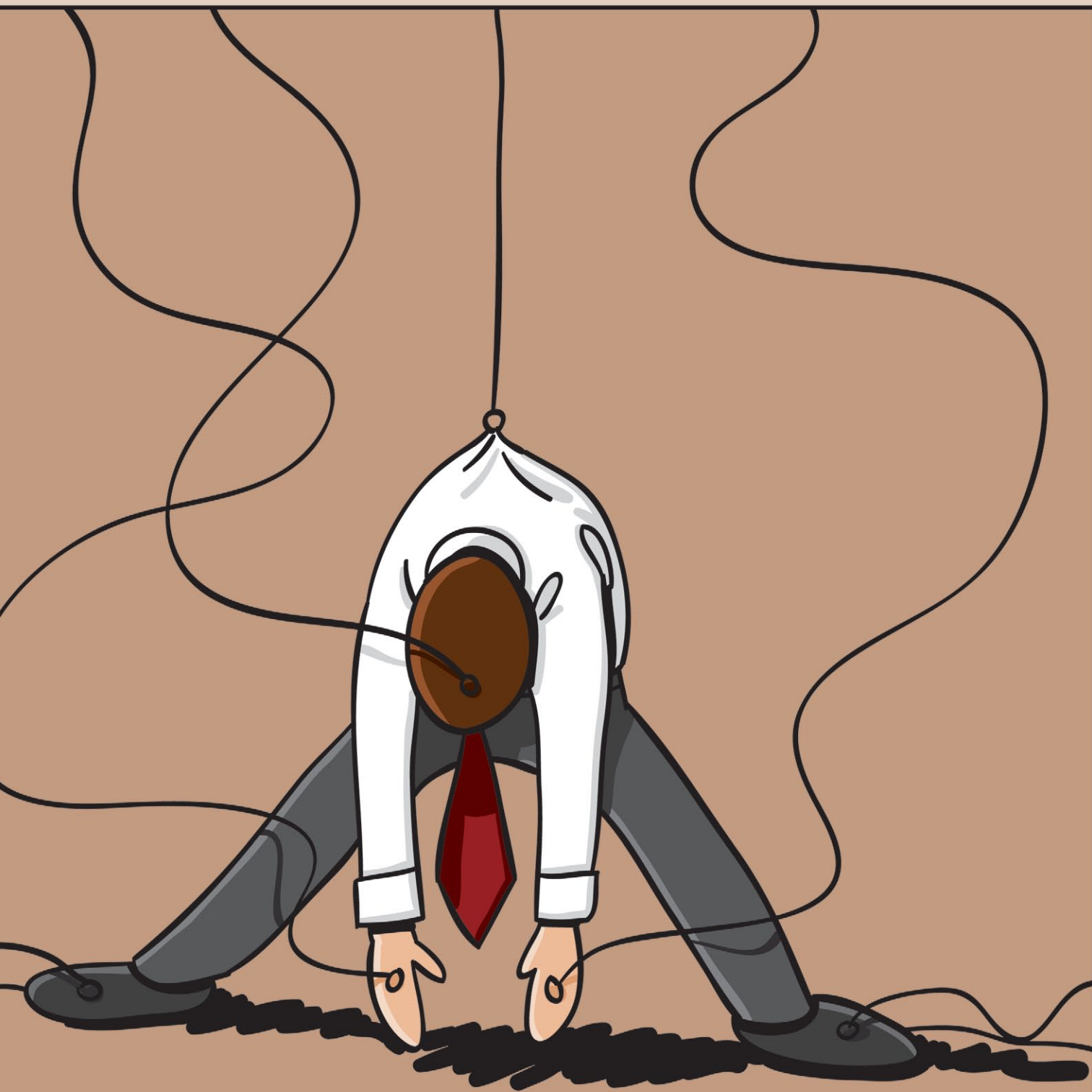


Fatigue after depression



responds to therapy

What are the next steps?

A sufficient base of evidence is often lacking to guide pharmacotherapy for fatigue

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Fatigue and depression can be viewed as a “vicious cycle”: Fatigue can be a symptom of major depression, and fatigue can be a risk factor for depression.¹ For example, fatigue associated with a general medical condition or traumatic brain injury can be a risk factor for developing major depressive disorder (MDD).¹⁻³ It isn't surprising that fatigue has been studied as a predictor of relapse after previous response to treatment in patients with MDD.

Despite the observed association between fatigue and depression, their underlying relationship often is unclear. The literature does not differentiate among fatigue associated with depression, fatigue as a treatment-emergent adverse effect, and fatigue as a residual symptom of depression that is partially responsive to treatment.^{4,5} To complicate the situation, many medications used to treat MDD can cause fatigue.

Patients often describe fatigue as (1) feeling tired, exhausted, or drained and (2) lacking energy and motivation. Fatigue can be related to impaired wakefulness but is believed to be a different entity than sleepiness.⁶ Residual fatigue can affect social, cognitive, emotional, and physical health.

