Clinical Evidence and Potential Neurobiological Underpinnings of Unresolved Symptoms of Depression

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Objective: Recent data indicate that more than 65% of patients with major depressive disorder (MDD) fail to achieve remission. This article reviews research on the current understanding and management of residual symptoms, i.e., subthreshold depressive symptoms present after recovery from a major depressive episode.

Data Sources: MEDLINE (1966 to June 2006) was searched using combinations of the following search terms: *major depressive disorder*, *residual symptoms*, *remission*, *response*, *tachyphylaxis*, *antidepressant*, *algorithm*, *treatment*, *responsiveness*, *serotonin*, *norepinephrine*, and *dopamine*.

Study Selection: All relevant articles that were published in English and reported original study data related to residual symptoms in MDD were included.

Data Extraction: Studies were examined for data related to the prevalence, presentation, consequences, treatment, and neurobiological underpinnings of residual symptoms associated with MDD.

Data Synthesis: Residual symptoms are common among patients treated for MDD who do not achieve full remission. Incomplete remission is associated with increased risk of relapse, suicide, functional impairment, and higher use of health care resources. Several factors, including "downstream" neurochemical mechanisms and clinical factors such as lack of adherence, contribute to the high prevalence of residual symptoms. Various clinical strategies, including switching and substitution antidepressant therapies, are used to address unresolved depressive symptoms. Individual differences in therapeutic response contribute to inadequate treatment and are linked to numerous clinical and neurobiological factors, including noncompliance, underdosing, intolerance, disturbances in neural circuitry, and genetic variability in neurotransmitters.

Conclusions: Future research is needed to more precisely characterize residual symptoms and their underlying biochemical and molecular mechanisms in order to develop more effective treatment methods.

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A common, disabling illness, major depressive disorder (MDD) has an estimated lifetime prevalence of about 17% in the U.S. population, according to data from the National Comorbidity Survey Replication.[1] MDD is characterized by a wide range of debilitating emotional and physical symptoms that are purported to be mediated predominantly through the serotonergic and noradrenergic pathways.[2] Although complete remission of symptoms is the goal of treatment, many patients fail to attain or maintain long-term, symptom-free status.[3] Recent findings from the National Institute of Mental Health's Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial indicate that approximately 50% of patients with MDD fail to respond to adequate first-line monotherapy with a selective serotonin (5-hydroxytryptamine [5-HT]) reuptake inhibitor (SSRI), and more than 65% fail to achieve remission.[4] Furthermore, even among patients who achieve remission, it has been estimated that more than half continue to experience 2 or more depressive symptoms.[5] Thus, residual symptoms (i.e., subthreshold depressive symptoms) persist at the end of therapy and are common among patients treated for MDD. Data are needed to understand and manage residual symptoms associated with MDD. The rates of remission remain modest even with a second-step treatment with either a switch to a new medication[6] or an augmentation with a second antidepressant agent.[7]

The objectives of this article are to (1) summarize the current understanding of the frequency of residual symptoms among patients with initial antidepressant treatment and the significance of the return of symptoms during long-term antidepressant treatment even after successful relief of symptoms during the acute phase treatment of depression (tachyphylaxis); (2) review the clinical evidence demonstrating successful approaches to managing unresolved symptoms and/or tachyphylaxis; (3) discuss potential neurobiological differences among these subgroups of patients and how these data could help guide clinical decision making; and (4) review relevant preclinical evidence exploring the short- and long-term neurobiological effects of various antidepressant strategies.

To achieve these objectives, we searched MEDLINE from 1966 to June 2006 using combinations of the following search terms: *major depressive disorder*, *residual symptoms*, *remission*, *response*, *tachyphylaxis*, *antidepressant*, *algorithm*, *treatment*, *responsiveness*, *serotonin*, *norepinephrine*, and *dopamine*. All relevant articles that were published in English and reported original study data related to residual symptoms in MDD were included. Studies were examined for data related to the prevalence, presentation, consequences, treatment, and neurobiological underpinnings of residual symptoms associated with MDD.

DEFINING RESPONSE

The primary goal of treatment of MDD is sustained remission and complete functional recovery.[3,4,8,9] Remission represents an absolute level of wellness, or an absence of symptoms, and is commonly quantified in clinical trials by such measures as a score of 7 or less on the 17-item Hamilton Rating Scale for Depression (HAM-D-17). A recent American College of Neuropsychopharmacology Task Force recommended that *full remission* be defined as an absence of both sad mood and reduced interest for at least 3 consecutive weeks in addition to the presence of 3 or fewer of the 7 remaining *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision symptoms of MDD.[8] *Partial remission* is defined as an improvement of symptoms that do not meet criteria for the disorder; however, more than minimal symptoms are present.[10]

In contrast to full remission, *response* is a relative reduction in pretreatment symptoms and is a less reliable measure of treatment outcome because it strongly depends on baseline measurement and severity of pretreatment symptoms.[8] In clinical trials, response has been typically defined as symptomatic improvement from baseline equal to or greater than 50%.[4,11] Clinical evidence indicates that many depressed patients improve with treatment but fail to attain acceptable levels of functioning and well-being; such patients experience a *partial response*, which has been defined as a 25% to 49% improvement in baseline symptoms.[11,12] *Nonresponse* is defined as less than a 25% improvement in symptoms.[11]

RESIDUAL SYMPTOMS

Frequency

Residual symptoms, i.e., subthreshold depressive symptoms present after recovery from a major depressive episode, are common among patients treated for MDD who do not achieve full remission. On the basis of long-term clinical trials of antidepressant response, Kupfer and Spiker[13] estimate that approximately two thirds of patients do not achieve full remission. Fava and Davidson[11] analyzed open-label and double-blind studies from 1993 to 1995 and found that 34% of patients met criteria for partial response or nonresponse, even after completing antidepressant therapy of adequate dose and duration. Using an intent-to-treat analysis to account for patients who may have withdrawn owing to lack of efficacy, they found that the mean rate of partial response or nonresponse increased to 46%.

