Neurotransmitter Targeting in the Treatment of Depression

Pierre Blier, MD, PhD

Residual symptoms are a common hindrance to daily life for patients with major depressive disorder. Even after antidepressant treatment has led patients to meet remission criteria, almost all patients have at least 1 symptom that remains unresolved. These symptoms can increase the risk for relapse, a chronic course, and suicide attempts. Residual symptoms are lingering symptoms that do not resolve with treatment of the depressive episode, and they should be distinguished from symptoms of comorbid psychiatric or medical conditions and medication side effects. By understanding how various antidepressants affect the 3 monoamine systems of serotonin, norepinephrine, and dopamine, clinicians can select treatments based on the most effective mechanism of action. Dual-action agents show promise for alleviating depressive symptoms that do not resolve with single-action agents. Medications that increase norepinephrine or dopamine neurotransmission may improve several common residual symptoms left after treatment with serotonin-specific agents. Treatment strategies like adjunctive therapies and dosing options are given for common residual symptoms, including sleep difficulties, sexual dysfunction, and pain. For patients to truly regain their quality of life, clinicians must target residual symptoms.
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After responding to antidepressant treatment, many patients with major depressive disorder (MDD) often have lingering symptoms but may no longer meet the criteria for a major depressive episode. According to the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*), a major depressive episode requires the presence of 5 or more symptoms during a consecutive 2-week timeframe.[1] Therefore, patients can be in remission and not meet MDD criteria while still experiencing residual, subthreshold symptoms.

Patients with unresolved symptoms have more functional and social impairments, more time with subthreshold depressive symptoms, and an increased risk of relapse, chronic course of illness, and suicide attempts than those with depression without residual symptoms.[2–5]

Therefore, the treatment goal for patients with MDD must be *complete remission* of symptoms rather than response. Response to antidepressant treatment is typically considered a 50% or more reduction in symptoms, often measured by a standardized rating scale, such as the Hamilton Depression Rating Scale (HDRS) or the Montgomery-Asberg Depression Rating Scale (MADRS).[2] Although that reduction may be a statistically significant improvement, many patients with MDD are left with clinically significant symptoms, showing that even the goal of remission does not guarantee that all depressive symptoms are resolved. In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial,[6] more than 90% of patients who met remission criteria had at least 1 residual symptom (median of 3 symptoms). Patients who remitted before 6 weeks of treatment had fewer residual symptoms than later remitters at 1 year, which lessened their risk of relapse, emphasizing why *complete* remission should be the treatment goal.

To help patients achieve asymptomatic remission, clinicians must recognize residual symptoms, understand the connection between monoamine systems and antidepressant treatments, and target common residual symptoms during treatment.

RECOGNIZE AND DIFFERENTIATE RESIDUAL SYMPTOMS

Residual symptoms are often milder versions of typical depressive symptoms[7] and fall into the same domains: emotional, physical, and cognitive.[1] Of these 3 symptom domains, the cognitive aspects of MDD are probably the most neglected in treatment. Cognitive impairments can include problems in attention, working memory, and executive function (eg, problem solving and task planning).[8] For example, difficulty concentrating or thinking has been cited as the third most common symptom for patients with MDD, behind only sleep problems and depressed mood (Figure 1).[9,10]

Residual symptoms in patients with MDD may be unresolved depressive symptoms or caused by a co-occurring psychiatric or medical condition or adverse events from medication. For example, patients with MDD often have comorbid substance dependence, anxiety disorders, personality disorders, cardiometabolic conditions, and diabetes.[11,12] Secondary psychiatric or medical conditions, as well as their treatments, may produce symptoms such as fatigue, cognitive impairment, or sexual dysfunction, which may also be residual symptoms of MDD.[7] Additionally, antidepressant-

From the Department of Psychiatry and Cellular/Molecular Medicine, University of Ottawa, and Mood Disorders Research, University of Ottawa Institute of Mental Health Research, Ottawa, Ontario, Canada.

