# Brain Circuits Determine Destiny in Depression: A Novel Approach to the Psychopharmacology of Wakefulness, Fatigue, and Executive Dysfunction in Major Depressive Disorder

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Recent advances in neuropharmacology and neuroimaging are mapping the topography of symptoms in major depressive disorder (MDD). Different malfunctioning neuronal circuits apparently mediate different symptoms in MDD. Since all patients with MDD do not have the same symptoms, this implies that they may not all have the same malfunctioning circuits. Furthermore, since MDD patients treated with antidepressants commonly experience residual symptoms that prevent them from attaining complete remission, this implies that not all circuits are successfully targeted by treatment in such patients. A new neurobiologically informed treatment strategy for such patients calls for targeting residual symptoms by augmenting antidepressants with agents capable of boosting specific neurotransmitters in the hypothetically malfunctioning circuits. With this approach, the frequently residual symptoms of sleepiness, fatigue, and executive dysfunction can be targeted with bupropion, atomoxetine, modafinil, atypical antipsychotics, and stimulants.

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Major depressive disorder (MDD) is a syndrome comprising, by definition, at least 5 symptoms (DSM-IV).[1] Each symptom may have a unique neurobiological mechanism mediated by different malfunctioning neurocircuits.[2,3] Certainly, not every patient has the same cluster of symptoms in MDD, implying that different circuits may malfunction in different patients with the same disorder. Furthermore, not every patient with MDD who takes an antidepressant medication will experience improvement of all symptoms, implying that some but not all malfunctioning circuits may respond to a given drug in a given patient. Thus, individual patients with MDD can have a unique portfolio of symptoms not only prior to treatment, but even following treatment with an antidepressant. Fatigue, sleepiness, and executive dysfunction are some of the commonest residual symptoms in patients who respond but do not remit with antidepressant treatment.[4–7] A novel strategy to reduce these residual symptoms and thus convert partial remitters to full remitters is to target the neurotransmitters in the circuits that hypothetically underlie those residual symptoms.[3] In this article, we review the hypothetical circuits that may mediate each of the symptoms associated with MDD. We also explore how the neurobiologically informed psychopharmacologist can utilize this information to select a portfolio of treatment options that rationally target all symptoms in MDD to maximize the chances of complete remission of symptoms and to optimize functional outcomes.

## DECONSTRUCTING THE SYMPTOMS OF MDD

It is well known that a major depressive episode is defined as at least 5 symptoms from a list of 9 possibilities, 1 of which must be depressed mood or loss of interest (Table 1).[1] These well-known diagnostic criteria allow a clinician to construct a diagnosis of MDD by compiling an inventory of all symptoms suffered by any patient during any specific period of time. Although making a diagnosis is important, the hierarchy that assigns greater importance to depressed mood and loss of interest over the other symptoms listed in Table 1 can distract treating clinicians from observing and monitoring the other symptoms associated with this disorder, particularly if mood improves

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**Table 1. Symptoms of Major Depressive Disorder[a]**

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|---|
| Required for diagnosis: |
| At least 1 of the required symptoms: |
| Depressed mood |
| Loss of interest or pleasure |
| At least 4 of the following symptoms: |
| Significant weight loss or gain, or decrease or increase in appetite |
| Insomnia or hypersomnia |
| Psychomotor agitation or retardation |
| Fatigue or loss of energy |
| Feelings of worthlessness or excessive or inappropriate guilt |
| Diminished ability to think or concentrate or indecisiveness |
| Recurrent thoughts of death or suicidal ideation |
| Commonly associated with major depressive disorder, but not part of formal diagnostic criteria: |
| Anxiety |
| Painful physical symptoms |

[a]Based on DSM-IV.[1]

but other symptoms remain following treatment. It is now well recognized that improving sadness and depressed mood alone in MDD is inadequate, because residual symptoms following treatment can interfere with functional outcomes and enhance the possibility of a relapse.[7–10] Also, treatments can give rise to side effects that can be easily confused with residual symptoms, making it difficult to know exactly how to eliminate residual symptoms in many patients.[11–13]

A novel strategy is evolving for how to approach the all-too-common situation of patients who continue to have residual symptoms following initial treatment of MDD. That strategy is to deconstruct the syndrome of MDD into the specific symptoms still being experienced by each individual patient and then to choose psychopharmacologic interventions to target those malfunctioning neuronal circuits that hypothetically mediate each residual symptom.[3]

