

Symptoms of Fatigue and Cognitive/Executive Dysfunction in Major Depressive Disorder Before and After Antidepressant Treatment

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Patients with major depressive disorder commonly experience fatigue and cognitive/executive dysfunction. These problems may be symptoms of the depression and persist despite effective antidepressant treatment, or these problems may emerge as adverse effects of some antidepressant treatments. A number of augmentation strategies can be employed to manage fatigue or cognitive/executive dysfunction, but the efficacy of these augmentation strategies must be researched further.

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Fatigue and cognitive symptoms are frequently observed among depressed patients. In fact, the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV)¹ classification includes, among the 9 key symptoms of major depressive disorder (MDD), fatigue or loss of energy and symptoms of psychomotor retardation such as slowed speech and thinking. Furthermore, the DSM-IV classification considers extreme fatigue/leaden paralysis (e.g., a heavy, leaden feeling in arms or legs) as 1 of the 5 key features of MDD with atypical features, a common depressive subtype.²

FATIGUE AND MDD

In addition to being a common symptom of MDD, fatigue was also found to be a prodromal symptom of MDD in an initial study by Fava and colleagues.³ Their findings have been supported by a recent study⁴ that has shown that individuals who report a history of unexplained fatigue are at a markedly increased risk for new onset major depression as compared with those who never report such fatigue risk ratio (RR = 28.4, 95% CI = 11.7 to 68.0).

Among those currently suffering from an episode of MDD, fatigue and lack of energy are typically present in

the majority of the patients. Interestingly, a twin study⁵ showed that fatigue during the most severe major depressive episode is more likely to be reported among women than men.

Typically, fatigue and lack of energy improve with antidepressant treatment, although their improvement may be less rapid than other symptoms of MDD.⁶ A study by Judge et al.⁷ demonstrated that antidepressant-treated patients experience an improvement in energy symptoms as their overall depression improves.

Besides being a common symptom of MDD or a prodromal symptom, fatigue can also be a side effect of antidepressant treatment, although this happens more typically with sedating antidepressants. For example, a double-blind controlled study⁸ of fluoxetine and trazodone showed that more adverse events suggesting sedation (somnia, asthenia) were reported with trazodone than with fluoxetine (42.6% vs. 21.5%, $p \leq .05$). Despite the frequent clinical perception that rates of treatment-emergent fatigue may vary across selective serotonin reuptake inhibitors (SSRIs), a double-blind study⁹ failed to show a statistically significant difference among fluoxetine, sertraline, and paroxetine in rates of asthenia/fatigue. In general, however, very little is known about the relative risk of experiencing treatment-related fatigue with the newer antidepressants. Clinicians, however, may tend to favor agents perceived to be less sedating and more activating for individuals who are concerned with this particular side effect. On the other hand, even activating agents may be associated with fatigue as a side effect; this has been generally thought to be the result of disruption of sleep architecture, with sleepiness and fatigue being the consequence of poor sleep quality and sleep deprivation.

Fatigue may also be a residual symptom of MDD. Data from 37 patients completing 2 to 3 years of maintenance

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antidepressant therapy showed that complaints of physical tiredness were related primarily to residual depression.¹⁰ Another study¹¹ showed that approximately one third of patients who had responded to fluoxetine treatment (Hamilton Rating Scale for Depression score < 8) reported fatigue as a subthreshold or threshold residual symptom of their MDD. Therefore, it appears that fatigue may persist despite effective antidepressant treatment.

When fatigue is a residual symptom of MDD or a side effect of otherwise effective antidepressant treatment, clinicians often use augmentation strategies to either boost the antidepressant effect¹² or manage such side effects. Activating antidepressants such as bupropion or atomoxetine may be added, or, perhaps more commonly, psychostimulants or modafinil. The psychostimulant strategy was first reported by Masand et al.,¹³ who showed that, in 7 patients with MDD who had a partial response to antidepressant treatment, a marked improvement in clinical symptoms of depression was noted following psychostimulant augmentation, particularly in apathy and feelings of fatigue. Later, Menza and colleagues¹⁴ reported a retrospective case series in which modafinil was used to augment partial or nonresponse to an antidepressant. At doses of 100 to 200 mg/day, all 7 patients achieved full or partial remission, generally within 1 to 2 weeks. All patients had some residual tiredness or fatigue prior to starting modafinil, and this symptom was particularly responsive to augmentation. Since this original observation, there have been other reports of open trials of modafinil for augmentation of antidepressants among partial or non-responders,¹⁵⁻¹⁷ and a double-blind, placebo-controlled study¹⁸ recently showed an advantage of modafinil over placebo in treating fatigue among partial responders to antidepressant treatment. Further studies are clearly needed to establish the efficacy of these augmentation strategies.