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***Corresponding author:** Pierre Blier, MD, PhD, Institute of Mental Health Research, 1145 Carling Ave, Ottawa, ON K1Z 7K4, Canada (pierre.blier@theroyal.ca).*

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Clinical Points

- Residual symptoms occur in most patients who have been treated for a major depressive episode and achieved remission.
- Many antidepressants increase 5-HT and trigger a decrease in NE and DA.
- Symptoms that did not respond to the initial antidepressant may respond to a medication with a different mechanism of action.
- Effective strategies for treating common residual symptoms include switching to a different antidepressant and adding adjunctive medications to target the symptom(s).

induced side effects may mimic residual symptoms and contribute to treatment discontinuation, causing previously controlled symptoms to emerge.[13] Common adverse effects that lead to discontinuation include drowsiness/fatigue, insomnia, sexual dysfunction, gastrointestinal symptoms, anxiety, headache, weight changes, nausea, and rash.[14,15]

Making a complete baseline assessment of depressive symptoms before initiating treatment can help clinicians differentiate between unresolved residual symptoms, comorbid conditions, and treatment-emergent side effects. If new symptoms arise after treatment is initiated, they are likely to be medication side effects or a result of a comorbidity such as substance use.[7] Whatever the cause of persistent or new-onset symptoms in patients being treated for MDD, clinicians must recognize and treat them to improve adherence and both short- and long-term outcomes.

UNDERSTAND THE CONNECTION BETWEEN MONOAMINE SYSTEMS AND ANTIDEPRESSANT TREATMENTS

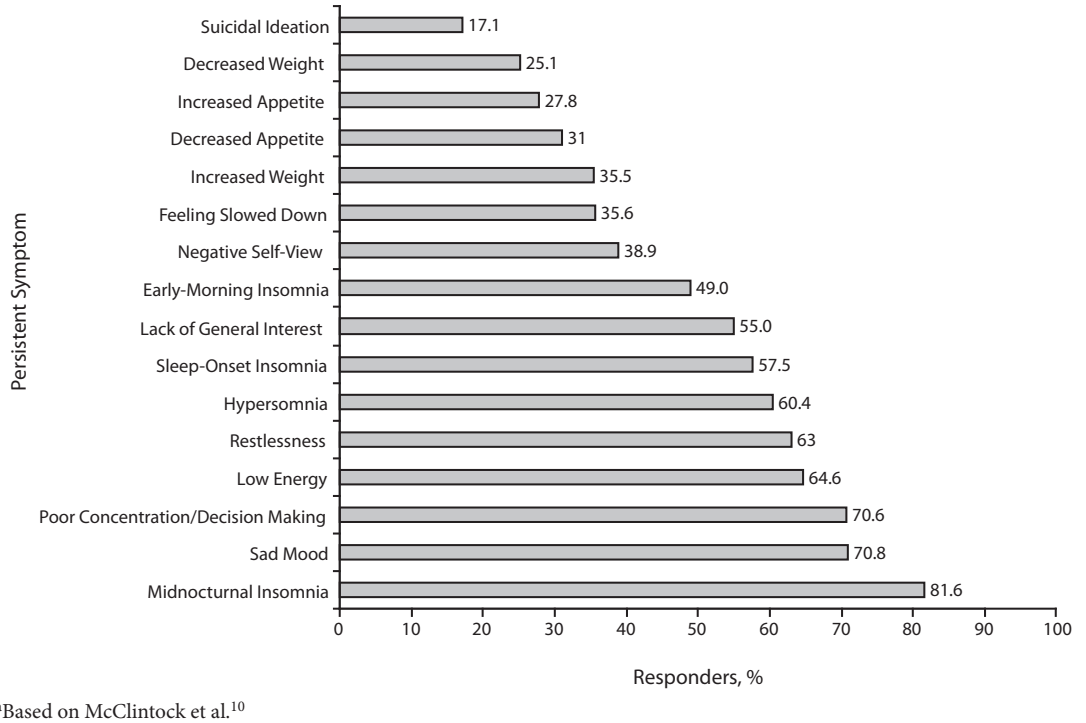
The 3 main monoamine systems associated with the pathophysiology of depression and the therapeutic effects of antidepressants are serotonin (5-HT), norepinephrine (NE), and dopamine (DA). These systems control specific aspects related to impulsivity, arousal, and reward effects in the brain, respectively. For example, people with 5-HT hypofunction can be at greater risk for committing suicide because of the 5-HT system's association with regulating impulsive aggression.[16,17]

Although each of these 3 neurotransmitter systems has specific associations, significant overlap exists in the signs and symptoms of depression. While an antidepressant may control some symptoms, such as depressed mood, new symptoms like anxiety or fatigue may be triggered by the medication's mechanism of action on 1 or more systems.