Individual clinical studies have assessed the prevalence rate of residual symptoms after antidepressant treatment; however, the studies vary with respect to methodology, such as patient population, duration of treatment, treatment modality, and measurement of residual symptoms. Paykel and colleagues[14] reported that approximately 32% of 60 patients aged 18 to 65 years who remitted from MDD experienced residual symptoms. In a long-term study of 61 elderly patients with MDD, Brodaty et al.[15] observed that 38% of patients exhibited residual symptoms 1 year after remission and 20% experienced residual symptoms after 4 years. Finally, in a 4-year follow-up study of 94 female outpatients who had received treatment for acute depression, 50% of patients experienced residual symptoms after treatment with amitriptyline and psychotherapy.[16]

Type and Nature

There are currently limited data and consensus about the types of symptoms most likely to persist as residual symptoms. Several categories of residual symptoms have been reported in the literature. Based on published literature, residual symptoms associated with partial response are generally mild and typical of depressive symptoms and include anxiety, insomnia, depressed mood, sexual dysfunction, and impairment of work and activities.[14] Residual symptoms associated with continuation treatment in elderly patients include depressed mood, insomnia, apathy, anxiety, feelings of guilt, and loss of libido.[17] The most common residual symptoms present despite full remission include fatigue, irritability, sleep disturbances, generalized and somatic anxiety, decreased interest or pleasure, lassitude, and inner tension.[5,18,19] In a separate

study, depressed mood, insomnia, somatic anxiety, and diminished interest in work and activities were identified as the most common residual symptoms present in elderly patients who achieved remission.[20]

Many residual symptoms are also physical in nature. Physical symptoms, such as backache, stomachache, muscle ache, and pain in the joints and limbs, are commonly reported by depressed patients.[21] In one study, 18 of 19 patients reported residual symptoms, and more than 90% had mild-to-moderate physical symptoms, as measured by item 13 of the HAM-D-17.[14]

Consequences

The consequences of residual symptoms include increased use of health care resources and disability benefits as well as a greater risk of functional impairment and suicide.[22] Residual symptoms are also associated with an increased risk of relapse of MDD. In a longitudinal study of patients with MDD who were followed every 3 months to remission and thereafter, residual symptoms (HAM-D-17 score ≥ 8) were present in 32% of patients (19/60) who remitted. Fifteen months after remission, 76% of patients (13/17) with residual symptoms had relapsed, compared with 25% of those (10/40) without residual symptoms ($p < .001$).[14] A 1-year prospective study found that after termination of successful treatment with cognitive-behavioral therapy (CBT) for MDD, rates of relapse were approximately 54% for patients with residual symptoms and approximately 10% for asymptomatic patients ($p = .009$).[23] In a study of 237 outpatients with MDD, significantly more asymptomatic patients remained well 10 years after recovery, compared with those who had residual symptoms (34.2% vs. 13.4%, $p = .001$).[24] Compared with asymptomatic patients, those with residual symptoms relapsed to a new major depressive episode more than 3 times faster (median = 231 weeks vs. 68 weeks, $p < .0001$), and to *any* depressive episode more than 5 times faster (median = 184 weeks vs. 33 weeks, $p < .0001$). Among patients with residual symptoms, risk of early relapse was more strongly associated with residual symptoms (OR = 3.68, 95% CI = 2.64 to 5.12) than history of recurrent MDD episode (OR = 1.64, 95% CI = 1.17 to 2.29).

Summary and Unresolved Issues

Sustained remission of all symptoms with complete functional recovery is the goal of treatment of MDD; however, residual symptoms, either emotional or physical in nature, are highly prevalent among patients treated for MDD. The presence of these symptoms is linked to multiple adverse outcomes for depression and may have significant implications for selection of treatment strategies. Several key issues regarding residual symptoms remain to be resolved. First, which specific symptoms must be present in order to be considered residual? For example, does mild depressed mood need to be present, or do other secondary symptoms qualify (without mild depressed mood) as residual symptoms? Furthermore, if the patient is much better but still experiences "absence of well-being," is that considered a residual symptom? Second, how should residual symptoms be measured? Third, what are the core target symptoms for treatment? And finally, what are the treatment options for residual symptoms?

TREATMENT OF UNRESOLVED SYMPTOMS

First-Line Therapy

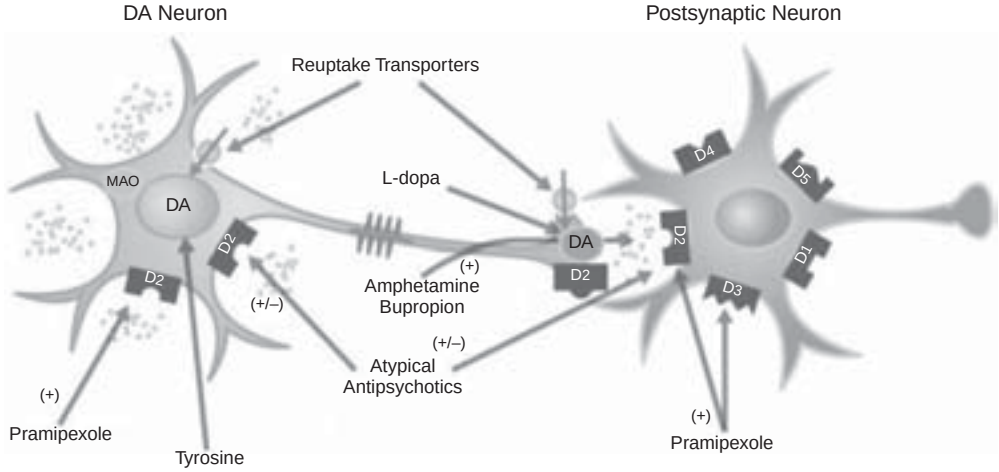
The correct choice of initial antidepressant therapy should provide the highest probability of achieving remission without residual symptoms. In clinical practice, achieving full remission often may require affecting more than 1 neurotransmitter thought to be involved in regulating mood and mediating a broad range of depressive symptoms.[25] The effects of norepinephrine, 5-HT, and dopamine overlap in the central nervous system; all 3 are involved in regulating mood, emotion, and cognition.[25] Depressive symptoms may result from dysregulation of any or all of these neurotransmitters.[25] Thus, treatment agents, such as the serotonin-norepinephrine reuptake inhibitors (SNRIs), which target 2 neurotransmitters, may offer therapeutic advantages over single-acting agents and improve responses for subgroups of patients. Several studies suggest a potential advantage for SNRIs relative to SSRIs with respect to higher remission rates,[26–29] resolution of a wide array of emotional and physical symptoms of depression,[30,31] and greater efficacy in a broad spectrum of patients, such as those depressed patients who are hospitalized[32] and those with treatment-resistant depression.[33] Few large-scale, head-to-head comparisons exist at the first antidepressant step for SSRIs versus the SNRIs. Combination antidepressants as a first step have also not been well studied.