## MATCHING SYMPTOMS WITH MALFUNCTIONING CIRCUITS

Neurotransmitters and receptors interact with each other within pathways or circuits to regulate various functions of the brain. Theoretically, dysfunction of certain distinct circuits can result in the symptoms of various psychiatric disorders.[14–16] In this section, we discuss those hypothetical circuits that may mediate each of the wide variety of emotional, cognitive, and physical symptoms associated with a major depressive episode. The classical theory to explain depression is the "monoamine hypothesis," which proposes that depression is related to a deficit of monoamines, particularly norepinephrine (NE) and serotonin (5-HT), at critical synapses.[17] However, the monoamine hypothesis may be a better theory for explaining the neurobiology of antidepressants than for explaining the neurobiology of the symptoms of depression.[18–24] That is, malfunctioning of monoamine pathways has been difficult to document in depression, but the antidepressant actions of currently available drugs and their ability to reduce or eliminate symptoms are definitely linked to boosting neurotransmission in monoamine pathways.[22]

A new paradigm is therefore evolving for the role of monoamines in depression as regulators of many of the hypothetically malfunctioning circuits causing the symptoms associated with a major depressive episode. Each monoamine arises from a common site in the brain stem, but is released in many projection areas throughout the brain.[25–30] Boosting monoamine actions with antidepressants in various specific sites of abnormal neuronal functioning could reduce the symptoms associated with that abnormal neuronal functioning. This paradigm would not necessarily require that input from monoamine pathways to be deficient prior to treatment with an antidepressant. It could, however, explain how boosting just one or two monoamines could reduce a whole portfolio of symptoms, since the circuits mediating those symptoms may all receive innervation from monoamine neurons.

It is well known that some symptoms in some patients with depression can clearly be reduced or eliminated by antidepressants capable of boosting 5-HT, NE, or both.[31,32] On the other hand, many patients nevertheless still have residual symptoms following treatment with such agents. A strategy to reduce these residual symptoms could be to target the pathways that are still hypothetically malfunctioning with a second agent capable of increasing 5-HT, NE, or both or by boosting the actions of other neurotransmitters known to be in the same circuit, which can include histamine, dopamine (DA), acetylcholine, and many others. Such an approach gives rise to a rational, hypothesis-driven, and testable action plan for selecting or combining pharmacologic agents tailored for the individual patient to eliminate whatever residual symptoms are unique to that patient and thus attain complete remission of symptoms for the patient.

### Depressed Mood and Sadness

Depressed mood is one of the required symptoms for the diagnosis of MDD, is the most widely recognized symptom of depression, and is the symptom most often targeted by treatment. Functional neuroimaging studies have recently associated sadness and depressed mood with abnormal neuronal activation in the medial prefrontal cortex, including the anterior cingulate cortex and orbitofrontal cortex.[33–38] These areas receive innervation from serotonergic projections from the midbrain raphe nucleus and from the noradrenergic projections from the locus ceruleus as well as from dopaminergic projections from the ventral tegmental area.[39–43] Antidepressants that act on 5-HT, NE, or both have been associated with normalization of these circuits and presumably could provide key regulatory influences on the symptom of sadness and potentially explain how antidepressants can improve sadness and depressed mood.[44,45]

### Sleep Disturbances: Sleepiness, Lack of Normal Wakefulness, Hypersomnia, and Insomnia

Another common symptom of depression is abnormal sleep, which ranges from insomnia to hypersomnia and can also include excessive daytime sleepiness and problems with normal wakefulness. The neurophysiology of sleep is complex, and only certain aspects of hypothetical circuits mediating sleep disturbances in depression are discussed here.