In the human brain, the cell bodies of these monoaminergic neurons are centered in the brainstem or in the mesencephalon, or midbrain. Specifically, 5-HT cell bodies are contained in the dorsal and medial raphe nuclei, NE neurons are located in the locus ceruleus (LC), and DA neurons are in the ventral tegmental area (VTA).

The 5-HT, NE, and DA neurons are interconnected both anatomically and functionally. These cells send reciprocal interactions and projections to common targets. Both the limbic system and the cortex are innervated by these 3 systems. The mechanism of action at various 5-HT, NE, and

Figure 1. Proportion of Responders Who Had Symptoms at Baseline That Persisted at Exit[a,b]



[a]Based on McClintock et al.[10]
[b]Response was defined as ≥ 50% reduction in 16-Item Quick Inventory of Depressive Symptomatology–Self Report ($QIDS\text{-}SR_{16}$).

DA receptors affects the efficacy and tolerability of many depression treatments, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).

Selective Serotonin Reuptake Inhibitors

An SSRI increases 5-HT transmission, which is sufficient to control depressive symptoms for some patients, but it can cause incomplete response or may not completely resolve all depressive symptoms. This increase in 5-HT inhibits NE neurons and decreases their firing rate, resulting in decreases in DA neuronal activity as well. Rat studies[18] have confirmed these effects with sustained use of SSRIs. When rats were administered citalopram or paroxetine for 2, 14, or 21 days, a gradual decrease in spontaneous firing activity of NE neurons in the LC resulted. Rats treated daily for 14 days with citalopram also showed reduction in NE levels in the basolateral nucleus of the amygdala and the LC.[19]

Another rat study[20] demonstrated the effects of SSRIs on DA neuronal firing in the VTA. The SSRI escitalopram, which has greater 5-HT reuptake inhibition potency than citalopram, decreased the firing rate and burst activity of DA neurons with sustained administration in anesthetized rats, but citalopram attenuated only burst activity, not the firing rate. Antagonists at 5-HT_{2C} receptors and agonists at DA receptors may prove to be effective adjunctive therapy because of their complementary mechanism of action with SSRIs.[20]

The effects of antidepressants on NE and DA receptors relate directly to depressive symptoms like cognitive impairment, anxiety, and fatigue.[21] NE and DA in the prefrontal cortex (PFC) regulate working memory and task performance, and too much or too little can lead to cognitive impairment. For example, excessive NE or DA release impairs PFC regulation and may cause anxiety or psychosis, whereas inadequate excitation of these receptors can lead to inattention and drowsiness.[21]

As more research is done on specific receptor subtypes within the 5-HT, NE, and DA systems, new pharmacologic options should emerge for treating partial responders and nonresponders to antidepressant treatment. For example, administering atypical antipsychotics at subtherapeutic doses can provide helpful supplemental pharmacologic properties without decreasing the D_2 transmission that is the basis for antipsychotic response.[22] Atypical antipsychotics may be used to block 5-HT_{2A} receptors, which are the pathways used by SSRIs to decrease NE transmission.[23] Therefore, using an adjunctive atypical antipsychotic to block the 5-HT_{2A} specific receptor subtype could prevent the potentially negative impact of SSRIs on NE transmission.

Dual-Acting Agents

Agents that target more than 1 monoamine system have the potential to more effectively treat depressive symptoms than single-action agents. For example, SNRIs increase the function of the 5-HT system, even at minimal doses, but higher doses also block NE transporters. Even though the NE firing will be decreased, the transporters at the other end of the neuron will be blocked.[24] This action is very different from an SSRI. Whereas an SSRI can increase only 5-HT, an SNRI can increase both 5-HT and NE transmission as long as it is administered at an adequate dose. The ability of SNRIs and norepinephrine reuptake inhibitors (NRIs) to enhance NE neurotransmission may improve residual symptoms of anhedonia and psychomotor retardation.