Partial and Nonresponse

Several treatment options have been proposed for patients who do not adequately respond to an initial antidepressant trial of optimal dose and duration. Treatment strategies for partial response and nonresponse include the following: (1) increase dose and extend duration, (2) use a multineurotransmitter mechanism agent, (3) switch or substitute 1 antidepressant for another, (4) augment (add another pharmacologic agent [e.g., lithium, triiodothyronine, dopaminergic agents, atypical antipsychotics; Figures 1 and 2], although when to start and how long to continue are controversial issues), (5) combine 2 antidepressants, and (6) use somatic treatments (initiate possibly after 2 or 3 treatment failures).[34–36]

When treating incomplete remission and residual symptoms, physicians may find it beneficial to determine the neural circuits associated with specific symptoms of

Figure 1. Diagram of the Dopamine (DA) System in the Central Nervous System[a]



[a]The cell bodies of the dopamine neurons are located in midbrain; the 2 most important ones are the bilateral A9 nuclei, or substantia nigra, which innervate the striatum, and the bilateral A10 nuclei in the ventral tegmental area, which give rise to the innervation of the limbic and cortical areas. The spikes on the axon represent the firing activity of the DA neurons. The small dots around the DA neuron represent DA molecules. These neurons have autoreceptors of the D_2 and D_3 subtypes that inhibit firing at the cell body level and of the D_2 subtype on terminals that inhibit release when activated by an excess amount of DA. The effects of DA on postsynaptic neurons are mediated by a variety of receptors belonging to 5 families. The cogwheels on the cell body and terminal represent the reuptake transporters. A (+) sign indicates an agonism or a stimulatory effect and a (–) sign indicates an antagonism or an inhibitory action. L-dopa is the immediate precursor for dopamine, the former being synthesized from tyrosine by a hydroxylase enzyme, which is a rate-limiting factor.
Abbreviation: MAO = monoamine oxidase.

depression, thus identifying possible targets of action for treatment. For example, the neural circuit associated with mood change symptoms, such as anhedonia and anxiety, may be different than that involved with cognitive impairment symptoms. Therefore, by matching an antidepressant therapy to the neural circuit associated with the type of symptom present, specific neural targets can be regulated.[37] The use of augmentation agents such as bupropion (presumed to increase dopamine and norepinephrine), atypical antipsychotics (dopamine blockade, 5-HT_2 receptor antagonism), or psychostimulants (presumed to increase dopamine neurotransmission) have been suggested to enhance dysfunctional neurocircuits and likely affect multiple neurotransmitters.[7,38]

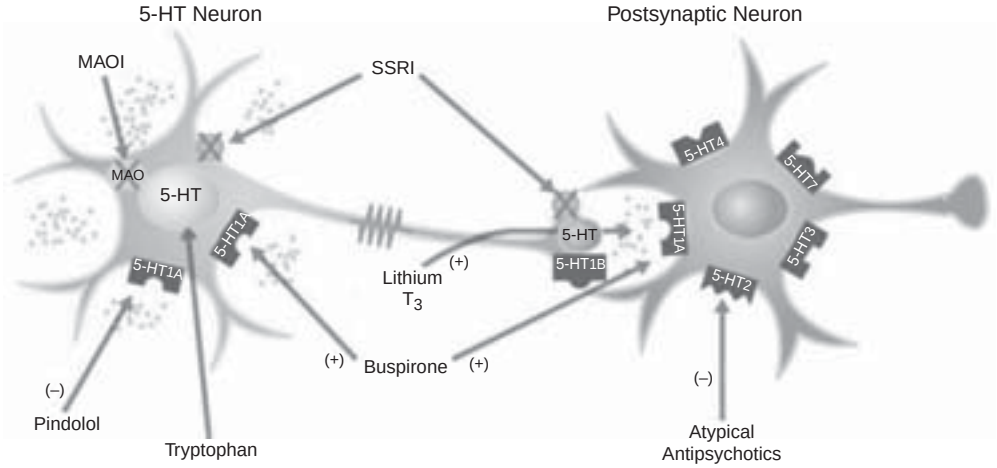
Tachyphylaxis

Some patients who initially respond to an antidepressant may not be able to sustain their response over time; that is, they experience tachyphylaxis.[39] Also referred to as "poop-out" or "breakthrough symptoms," tachyphylaxis is the emergence of a specific constellation of symptoms (e.g., emotional blunting and anhedonia) rather than a return of the full gamut of symptoms. Although the frequency of this kind of reaction is not well documented, it is sometimes found in patients taking newer antidepressants. Tachyphylaxis is sometimes associated with comorbid conditions, such as bipolar spectrum disorders.[40] Furthermore, in order to increase the clinical utility, it is important to distinguish tachyphylaxis from residual symptoms in terms of nature, frequency, number of symptoms, and, above all, the time course of the symptoms. It may also be unclear if the return of symptoms is a natural progression of the disease state rather than a lack of efficacy. Another possibility is that symptoms that emerge over time on SSRIs may reflect delayed emergence of SSRI side effects. Additional research is needed to address these issues. Suggested treatment options for tachyphylaxis have been similar to those for partial response and include increasing the antidepressant dose, using a pharmacologic combination, adding CBT, matching residual symptoms, treating potential side effects, and using pharmacologic intervention with a different mechanism of action.

