



Depression and Multiple Sclerosis An Immunomodulatory Connection?

Randolph B. Schiffer, MD

Guest Editor

It is generally accepted that depressive disorders occur among people with multiple sclerosis (MS) at rates higher than in most other populations with chronic neurologic disorders. Reported measures of lifetime risk for depressive spectrum disorders in MS patients are very high, in some cases exceeding 50%.¹ Point prevalence rates for major depressive syndromes in MS clinic populations are in the range of 14% but are probably higher in community samples. It is fair to say that the significance of this depressive diathesis in MS is not yet fully understood.

There is evidence that the comorbidity of depression and MS adversely affects functional status in several neuropsychiatric domains. Depressed MS patients perform worse than nondepressed MS patients on tests of cognitive function. In addition, standardized measures of quality of life are lower in depressed MS patients than in nondepressed MS patients. Intercurrent depression in MS populations is associated with unemployment. Depressed MS patients experience disruption of their social support and family systems beyond what can be attributed to neurologic disease factors alone. Moreover, the comorbidity of depression and MS may adversely affect adherence to medical treatment regimens for MS.

These documented adverse effects on function in themselves would be enough to stimulate clinical interest in improving the diagnosis and treatment of depression in individuals with MS. Could it be, however, that the functional implications of intercurrent depression among MS patients may extend further than this to include adverse immunomodulatory effects on the MS syndrome

itself? Anecdotal reports have appeared for centuries suggesting that psychological distress or depression might cause, or worsen, core neurologic diseases. Could these reports have merit?

People with depression have been shown to have increased levels of circulating proinflammatory cytokines (IL-6, IL-1, tumor necrosis factor [TNF]), acute phase proteins (C-reactive protein), and circulating adhesion molecules in plasma, serum, and cerebrospinal fluid.² Such patients have decreased levels of anti-inflammatory cytokines (IL-4, IL-10). Successful antidepressant therapy attenuates these proinflammatory changes in some patients.³

There is also evidence that MS patients may have altered profiles of cytokine signaling similar to those described in depressed patients, at least during certain phases of disease activity. In relapsing-remitting phases, these MS patients demonstrate up-regulation of circulating adhesion molecules prior to attacks, and in more chronic phases of disease activity, they may demonstrate elevated levels of circulating proinflammatory cytokines (TNF, IL-6).⁴

A few “bridging” reports have been published of correlations between clinical depressive syndromes and alterations of certain neuroimmunologic parameters in people with MS. For example, Foley and colleagues⁵ reported that depressed and anxious MS patients demonstrate a relative depletion of peripheral CD8⁺ lymphocytes compared with MS patients with no affective or anxiety disorder.

Other observations suggest that there may be interactions between such states of altered emotional tone and certain pathologically altered immune functions in MS patients. The exogenous up-regulation of certain cytokine levels as a treatment for MS (interferons) is sometimes associated with a clinical depressive syndrome,

From the Cleveland Clinic Lou Ruvo Center for Brain Health, Cleveland, OH, USA. *Correspondence:* Randolph B. Schiffer, MD, Cleveland Clinic Lou Ruvo Center for Brain Health, 9500 Euclid Ave., Cleveland, OH 44195; e-mail: schiffer@ccf.org.

and even suicide.^{6,7} Corroborating reports from the internal medicine literature concerning a relationship between affective disorders and interferons have appeared, with rates of new-onset major depression in association with the use of interferon alpha to treat infectious and malignant syndromes approaching 50%.⁸

It has long been reported that emotionally stressful experiences may be harbingers of clinical exacerbations in MS. Almost all MS experts have observed this phenomenon clinically. Several prospective studies have found a relationship between stressful life events and increased exacerbation rates among people with MS.¹ In at least one of these studies, gadolinium-enhancing magnetic resonance imaging lesions also appeared in association with clinical measures of stress and conflict. While not a depressive syndrome per se, stressful emotional experiences have been correlated with depression.