COGNITIVE AND EXECUTIVE DYSFUNCTION IN MDD

Over the past couple of decades, several neuropsychological studies have demonstrated that cognitive and executive function deficits are relatively common in MDD.

One of the first reports in the literature on cognitive symptoms in MDD came from Rush and colleagues.¹⁹ They assessed 22 patients who had unipolar, nonpsychotic major depression by using a neuropsychological test battery. The endogenously depressed patients performed more poorly than those without endogenous depression did on the test battery as a whole, and, when compared with performance norms obtained from nondepressed controls, both groups showed performance impairments on the majority of subtests in the battery.

A subsequent study by Roy-Byrne et al.²⁰ assessed 10 patients with MDD and 10 age- and sex-matched normal controls by using 2 contrasting cognitive tasks: one re-

quired sustained effort and information processing, and the other required only superficial information processing that could be accomplished automatically with little effort. Depressed patients performed more poorly only on the effort-demanding cognitive task. These findings were supported by a study by Tancer et al.,²¹ which showed that depressed patients performed significantly more poorly than the controls on effort-demanding tasks, while not differing on the effortless tasks. Another study²² showed that depression in old adults may result in deficits in effortful, elaborate processes at encoding and retrieval.

A study by Richards and Ruff²³ showed that depressed patients were impaired on visuospatial short-term memory and learning and on verbal learning, and Isley et al.²⁴ found that depressed patients demonstrated deficits in psychomotor speed and in free recall of material (both immediate and delayed). Finally, a study²⁵ examining working memory function in untreated major depression by using a digit probe identification and matching task provided objective evidence that MDD significantly affects working memory.

While neuropsychological studies have consistently reported impaired cognition in elderly patients with unipolar depression, studies of cognitive function in younger patients with depression have shown more subtle results. For instance, in a study by Purcell et al.,²⁶ young patients showed impaired subsequent movement latencies on the Tower of London task, suggesting deficits in the ability to sustain motor responses in depression. Patients also showed impaired subsequent movement latencies on the task of attentional set shifting, requiring more trials to meet the criterion at the intradimensional stage of the task and being more likely to fail the task at the extradimensional shift stage than controls.

A 1997 meta-analysis by Veiel²⁷ of all neuropsychological studies published since 1975 showed that the neuropsychological deficits of individuals with MDD are consistent with a global-diffuse impairment of brain functions, with particular involvement of the frontal lobes. The severity and the profile of cognitive deficiencies in depression were postulated to be similar to those seen in moderately severe traumatic brain injury. In another study,²⁸ depressed patients also showed significantly more anomia, or word-finding difficulty, and made more naming errors (i.e., semantically related substitution words) than control subjects.

It is unclear whether the presence of cognitive and executive dysfunction in MDD has any relationship to fatigue and disruption of the sleep-wake cycle. Future studies will need to address this question.

Not all studies have shown neuropsychological impairments in patients suffering from MDD. For example, a study²⁹ of 28 unmedicated inpatients with MDD showed that cognitive functioning in depressed patients did not differ significantly from that in carefully matched con-

trols. Similarly, Grant et al.³⁰ administered a comprehensive battery of standard neuropsychological tests and experimental computerized measures of cognitive functioning to unmedicated ambulatory younger adults with mild to moderate nonbipolar depression and to a group of age- and gender-equated healthy subjects. They found that the patients demonstrated a notable absence of widespread cognitive impairment, with deficits in executive functions observed on the Wisconsin Card Sort Test but not on several other tests. However, a recent study³¹ involving 22 nonhospitalized patients with DSM-III-R–defined nonpsychotic unipolar major depressive disorder and 30 healthy controls showed that the patients performed significantly below controls in terms of selective attention, working memory, verbal long-term memory, and verbal fluency, in accordance with the hypothesis that in MDD there is a global-diffuse impairment of brain function with particular involvement of the frontal lobes.