Treatment Algorithms, Critical Decision Points, and Measurement-Based Care

The use of treatment algorithms, critical decision points, and measurement-based care can enhance adequacy of treatment and overall outcomes. A comprehensive, evidence-based treatment algorithm for chronic major depression can promote efficient and efficacious therapy by providing clinicians with a tool for making and simplifying treatment decisions.[36] On the basis of the Texas Medication Algorithm Project (TMAP),[34] Trivedi and Kleiber[36] recommend a flexible, step-by-step guide for the treatment of chronic depression in a broad range of patients. Each algorithm stage is accompanied by a range of critical decision points, which offer clinicians strategic

Figure 2. Diagram of the Serotonin (5-HT) System in the Central Nervous System[a]



[a]The cell bodies of the 5-HT neurons are located in several nuclei on midline of the brainstem, the most important ones being the dorsal and median raphe nuclei below the Sylvius aqueduct. The spikes on the axon represent the firing activity of the 5-HT neurons. The small dots around the 5-HT neuron represent 5-HT molecules. These neurons have autoreceptors of the 5-HT_{1A} subtype that inhibit firing when activated by an excess amount of 5-HT. The effects of 5-HT on postsynaptic neurons are mediated by distinct receptors belonging to 7 families, only 4 of which are illustrated here. Each family of 5-HT receptors has different subtypes that may be denoted from A to E. The cogwheels on the cell body and terminal represent the reuptake transporters. A (+) sign indicates an agonism or a stimulatory effect and a (–) sign indicates an antagonism or an inhibitory action. Tryptophan is the amino acid precursor for 5-HT.
Abbreviations: MAO = monoamine oxidase, MAOI = monoamine oxidase inhibitor, SSRI = selective serotonin reuptake inhibitor.

and tactical options for managing therapy. Stage 1 consisted of monotherapy with the SSRIs, bupropion sustained release, venlafaxine extended release, mirtazapine, or psychotherapy. In the absence of remission, subsequent stages include treatment with tricyclic antidepressants, combination therapy, electroconvulsive therapy, atypical antipsychotics, and novel therapies, such as vagus nerve stimulation.

In addition to TMAP, the National Institute of Mental Health's STAR*D study was an algorithm-based, clinical trial for the treatment of depression.[4] In the STAR*D treatment algorithm, patients were initially treated with an SSRI (citalopram) and then randomly assigned to 1 of 6 therapeutic options. In the absence of remission, patients were then progressively eligible to enter 3 subsequent treatment stages. To help ensure high quality, consistent care, the investigators used measurement-based care, including a treatment manual and a Web-based treatment monitoring program, to assess symptoms and tolerability. Such measurement-based tools can assist researchers and clinicians in making treatment decisions and monitoring patient progress to enhance treatment outcomes.

Summary

Treatment of MDD should maximize the probability of achieving complete remission with the first choice of therapy. When selecting an appropriate first-line antidepressant agent, the clinician should consider its mechanism of action and clinical evidence for attaining remission with the resolution of all emotional and physical symptoms of depression. For patients who do not respond adequately to therapy or who experience tachyphylaxis, several treatment options have been proposed to address unresolved symptoms. While more research is needed to better understand tachyphylaxis, it is important to distinguish residual symptoms from tachyphylaxis in order to increase clinical utility of antidepressant agents and to improve long-term treatment outcomes. Additionally, the use of measurement-based care and an evidence-based treatment algorithm for MDD, such as the TMAP decision-tree algorithm, can facilitate provision of effective treatment options and enhance response to pharmacotherapy.

CLINICAL AND NEUROBIOLOGICAL DIFFERENCES IN ANTIDEPRESSANT RESPONSIVENESS

Various factors have been linked to differences in responsiveness and endurance of effect of pharmacotherapy. Clinical factors commonly associated with poor response to antidepressant therapy include noncompliance, underdosing, adverse events (intolerability), excessive psychosocial stress, and lack of effective augmentation with psychotherapy.[41] Comorbidities, such as anxiety disorder, drug/alcohol abuse, personality disorder (Axis II), and medical illness, may also negatively impact response to antidepressant therapy, worsen prognosis, and increase the risk of suicide. Clinical outcomes

can also be significantly influenced by medication choice, as previously discussed.

Neurobiological Factors

Sleep abnormalities. In addition to clinical factors, growing evidence suggests that several neurobiological factors may contribute to differences in therapeutic response and tolerability. For example, neurobiological disturbances, such as sleep abnormalities, may play a role in responsiveness to therapy. In a prospective, case-control study of 90 outpatients who received CBT for MDD, the percentage of patients remaining well at 100 weeks following recovery was approximately 70% for patients with normal electroencephalographic sleep profiles yet only approximately 30% for patients with abnormal sleep profiles. During a 36-month prospective follow-up, sleep abnormalities were predictive of a decreased recovery rate and an increased risk of depressive recurrence.[42]

Genetic variables. Genetic variability among patients, such as variations in the CYP450 genes, has been linked to differences in clinical effects and antidepressant tolerability. The 2D6 gene, which regulates the enzymes responsible for clearing toxins from food and eliminating drugs from plasma, varies substantially among different populations. For example, Ethiopian and Saudi Arabian populations are much more likely to have multiduplicated copies of 2D6 genes compared with Westerners.[43,44] Dalen and colleagues[45] found a linear relationship between plasma levels of the drug nortriptyline and 2D6 functionality: individuals without the 2D6 gene had the highest levels of nortriptyline, while those with 13 duplicates of the 2D6 gene had the lowest levels of nortriptyline. Drug metabolism involving the 2D6 gene may contribute to treatment refractoriness. In a Swedish study by Kawanishi et al.,[46] 2 different 2D6 genotypes—extensive metabolizers and poor metabolizers—were examined, and approximately 90% of the patients who were refractory to treatment with 2D6 substrate antidepressant drugs were found to be extensive metabolizers.

