

# Is multiple sclerosis patient depressed, stressed, or both?

## How to sort through overlapping symptoms and provide appropriate treatment

**M**rs. S, age 50, has had relapsing-remitting multiple sclerosis (MS) for approximately 10 years. She describes her mood as “up and down” and is referred by her neurologist for psychiatric assessment of mood swings and possible depression. Fatigue limits her ability to work full-time, perform household duties, socialize with friends and family, and enjoy mental or physical exercise. In addition, her 18-year-old daughter—an important source of psychological support—is planning to leave home.

Mrs. S experienced depression 5 years ago during her divorce. She was prescribed paroxetine, 20 mg/d, and had a positive response. She took the medication for 6 months, then discontinued.

One-half of MS patients experience major depression in their lifetimes,<sup>1</sup> and the suicide rate is approximately doubled in MS patients compared with the general population.<sup>2</sup> Depression in MS patients often has an atypical presentation, with irritability and anger being as prominent as sadness.<sup>3</sup> Not all emotional changes experienced by MS patients represent depressive disorders, however.

When evaluating MS patients who are struggling with depression, you can help them by diagnosing comorbid mood disorders, determining suicide risk, and

providing psychological support as they cope with the impact of their illness.

### MS disease course

MS is a disease of the brain and spinal cord, characterized by:

- inflammatory demyelination and gliosis
- neuronal and axonal loss
- a variety of presenting symptoms as different CNS regions are affected.

Focal areas of demyelination followed by a reactive gliosis cause white matter lesions in the brain, spinal cord, and optic nerve. Neurologic dysfunction can manifest as visual changes, spastic paresis, hypoesthesia and paresthesia, ataxia, and bowel and bladder dysfunction. MS presentation also can include optic neuritis and transverse myelitis. MS symptoms often are intensified by heat exposure.

After the initial episode, months or years may pass before additional neurologic symptoms appear. Based on its course, MS can be classified as:

- relapsing-remitting, when the disease does not progress between attacks
- secondary progressive, characterized by a gradually progressive course after an initial relapsing-remitting pattern
- primary progressive, when patients experience gradual progressive disability from symptom onset (*Table 1, page 80*).

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Table 1

## Clinical classification of multiple sclerosis (MS)

Type	Characteristics
Relapsing-remitting*	Symptoms appear during relapses, resolve during remissions, and do not progress between relapses
Secondary progressive	MS symptoms that previously followed a relapsing-remitting pattern steadily become more severe and progress without relapse
Primary progressive	Gradual progression from symptom onset, without relapses or remission
Clinically isolated syndrome	A single attack that may indicate MS has occurred—such as optic neuritis or transverse myelitis—but clinical requirements for the diagnosis have not been met

\* Patients often progress from relapsing-remitting to secondary progressive MS

### Clinical Point

MS can diminish enjoyment of some activities, but lack of enjoyment in almost all activities remains a valid indicator of depression

#### CASE CONTINUED

#### Progressing symptoms

Mrs. S has had multiple MS presentations, including optic neuritis, lower extremity weakness, balance problems, and urinary incontinence. Recently, her MS symptoms have gradually progressed even in the absence of attacks, and her diagnosis has been revised to secondary progressive MS.

During psychiatric evaluation, Mrs. S denies persistent changes in sleep or appetite. She describes fatigue that starts after physical exertion and increases as the day progresses. She denies feelings of worthlessness, helplessness, excessive guilt, and suicidal ideation and does not have a history of inappropriate anger or irritability.