Perhaps the most intriguing of such “interaction” reports are those suggesting the possibility of a causal relationship between the treatment of depression in MS and favorable alterations in pathologic neuroimmunologic measures. For example, Mohr and colleagues⁹ reported that the stimulation of interferon gamma production by lymphocytes decreases in depressed MS patients as the depression improves. In addition, in a study of the selective serotonin reuptake inhibitor (SSRI) antidepressant fluoxetine as a treatment for MS in 40 mixed MS patients, a trend was observed toward a decrease in numbers of gadolinium-enhancing lesions in the SSRI-treated group.¹⁰

Our knowledge of the relationship between the depressive spectrum disorders and the cluster of syndromes currently known as MS is still in its infancy. In this issue of the IJMCS, we present selected manuscripts focused on this topic, in the hope that both clinicians and scientists will find them interesting and useful. An algorithm for the treatment of depression in patients with MS appears on the following pages. □

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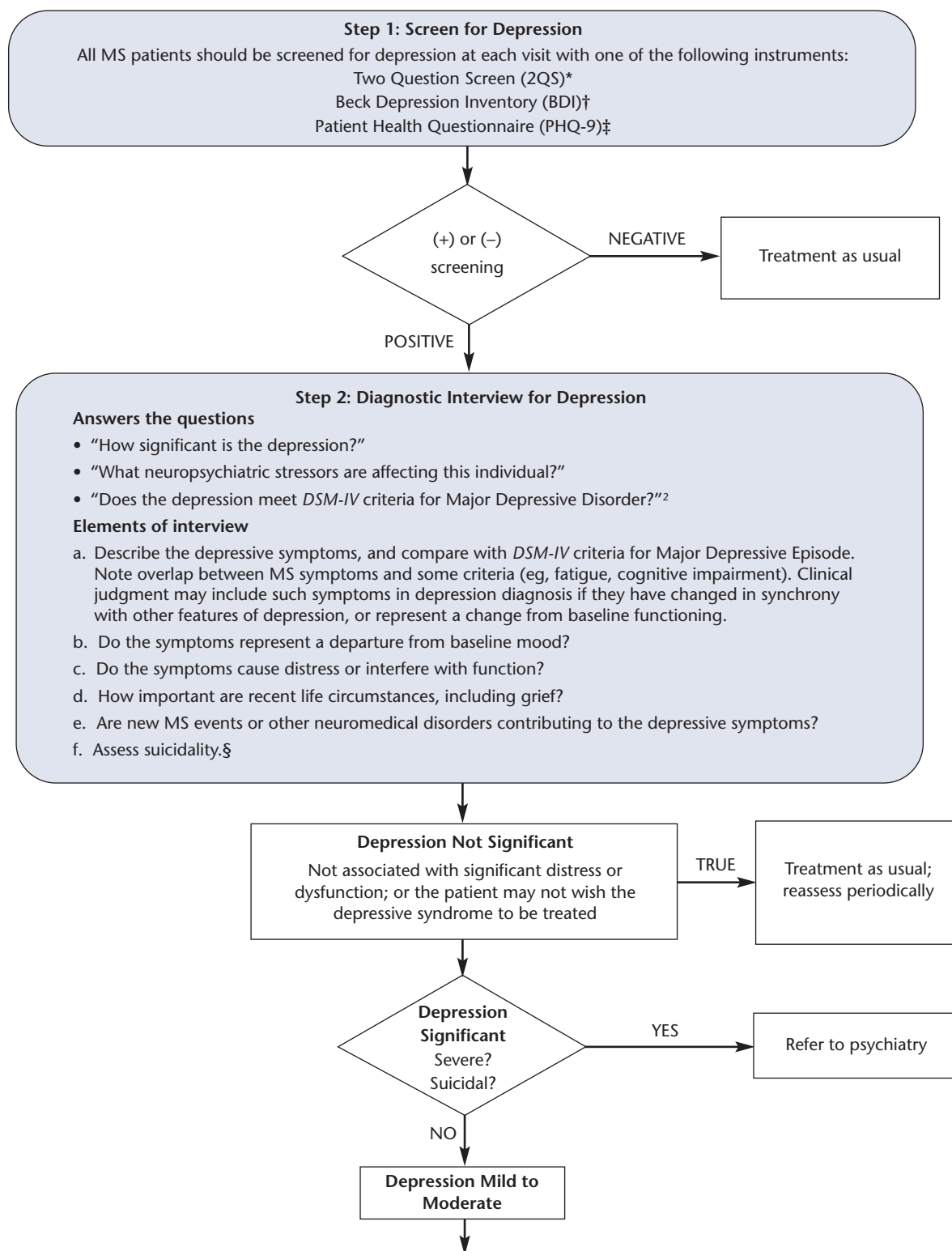
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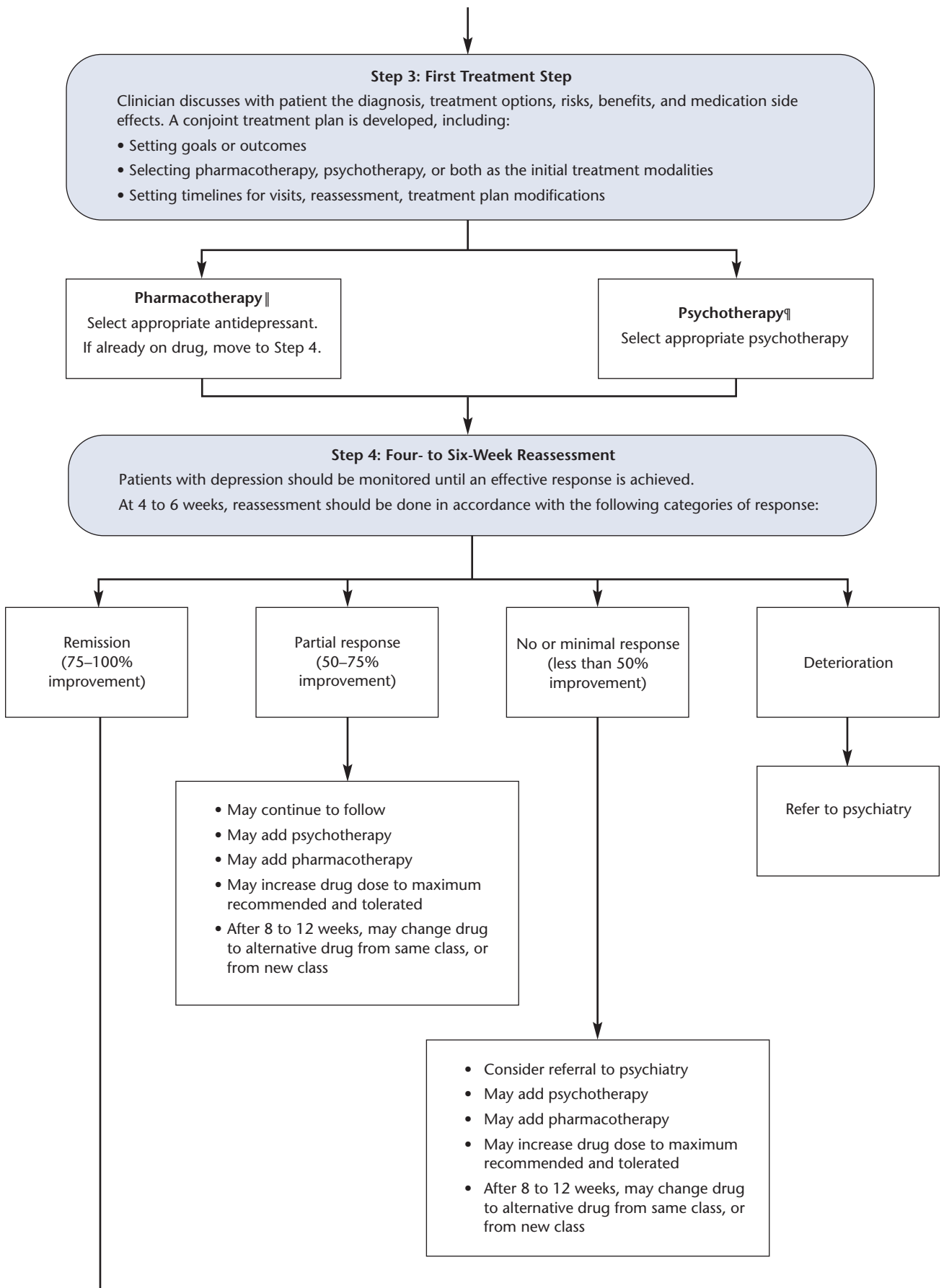
The Goldman Algorithm for the Treatment of Depression in Multiple Sclerosis

The Goldman Algorithm is aimed at the identification and treatment of MS patients with depression as they appear in neurologic care systems. It is intended to be used by neurologists/physician assistants/nurse practitioners/advanced practice nurses who care for patients with MS. We assume that the algorithm will be used in the context of an ongoing, supportive, and educational relationship with the treating neurologist and staff.