We reviewed the literature about fatigue as a symptom of MDD by conducting a search of Medline, PubMed, and Google Scholar, using keywords *depression*, *fatigue*, *residual symptoms*, and *treatment*. We chose the papers cited in this article based on our consensus and because these publications represent expert opinion or the highest quality evidence available.

Residual fatigue has an effect on prognosis

Fatigue is a common symptom of MDD that persists in 20% to 30% of patients whose symptoms of depression otherwise remit.^{4,7-9} Several

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studies have linked residual fatigue with the overall prognosis of MDD.⁵ Data from a prospective study demonstrate that depressed patients have a higher risk of relapse when they continue to report symptoms of fatigue after their symptoms of depression have otherwise entered partial remission.¹⁰ Another study demonstrated that the severity of residual symptoms of depression is a strong predictor of another major depressive episode.¹¹

In a large-scale study, the prevalence of residual fatigue after adequate treatment of MDD in both partial responders and remitters was 84.6%.¹² The same study showed that one-third of patients who had been treated for MDD had persistent and clinically significant fatigue, which could suggest a relationship between fatigue and selective serotonin reuptake inhibitors (SSRIs) and other antidepressants.

Another study demonstrated that 64.6% of patients who responded to antidepressant treatment and who had baseline fatigue continued to exhibit symptoms of fatigue after an adequate trial of an antidepressant.¹³

Neurobiological considerations

Studies have shown that the neuronal circuits that malfunction in fatigue are different from those that malfunction in depression.¹⁴ Although the neurobiology of fatigue has not been determined, decreased neuronal activity in the prefrontal circuits has been associated with symptoms of fatigue.¹⁵

In addition, evidence from the literature shows a decrease in hormone secretion¹⁶ and cognitive abilities in patients exhibiting symptoms of fatigue.¹⁷ These findings have led some experts to hypothesize that symptoms of fatigue associated with depression could be the result of (1) immune dysregulation¹⁸ and (2) an inability of available antidepressants to target the underlying biology of the disorder.²

Despite the hypothesis that fatigue associated with depression might be biologically related to immune dysregulation, some authors continue to point to an imbalance in neurotransmitters—norepinephrine, histamine, dopamine, acetylcholine—as being

Pharmacotherapeutic options for fatigue associated with depression

Drug (class)	Neurobiological mechanism targeting fatigue ^a	First-line therapy	Augmentation therapy
Sertraline ³⁴ (selective serotonin reuptake inhibitor)	Dopamine ^a	Yes	–
Bupropion ³⁵ (norepinephrine-dopamine reuptake inhibitor)	Norepinephrine, dopamine	Yes	–
Venlafaxine ³⁶ (serotonin-norepinephrine reuptake inhibitor)	Norepinephrine, dopamine ^a	Yes	–
Modafinil ³⁷	Histamine ^a	–	Yes
Amphetamine/dextroamphetamine, methylphenidate (stimulant) ³⁴	Norepinephrine, dopamine	–	Yes

^aThe principal mechanism of action of these drugs occurs by a different neurotransmitter system than what is listed. For example, the principal mechanism of action of sertraline is by serotonin reuptake inhibition. However, at higher dosages, sertraline might have limited activity on the dopaminergic system

Note: The drugs in this table might target fatigue through a mechanism of action involving the receptors listed. However, such receptor modulation may only occur at a higher dosage, and the clinical significance of this action is unclear

associated with fatigue.¹⁴ For example, a study demonstrated that drugs targeting noradrenergic reuptake inhibition were more effective at preventing a relapse of fatigue compared with serotonergic drugs.¹⁹ Another study showed improvement in energy with an increase in the plasma level of desipramine, which affects noradrenergic neurotransmission.²⁰

Inflammatory cytokines also have been explored in the search for an understanding of the etiology of fatigue and depression.²¹ Physical and mental stress promote the release of cytokines, which activate the immune system by inducing an inflammatory response; this response has been etiologically linked to depressive disorders.²² Furthermore, studies have demonstrated an elevated level of inflammatory cytokines in patients who have MDD—suggesting that MDD is associated with a chronic low level of inflammation that crosses the blood–brain barrier.²³

Clinical considerations: A role for rating scales?

Despite the significance of residual fatigue on the quality of life of patients who have MDD, most common rating scales, such as the Hamilton Depression Rating Scale²⁴ and the Montgomery-Åsberg Depression Rating Scale,²⁵ have limited sensitivity for

measuring fatigue.²⁶ The Fatigue Associated with Depression (FAsD)²⁷ questionnaire, designed according to FDA guidelines,²⁸ is used to assess fatigue associated with depression. The final version of the FAsD includes 13 items: a 6-item experience subscale and a 7-item impact subscale.

Is the FAsD helpful? The experience subscale of the FAsD assesses how often the patient experiences different aspects of fatigue (tiredness, exhaustion, lack of energy, physical weakness, and a feeling that everything requires too much effort). The impact subscale of the FAsD assesses the effect of fatigue on daily life.

The overall FAsD score is calculated by taking the mean of each subscale; a change of 0.67 on the experience subscale and 0.57 on the impact subscale are considered clinically meaningful.²⁷ The measurement properties of the questionnaire showed internal consistency, reliability, and validity in testing. Researchers note, however, that FAsD does *not* include items to assess the impact of fatigue on cognition. This means that the FAsD might not distinguish between physical and mental aspects of fatigue.