#### Diagnosing depression in MS

Normal emotional adjustment to MS can include reactions to loss of function or changes in social or occupational roles. Further, MS patients—similar to non-MS patients—experience life changes and transitions not related to the illness, such as divorce or a grown child moving away. Emotional responses to life stressors often are self-limited but may warrant an adjustment disorder diagnosis if they are associated with excessive distress or substantial impairment in social, occupational, or academic functioning (Table 2, page 82).<sup>4</sup>

Female MS patients and those who report high stress or a family history of affective disorder may be more likely to develop clinical depression.<sup>5</sup> Several studies

have reported correlations between structural brain abnormalities and depression in MS. Feinstein et al<sup>6</sup> reported that extensive hyperintense lesion volume in the left medial inferior prefrontal region with atrophy affecting the dominant anterior temporal lobe was associated with major depression. However, a depression diagnosis in MS patients remains a clinical one that does not require brain imaging studies.

Lack of interest or enjoyment as a symptom of depression can be difficult to identify because MS can diminish enjoyment of some activities. Although patients with MS may need to change their activity patterns to accommodate their illness, the lack of enjoyment in all—or almost all—activities remains a valid indicator of depressive disorder.

MS treatment includes the use of disease-modifying medications such as interferon beta-1b and interferon beta-1a. Several years ago researchers were concerned that interferon beta might cause depression in MS patients based on reports of a suicide and attempted suicide during an early trial of interferon beta-1b in relapsing-remitting MS.<sup>7</sup> Subsequent studies did not substantiate this concern, however (Box 1, page 83).<sup>8,9</sup>

**Overlapping symptoms** such as fatigue and cognitive deterioration could complicate the diagnosis. Look for changing patterns of these symptoms and other signs of depression. Rating scales that do not emphasize fatigue and cognitive impairment—such as the Beck Depression Inventory<sup>10</sup> and

continued on page 82

continued from page 80

**Table 2**

## Questions to consider when assessing MS patients for depression

Ask yourself	Reason
Are symptoms part of normal emotional changes?	Not all mood changes are pathologic or meet criteria for major depression
Is this an adjustment disorder?	Mood symptoms can be caused by a major stressor such as a recent diagnosis or personal loss
Is fatigue secondary to MS or depression?	MS typically causes fatigue after physical activity and heat exposure; fatigue early in the day points to depression
Are cognitive deficits related to MS or depression?	Negative thoughts point to depression whereas cognitive deficits may be caused by depression, MS, or both
Is this an atypical presentation?	MS patients may present with anger or irritability
Is this a pseudobulbar problem?	Patients with IEED might describe more concern about affect dysregulation than mood swings

MS: multiple sclerosis; IEED: involuntary emotional expression disorder

### Clinical Point

Feelings of worthlessness and guilt or suicidal ideation are not normal MS symptoms and point to depression

the Center for Epidemiologic Studies Depression Rating Scale<sup>11</sup>—can help identify depression in MS patients.

**Fatigue** is one of MS' most common and troublesome symptoms.<sup>12,13</sup> It typically mounts gradually during the day and after activity or heat exposure. Thus, fatigue early in the morning or manifesting as diminished motivation may point to a depressive disorder.

**Cognitive deterioration.** Clinically significant cognitive dysfunction occurs in 45% to 65% of MS patients.<sup>14</sup> The disease can cause losses in short-term memory, attention, information processing, problem solving, multitasking, and language function.

Bedside cognitive function tests such as the Mini-Mental State Examination<sup>15</sup> often are not sensitive enough to detect MS-related cognitive dysfunction. Be alert for changes in cognitive style when assessing for depressive disorders in these patients. Feelings of worthlessness and guilt or suicidal ideation are not normal MS symptoms and point to depression.

MS patients may experience pathological laughing and crying—also known as

involuntary emotional expression disorder (IEED)—a neurologic phenomenon that causes uncontrollable laughing, crying, or anger in the absence of subjective emotional distress. IEED has been reported in approximately 10% of patients with MS (*Box 2, page 84*).<sup>16-22</sup>

### CASE CONTINUED

#### Learning to adjust

Since discontinuing paroxetine 5 years ago, Mrs. S has not experienced another depressive episode. However, she describes a history of mood changes associated with pressured speech, increased activity, irritability, and insomnia during cortisone treatment for idiopathic thrombocytopenic purpura 4 years earlier. These episodes were mild, and she did not seek psychiatric treatment.

