

# Is a medical illness causing your patient's depression?

## Endocrine, neurologic, infectious, or malignant processes could cause mood symptoms

**M**s. G, age 56, presents with the chief complaint of "depression." Review of symptoms reveals 6 months of depressed mood, anhedonia, tearfulness, 30-pound weight gain, low energy, and bilateral ankle edema. Her psychiatrist orders a thyroid stimulating hormone (TSH) level, which shows 9.51 mU/L (normal range 0.35 to 4.94 mU/L), indicating hypothyroidism. After 1 month of treatment with levothyroxine, Ms. G's mood symptoms and edema resolve and her weight stabilizes.

A patient who comes to you for treatment of depression might also present with physical symptoms (such as, fatigue, nausea, balance problems, etc.) that could point to a medical illness. Endocrine, neurologic, infectious, and malignant processes (*Table 1, page 44*) and vitamin deficiencies (*Table 2, page 45*) could be causing your patient's depression. To help differentiate various etiologies of depressive symptoms, we review common medical causes of depression, their distinguishing characteristics, and pertinent treatment issues.

DSM-IV-TR considers major depression secondary to a general medical condition to be diagnostically separate from a major depressive episode. When considering nonpsychiatric causes of depression, begin with a thorough medical history including current and past medications (*Table 3, page*

*51*),<sup>1-7</sup> illicit substance use, review of systems, and a detailed neurologic exam.

### Endocrine disorders

**Hypothyroidism** increases a patient's risk of a mood disorder 7-fold, compared with the general population.<sup>8</sup>

**Signs and symptoms.** Patients with hypothyroidism may complain of constipation, thinning hair, dry skin, edema, sensitivity to cold, goiter, thyroid nodule, or hoarse voice. Symptoms such as fatigue, weight gain, and sleep disturbance overlap with depressive symptoms. A TSH value >4.94 mU/L indicates hypothyroidism and warrants referral to a primary care provider or endocrinologist.

Although the pathophysiology is unclear, 1 study found elevated thyroid peroxidase antibodies in depressed postmenopausal women who had abnormal thyroid function tests, suggesting an autoimmune link between depression and hypothyroidism.<sup>9</sup> In another study, 2.5% of depressed patients had abnormal serum TSH or thyroxine levels indicating hypothyroidism.<sup>10</sup> Thyroid hormones have been used to augment treatment of refractory depression.<sup>11</sup>

**Hyperparathyroidism.** "Moans, groans, stones, and psychiatric overtones" describes the constellation of hyperpara-

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### Clinical Point

Decreased morning serum cortisol level, hyponatremia, and hyperkalemia confirm Addison's disease

**Table 1**

## Medical conditions with evidence of causing depression

<b>Endocrine</b>
Hypothyroidism
Hyperparathyroidism
Cushing's syndrome
Addison's disease
<b>Neurologic</b>
Stroke
Seizures
Huntington's disease
Wilson's disease
Multiple sclerosis
Parkinson's disease
Traumatic brain injury
<b>Infectious</b>
Human immunodeficiency virus
West Nile virus
Creutzfeldt-Jakob disease
Lyme disease
Neurosyphilis
Hepatitis C
<b>Malignancy</b>
Paraneoplastic syndromes
Pancreatic cancer

thyroidism symptoms. As serum calcium levels rise, mood and physical symptoms worsen (*Table 4, page 52*).

**Signs and symptoms.** Elevated serum calcium (normal range 8.7 to 10.7 mg/dL) and parathyroid hormone (PTH) levels support the diagnosis. Depressive symptoms may diminish or even resolve when calcium levels return to normal after parathyroidectomy.<sup>12</sup>

**Cushing's syndrome (CS).** As many as 80% of patients exhibit depressive symptoms when CS is active.<sup>13</sup>

**Signs and symptoms.** Distinguishing CS symptoms include:

- hirsutism
- truncal obesity
- acne
- hypertension
- facial flushing
- purple striae.

Elevated serum cortisol, the condition's hallmark, may be caused by pituitary adenomas, adrenal tumors or hyperplasia, or ectopic adrenocorticotrophic hormone secretion. The most common cause is exogenous administration of glucocorticoids. A dexamethasone suppression test or 24-hour urine cortisol confirms CS diagnosis.