Several studies suggest that the molecular mechanisms underlying response to antidepressant treatment may also include complex interactions involving the genetic regulation of neurotrophins, such as brain-derived neurotrophic factor (BDNF).[47] A target of antidepressant therapy, BDNF affects synaptic plasticity as well as the maintenance and survival of neurons.[48] Preclinical studies show that chronic antidepressant administration blocks stress-induced reductions in BDNF expression and also increases BDNF expression in the hippocampus,[47,49] a primary site of depression-induced damage, particularly in recurrent MDD.[50] The increased BDNF expression may promote hippocampal neurogenesis and neuronal sprouting.[47]

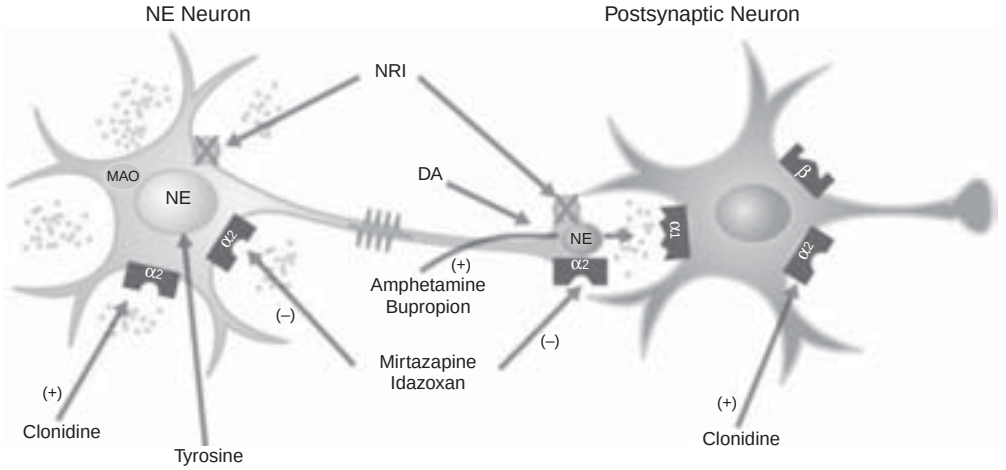
Emerging pharmacogenetic data from the STAR*D cohort[4,51] suggest that additional genetic variables may be correlated with antidepressant treatment outcomes. Recently published STAR*D findings indicate that a glutamate-receptor encoding gene may modulate response to SSRI treatment and contribute to treatment-resistant depression.[52] These preliminary data offer novel insights into the genetic correlates of depression and the mechanism of action of antidepressants. Additional research is warranted to further explore the findings and their clinical relevance.

5-HT transporters and receptors. Alterations in the function and density of brain 5-HT transporters and receptors have been associated with MDD, according to recent imaging studies, and may impact treatment outcomes. Malison and colleagues[53] were the first to find a statistically significant reduction in the density of 5-HT transporter binding sites in the brainstems of living patients with MDD compared with healthy controls. This reduction may be an adaptive response by the brain to increase 5-HT availability, and the findings provide support for the critical link between alterations in serotonergic neurons and the pathophysiology of depression (Figure 2). Sargent and colleagues[54] found that the binding potential of 5-HT_{1A} receptors was modestly but substantially reduced in several brain regions, including the frontal, temporal, and limbic cortex, in unmedicated patients with acute MDD and that this reduction remained despite successful SSRI treatment. Subsequently, the same group, Bhagwagar et al.,[55] showed that these changes persist even after recovery from MDD; their study revealed a 17% decrease in 5-HT_{1A} receptor binding potential in the cortical areas of 14 recovered male patients. While the underlying causes remain unclear, the failure of 5-HT_{1A} receptors to normalize may potentially contribute to a less than full recovery in some patients.

Interactions between 5-HT transporter genotype and exposure to stress may also impact vulnerability to depression. In a prospective longitudinal study of a representative birth cohort, Caspi and colleagues[56] examined the association between number of stressful life events and depression outcomes as a function of 5-HT transporter genotype. A functional polymorphism in the promoter region of the 5-HT transporter gene was found to mediate the effects of life stress on depression. Individuals carrying 1 or 2 copies of the short allele of the 5-HT transporter promoter polymorphism had more depressive symptoms and diagnosable depression, as well as an increased probability of suicide ideation or attempt, compared with individuals homozygous for the long form of the 5-HT transporter genotype. Thus, ongoing stress is a potential contributor to depression and the long form of the 5-HT transporter genotype may confer protection against it, possibly decreasing the probability of a major depressive episode.

Polymorphisms in the promoter region of the 5-HT transporter gene also influence antidepressant efficacy

Figure 3. Diagram of the Norepinephrine (NE) System in the Central Nervous System[a]



[a]The cell bodies of the NE neurons are located in several nuclei in the brainstem, the most important ones being the locus ceruleus. These are located bilaterally immediately below the floor of the lateral arms of the fourth ventricle and give rise to about 90% of the forebrain innervation. The spikes on the axon represent the firing activity of the NE neurons. The small dots around the NE neuron represent NE molecules. These neurons have autoreceptors of the α_2-adrenergic subtype that inhibit firing and release when activated by an excess amount of NE. The effects of NE on postsynaptic neurons are mediated by receptors belonging to 2 families, each family with several subtypes. The cogwheels on the cell body and terminal represent the reuptake transporters. A (+) sign indicates an agonism or a stimulatory effect and a (–) sign indicates an antagonism or an inhibitory action. Tyrosine is the amino acid precursor for dopamine and NE.
Abbreviations: DA = dopamine, MAO = monoamine oxidase, NRI = norepinephrine reuptake inhibitor.

and tolerability. In a double-blind, randomized, 8-week study of 246 elderly patients with MDD, Murphy and colleagues[57] found that the short form of the 5-HT transporter gene was associated with adverse events and modest reductions in efficacy among patients treated with paroxetine. However, among mirtazapine-treated patients, carriers of the short allele experienced fewer and less severe adverse events compared with short allele carriers treated with paroxetine. Thus, differences in both polymorphisms and antidepressant mechanisms of action may account for variations in treatment outcomes among patients.

Neurotransmitter availability. Antidepressant mechanism of action and treatment outcomes may also be influenced by individual differences in neurotransmitter availability, such as the availability of 5-HT, which is dependent on plasma levels of the essential amino acid tryptophan. 5-HT synthesis requires tryptophan from dietary sources. In order for tryptophan to enter the brain, it has to cross the blood brain barrier in a transporter that is also used by some other large neutral amino acids. If the levels of these other amino acids rise, then this limits the entry of tryptophan into the brain, thus causing an acute depletion of brain 5-HT. When this tryptophan-depletion approach was used in SSRI-treated patients, it was shown that it can lead to a return of depressive symptoms within 5 hours, owing to a rapid 5-HT drop in the brain.[58] Similarly, norepinephrine depletion using the synthesis inhibitor α-methyl paratyrosine has been shown to lead to depressive relapse in patients treated with noradrenergic reuptake inhibitors (NARIs, Figure 3).[59] Intriguingly, if 5-HT is depleted in NARI-recovered patients or norepinephrine is depleted in SSRI-recovered patients, relapse is not seen. This result suggests a degree of selectivity to the therapeutic mechanisms by which these different drugs act, characterized as "the neurotransmitter that gets you well, keeps you well."