Mrs. S' mood episode does not seem to be a recurrence of major depressive disorder because she lacks persistent depressed mood and major depressive symptoms. Her diagnosis is best understood as an adjustment disorder to the progression of her illness and her daughter leaving home. Fatigue is her most debilitating MS symptom.



#### For more on IEED, read

**"A cry for help: Treating involuntary emotional expression disorder"**

CURRENT PSYCHIATRY, March 2008, p. 101-11 or CurrentPsychiatry.com.

#### Medication options

Use a cautious approach to pharmacotherapy. MS patients may have diminished cognitive reserves and might be at increased risk of medication-related delirium.

**Depression.** Two randomized, controlled trials have confirmed antidepressants' efficacy for treating depression in MS patients. The studies investigated the tricyclic antidepressant desipramine<sup>23</sup> and the selective serotonin reuptake inhibitor (SSRI) sertraline.<sup>24</sup>

In a double-blind clinical trial, 28 patients were randomly assigned to a 5-week trial of desipramine and individual psychotherapy or placebo and psychotherapy. Patients receiving desipramine showed significantly greater improvement than the placebo group, as measured by clinical judgment.

A 16-week study compared the efficacy of cognitive-behavioral therapy (CBT), supportive-expressive group therapy (SEG), and sertraline in 63 MS patients with major depressive disorder. Results showed that CBT and sertraline were more effective in reducing depression than SEG.<sup>24</sup>

SSRIs are a common first choice because of their ease of use and general tolerability among MS patients.<sup>25</sup> Recommended dosages include:

- citalopram, 20 to 40 mg/d
- fluoxetine, 20 to 40 mg/d
- fluvoxamine, 50 to 300 mg/d
- paroxetine, 20 to 50 mg/d
- sertraline, 50 to 200 mg/d.

There is no consensus that any one antidepressant is best for all MS patients, however. When selecting an antidepressant, consider side-effect profiles, potential for drug-drug interactions, and a history of response to a particular antidepressant. Highly sedating antidepressants such as mirtazapine could aggravate fatigue. Highly anticholinergic agents such as amitriptyline may impair cognitive function.

**Fatigue.** Amantadine is the mainstay pharmacologic treatment for fatigue in MS, but evidence for its efficacy is weak.<sup>26</sup> Clinical trials of psychostimulants generally have reported disappointing results. One randomized, double-blind trial found no significant differences in fatigue levels between patients receiving pemoline or placebo.<sup>27</sup>

Some studies have reported reduced MS-related fatigue with modafinil,<sup>28-30</sup> but

### Box 1

## Neuropsychiatric effects of multiple sclerosis medications

**D**o interferon beta-1a and 1b—agents used to treat relapsing-remitting MS—cause or aggravate depression?

Two large-scale clinical trials of interferon beta-1a included a validated measure of depressive symptoms—the Center for Epidemiologic Studies Depression Rating Scale.<sup>8,9</sup> This scale allowed researchers to conduct a detailed analysis that compared changes in depression symptoms over time in study participants treated with interferon or placebo. Evidence did not indicate increased depressive symptoms in association with interferon treatment.

**Conclusion.** Depression symptoms that emerge during treatment with one of these agents are not likely caused by the treatment and usually can be managed without discontinuing the drug.

the only double-blind, placebo-controlled trial showed no significant difference between modafinil and placebo in patient fatigue levels.<sup>31</sup> In this study, modafinil reduced physical fatigue only in patients with daytime somnolence.

### Other psychiatric disorders

**Bipolar disorder** occurs more frequently in MS patients than in the general population.<sup>32</sup> Additionally, some patients with advanced MS might experience benign feelings of euphoria.<sup>33</sup> Euphoria can be differentiated from mania by assessing for mania's other symptoms, such as erratic and disinhibited behavior, rapid speech, increased libido, decreased need for sleep, and excessive energy.