Important circuits that may malfunction during depression are those that interconnect key sites of the hypothalamus, brain stem, and cortex. For example, states of arousal are regulated by both the hypothalamic sleep-wake switch and the brain stem monoamine projections to the cortex.[46–48] If the normal oscillations between sleep and wakefulness are disrupted in depression, this can lead to insomnia at night and hypersomnia and sleepiness in the day. Sleep-promoting neurons in the ventrolateral preoptic area and wake-promoting neurons in the tuberomamillary nucleus (TMN) comprise the hypothalamic sleep-wake switch.[46,48,49] Important histaminergic projections from TMN to cortex must be activated for normal wakefulness to occur.[50–53] Malfunctions in this pathway can theoretically lead to disruptions in normal sleep-wake rhythms and diminished cortical arousal and sleepiness in depression.[54] Malfunctions of ascending monoamine neurons to cortex via the ascending reticular activating system may also cause disruptions in normal wakefulness and sleep.[55–58] The enhancement of cortical activity through various pharmacotherapies, including antidepressants that enhance monoamine neurotransmission as well as the novel wake-promoting drug modafinil, which enhances histaminergic neurotransmission from the TMN,[59,60] could explain the beneficial actions of these therapies in improving sleep disturbances, as well as problems with sleepiness in depression.

### Problems Concentrating and Executive Dysfunction

Cognitive dysfunction, particularly difficulty in paying attention, organizing, and problem solving, is strongly associated with hypoactivity in the frontal and prefrontal cortex, especially dorsolateral prefrontal cortex (DLPFC).[61–69] Abnormal functioning of DLPFC may predict treatment response to and stability of antidepressant therapy of patients with MDD.[70–72]

Executive functioning may control a wide range of mental processes, including motivation, focus, emotion, learning, and working memory, and may be regulated in turn by numerous neurotransmitters projecting to DLPFC, including NE, DA, histamine, acetylcholine, and perhaps others.[50,73–75] Decreased neuronal activity in prefrontal circuits may be associated with diminished concentration, indecisiveness, diminished ability to think, and executive dysfunction, symptoms associated not only with MDD but also with many other disorders including attention deficit disorder, schizophrenia, sleep deprivation, and dementia.[76–80]

### Fatigue and Loss of Energy

Symptoms of fatigue and low energy may be among the least understood and least emphasized symptoms associated with a major depressive episode.[81] However, the symptoms of fatigue and low energy are extremely important in MDD and contribute significantly to disability associated with depressed patients.[82–84]

Physical fatigue and lack of physical energy with a sense of tiredness or exhaustion arising from the body may be related to some other symptoms associated with a major depressive episode, namely psychomotor retardation and painful somatic symptoms, and may be difficult to distinguish from them. Mental fatigue and lack of mental energy may also be related to some other symptoms associated with a major depressive episode, namely cognitive dysfunction, apathy, and lack of motivation, and may likewise be difficult to distinguish from them. Furthermore, patients and clinicians sometimes have difficulty distinguishing physical fatigue from mental fatigue, adding to the complexity of determining whether such symptoms improve with antidepressant treatment.

Not only are the symptoms of fatigue and loss of energy sometimes difficult to distinguish from several other symptoms of MDD, but their exact neurobiological basis has been difficult to associate with specific neuronal circuits. Nevertheless, evolving knowledge about the topography of brain functions suggests several reasonable possibilities. Thus, brain areas regulating motor functioning, such as striatum and cerebellum, are reasonable candidates for mediating physical fatigue and lack of energy that arise from the body. Serotonin and DA both project to striatum and NE projects to cerebellum,[85–87] and these monoamine neurotransmitters in the brain areas controlling motor function may hypothetically provide regulatory influences on the symptoms of physical fatigue.[2,88] Sensory input from the body enters the spinal cord, where serotonergic and noradrenergic descending fibers may hypothetically regulate the perception of physical tiredness.[89,90] On the other hand, diffuse cortical projections of several key neurotransmitters, especially NE, DA, acetylcholine, and histamine, may all regulate the symptom of mental fatigue at the cortical level.[50,73–75,91] Reduced neuronal activities in prefrontal cortex, especially DLPFC, might explain the symptom of mental fatigue in MDD.[92]

### Loss of Interest, Loss of Pleasure

Many patients with MDD experience diminished interest in performing their daily activities or derive little pleasure from things they once enjoyed. Interest and pleasure are normally regulated by at least 2 key brain areas,

namely the hypothalamus and the "pleasure center" in the nucleus accumbens. The hypothalamus, which receives important input from both noradrenergic and serotonergic neurons, regulates various appetitive drives and vegetative functions, including sexual functioning.[93–95] The mesolimbic DA pathway is a key regulator of pleasure, including the pleasure received from substances of abuse.[96,97] Dysfunctioning neuronal circuits in these brain areas may underlie the symptoms of lack of interest, lack of experiencing pleasure, and decreased libido in MDD.