Norepinephrine reuptake inhibitors also affect DA. Norepinephrine is synthesized from DA, and the only chemical difference between them is that NE has an extra hydroxyl group on the side chain. The PFC has few DA transporters, and NE transporters are probably the primary mechanism for DA reuptake in the PFC.[25] Therefore, blocking NE reuptake transporters with an NRI (eg, desipramine, reboxetine, atomoxetine) can elevate levels of DA in the PFC or hippocampus. Reboxetine enhances DA output in the PFC but not in the nucleus accumbens.[26] A study[27] comparing agents (eg, fluoxetine, clomipramine, imipramine, and desipramine) that increase extracellular concentrations of DA in the PFC but not in the medial nucleus accumbens revealed that stimulating DA transmission in the PFC may have a role in the effectiveness of these drugs independent of an action in the nucleus accumbens.

In addition to SNRI and NRI agents, the antidepressant mirtazapine is a presynaptic α_2 antagonist with dual action on NE and 5-HT neurotransmission.[28] Mirtazapine has postsynaptic antagonism at 5-HT_2 and 5-HT_3 receptors, which contributes to its antidepressant effects without typical SSRI side effects.[28]

TARGET COMMON RESIDUAL SYMPTOMS

Applying what is known about the effects of drugs on the 5-HT, NE, and DA systems, clinicians can target specific residual symptoms that are the most common or troublesome for patients with MDD.

Fatigue/Sleepiness

Agents that increase NE and DA neurotransmission in relevant pathways may improve symptoms of fatigue, sleepiness, and cognitive impairment. Fatigue may be a symptom of the depression or a side effect of antidepressant treatment.[29,30] Although tricyclic antidepressants (TCAs) are more commonly associated with sedating effects, some SSRIs and SNRIs can also cause treatment-emergent fatigue.[31] For patients who present with fatigue at baseline, antidepressant medications that are more likely than others to resolve fatigue symptoms can be used as monotherapy. These include bupropion, venlafaxine, sertraline, and fluoxetine.[32] As a norepinephrine-dopamine releaser, bupropion has been shown to significantly improve fatigue scores compared with SSRIs and placebo in patients with MDD.[33] Patients who experienced remission with bupropion also had fewer residual hypersomnia or fatigue symptoms compared with SSRI remitters.[33] SSRI treatment for fatigue comes mainly from studies in special populations.[34]

Another treatment strategy is to use adjunctive therapy with agents that increase NE and/or DA neurotransmission

to target fatigue and sleepiness.[31] Adjunctive treatments include psychostimulants (eg, methylphenidate), atomoxetine, or atypical antipsychotics (at lower doses).[7,35] Some atypical antipsychotics (eg, olanzapine, risperidone, quetiapine) can alleviate daytime fatigue by improving sleep quality at night.[36] Similarly, pramipexole, a presynaptic DA agonist, has been shown to safely improve poor sleep quality in patients with restless leg syndrome and in patients with MDD.[37,38]

In contrast to the sedative effects of atypical antipsychotics and pramipexole, atomoxetine is an NRI used to treat attention deficit/hyperactivity disorder (ADHD). A study[39] of adjunctive atomoxetine in 12 patients with MDD suggests a promising role for treating residual fatigue. Patients taking atomoxetine had significant reductions on the fatigue measure, and 5 of the 12 patients had a 50% or more decrease in fatigue measurement scores. All 12 patients remitted by follow-up.

An adjunctive treatment that increases histamine (H) and DA is the wake-promoting agent modafinil, which can improve fatigue and sleepiness in patients with MDD.[32,35] In partial responders to antidepressant therapy, adjunctive modafinil significantly improved sleepiness and residual fatigue.[40] Because modafinil (200–400 mg/d) interferes with DA reuptake inhibition and may be associated with dependence and abuse, it should be used with caution in certain populations.[41]

Insomnia

Another common sleep disturbance that often persists in patients with MDD even after remission is insomnia.[42] In an 8-week study[43] of residual MDD symptoms in responders to a fixed dose of fluoxetine, 92% of patients with posttreatment insomnia had pretreatment insomnia. The persistence of insomnia throughout treatment indicates a significant problem.