Antidepressants and corticosteroids could aggravate the course of bipolar disorder, and drug-illness interactions with lithium could make side effects such as tremor, diarrhea, and polyuria more difficult to tolerate. Mood stabilizing anticonvulsants such as valproate and carbamazepine are a useful alternative for treating the bipolar patient with comorbid MS. To avoid sedation, start with a low dose and increase gradually.

### Clinical Point

When selecting an antidepressant, consider side effects, drug-drug interactions, and history of response to the antidepressant

## Box 2

## Uncontrollable crying may be pseudobulbar affect, not depression

Approximately 10% of multiple sclerosis (MS) patients develop inappropriate affective expression—anger, laughing, or crying—in the absence of prominent mood changes.<sup>16</sup> Involuntary emotional expression disorder (IEED)—or pathologic laughing or crying—is a form of pseudobulbar affect. IEED occurs when affective motor control becomes disinhibited as a result of brain damage from neurologic disease or injury. Conditions associated with IEED include amyotrophic lateral sclerosis, MS, traumatic brain injury, stroke, and dementia.<sup>17</sup>

IEED can prompt a psychiatric evaluation because uncontrolled crying can seem like intense depression. Symptoms range in severity and include exaggerated and inappropriate affective responses and perceived lack of control over responses. IEED episodes are paroxysmal, occurring

in a brief and stereotyped manner, whereas crying in depression is more sustained, less stereotyped, and relates to the underlying mood.<sup>17,18</sup> In addition, patients with depressive disorders often suffer difficulties with sleep and appetite as well as thoughts of guilt, hopelessness, and worthlessness not present in IEED.<sup>17,19</sup>

Studies have shown successful treatment of IEED with antidepressants including tricyclic antidepressants and serotonin reuptake inhibitors.<sup>20</sup> A recent randomized, controlled trial suggested that dextromethorphan and quinidine may be beneficial in treating potentially disabling pseudobulbar affect in MS.<sup>21</sup> Rating scales such as the 7-item Center for Neurologic Study Lability Scale may help establish a baseline against which to monitor treatment response.<sup>22</sup>

## Clinical Point

MS patients might use avoidance and denial to cope, but they usually need to learn active coping strategies as the disease progresses

**Insomnia.** Sedative hypnotics such as zopiclone can be used for short-term treatment of sleep disturbances. Carefully consider hypnotics' possible negative effects on balance, coordination, and memory, however.

**Psychotic disturbances** are rare in MS but occur more frequently in MS patients than in the general population.<sup>34</sup> Use low doses of antipsychotics such as olanzapine, quetiapine, or risperidone in MS patients with psychosis. These atypical agents are associated with a lower risk of parkinsonian side effects than typical antipsychotics.

## CASE CONTINUED

## Coping mechanisms

Mrs. S has difficulty coping with her increasing symptom burden and functional limitations, but she says it is hard for her to ask for help. Her treatment plan includes recruiting support to help her deal with feelings of loss over her daughter's move. We encourage her to reconnect with friends and family and use community supports for MS patients.

We discuss her treatment options, including biological treatments for fatigue, CBT, and behavioral activation therapy for her mood symptoms. She chooses a course of modafinil,

50 mg/d, and weekly CBT incorporating behavioral activation therapy to increase her activity level and target depressive symptoms and fatigue.

## Psychosocial interventions

**CBT** is an effective treatment for depression in MS patients<sup>24</sup> and is preferred for most patients with mild depression. CBT focuses on improving coping through behavioral activation and cognitive restructuring.<sup>35</sup> CBT can incorporate teaching patients skills for managing MS-related problems such as fatigue, mild cognitive impairment, pain, stress, communication, sexual dysfunction, intimacy, and social difficulties secondary to MS.