### Feelings of Worthlessness or Guilt and Thoughts of Suicide

Substantial research has been done on the symptoms of guilt and suicidal ideation of depressed patients due to their extreme consequences. It has been predicted that these symptoms might result from a limbic malfunction controlled not only by mesolimbic dopaminergic pathways but also by projections from the serotonergic raphe and the noradrenergic locus ceruleus to both the amygdala and the anterior cingulate cortex.[36] In fact, a recent neuroimaging study by Arango et al.[98] found that a deficiency of serotonin transporter binding in ventral prefrontal cortex might be the pathobiological mechanism underlying suicidal thoughts. Also, Oquendo et al.[99] have recently reported that prefrontal abnormalities and impaired 5-HT responsivity are proportional to the lethality of suicide attempts. Thus, the same areas of cortex associated with sadness and depressed mood may have a role in mediating suicidal ideation and acts.

### Loss of Appetite or Weight Loss

Although patients with MDD may experience either gain or loss of appetite or weight, only losses of these are considered criteria for MDD. Since the hypothalamus regulates appetitive drives, this area of the brain is an excellent hypothetical candidate for the region likely to regulate abnormal appetite in MDD.[94,95,100,101] Serotonergic and noradrenergic projections to hypothalamus may thus regulate appetite and weight in MDD as they are hypothesized to do for the other hypothalamically linked symptoms such as lack of interest and pleasure discussed above.[93–97,102,103]

### Psychomotor Agitation or Retardation

Psychomotor agitation and retardation are two nearly opposite motor disturbances that can be seen in depressed patients and can also be among the earliest symptoms of MDD.[104] As discussed in the section on physical fatigue, normal motor activity is regulated in part by the striatum and the cerebellum, and these areas and their incoming monoaminergic projections may be hypothetical sites for the pathways mediating psychomotor symptoms in MDD.[2,85–88] Numerous neuroimaging studies of depressed patients have shown abnormal neural activities in the basal ganglia and its neurocircuitry with the cortex, especially decreased activity in the left prefrontal area.[105,106] However, the exact abnormality of neuropathway and neurotransmission behind these symptoms is still obscure.

### Anxiety

MDD and anxiety disorders are highly comorbid.[107–109] Although not a formal criterion for a major depressive episode, the symptom of anxiety is nevertheless a frequently associated symptom.[110]

Recently, the neurocircuitry of fear has been elucidated, centering on the amygdala.[111–114] Abnormalities in the fear circuit may underlie anxiety in MDD as well as in anxiety disorders. Noradrenergic projections from locus ceruleus to the amygdala are well known to regulate anxiety, based on evidence that direct electrophysiologic or pharmacologic stimulation of locus ceruleus in animal brains results in behaviors similar to those of human anxiety patients.[115–118] Serotonergic projections from midbrain raphe nuclei to limbic system are another set of neurocircuits that have been proposed to modulate fear and anxiety.[119] Malfunctioning of these projections, especially the ones to amygdala, may underlie the symptom of anxiety in MDD and be regulated in part by monoamine inputs to the fear circuit.[2,120,121]

### Painful Somatic Symptoms

Although more than half of patients with MDD complain of a variety of chronic pain symptoms,[122] such as headache, backache, stomachache, musculoskeletal pain, and pain in the joints and neck, such symptoms are not part of the formal diagnostic criteria for MDD. Candidates for the pathways that may mediate such symptoms include the same pathways that carry sensory input from the body into the spinal cord and were discussed in the section on physical fatigue. Also, descending serotonergic and noradrenergic fibers into the spinal cord may not only regulate the sensation of fatigue or loss of energy that derives from input from the body, but may also have a key role in whether these inputs are perceived as painful physical symptoms.[90,123–125] Malfunctions of the sensory input into the spinal cord, or of how these inputs are perceived in cortical sites, may underlie the sensation of painful somatic symptoms in MDD and may be modulated by monoamine systems.[125,126]