Clinicians may select sedative or sleep-promoting antidepressants or atypical antipsychotics to help patients with MDD and insomnia. Trazodone at low doses (25–150 mg) at bedtime could be used as an adjunctive treatment because it blocks 5-$HT_{2A/C}$ receptors as well as α_1 receptors. Blocking H_1 receptors may also cause sedating effects, therefore doxepin, a probable H_1 and 5-HT_2 antagonist, in small doses (eg, 10–20 mg/d) and quetiapine, a probable H_1, 5-HT_2, and α_1 antagonist, (25–50 mg/d) could be used in conjunction with depression treatment to alleviate insomnia. Benzodiazepine hypnotics can improve sleep disturbances, although some are more selective than others. For example, zolpidem augmentation (10 mg/qhs) of an SSRI (ie, fluoxetine, sertraline, or paroxetine) improved sleep quality and duration in patients with persistent insomnia.[44]

Cognitive Impairment

Although cognitive symptoms usually improve with antidepressant treatment, they may remain unresponsive or emerge as a treatment side effect.[29,31] Attention and memory problems are often present in patients with MDD,[45] although prevalence rates for residual cognitive impairment have not been established for patients with remitted MDD. Anecdotal augmentation strategies to alleviate cognitive symptoms include cholinesterase inhibitors, bupropion, DA receptor agonists, psychostimulants, and modafinil.[29] Like the treatment of fatigue and sleepiness, cognitive impairment should improve with increased NE and DA neurotransmission. For example, augmenting SSRI treatment with the NRI atomoxetine, although not FDA-approved for the treatment of depression, has alleviated concentration and sleep problems in a case study including 3 patients who could not tolerate dual-acting medications.[46] By augmenting an SSRI with an NRI, clinicians can also create a dual-acting regimen.

Sexual Dysfunction

Sexual dysfunction is a common side effect of agents that block the 5-HT reuptake transporter.[47] This means that many antidepressants are associated with sexual problems related to desire, arousal, and orgasm/ejaculation.[48] Many patients are unlikely to spontaneously report sexual dysfunction to their physician, and up to 42% of patients waited for the symptoms to resolve themselves.[47] As a result, sexual dysfunction symptoms contribute to patient dissatisfaction and treatment noncompliance.[49]

Several strategies are available to treat sexual dysfunction, although many lack substantial evidence for efficacy. For example, adding a medication to an antidepressant has yielded mostly negative results with the exceptions of bupropion and sildenafil.[50,51]

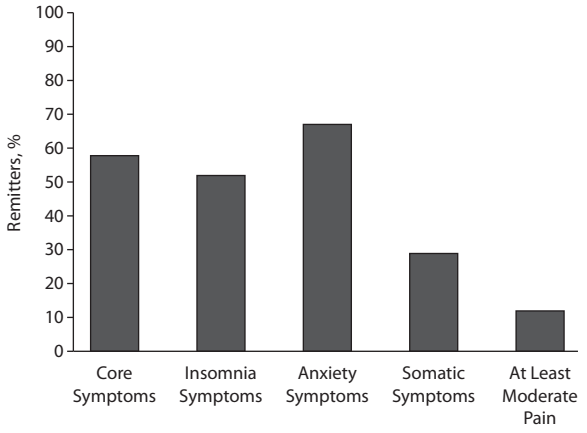
Dosing reductions may be used to eliminate sexual dysfunction, as long as antidepressant efficacy is not sacrificed.[48] When titrating down the antidepressant dose, clinicians should always monitor depressive symptoms to ensure that efficacy is maintained and relapse is prevented.

Another strategy is to switch to another antidepressant that does not have a propensity to cause sexual dysfunction. For example, nefazodone, bupropion, and mirtazapine are associated with less sexual dysfunction than SSRIs and venlafaxine.[52,53] Of course, any switching strategy requires careful monitoring for discontinuation symptoms or loss of efficacy.[49] An optimal strategy is a plateau switch in which the drug inhibiting 5-HT reuptake is continued while the new antidepressant is introduced and titrated up to a therapeutic dose. This approach must not be used with a monoamine oxidase inhibitor (MAOI) because monoamine oxidase should not be inhibited at the same time as blocking the reuptake of 5-HT. The initial antidepressant would have to be completely discontinued, typically with a washout period, before starting an MAOI.

Pain

Patients with MDD often have comorbid pain symptoms. A review[54] found that an average of 65% of patients with depression experienced 1 or more pain complaints (eg, headache, back ache, joint pain, or general pain). Among patients whose MDD had remitted after 3 months of treatment, about 10% reported residual pain symptoms (Figure 2).[42]

Figure 2. Prevalence of Residual Symptoms in Remitters (N = 412)[a,b]



[a]Reprinted with permission from Romera et al.[42]
[b]Remission is defined as a score of ≤ 7 on the 17-item Hamilton Depression Rating Scale.

