

A mood disorder complicated by multiple sclerosis

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How would you handle this case?

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Ms. A, age 56, presents with depressed mood, anhedonia, irritability, agitation, and recent self-injurious behavior. She also has multiple sclerosis. How can you best help her?

CASE Depression, or something else?

Ms. A, age 56, presents to the emergency department (ED) with depressed mood, poor sleep, anhedonia, irritability, agitation, and recent self-injurious behavior; she had superficially cut her wrists. She also has a long-standing history of multiple sclerosis (MS), depression, and anxiety. She is admitted voluntarily to an inpatient psychiatric unit.

According to medical records, at age 32, Ms. A was diagnosed with relapsing-remitting MS, which initially presented with facial numbness, and later with optic neuritis with transient loss of vision. As her disease progressed to the secondary progressive type, she experienced spasticity and vertigo. In the past few years, she also had experienced cognitive difficulties, particularly with memory and focus.

Ms. A has a history of recurrent depressive symptoms that began at an unspecified time after being diagnosed with MS. In the past few years, she had greatly increased her alcohol use in response to multiple psychosocial stressors and as an attempt to self-medicate MS-related pain. Several years ago, Ms. A had been admitted to a rehabilitation facility to address her alcohol use.

In the past, Ms. A's depressive symptoms had been treated with various antidepressants, including fluoxetine (unspecified dose), which for a time was effective. The most recently

prescribed antidepressant was duloxetine, 60 mg/d, which was discontinued because Ms. A felt it activated her mood lability. A few years before this current hospitalization, Ms. A had been started on a trial of dextromethorphan/quinidine (20 mg/10 mg, twice daily), which was discontinued due to concomitant use of an unspecified serotonin-norepinephrine reuptake inhibitor (SNRI) and subsequent precipitation of serotonin syndrome.

At the time of this current admission to the psychiatric unit, Ms. A is being treated for MS with rituximab (10 mg/mL IV, every 6 months). Additionally, just before her admission, she was taking alprazolam (.25 mg, 3 times per day) for anxiety. She denies experiencing any spasticity or vision impairment.

What is your differential diagnosis?

- a) major depressive disorder (MDD)
- b) unspecified bipolar disorder
- c) unspecified personality disorder
- d) mood disorder due to another medical condition (MS)
- e) adjustment disorder with mixed disturbance of emotions and conduct

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Disclosures

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The authors' observations

We initially considered a diagnosis of MDD due to Ms. A's past history of depressive episodes, her recent increase in tearfulness and anhedonia, and her self-injurious behaviors. However, diagnosis of a mood disorder was complicated by her complex history of long-standing MS and other psychosocial factors.

While MS is defined by neurologic episodes resulting from CNS demyelination (Table,¹ page 40), psychiatric symptoms are also highly prevalent in patients with MS but can be overlooked in clinical settings. MDD seems to be particularly common, with a lifetime prevalence of up to 50% in patients with MS,^{2,3} along with a lifetime prevalence of suicide 7.5 times higher than in the general population.⁴ Some studies have found that depressive symptoms supersede physical disability and cognitive dysfunction as significant determinants of quality of life in MS patients.⁵ Additionally, in patients with MS, bipolar disorder and psychosis have a lifetime prevalence 2 to 3 times that of the general population.² While past literature has described a subgroup of patients with MS who present with euphoria as the predominant mood state, contemporary researchers regard this presentation as rare and most likely reflecting a change in the definition of euphoria over the past century.⁶ Although MDD is the most prevalent and most studied MS-associated psychiatric diagnosis, other mood symptoms can be similarly disruptive to daily functioning. Therefore, early recognition and management of psychiatric manifestations in patients with MS is essential, because psychiatric conditions such as depression can predict morbidity, treatment adherence, and overall quality of life.⁷

Several factors contribute to the neuropsychiatric course of patients with MS, including the impact of the patient accepting a chronic and incurable diagnosis, the toll of progressive neurologic/physical disability and subsequent decline in functioning,

and the availability of a support system.² As opposed to disorders such as Parkinson's disease, where disease progression is relatively more predictable, the course of MS involves the obscurity of symptom fluctuation, both from the patient's and/or clinician's viewpoint. Psychiatric and neurologic symptoms may be difficult to predict, leading to speculation and projection as to the progression of the disease. The diagnosis of psychiatric conditions, such as depression, can be complicated by the fact that MS and psychiatric disorders share presenting symptoms; for example, disturbances in sleep and concentration may be seen in both conditions.

While studies have examined the neurobiology of MS lesions and their effects on mood symptoms, there has been no clear consensus of specific lesion distributions, although lesions in the superior frontal lobe and right temporal lobe regions have been identified in depressed MS patients.⁸ Lesions in the left frontal lobe may also have some contribution; studies have shown hyperintense lesion load in this area, which was found to be an independent predictor of MDD in MS.⁹ This, in turn, coincides with the association of left frontal cortex involvement in modulating affective depression, evidenced by studies that have associated depression severity with left frontal lobe damage in post-stroke patients¹⁰ as well as the use of transcranial magnetic stimulation of the left prefrontal cortex for treatment-resistant MDD.¹¹ Lesions along the orbitofrontal prefrontal cortex have similarly been connected to mood lability and impulsivity, which are characteristics of bipolar disorder.⁸ Within the general population, bipolar disorder is associated with areas of hyperintensity on MRI, particularly in the frontal and parietal white matter, which may provide clues as to the role of MS demyelinating lesions in similar locations, although research concerning the relationship between MS and bipolar disorder remains limited.¹²

Clinical Point

Up to 50% of patients with multiple sclerosis will experience major depressive disorder

continued

Clinical Point

Multiple sclerosis and psychiatric disorders can share presenting symptoms, such as disturbances in sleep and concentration