Hypothalamic-pituitary-adrenal (HPA) axis dysfunction. Disturbances in the HPA axis, including hyperactivity, have been implicated as driving factors for depression and may account for variability in drug responsiveness.[60] Nemeroff and colleagues[61] measured concentrations of corticotrophin-releasing factor (CRF) in normal healthy volunteers and in unmedicated patients with *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition–diagnosed MDD, schizophrenia, or dementia. Patients with MDD exhibited significantly increased concentrations of CRF compared with controls and other diagnostic groups.

HPA axis hyperactivity has been associated with alterations in the number and function of glucocorticoid receptors in patients with MDD.[62] Research suggests that some antidepressants may act in part by enhancing glucocorticoid receptor function via membrane steroid transporters, such as P-glycoprotein (Pgp). A major constituent of the blood brain barrier, Pgp modulates penetration, retention, and drug-drug interactions of medications.[63,64] The actions of this efflux transporter alter the pharmacokinetics of both SSRI and SNRI antidepressants. Studies suggest that

fluoxetine, paroxetine, and venlafaxine are Pgp substrates, while citalopram may not be.[65,66] Individual mutations in the Pgp transporter may account for differences in drug responsiveness as different genotypes have varying effects on plasma levels of antidepressants. Uhr and colleagues[67] reported substantial differences in brain penetration of doxepin, venlafaxine, paroxetine, and mirtazapine in mice with a genetic disruption of the multiple drug resistance gene 1ab, which encodes the Pgp transporter. Additional evidence for the role of steroid receptors in depression is suggested by Boyle and colleagues' study,[68] which demonstrated in mice that when forebrain glucocorticoid reception function is switched off, a depressive behavioral response is observed.

Summary

Individual differences in therapeutic response and tolerability to antidepressant treatment are linked to numerous clinical factors, such as noncompliance, underdosing, intolerance, and medication choice. In addition, studies suggest responsiveness to pharmacotherapy and risk of depression may be influenced by sleep abnormalities; disturbances in the HPA axis; and variability in neurotransmitter receptors, transporters, and levels. Emerging data also suggest a potential role for complex molecular mechanisms involving neurotrophins, neurogenesis, and specific genetic variants. Additional studies are warranted to further elucidate the etiology of neurobiological factors in depression and their clinical relevance for treatment outcomes, including predictors of residual symptoms.

PRECLINICAL EVIDENCE: IMPLICATIONS FOR TREATMENT OF UNRESOLVED DEPRESSION

The therapeutic effects of current antidepressants are mediated by an enhancement of 5-HT and/or norepinephrine transmission, and deficient elements in these systems may prevent a full antidepressant response.

The 5-HT System

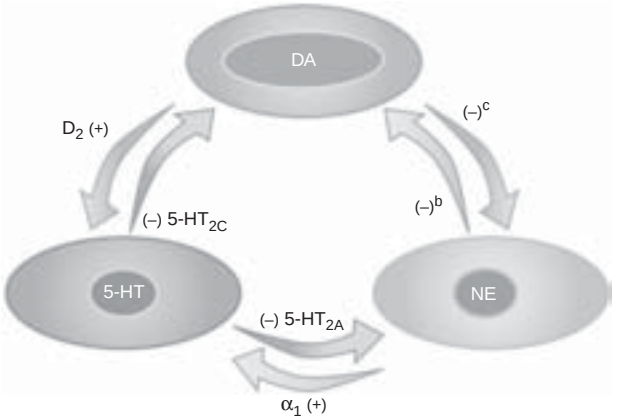
Acute administration of SSRIs results in a rapid accumulation of 5-HT in most brain structures as a result of the inhibition of 5-HT transporters. This surge of 5-HT in the midbrain raphe nuclei causes 5-HT neurons to decrease their firing rate, which limits the capacity of SSRIs to maintain the initial increase in 5-HT level in postsynaptic areas. This happens because the electrical impulse flow of 5-HT neurons is one of the main determinants in controlling 5-HT release throughout the brain. With prolongation of the administration of SSRIs, the accumulation of 5-HT at the cell body level is maintained. However, the firing rate of 5-HT neurons recovers because 5-HT_{1A} autoreceptors located on 5-HT cell bodies, which normally inhibit their electrical activity, desensitize. This adaptive change allows a net enhancement of 5-HT transmission to occur in part because the firing of 5-HT neurons has been normalized in the presence of sustained 5-HT reuptake inhibition.[69,70]

A key target for SSRI antidepressant therapy is the 5-HT transporter. Smeraldi and colleagues[71] were the first to show that allelic variation of the 5-HT transporter promoter is related to antidepressant response to an SSRI. In a 6-week, randomized controlled trial of 102 patients with MDD, both homozygotes and heterozygotes for the long allele of the 5-HT transporter promoter demonstrated a better response to fluvoxamine compared with homozygotes for the short allele. In the group augmented with pindolol (a 5-HT_{1A} autoreceptor antagonist), all genotypes responded as well as the group homozygous for the long allele and treated with fluvoxamine alone. Since this initial report, the vast majority of studies examining this relationship in depressed patients have replicated the finding. Similar genotype results were recently reported in a study of SSRI-treated patients with panic disorder.[72] While additional research is needed, especially with the recent identification of a nonfunctional long allele, the data suggest that genotyping of the 5-HT transporter promoter may be a potential means of individualizing antidepressant therapy.[71]

