic effects of chronic antidepressant treatment with fluoxetine or imipramine. Recent work using X-ray irradiation to block neurogenesis, and therefore determine whether it was necessary for various stress and antidepressant-mediated behaviors, extends these findings. The adverse behavioral effects of unpredictable chronic, mild stress were not blocked by X-ray treatment, suggesting that reduced neurogenesis was not the cause of the stress-related behaviors. However, as in prior studies, the ability of either fluoxetine or imipramine to reverse the behavioral effects of unpredictable chronic, mild stress was blocked. These data suggest that, at least in certain animal models of MDD, neurogenesis was required for the antidepressant response. Also, existing data show little quantitative differences in amount of neurogenesis among NRIs, SSRIs, and SNRIs.

MDD AS A GENETICALLY COMPLEX DISORDER

New research has led to important questions about the very nature of the construct of MDD. The modern construct of MDD evolved from an attempt to improve the reliability of clinical diagnosis and communication among clinicians and researchers. To that end, it has been effective, and considerable research supports the clinical validity of MDD. However, as for many other disorders in medicine, overinclusive definitions increase the likelihood of greater heterogeneity of environmental and genetic causal pathways. Some suggest that some or all of the difficulty in identifying the genetic or neurobiological basis for MDD is related to how broadly this condition is defined. If the definition of a condition is overly broad, it may include a large group of underlying conditions that happen to share some of the symptoms used to define the index condition but have different neurobiological origins. Such a situation would make it unlikely that any given
study investigating underlying causal factors would identify a single biological abnormality or set of genes. Additionally, heterogeneity will likely influence qualitative and quantitative aspects of treatment response as well as the tolerability of treatments.

The possibility that MDD includes a large number of etiologically narrower subtypes that share some but not all the characteristics is not new. The bipolar-unipolar distinction and the subtypes of melancholic, seasonal, atypical, psychotic, brief recurrent, postpartum, childhood onset, early and late adult onset and double are some prominent examples of attempts to define narrower subtypes that may be more homogeneous. More research is needed to determine if some of these proposed subtypes are sufficiently distinct to warrant being formally designated as a separate condition or a causally-distinct subtype.

New methods for measuring genetic differences between people have fueled much research into individual genetic differences that contribute to risk of major mental disorders, as well as treatment response and safety. This exponentially growing body of research suggests that individual differences in genetically determined biological factors may underlie differences among people in therapeutic drug responsiveness and treatment-related adverse events. Much of the current work in this regard has focused on small variations in the genetic sequence for genes, such as single nucleotide polymorphisms and restriction fragment length polymorphisms, but new research suggests that larger structural variation may be more common among people. Complicating this research, many polymorphisms do not modify gene function while genetic variation in distant sites or rare variants can sometimes alter the expression of gene products, justifying the measurement of gene expression using microarrays. The number of highly idiosyncratic variables that could modify gene expression, or subsequent protein synthesis as well as the possible interactions between different genetic variants in different people, markedly raises the levels of complexity and suggests that investigators and clinicians will need to be patient as this research continues to unfold and mature. Its full implications extend beyond psychiatry and are generally discussed under the rubric of “personalized medicine.” The lack of methods and/or resources to simultaneously consider all of the polymorphisms and structural genomic variations among people is most likely responsible for the high degree of variability in prior study outcomes of the effect of single genetic polymorphisms and antidepressant treatment response. However, it is worth noting that some studies (although other studies have not confirmed these findings) have found significant associations between antidepressant treatment response and genetic polymorphisms of the NE and D transporters, the 5-HT transporter promoter 5-HT, catecol-O-methyltransferase, enzymes, corticotropin-releasing hormone signaling systems, glucocorticoid receptor, and the propeptide region of the brain-derived neurotrophic factor gene. Antidepressant side effects have been associated with polymorphisms of the 5-HT and the cytochrome P450 isozymes.

CONCLUSION

The literature reviewed strongly suggests that increasing brain NE and/or 5-HT is a pharmacologic characteristic that contributes substantially to the efficacy of currently available antidepressants. This most likely includes a temporal sequence with increased monoamine levels causing alterations in presynaptic autoreceptor density and sensitivity, which allow further increases in synaptic levels of the monoamines, culminating in postsynaptic receptor adaptations and changes in neuronal plasticity and neurogenesis. The postsynaptic areas affected by these processes notably include most of the brain areas involved in emotion regulation.

Given that the projections and function of the NE and 5-HT systems are not identical, it would be anticipated that SSRIs, NRIs, and SNRIs should have marked differences in the quality of antidepressant response and tolerability, as well as the overall proportion of patients that respond. SNRIs should be effective in a larger number of patients, and patients should have a more complete response to treatment with SNRIs. However, while greater efficacy of SNRIs in MDD has been reported, the magnitude of this effect is significantly smaller than one may have predicted based on the neurobiological data. The more robust magnitude of the relative benefit of SNRIs versus SSRIs for treatment of neuropathic pain is closer to what one would have expected for MDD and is likely explained by the dual modulation of pain centers in the brain and spinal cord by NE and 5-HT.

The SNRIs as an antidepressant class exhibit affinity toward both 5-HT and NE transporter molecules, but their selectivity differs among members of the class, possibly leading to differences in their effects on central and peripheral targets. Recent advances in pharmacogenomics demonstrate that polymorphisms of gene loci involved in monoamine signaling pathways are associated with changes in the efficacy, safety, and tolerability of SNRIs. As this area of investigation matures, it may be possible to select patients who will be more likely to respond to specific classes of drugs based on the presence of certain genes or biomarkers. Until such time, data suggest that there are theoretical reasons why medications with a broader profile of effects on monoamine systems may have a slight advantage over the more neurotransmitter-selective compounds.

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