Table

Signs and symptoms of multiple sclerosis

Visual	Blurred vision Unilateral vision loss Oscillopsia Diplopia
Motor	Trunk/limb weakness Spasticity Hyperreflexia Gait disturbance Balance problems
Sensory	Numbness Paresthesias Dysesthesias Lhermitte’s sign “MS hug” (feeling of having a tight band around the ribs or chest) Trigeminal neuralgia Allodynia Hyperpathia Proprioception deficits
Cerebellar	Tremor Ataxia Incoordination
Genitourinary	Urgency/frequency/retention Incontinence Frequent UTI Constipation Impotence Anorgasmia Dyspareunia
Neuropsychiatric	Impairment of memory, concentration, attention, and/or processing speed Depression Irritability Anxiety
Other symptoms	Prominent intractable fatigue with no other cause

Source: Reference 1
MS: multiple sclerosis; UTI: urinary tract infection

EVALUATION No exacerbation of MS

Upon admission, Ms. A’s lability of affect is apparent as she quickly switches from being tearful to bright depending on the topic of discussion. She smiles when talking about the hobbies she enjoys and becomes tearful

when speaking of personal problems within her family. She denies suicidal ideation/intent, shows no evidence of psychosis, and denies any history of bipolar disorder or recollection of hypomanic/manic symptoms. Overall, she exhibits low energy and difficulty sleeping, and reiterates her various psychosocial stressors, including her family history of depression and ongoing marital conflicts. Ms. A denies experiencing any acute exacerbations of clinical neurologic features of MS immediately before or during her admission. Laboratory values are normal, except for an elevated thyroid stimulating hormone (TSH) value of 11.136 uIU/mL, which is expected given her history of hypothyroidism. Results of the most recent brain MRI scans for Ms. A are pending.

The authors’ observations

Although we considered a diagnosis of bipolar disorder–mixed subtype, this was less likely to be the diagnosis considering her lack of any frank manic/hypomanic symptoms or history of such symptoms. Additionally, while we also considered a diagnosis of pseudobulbar affect due to her current mood swings and past trial of dextromethorphan/quinidine, this diagnosis was also less likely because Ms. A’s affect was not characterized by uncontrollable outbursts of emotion but was congruent with her experiences and surroundings. For example, Ms. A smiled when talking about her hobbies and became tearful when speaking of conflicts within her family.

Given Ms. A’s mood dysregulation and lability and her history of depressive episodes that began to manifest after her diagnosis of MS was established, and after ruling out other etiologic psychiatric disorders, a diagnosis of mood disorder secondary to MS was made.

How would you manage Ms. A’s mood disorder secondary to MS?

- a) start an antidepressant

- b) start a mood stabilizer
- c) start an atypical antipsychotic
- d) start cognitive-behavioral therapy (CBT)

TREATMENT Mood stabilization

We start Ms. A on divalproex sodium, 250 mg 2 times a day, which is eventually titrated to 250 mg every morning with an additional daily 750 mg (total daily dose of 1,000 mg) for mood stabilization. Additionally, quetiapine, 50 mg nightly, is added and eventually titrated to 300 mg to augment mood stabilization and to aid sleep. Before being admitted, Ms. A had been prescribed alprazolam for anxiety; she is switched to longer-acting clonazepam, .5 mg/d, to minimize the potential for withdrawal symptoms while she is hospitalized.

The authors' observations

Definitive treatments for psychiatric conditions in patients with MS have been lacking, and current recommendations are based on regimens used to treat general psychiatric populations. For example, selective serotonin reuptake inhibitors are frequently considered for treatment of MDD in patients with MS, whereas SNRIs are considered for patients with concomitant neuropathic pain.¹³ Similarly, lithium and valproic acid (divalproex sodium) are the pharmacotherapies of choice for mood stabilization,² while CBT appears to be the main psychotherapy showing benefit for patients with MS who are depressed.¹⁴ As with any patient, response and reactions to treatment should be closely monitored. Given the lack of definitive regimens, along

Clinical Point

Treatments for mood disorders in patients with MS include SSRIs, SNRIs, mood stabilizers, and CBT

Clinical Point

Ms. A improved after receiving divalproex sodium and quetiapine

Related Resources

- National Multiple Sclerosis Society. <http://www.nationalmssociety.org>.
- Fitzgerald C. Is multiple sclerosis patient depressed, stressed, or both? *Current Psychiatry*. 2008;7(4):79-86.

Drug Brand Names

Alprazolam • Xanax	Fluoxetine • Prozac
Clonazepam • Klonopin	Lithium • Eskalith, Lithobid
Dextromethorphan/ quinidine • Nuedexta	Quetiapine • Seroquel
Divalproex sodium • Depakote	Rituximab • Rituxan,
Duloxetine • Cymbalta	Rituxan Hycela

with the ambiguity of neurologic and psychiatric symptom etiology in terms of physiologic vs psychosocial contributions, the need for trial and error in terms of choice of treatment and optimal dosages becomes essential.

OUTCOME Improved mood, energy

After 2 weeks of inpatient treatment, Ms. A shows improvement in mood lability and energy levels, and she is able to tolerate titration of divalproex sodium and quetiapine to therapeutic levels. She is referred to an outpatient psychiatrist after discharge, as well as a follow-up appointment with her neurologist. On discharge, Ms. A expresses a commitment to treatment and hope for the future.

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Bottom Line

Evaluation and treatment of psychiatric manifestations in patients with multiple sclerosis (MS) requires careful attention and focus on the individual's unique pattern of symptoms, psychosocial stressors, and response to treatment, among other considerations. Treatment for mood disorders in patients with MS are the same as those used for the general psychiatric population.