Why are cognitive symptoms not always present in MDD? One possible explanation may be the variability in symptom severity. In a study³² examining the relationship between memory function and depression in 23 unmedicated patients with MDD, poor memory was associated with greater depression severity. Similarly, a study by Van Londen et al.³³ showed that melancholic depressed patients performed less well on the neuropsychological battery than did the nonmelancholic patients, but these differences could be accounted for by the severity of the illness. Van Londen and colleagues also found that global intellectual functioning was negatively correlated with mean baseline plasma concentrations of cortisol.

Another explanation is that recurrent depression may be relatively more likely to be associated with neuropsychological deficits. In a study by Basso and Bornstein,³⁴ young-adult, nonpsychotic, depressed inpatients were divided into 2 groups: those with a single episode ($N = 20$) and those with a recurrent episode ($N = 46$); these 2 groups—equivalent in age, education, estimated IQ, severity of depression, and demographic composition—were then administered the California Verbal Learning Test within a broader battery of neuropsychological tests. The recurrent-episode group demonstrated memory deficits relative to both the single episode group and published norms, but no other significant difference was found across the battery.

Finally, the presence of psychotic features may increase the probability that depressed patients may present with significant neuropsychological deficits. A recent study³⁵ examining differences in performance on a verbal memory test and in cortisol levels between patients with psychotic and nonpsychotic major depression and healthy volunteers found that subjects with psychotic major depression had a higher rate of errors of commission on the verbal memory test (i.e., they incorrectly identified distracters as targets) than did subjects with nonpsychotic major depression or

healthy volunteers, with errors of omission being similar among the 3 groups. Subjects with psychotic major depression had higher cortisol levels throughout the afternoon than subjects with nonpsychotic major depression or healthy volunteers.

Similarly, cognitive symptoms typically improve with antidepressant treatment. For example, in a study³⁶ among inpatients with MDD who were tested when depressed and after recovery, the majority of the cognitive function test results showed impaired performance during depression, with improvement after recovery. However, at times, the improvement in cognitive symptoms as a result of symptom improvement may be masked by the emergence of treatment-related cognitive effects, particularly with highly anticholinergic antidepressants. For example, in a double-blind study³⁷ comparing the SSRI fluoxetine with the tricyclic antidepressant amitriptyline, there was significant improvement in patient and observer ratings of depression in both groups, with no difference between groups; however, recent memory improved significantly in the fluoxetine group but not in the amitriptyline group. Similarly, another study³⁸ found that, although clinically both drugs were equally effective, the improvement of memory performance in fluoxetine-treated patients was significantly greater compared with that of desipramine-treated patients. In a study³⁹ comparing the effects of nortriptyline on memory with those of placebo, average immediate—but not delayed—free recall on a 20-item selective reminding test was adversely affected by medication, while performance on measures of immediate and delayed recognition memory was comparable between groups. Discontinuation of nortriptyline resulted in significant improvement on a subset of 9 memory self-assessment items.

However, there have been reports of memory difficulties during treatment with SSRIs as well. For example, Bangs et al.⁴⁰ described the case of a 14-year-old male patient who complained of memory problems during treatment with fluoxetine for MDD. The patient showed impairment on all 5 scales of the Wechsler Memory Scale-Revised during fluoxetine treatment, with 3 of the scales—Verbal Memory, Visual Memory, and General Memory—showing statistically significant improvements after fluoxetine was discontinued. In a double-blind study⁴¹ of healthy subjects, paroxetine specifically impaired delayed recall on a word-learning test at doses of 20 and 40 mg/day, while sertraline did not affect word learning but improved performance on a verbal fluency task at doses of 50 and 100 mg/day. Neither drug affected performance on a short-term memory scanning task.