The therapeutic effects of various classes of antidepressant treatments are also mediated by enhanced 5-HT neurotransmission due to various adaptive changes within the 5-HT system. Preclinical studies indicate that repeated administration of monoamine oxidase inhibitors (MAOIs) and SSRIs desensitizes the somatodendritic 5-HT_{1A} autoreceptors in the dorsal raphe nucleus, permitting firing rate to recover in response to drugs.[70] In addition, chronic treatment with various types of antidepressant therapy, including the SSRI paroxetine, the tricyclic antidepressant imipramine, the α_2-adrenergic antagonist mirtazapine, the reversible type A MAOI befloxatone, the 5-HT_{1A} receptor agonist gepirone, and electroconvulsive therapy, enhances tonic activation of postsynaptic 5-HT_{1A} autoreceptors in the forebrain.[73]

However, postsynaptic 5-HT_{1A} autoreceptors may have the capacity to adapt, or to desensitize, and it may be possible that some postsynaptic autoreceptors desensitize after long-term exposure to enhanced 5-HT levels. Despite increasing overall 5-HT transmission, it was observed in electrophysiologic studies of the rat brain that clorgyline, a potent type A MAOI, desensitized postsynaptic 5-HT_{1A} receptors in the hippocampus after sustained administration.[74] With regards to interfering with the 5-HT transporter, it was reported that the responsiveness of postsynaptic 5-HT_{1A} receptors in the hippocampus was also dampened in mice lacking the 5-HT transporter gene.[75] The desensitization of some postsynaptic 5-HT_{1A} autoreceptors during prolonged treatment may thus explain, in part, the occasional encounter of fading responses ("poop out") to antidepressants, including SSRIs.

Figure 4. Diagram Representing the Reciprocal Interactions Between the Cell Bodies of Serotonin (5-HT), Norepinephrine (NE), and Dopamine (DA) Neurons[a]



[a]A (+) sign indicates a stimulatory pathway and a (–) sign indicates an inhibitory pathway. The nature of these projections was derived from lesion experiments, electrical stimulations of these neurons, and pharmacologic experiments using systemic and local application of agonists and antagonists. Current knowledge indicates that the outside arrows represent monosynaptic pathways, whereas the inside arrows would involve at least an interneuron.
[b]Presumed effect from an enhancement of firing of DA neurons in NE-lesioned rats.
[c]Presumed effect from an enhancement of firing of a subpopulation of NE neurons in DA-lesioned rats.

In addition, anomalies of 5-HT_{1A} autoreceptors may underlie inadequate response to SSRIs. Activation of these autoreceptors inhibits the firing of 5-HT neurons and decreases 5-HT release in forebrain structures. Stockmeier et al.[76] found a higher density of 5-HT_{1A} autoreceptors in the dorsal raphe of suicide victims with MDD compared with normal controls, suggesting an increased function of 5-HT_{1A} autoreceptors and a reduced activity of 5-HT neurons at least in some depressed patients.

The Norepinephrine System

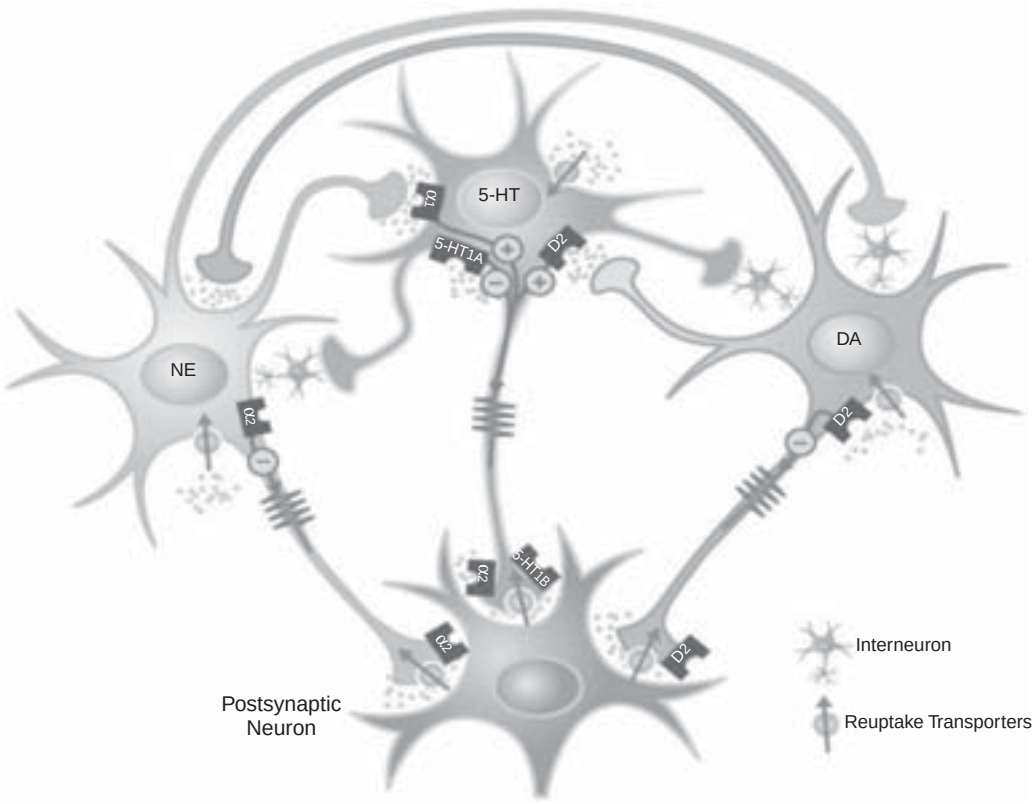
The norepinephrine system may also act as a mediator for incomplete response (Figure 3). Serotonin exerts an inhibitory influence on the noradrenergic tone as preclinical research indicates that 5-HT synthesis inhibition and a lesion of 5-HT neurons increases norepinephrine firing.[77,78] Sustained administration of SSRIs lowers the firing rate of norepinephrine neurons. Citalopram, fluoxetine, and paroxetine reduce the spontaneous firing rate in a time-dependent manner: 2-day regimens are without effect, whereas a 3-week administration period can decrease firing by as much as 50%.[79,80] In contrast, escitalopram, which was reported to enhance 5-HT levels to a greater extent than citalopram,[81] decreases norepinephrine firing by 65% in only 2 days.[78] Taken together, the data suggest that if a patient is not responding to an SSRI, it may be due to a decreased noradrenergic tone despite an increase in 5-HT transmission (Figure 4).