When antidepressants increase levels of NE and 5-HT in certain brain areas, they help modulate pain signals.[54] This explains the efficacy of certain antidepressants in alleviating pain symptoms. But, if an antidepressant has not reduced pain symptoms, clinicians must consider other options. If the patient was taking an SSRI, then a crossover to a dual reuptake inhibitor (eg, duloxetine, milnacipran, venlafaxine) can be used. The SNRI dose should be increased to the upper range to ensure significant NE reuptake inhibition along with 5-HT reuptake inhibition.[55] In a study[56] of patients with MDD and painful physical symptoms (N = 86), venlafaxine extended-release (75–225 mg/d) significantly decreased total $HDRS_{17}$ scores ($P < .0001$) and overall pain ($P < .0001$) at every visit. Pain responders demonstrated a better depression remission rate than pain nonresponders (56% vs 20%; $P = .0001$).

Of a similar structure to venlafaxine, tramadol is a 5-HT and NE reuptake inhibitor and a μ-opoid agonist available in slow-release formulations. Widely prescribed as an analgesic comparable to codeine, tramadol acts only on the μ-opioid receptors, unlike other opioids that act on multiple opioid receptors. Due to its unique mechanism of action, tramadol shows promise for patients with depression and chronic pain.[57] Although the abuse incidence for tramadol is low, agonists of μ-receptors still carry a risk for addiction.[57,58] Serotonin syndrome is another risk if tramadol is combined with other agents that increase 5-HT activity,[57] but it is not necessarily contraindicated with SSRIs if it is uptitrated slowly.

The TCAs amitriptyline or nortriptyline could be used adjunctively at low doses (ie, 25–50 mg/d) for pain management,[59] and gabapentin and pregabalin, anticonvulsants that target the $\alpha_2\delta$ subunit of voltage-gated calcium channels, may be beneficial for pain as well as for comorbid anxiety.[60] Gabapentin and pregabalin lower neurotransmission in pain pathways and are FDA-approved to treat pain in a variety of conditions.[60]

CONCLUSION

Residual symptoms are a common and problematic issue in patients with MDD who remit with antidepressant treatment. Residual symptoms increase the risk of relapse, suicide, and continued functional impairments in relationships and work. Although the severity of the symptoms may be decreased through treatment, many physical, emotional, and cognitive symptoms can remain. These unresolved symptoms from the major depressive episode should be distinguished from symptoms of comorbid psychiatric or medical conditions and from side effects of treatment.

Most antidepressant medications alleviate depressive symptoms by acting at 5-HT receptors in the brain. Because the 5-HT system is interconnected with the NE and DA systems, medications that increase 5-HT often decrease NE and DA, resulting in certain persistent symptoms. Dual-action medications, like SNRIs, are more effective than SSRIs at controlling some residual symptoms. For patients who cannot tolerate dual-action agents, clinicians can target specific residual symptoms using a variety of adjunctive medications or dosing strategies. Adding low doses of medications with a different mechanism of action can supplement the antidepressant effects by targeting unresolved symptoms such as fatigue, insomnia, sexual dysfunction, or pain.

Drug names: atomoxetine (Strattera), bupropion (Wellbutrin, Aplenzin, and others), citalopram (Celexa and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), doxepin (Zonalon, Silenor, and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), gabapentin (Neurontin, Gralise, and others), imipramine (Tofranil and others), methylphenidate (Focalin, Daytrana, and others), milnacipran (Savella), mirtazapine (Remeron and others), modafinil (Provigil and others), nortriptyline (Pamelor, Aventyl, and others), olanzapine (Zyprexa and others), paroxetine (Paxil, Pexeva, and others), pramipexole (Mirapex and others), pregabalin (Lyrica), quetiapine (Seroquel and others), risperidone (Risperdal and others), sertraline (Zoloft and others), sildenafil (Viagra and Revatio), tramadol (Ultram, Ryzolt, and others), trazodone (Oleptro and others), venlafaxine (Effexor and others), zolpidem (Ambien, Zolpimist, and others).

Disclosure of off-label usage: Dr Blier has determined that, to the best of his knowledge, atomoxetine, gabapentin, methylphenidate, milnacipran, modafinil, pramipexole, pregabalin, quetiapine, sildenafil, and trazodone are not approved by the US Food and Drug Administration for the treatment of depression.

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