Treatment

It isn't surprising that residual depression can increase health care utilization

Clinical Point

Treatment with SSRIs has been associated with a low probability of achieving remission when targeting fatigue as a symptom of MDD



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Fatigue in depression

Clinical Point

Psychostimulants have been shown to be efficacious for depression and fatigue, both as monotherapy and adjunctively

and economic burden, including such indirect costs as lost productivity and wages.²⁹ Despite these impacts, there is a paucity of studies evaluating the relationship between residual symptoms, such as fatigue, and work productivity. It has been established that improving a depressed patient's level of energy correlates with improved performance at work.

Treating fatigue as a residual symptom of MDD can be complicated because symptoms of fatigue might be:

- a discrete symptom of MDD
- a prodromal symptom of another disorder
- an adverse effect of an antidepressant.^{2,30}

It is a major clinical problem, therefore, that antidepressants can alleviate *and* cause symptoms of fatigue.³¹ Treatment strategy should focus on identifying antidepressants that are less likely to cause fatigue (ie, noradrenergic or dopaminergic drugs, or both). Adjunctive treatments to target residual fatigue also can be used.³²

There are limited published data on the effective treatment of residual fatigue in patients with MDD. Given the absence of sufficient evidence, agents that promote noradrenergic *and* dopaminergic neurotransmission have been the treatment of choice when targeting fatigue in depressed patients.^{2,14,21,33}

The *Table*³⁴⁻³⁷ (page 29) lists potential treatment options often used to treat fatigue associated with depression.

SSRIs. Treatment with SSRIs has been associated with a low probability of achieving remission when targeting fatigue as a symptom of MDD.²¹

One study reported that, after 8 weeks of treatment with an SSRI, treatment-emergent adverse events, such as worsening fatigue and weakness, were observed—along with an overall lack of efficacy in targeting all symptoms of depression.³⁸

Another study demonstrated positive effects when a noradrenergic agent was added to an SSRI in partial responders who continued to complain of residual fatigue.³³

However, studies that compared the effects of SSRIs with those of antidepressants that have pronoradrenergic effects

showed that the 2 mechanisms of action were not significantly different from each other in their ability to resolve residual symptoms of fatigue.²¹ A limiting factor might be that these studies were retrospective and did not analyze the efficacy of a noradrenergic agent as an adjunct for alleviating symptoms of fatigue.³⁹

Bupropion. This commonly used medication for fatigue is believed to cause a significantly lower level of fatigue compared with SSRIs.⁴⁰ The potential utility of bupropion in this area could be a reflection of its mechanism of action—ie, the drug targets both noradrenergic and dopaminergic neurotransmission.⁴¹

A study comparing bupropion with SSRIs in targeting somatic symptoms of depression reported a small but statistically significant difference in favor of the bupropion-treated group. However, this finding was confounded by the small effect size and difficulty quantifying somatic symptoms.⁴⁰

Stimulants and modafinil. Psychostimulants have been shown to be efficacious for depression and fatigue, both as monotherapy and adjunctively.^{39,42}

Modafinil has demonstrated efficacy in open-label trials for improving residual fatigue, but failed to separate from placebo in controlled trials.⁴³ At least 1 other failed study has been published examining modafinil as a treatment for fatigue associated with depression.⁴³

Adjunctive therapy with CNS stimulants, such as amphetamine/dextroamphetamine and methylphenidate, has been used to treat fatigue, with positive results.¹⁶ Modafinil and stimulants also could be tried as an augmentation strategy to other antidepressants; such use is off-label and should be attempted only after careful consideration.¹⁶

Exercise might be a nonpharmacotherapeutic modality that targets the underlying physiology associated with fatigue. Exercise releases endorphins, which can affect overall brain chemistry and which have been theorized to diminish symp-

toms of fatigue and depression.⁴⁴ Consider exercise in addition to treatment with an antidepressant in selected patients.⁴⁵

To sum up

In general, the literature does not recommend one medication as superior to any other for treating fatigue that is a residual symptom of depression. Such hesitation suggests that more empirical studies are needed to determine what is the best and proper management of treating fatigue associated with depression.

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Drug Brand Names

Amphetamine/ dextroamphetamine	Adderall	Methylphenidate	Ritalin
Bupropion	Wellbutrin	Modafinil	Provigil
Desipramine	Norpramin	Sertraline	Zoloft
		Venlafaxine	Effexor

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continued

Clinical Point

The literature does not recommend 1 medication as superior to any other for treating residual symptoms of fatigue

Bottom Line

Fatigue can be a symptom of major depressive disorder (MDD) or a risk factor for depression. Fatigue has been studied as a predictor of relapse after previous response to treatment in patients with MDD. Residual fatigue can affect social, cognitive, emotional, and physical health and can result in increased utilization of health care services. A number of treatment options are available; none has been shown to be superior to the others.



Fatigue in depression

Clinical Point

Consider exercise in addition to treatment with an antidepressant in selected patients

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