

# The Psychopharmacology of Energy and Fatigue

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**Issue:** *Second only to depressed mood itself, tiredness, low energy, and listlessness are the most common symptoms associated with depression. Recent understanding of interactions between monoaminergic neurons may help explain why some antidepressants may be more rapidly energy restoring than others.*

## Role of Energy and Fatigue in Depression

In recent years, great emphasis has been placed on treating the subgroup of depressed patients who experience anxiety, transforming not only the treatment of anxiety comorbid with depression, but also the treatment of numerous anxiety disorders with a variety of antidepressants. On the other hand, another subgroup of depressed patients has been largely neglected, namely those with fatigue, lack of energy, and lack of motivation.<sup>1</sup> One possible reason for this neglect is that such complaints may be interpreted as symptoms of a somatic illness and lead to exhaustive searches for medical illness rather than to treatment as depression.

Patients with low energy and fatigue are actually more common than patients with anxiety, fearfulness, and worry.<sup>1</sup> Given that the new standard of care in the treatment of depression is to attain complete remission of all symptoms,<sup>2</sup> it is noteworthy that baseline fatigue and loss of interest in activities—and not baseline anxiety—prior to antidepressant treatment may be the best predictors of lack of remission with antidepressant treatment.<sup>3</sup> Energy loss in depression is the factor that correlates most strongly with days in bed, days of lost work, low work productivity, and lack of social functioning.<sup>4</sup> Failure to treat low energy in depressed patients can therefore lead to unsatisfactory outcomes, without return to normal social and occupational functioning.

## Energy Spectrum and Monoamine Neurotransmission

Energy can be thought of across a spectrum, from low energy characterized by fatigue, lack of motivation, listlessness, and lack of interest, merging eventually with sleepiness and sedation. At the other end of the spectrum are states of too much energy such as

agitation or even mania. Lesser degrees of excessive energy may be described as anxiety states. The ideal state is one of balance, having the energy and motivation to be engaged but relaxed.

The biological basis of energy, motivation, and fatigue in association with depression remains unknown, but a wide variety of data link these symptoms to the 3 monoamine neurotransmitters serotonin, norepinephrine, and dopamine. Low amounts of all 3 may be associated with mood complaints, but reductions of norepinephrine and dopamine are particularly associated with symptoms of fatigue, low energy, and lack of motivation.<sup>5,6</sup> Interactions of antidepressants with these monoamine neurotransmitters may explain not only antidepressant actions, but also actions on energy, motivation, and fatigue. Thus, agents such as selective serotonin reuptake inhibitors (SSRIs) that increase serotonin selectively can actually *decrease* both norepinephrine and dopamine neurotransmission acutely, via stimulation of 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors.<sup>7,8</sup> This action may explain the apathy and listlessness some patients experience

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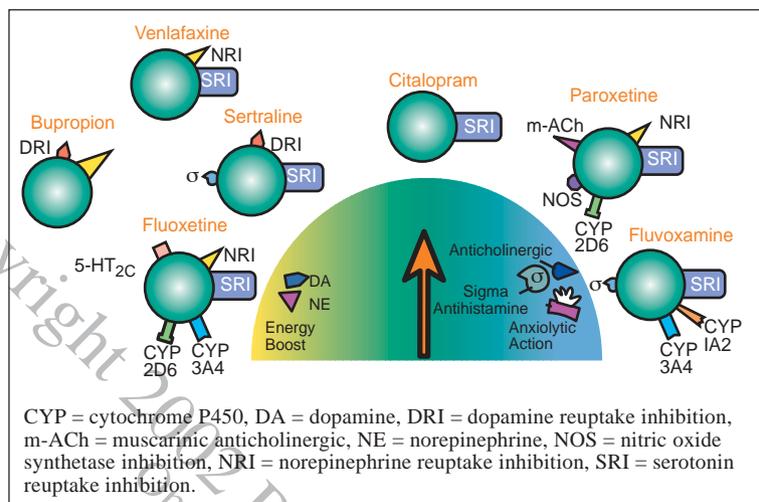
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when taking certain antidepressants, especially early in treatment.

On the other hand, agents that rapidly improve dopamine or norepinephrine functioning early in treatment may enhance the odds of having an early boost in energy (left side, Figure 1), whereas agents that block acetylcholine, histamine, or sigma receptors seem to enhance the odds of having an early anxiolytic action (right side, Figure 1).<sup>9</sup> Agents that can rapidly improve either dopamine or norepinephrine functioning include not only bupropion, which increases both norepinephrine and dopamine without increasing serotonin, but also venlafaxine, which increases serotonin as well as norepinephrine as a result of dual serotonin and norepinephrine reuptake blockade. The SSRI sertraline may have secondary direct and acute actions on dopamine reuptake in some patients and increase their energy. Fluoxetine has potent actions on 5-HT<sub>2C</sub> receptors, leading to a ro-

Figure 1. Spectrum of Antidepressants With Neurotransmitter Actions That May Boost Energy or Lead to Early Anxiolytic Action



bust and early increase in both norepinephrine and dopamine release, which may explain the rapid boost in energy that is not uncommonly observed with this agent.

Although any antidepressant may be as likely to work for any given patient in the long run, few studies address the fact that symptom improvement early in treatment is likely to enhance compliance, whereas a worsening of symptoms is likely to reduce compliance, even if the ultimate outcome months later is destined to be the same.<sup>10</sup> Thus, a fatigued pa-

tient with low motivation would not welcome reduced energy and sedation prior to getting better. Fortunately, a plethora of antidepressants have differing mechanisms of action that can be exploited to enhance the chances of short-term as well as long-term symptomatic relief in some cases.

**Summary**

In summary, low energy, fatigue, and lack of motivation are important symptoms in many patients with depression and must be eliminated in those patients to attain complete remission and a return to normal work and social functioning. One strategy for treating such patients is to utilize agents that boost noradrenergic or dopaminergic neurotransmission in order to get a rapid boost in energy, enhancing compliance and leading ultimately to the complete remission of symptoms by restoring energy, motivation, and interest and eliminating fatigue. ♦

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**Take-Home Points**

- ◆ Although symptoms of lack of energy, fatigue, and lack of motivation in depressed patients are actually more common than symptoms of anxiety, fearfulness, and worry, they are often less targeted for elimination by treatments.
- ◆ Not only are baseline fatigue and loss of interest in activities prior to antidepressant treatment predictors of lack of remission with antidepressant treatment, but loss of energy in depression also most strongly correlates with days in bed, days of lost work, low work productivity, and diminished social functioning.
- ◆ Antidepressant agents that enhance noradrenergic or dopaminergic functioning early in treatment may also be associated with a welcome early boost in energy.