How would SSRIs and other serotonergic agents affect cognitive performance? As pointed out by Buhot et al.⁴² in their recent review, despite a relative lack of functional specialization, the serotonergic system plays a significant role in learning and memory, in particular by interacting

with the cholinergic, glutamatergic, dopaminergic, or GABAergic systems. "Converging evidence suggests that the administration of 5-HT_{2A/2C} or 5-HT₄ receptor agonists or 5-HT_{1A} or 5-HT₃ and 5-HT_{1B} receptor antagonists prevents memory impairment and facilitates learning in situations involving a high cognitive demand, while antagonists for 5-HT_{2A/2C} and 5-HT₄ or agonists for 5-HT_{1A} or 5-HT₃ and 5-HT_{1B} generally have opposite effects."⁴²

Finally, cognitive symptoms may also be a residual symptom of MDD. Unfortunately, very little is known about the prevalence of cognitive and executive dysfunction in remitted depressives. Colleagues and I are currently conducting a study to assess rates of cognitive dysfunction among outpatients with remitted MDD who are continuing their maintenance antidepressant treatment. Although our study will not be able to distinguish residual symptoms from treatment-related symptoms, at least we will be able to evaluate how commonly clinicians may be faced with the challenge of having to address such symptoms.

Some researchers believe that the duration of depressive symptoms may contribute to the presence of cognitive symptoms that may not abate despite effective antidepressant treatment. For example, a recent study⁴³ showed no normalization of cognitive test performance in spite of complete recovery of affective symptoms, questioning the reversibility of low cognitive test performance in depression. Animal studies⁴⁴ suggest that chronic elevation of glucocorticoid levels can lead to the loss of hippocampal neurons and irreversible decline in declarative memory. Sheline et al.⁴⁵ assessed 24 women ranging in age from 23 to 86 years with a history of recurrent major depression but no medical comorbidity, as well as 24 case-matched controls, by using MRI scanning and neuropsychological testing. Subjects with a history of depression (post-depressed) had smaller hippocampal volumes bilaterally than controls and scored lower in verbal memory, a neuropsychological measure of hippocampal function, suggesting that the volume loss was related to an aspect of cognitive functioning. Repeated stress during recurrent depressive episodes may result in cumulative hippocampal injury as reflected in volume loss. A recent study⁴⁶ compared hippocampal function, which was assessed both by performance on hippocampal-dependent recollection memory tests and by hippocampal volumes as measured in a 1.5-T magnetic resonance imager, in 3 groups: depressed subjects with multiple past episodes of depression, never-treated depressed subjects in a first episode of depression, and matched healthy control subjects. Both first- and multiple-episode depressed groups displayed hippocampal dysfunction on several tests of recollection memory, but only depressed subjects with multiple depressive episodes had hippocampal volume reductions, with curve-fitting analysis revealing a significant logarithmic association between illness duration and hippocampal volume.

An alternative explanation for these findings is that neuronal loss and damage may occur first and hypercortisolemia may follow.⁴⁶

When cognitive and executive dysfunctions are residual symptoms of MDD or side effects of otherwise effective antidepressant treatment, clinicians often use augmentation strategies either to boost the antidepressant effect¹² or to manage such side effects, although little is known about the efficacy of augmentation strategies. Cholinesterase inhibitors, bupropion, dopamine receptor agonists, psychostimulants, and modafinil have all been used with this goal in mind, although primarily on the basis of anecdotal reports. Colleagues and I are currently conducting an open trial of modafinil for the treatment of cognitive symptoms in outpatients taking continued antidepressant treatment for remitted MDD. Further studies are clearly needed to establish the efficacy of these augmentation strategies.

SUMMARY

In conclusion, fatigue and cognitive/executive dysfunction are common symptoms in patients with MDD, which may either persist due to the disorder despite effective antidepressant treatment or emerge as a side effect of the antidepressant treatment itself. In order to address these symptoms, clinicians can use a number of augmentation strategies whose efficacy needs to be evaluated in a systematic fashion.

Drug names: amitriptyline (Enderp, Elavil, and others), atomoxetine (Strattera), bupropion (Wellbutrin and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), modafinil (Provigil), nortriptyline (Aventyl, Pamelor, and others), paroxetine (Paxil), sertraline (Zoloft), trazodone (Desyrel and others).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, atomoxetine and bupropion are not approved by the U.S. Food and Drug Administration for the treatment of fatigue, and modafinil is not approved for the treatment of fatigue and cognitive symptoms.

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