## RESIDUAL SYMPTOMS AFTER TREATMENT OF DEPRESSION

### What Is the Importance of Residual Symptoms?

Although response to an antidepressant in MDD can range from complete abolition of all symptoms (i.e., full remission) to lack of any substantial relief of any symptoms (i.e., treatment resistance), most patients have a treat-

ment response that falls somewhere between these extremes. Full remission of symptoms is the goal of treatment for MDD, but only 25% to 50% of patients in clinical trials achieve it.[6] Over 73% of patients continue to experience at least one residual symptom after 2 months of treatment.[5] Rating scales widely utilized in clinical trials, such as the Montgomery-Asberg Depression Rating Scale and the Hamilton Rating Scale for Depression (HAM-D), may not be very useful for detecting such residual symptoms in clinical practice. That is, rating scales often define "remission" as a low score, but not as "normal" or "symptom-free." As long as the evaluation score on the rating scale is below a certain cut-off point (e.g., 7 or 8), a patient could be considered in "remission" even though some residual symptoms may still exist.[127] For example, among a total of 108 depressed patients who responded acutely to fluoxetine and achieved "remission" according to the criterion HAM-D score of ≤ 7, only 19% finally reached an asymptomatic state after 8-week treatment.[5] All others experienced residual symptoms.

In fact, all current antidepressant drugs leave most patients with residual symptoms after 2 months of treatment.[4,31,32] Thus, an important challenge is to recognize residual symptoms, because even among the patients who no longer meet criteria for MDD, the presence of residual symptoms can nevertheless contribute to continued impairment.[128,129] Residual symptoms are a serious discomfort affecting the quality of life for depressed patients and their families. These symptoms generate more health care visits and the need for public disability benefits. Moreover, they increase the risk of suicide, are responsible for long duration of functional impairment, and appear to be one of the most accurate and consistent predictors of early relapse and recurrence.[130,131]

### Why Are There Residual Symptoms?

One reason that residual symptoms of MDD persist following treatment might be that clinicians tend to focus on relief of depressed mood as the hallmark of treatment. On the one hand, if mood does not improve, this is readily observed and different strategies, such as optimization, augmentation, and switching, are then used to target improvement in mood.[132] On the other hand, both the psychiatrist and patient may be satisfied if mood alone improves. However, as noted above, in most cases, when mood improves, several residual symptoms are likely to persist even if unnoticed.

A second factor leading to residual symptoms of MDD following treatment is that antidepressants are frequently associated with side effects that can be confused with symptoms of MDD (e.g., sleepiness, fatigue, sexual dysfunction, changes in appetite or weight). Sometimes the improvement in cognitive symptoms in MDD may be masked by the emergence of treatment-related cognitive effects, especially with highly anticholinergic antidepressants.[133,134] Taking a good baseline inventory of symptoms and determining whether symptoms are treatment emergent, and also whether they abate with time, can help distinguish side effects of medication from residual and undertreated symptoms of MDD.

A third possible reason for the persistence of residual symptoms following treatment of MDD is the treatment strategy. The most frequently used strategy for treating residual symptoms of depression is to increase the dose of the antidepressant already prescribed.[135–138] This might work for those patients who are underdosed, but would not be expected to work for those patients who need a boost to a different neurotransmitter in a different pathway. Although the reasons are still not understood, it is nevertheless clear that some patients require different neurotransmitters to be boosted in order to get symptom relief than do other patients. Currently, there is no way to predict whether a patient will need a single neurotransmitter action or multiple neurotransmitter actions with multiple agents to attain symptom remission, but remaining vigilant to the presence of residual symptoms can allow the clinician to embark on a strategy to hunt down and remove all symptoms.

That strategy consists of deconstructing the diagnosis of MDD in a given patient into the specific symptoms experienced by that patient, and then utilizing case-based psychopharmacologic interventions to target the hypothetically malfunctioning neuronal circuits mediating each symptom. The key is to have a neurobiologically informed treatment strategy that targets every symptom in every circuit, utilizing rational drug selections and combinations from the therapeutic armamentarium at hand with the idea that achieving and retaining full remission is the endpoint of treatment in MDD.