Behavioral activation strategies focus on the relationship between activity and mood. They target a common pattern of avoidance and withdrawal from social, occupational, and physical demands that relieves MS patients' anxiety in the short term but leads to problems associated with inactivity.<sup>35</sup> Behavioral activation strategies—including exercise—have a strong evidence base supporting their use alone to manage depression and as a component of CBT.<sup>36</sup>

**Active coping strategies.** In early MS, patients often use avoidance and denial to cope with their disease. As symptoms become more intrusive, however, patients usually need to learn active coping strategies. These often begin with symptom management and evolve to include individually meaningful tasks such as reevaluating personal goals, values, and priorities.

**Other psychotherapy modalities.** In one study, patients randomized to an insight-oriented treatment group improved more than those in a placebo intervention based on discussing current events.<sup>37</sup> Although not formally assessed in the literature, psychoeducation can help the patient maintain a sense of control over his or her treatment. Interpersonal therapy can help patients deal with role transitions caused by their illness and subsequent disabilities, although its use in this population has not been studied.

Although the literature does not favor supportive psychotherapy for treating depression in MS patients,<sup>24</sup> this modality can help alleviate feelings of grief and loss that can emerge when MS symptoms worsen. Patients often appreciate having an opportunity to articulate their feelings and fears in a professional therapeutic relationship. MS patients often value validation and normalization of their emotional responses, and many therapists choose to integrate supportive strategies with CBT's more "action oriented" elements.

**Exercise** is an effective treatment for fatigue in MS<sup>38</sup> and also helps combat loss of physical fitness. MS patients who use energy conservation strategies to manage fatigue can participate in suitably paced physical exercise. Aquatic exercise is a popular option because it often does not cause overheating.

#### CASE CONTINUED

#### Energy surge

At the second follow-up appointment, Mrs. S notes that her energy level is better early in the day but decreases by late afternoon. An additional dose of modafinil, 50 mg, is added at noon, which increases her overall energy level.

## Related Resources

- National Multiple Sclerosis Society. [www.nationalmssociety.org](http://www.nationalmssociety.org).
- The Goldman Consensus Group. The Goldman Consensus statement on depression in multiple sclerosis. *Mult Scler* 2005;11:328-37.
- Feinstein A. *The clinical neuropsychiatry of multiple sclerosis*. Cambridge, UK: Cambridge University Press; 2007.

#### Drug Brand Names

Amantadine • Symmetrel	Modafinil • Provigil
Amitriptyline • Elavil	Olanzapine • Zyprexa
Carbamazepine • Tegretol	Paroxetine • Paxil
Citalopram • Celexa	Pemoline • Cylert
Desipramine • Norpramin	Quetiapine • Seroquel
Fluoxetine • Prozac	Risperidone • Risperdal
Fluvoxamine • Luvox	Sertraline • Zoloft
Interferon beta-1a • Avonex, Rebif	Valproate • Depacon
Interferon beta-1b • Betaseron	Zopiclone • Imovane,
Lithium • Eskalith, Lithobid	Zimovane
Mirtazapine • Remeron	

#### Disclosure

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

CBT helps Mrs. S to develop reasonable expectations of herself and others and addresses the possibility that she could try part-time work. Including exercise as behavioral activation also lessens her fatigue. Reconnecting with family and friends helps relieve feelings of isolation resulting from her daughter moving away.

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continued

## Clinical Point

Many therapists choose to integrate supportive strategies with cognitive-behavioral therapy's more 'action oriented' elements

### Clinical Point

**Aquatic exercise is a popular option for behavioral activation because it often does not cause overheating**

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## Bottom Line

When diagnosing depression in multiple sclerosis patients, tease out overlapping symptoms such as fatigue and cognitive deterioration. Take a cautious approach to pharmacotherapy, and provide psychological support—such as cognitive-behavioral therapy, active coping strategies, or exercise—to help patients cope with the impact of their illness.