The Goldman Algorithm has been constructed wherever possible from the current evidence base for the treatment of depression in MS.¹

Source: Schiffer R, Arnett P, Ben-Zacharia A, et al. Goldman Algorithm. Poster presented at: 21st Annual Meeting of the Consortium of Multiple Sclerosis Centers; June 1, 2007; Washington, DC.





Step 5: Continuation Phase

- Continue medication for 10 to 12 months and continue psychotherapy as benefits the patient
- For pharmacotherapy alone, may reduce visits to monthly or bimonthly
- For psychotherapy, determine frequency as befits the individual patient

Step 6: Maintenance or Surveillance

- For patients with no or limited history of depressive episodes, drug should be tapered and discontinued at 1 year. If patient relapses, medication should be restarted.
- For patients with history of chronic depression, or more than three depressive episodes, indefinite continuation of drug is recommended, although dose may be reduced
- Psychotherapy should continue as long as patient benefits

NOTES

*Two Question Screen (2QS)

1. "During the past two weeks, have you often been bothered by feeling down, depressed, or hopeless?"
2. "During the past two weeks, have you often been bothered by little interest or pleasure in doing things?"

A positive answer to either question is a **positive screening response**. Brevity is a major strength of this screen.

† Beck Depression Inventory (BDI)

The BDI consists of 21 items, each rated from 0 to 3, with a higher score indicating greater severity. Ratings are summed, and cutoff scores recommended by the authors are as follows: <10 = no or minimal depression; 10–17 = mild-to-moderate depression; 18–29 = moderate-to-severe depression; 30–63 = severe depression. Test-retest reliability for psychiatric patients ranges from 0.48 to 0.86, and scores correlate 0.72 with clinical ratings of depression in psychiatric patients.³

The BDI has been used extensively with MS patients, in both clinical and research settings, as well as with many other medical and psychiatric populations. We consider a positive screen to be a score above 20 and/or endorsement of any rating above 0 for the suicidality item. In a sample of 510 ambulatory MS patients attending a hospital outpatient MS center, this approach identified 16% as depressed (unpublished data).

‡ Patient Health Questionnaire (PHQ-9)

The PHQ-9 has also been validated in both non-neurologic and neurologic populations.⁴ It consists of the nine *DSM-IV* Major Depressive Disorder (MDD) items, which patients rate on a 4-point scale the extent to which they have been bothered by the symptom over the past 2 weeks (Not at All, Several Days, More Than Half the Days, Nearly Every Day). Scores range from 0 to 27, with higher scores indicating greater severity. Spitzer et al.⁵ report that the PHQ-9 had a sensitivity of 73% and a specificity of 94% for identifying MDD in a sample of 585 patients using an algorithm, and Williams and colleagues⁴ reported a sensitivity of 91% and a specificity of 89% using a cutoff of 10 in stroke patients.

In MS patients a PHQ-9 score of 10 identified 19.1% of ambulatory MS patients as depressed.⁶ The PHQ-9 has the advantage of being closely tied to *DSM-IV* criteria. We consider a positive screen to be a score of 10 or more and/or a rating of at least "Several Days" for the suicidality item.

§ Assess suicide potential by evaluating several factors. Does the patient have a plan? Is intent serious? Are lethal means available? Do other factors increase risk (eg, previous or family history of suicide, history of violence, intercurrent alcohol or drug use, psychotic features, social isolation, elderly or adolescent)?

|| **Sertraline** has Class A supporting evidence, with dosing beginning at 50 mg/day, followed by escalation to 150 mg/day if appropriate. Other SSRI category drugs are used based on anecdotal evidence. Desipramine 25 mg twice a day also has Class A supporting evidence.

¶ **Cognitive-behavioral therapy** has the best supporting evidence,⁷ although all types of psychotherapy are commonly used, including supportive and insight-oriented therapies.

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