Because there are reciprocal interactions between 5-HT and norepinephrine neurons, it is important to consider the effects of drugs altering the norepinephrine system on 5-HT neurotransmission. Blocking the norepinephrine reuptake pump has no effect on 5-HT neuronal firing. A 2-day and a 21-day treatment with reboxetine, a selective norepinephrine reuptake inhibitor, dose-dependently decreased the firing of noradrenergic neurons but did not affect 5-HT firing activity.[82] However, certain drugs that boost norepinephrine transmission by blocking presynaptic α_2-adrenoceptors enhance 5-HT transmission and enhance treatment response. Preclinical research indicates that sustained treatment with the antidepressant mirtazapine, a nonselective α_2-adrenoreceptor antagonist, increases the firing rate of 5-HT. This effect is mediated via increased norepinephrine release, which is a result of blocked α_2-adrenergic autoreceptors of locus ceruleus neurons.[83] Combining mirtazapine to either 6-week SSRI or SNRI therapy from treatment initiation improves remission in patients with MDD. Significantly greater improvements in HAM-D-17 scores were observed for combination drug groups that included mirtazapine compared with fluoxetine alone ($p = .011$). The combination drug groups were fluoxetine and mirtazapine, bupropion and mirtazapine, and venlafaxine and mirtazapine. Remission rates (HAM-D-17 ≤ 7) for the groups were 25% for fluoxetine alone, 52% for fluoxetine and mirtazapine, 46% for bupropion and mirtazapine, and 58% for venlafaxine and mirtazapine.[84] The underlying mechanism of action of the mirtazapine combination could be an increased 5-HT and/or norepinephrine firing, norepinephrine autoreceptor antagonism on norepinephrine terminals, and norepinephrine heteroreceptor on 5-HT terminals.

Reciprocal Interactions Between 5-HT, Norepinephrine, and Dopamine

Reciprocal interactions between 5-HT, norepinephrine, and dopamine systems may account for the full manifestation of an antidepressant response (Figure 5). The neurocircuitry between 5-HT, norepinephrine, and dopamine is now better understood. For example, there is a direct pathway from dopamine to 5-HT neurons exerting an excitatory effect via D_2 heteroreceptors located on 5-HT neurons. However, the effects of long-term SSRI treatment on certain aspects of the monoaminergic circuitry, particularly the dopamine system, are unknown. Treatment with bupropion, the most commonly used augmentation strategy in the United States, is thought to produce potent 5-HT and norepinephrine effects that are not mediated through transporters. Positron emission tomography scan studies show that up to 300 mg/day of bupropion occupies less than 20% of dopamine reuptake sites.[85] Bupropion therefore decreases norepinephrine firing by enhancing

Figure 5. Detailed Diagram of the Reciprocal Interactions Between the Cell Bodies of Serotonin (5-HT), Norepinephrine (NE), and Dopamine (DA) Neurons Showing the Various Types of Cell Body and Terminal Autoreceptors Controlling the Function of These Neurons[a]



[a]A (+) sign indicates a stimulatory effect and a (–) sign indicates an inhibitory effect. The interneurons have been identified as γ-aminobutyric acid neurons mediating an inhibitory action on target neurons.

norepinephrine release via mechanisms not involving reuptake inhibition.[86] Sustained bupropion administration, while not affecting the firing rate of dopamine neurons, can have some effect on the dopamine system: it increases dopamine release in the nucleus accumbens, but not in the striatum. In the locus ceruleus, with sustained bupropion treatment, there is a recovery of norepinephrine neuron firing (a gradual increase) in 7 to 14 days; importantly, there is an increase in the percentage of neurons firing in bursts. With sustained bupropion treatment, the increase in 5-HT neuron firing in the locus ceruleus is rapid (2 days) and sustained (over 14 days), which is accompanied by an increase in the percentage of neurons firing in bursts. This mode of firing, in comparison to the single-action potential mode of firing, produces greater norepinephrine release in projection areas. Finally, the combination of the SSRI escitalopram with bupropion significantly increases 5-HT neuronal firing when compared with the control saline value and even with bupropion alone.[87] Taken together, these findings underscore the importance of the various interactions between the monoaminergic systems.

Summary

Depression affects integrated neural pathways shared by monoaminergic neurotransmitter systems. Research indicates that the therapeutic effects of antidepressant agents may be mediated by enhancement of serotonergic and noradrenergic transmission as well as by various reciprocal interactions between the serotonergic, noradrenergic, and dopaminergic neural circuits. Abnormalities in any of these neurotransmitter systems can potentially contribute to an incomplete response to antidepressant therapy. Although the pathogenesis of MDD and unresolved depressive symptoms is complex, it may be possible to identify the specific neural pathways and/or deficient elements of the monoaminergic circuits affected by depression and target them for treatment. Additional research is needed.

CONCLUSIONS

The goal of treatment for MDD is remission; however, many patients fail to attain or maintain symptom-free status. Residual depressive symptoms are common among

patients treated for MDD and are associated with negative outcomes. Additional research is needed to identify which symptoms must be present in order to be considered residual, how to measure residual symptoms, and what core target symptoms and treatment options exist for residual symptoms. Differences in therapeutic response and tolerability are linked to numerous clinical and neurobiological factors. Various types of treatment strategies, including the use of measurement-based care and enhancing monoaminergic transmission, offer rational means to improve or restore antidepressant response. In addition, exploration of the biochemical and molecular mechanisms involved in the neurophysiology of MDD is an emerging area of research and will provide novel insights into the pathophysiology and treatment of MDD and unresolved depressive symptoms.

Drug names: bupropion (Wellbutrin and others), buspirone (BuSpar and others), citalopram (Celexa and others), doxepin (Sinequan, Zonalon, and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), lithium (Lithobid, Eskalith, and others), mirtazapine (Remeron and others), norepinephrine (Levophed and others), nortriptyline (Pamelor and others), paroxetine (Paxil, Pexeva, and others), pindolol (Visken and others), pramipexole (Mirapex), venlafaxine (Effexor and others).

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