### Sleepiness, Fatigue, and Executive Dysfunction as Common Residual Symptoms

Although it may be relatively easy to determine when a patient's depressed mood or sadness is improving, especially if this was the patient's presenting complaint, it can be more difficult in practice to determine whether other symptoms of a major depressive episode are improving. For example, sleepiness, fatigue, and executive dysfunction can be among the most neglected symptoms in the treatment of depression, particularly if they persist following treatment with an initial antidepressant,[139–141] and will therefore be emphasized here in the discussion of targeting residual symptoms to attain remission in MDD.

The most common residual symptoms reported in studies that measure symptoms following antidepressant treatment are sleep disturbances and fatigue; other residual symptoms may include executive dysfunction, anxiety, decreased motivation, anhedonia, and dysfunctional attitudes.[82,141,142] Nierenberg et al.[5] reported that nearly 44% of depressed patients complained of persistent sleep

disturbance as a residual symptom following treatment with fluoxetine. Furthermore, sleep disturbances have often resulted from taking various antidepressants, including some monoamine oxidase inhibitors[143] and selective serotonin reuptake inhibitors (SSRIs).[144] Thus, sleep disturbances are some of the most common symptoms of MDD both before and after treatment, and it is important to try to distinguish whether they are residual symptoms of MDD or side effects of antidepressant medication.

Besides sleep disturbances, fatigue is another major complaint of depressed patients after treatment. Several studies have found that 10% to 35% of patients with MDD who reached remitted treatment results continued to complain of fatigue.[145] Fatigue and lack of energy are significantly related to a reduction in work and social functioning of depressed patients.[84,146] Changes in energy were more strongly correlated with percent effectiveness at work, output demands, interpersonal demands, and time management than was depression symptom change.[84] Thus, improvement in energy may be as important as or even more important than changes in depressed mood in terms of improving work productivity.[84]

Residual cognitive impairment or executive dysfunction can severely affect the patient's ability to function effectively at work. Executive impairment may emerge independent of age, depression severity and subtype, task difficulty, motivation, and response bias; some executive dysfunction may persist on clinical recovery.[147] In a study by Porter et al.,[148] neurocognitive impairment was present in young, predominantly first-episode outpatients without melancholia and was not due to the effects of psychotropic medication. Furthermore, poor memory has been found to be associated with greater depression severity.[149] Recurrent depression may be relatively more likely to be associated with neuropsychological deficits.[150] Thus, neurocognitive impairment is an objective measure that may be used as a tool to investigate the abnormalities in brain function underlying MDD.

## TREATING RESIDUAL SYMPTOMS BY TARGETING NEUROTRANSMITTERS IN SYMPTOM-GENERATING CIRCUITS

When a depressive patient has residual symptoms following treatment with an antidepressant, several treatment options are available for targeting remission of these symptoms. One option is to optimize the dose of the current antidepressant or lengthen therapy with that agent. In a recent survey of 432 psychiatrists and other medical specialists who treat depression,[132] the majority of participants preferred to raise the dose of the current treatment in patients who were partial responders before other strategies were tried. Approximately 14% preferred to add an augmenting agent, while very few preferred to switch treatments. Although raising the dose may increase efficacy for all symptoms and lead to remission, this is not always the case. It may only increase efficacy for symptoms that have already improved somewhat, without necessarily alleviating symptoms that have not responded at all to treatment.

Another possibility for treating residual symptoms is to switch to another antidepressant treatment or add another agent. Augmenting agents in the past have classically included buspirone, thyroid hormone, and lithium, based largely on empirical observations.[151] A new set of augmenting agents can now be added to the treatment armamentarium by utilizing the strategy of targeting residual symptoms in hypothetically malfunctioning circuits regulated by specific neurotransmitters.

### Norepinephrine Reuptake Inhibitors

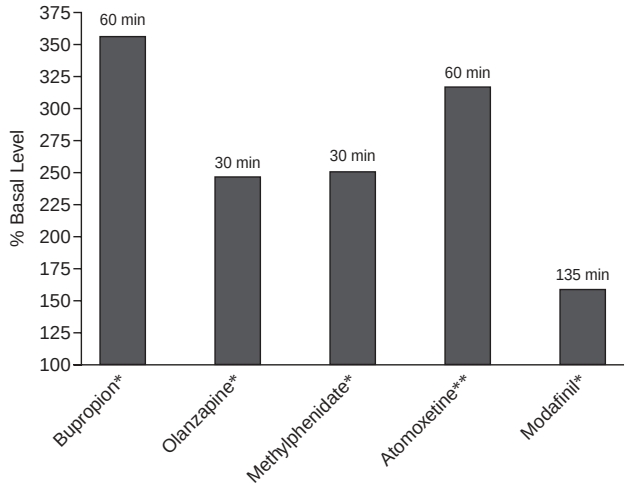
One of the best known and most frequently utilized approaches to the treatment of residual symptoms in MDD is to augment an SSRI or a serotonin-norepinephrine reuptake inhibitor (SNRI) with bupropion, a norepinephrine and dopamine reuptake inhibitor.[2] By blocking reuptake of NE, bupropion can increase both DA and NE in the frontal cortex, as well as in other areas of the brain (Figures 1 and 2).[152–158] Bupropion may be especially effective in improving sleep efficiency,[159] energy and fatigue,[160,161] and executive function.[156,160] Besides bupropion, a new selective norepinephrine reuptake inhibitor, atomoxetine, is also beginning to be used to augment SSRIs and SNRIs. By enhancing both NE and DA actions, both bupropion and atomoxetine could boost theoretically deficient circuits in DLPFC and improve residual executive dysfunction in MDD (see Figures 1 and 2).[152–155] By enhancing these neurotransmitters both in cortex and in subcortical areas, bupropion and atomoxetine may also improve residual fatigue and loss of energy. No studies of this use of atomoxetine have yet been reported, however.

### Modafinil

A novel approach to increasing not only monoamine neurotransmitters but also histamine in pathways theoretically mediating residual symptoms is to administer the novel wake-promoting agent modafinil. This drug selectively activates orexin-containing and histaminergic neurons in the hypothalamus and releases histamine in the hypothalamus (Figure 3)[60] as well as DA and NE in cortex (see Figures 1 and 2)[152–155] but not notably in nucleus accumbens.[162] Modafinil also releases 5-HT in cortex.[163,164] This neuropharmacologic profile is distinct from that of antidepressants and that of stimulants[165] and predicts potential actions in relieving not only sleepiness but also fatigue and executive dysfunction in MDD without substantial abuse potential.

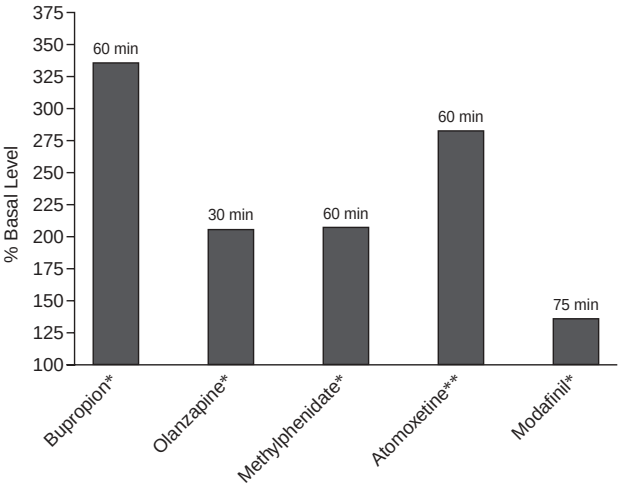
Preliminary studies suggest that modafinil can relieve residual symptoms of sleepiness and fatigue following treatment with a variety of antidepressants in

**Figure 1. Dopamine in the Prefrontal Cortex: Peak Effects of Various Drugs[a]**




[a]Data from Li et al.,[152] Zhang et al.,[153] Bymaster et al.,[154] and De Saint Hilaire et al.[155]
*p < .05 vs. basal level.
**p < .025 vs. basal level.

**Figure 2. Norepinephrine in the Prefrontal Cortex: Peak Effects of Various Drugs[a]**

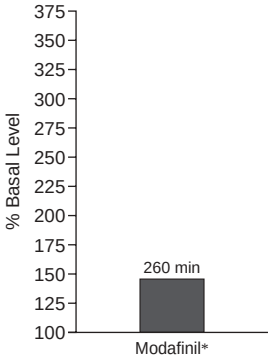



[a]Data from Li et al.,[152] Zhang et al.,[153] Bymaster et al.,[154] and De Saint Hilaire et al.[155]
*p < .05 vs. basal level.
**p < .025 vs. basal level.

MDD.[161,166,167] This is consistent with its known actions in reducing daytime sleepiness associated with a number of sleep disorders, including narcolepsy,[168,169] obstructive sleep apnea,[170] and shift work sleep disorder.[171] Indeed, a recent study[172] suggests that fatigue in obstructive sleep apnea may be driven by depressive symptoms rather than by apnea severity, so the actions of modafinil in relieving fatigue in both obstructive sleep apnea and depression may be due to a common action on a common neurotransmitter in a common pathway. Modafinil also relieves sleepiness and fatigue in patients with myotonic dystrophy[173,174] and patients with multiple sclerosis,[175] suggesting an action to reduce fatigue mediated by a common pathway that may be malfunctioning in a number of neurologic and psychiatric disorders in addition to MDD.

Finally, early results suggest that modafinil may improve executive dysfunction. Although this has only been anecdotally noted in MDD, modafinil has been shown to enhance cognitive functioning in a number of potentially related conditions, from normal aging in experimental animals[177] to normal human volunteers[178] to sleep-deprived normal volunteers[178,179] to both children and adults with attention-deficit/hyperactivity disorder.[180,181] Modafinil may also improve the cognitive dysfunction and sleepiness associated with medication side effects from antipsychotics[182] or opioids.[183] To the extent that these improvements in cognitive dysfunction are due to actions in circuits that are also malfunctioning in patients with residual cognitive symptoms in MDD, modafinil may be a promising treatment option to improve cognition in such patients.

**Figure 3. Histamine in the Anterior Hypothalamus: Peak Effects of Modafinil[a]**




[a]Data from Ishizuka et al.[60]
*p < .01 vs. basal level.

## Atypical Antipsychotics

The 5 atypical antipsychotics (olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole) may also be used as adjunctive agents for residual symptoms in MDD.[184] Since these agents can all increase extracellular levels of NE, DA, and acetylcholine, but not 5-HT, in the prefrontal cortex, they may be effective in improving executive dysfunction in MDD.[153,185,186] These actions of releasing prefrontal neurotransmitters are theoretically linked to the ability of atypical antipsychotics to improve cognition in schizophrenia and may thus be useful in improving residual cognitive symptoms in MDD as well.

### Stimulants

Central nervous system (CNS) stimulants, such as amphetamine and methylphenidate, have been used for many years to improve residual symptoms of sleepiness, fatigue, and executive dysfunction in MDD. CNS stimulants not only block NE and DA reuptake but also increase the release of these 2 neurotransmitters by interfering with the transport of these agents into synaptic vesicles.[187,188] However, CNS stimulants can increase the release of DA and NE not only in the cortex, but also in subcortical limbic areas such as nucleus accumbens, which is responsible for the significant abuse potential of these drugs.[189–191] Clinical data have shown some positive results of adjunctive therapy with CNS stimulants for treatment of fatigue in depression[192–194]; however, no studies have been found to examine the role of CNS stimulants as a drug treatment for executive dysfunction in depression. Given their known actions in attention deficit disorder, though, a positive effect on residual symptoms of cognitive dysfunction in MDD could be expected.

## SUMMARY

Symptoms of MDD are hypothetically mediated by different malfunctioning neurocircuits. Fatigue, sleep disturbances, and executive dysfunction are important residual symptoms that often persist following treatment but must be eliminated to achieve the goal of an asymptomatic state of full remission. A novel treatment approach for treating the symptoms of MDD is to augment antidepressants with agents that increase neurotransmission of 5-HT, NE, DA, acetylcholine, and/or histamine in the hypothetically malfunctioning brain circuits mediating those symptoms.

*Drug names:* aripiprazole (Abilify), atomoxetine (Strattera), bupropion (Wellbutrin and others), buspirone (BuSpar and others), fluoxetine (Prozac and others), methylphenidate (Ritalin, Metadate, and others), modafinil (Provigil), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

*Disclosure of off-label usage:* The authors of this article have determined that, to the best of their knowledge, aripiprazole, atomoxetine, buspirone, methylphenidate, modafinil, olanzapine, quetiapine, risperidone, and ziprasidone are not approved by the U.S. Food and Drug Administration for the treatment of symptoms of depression.

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