Depressed CS patients often experience poor concentration, early morning waking, and decreased libido. Compared with nondepressed individuals with CS, those with depression tend to be older (average age 37.5) and more likely to be female, have more severe CS-related symptoms, and exhibit higher urine cortisol levels at diagnosis (average 1.694 pmol/L).<sup>14,15</sup>

Antidepressants typically will not resolve depression in patients with CS unless you also correct the hypercorticalism.<sup>16</sup>

**Addison's disease (AD).** Major depressive disorder is >2 times more prevalent in AD patients compared with matched controls.<sup>17</sup>

**Signs and symptoms.** Hyperpigmentation, salt cravings, low blood pressure, nausea, and vomiting are AD hallmarks. AD patients present with fatigue, vegetative symptoms, weight loss, and weakness that mimics a major depressive episode.

AD is caused by damage to the adrenal cortex. These patients do not have enough of the mineralocorticoid aldosterone, which maintains sodium and potassium balance and regulates blood pressure via the renin-angiotensin-aldosterone pathway. Decreased morning serum cortisol level, hyponatremia, and hyperkalemia confirm the diagnosis. AD can be serious—possibly fatal—so prompt referral to an endocrinologist is warranted.

### Neurologic disorders

**Stroke.** Post-stroke depressive symptoms generally do not differ from endogenous depression. Apathy, catastrophic reactions, hyperemotionalism, and diurnal mood variations are more prevalent in stroke patients,<sup>18</sup> although some of these features have been noted in other neurologic conditions.

**Signs and symptoms.** Look for depression onset or a change in existing depression

symptoms that occurs in the context of a clinically apparent stroke.<sup>19</sup> Antidepressants such as serotonin reuptake inhibitors may relieve post-stroke depression.

**Seizures.** Depressive symptoms could appear before or after a seizure or may be the clinical presentation of a simple or complex partial seizure.<sup>1</sup>

**Signs and symptoms.** Episodic, short-lived depression that resolves rapidly may warrant a seizure evaluation. Prodromal depressive symptoms such as irritability, depression, fear, or anger<sup>20</sup> may precede a seizure by 1 to 3 days and could improve after the seizure.

Caused by a simple partial seizure, ictal depression is characterized by guilt, anhedonia, or sudden-onset suicidal ideation without an environmental trigger. Symptoms are fairly short-lived, lasting from a few hours to a few days.<sup>5</sup>

Depressive symptoms also may develop minutes before a complex partial seizure or a secondarily generalized seizure.<sup>2</sup> Mood changes typically are brief, stereotypical, and associated with other ictal phenomena. Interictal depression involves mild chronic symptoms similar to dysthymia. Postictal depression may last for several days.

Prodromal and ictal depression often improve when antiepileptic therapy reduces seizure frequency.

**Huntington's disease (HD)** is a hereditary chorea caused by expanded trinucleotide repeats and characterized by abnormal movements, cognitive impairment, and neuropsychiatric symptoms. The suicide rate among HD patients is 4 times higher than in the general population.<sup>21</sup>

**Signs and symptoms.** Depression concurrent with neurologic symptoms such as chorea or dystonia may warrant an HD evaluation. Patients may present with psychiatric complaints such as depression, apathy, insomnia, or anxiety that may coincide with or precede other neurologic symptoms.<sup>22</sup> Mood-congruent delusions and auditory hallucinations also have been reported.<sup>23</sup> In one study, 98% of HD patients exhibited psychiatric symptoms—including dysphoria, agitation, irritability, apa-

**Table 2**

## Vitamin deficiencies that can lead to depression

Vitamin	Symptom
<b>B<sub>12</sub></b>	Megaloblastic anemia
	Decreased appetite
	Unexplained pancytopenia
	Paresthesias
	Dementia
	Glossitis
	Depressed mood
	Ataxia
	Irritability
	<b>Folate</b>
Depressed mood	
Dementia	
Impaired vibratory sensation	
Hyper- or hyporeflexia	
Macrocytic anemia	

thy, and anxiety—that occurred irrespective of cognitive or motor symptoms.<sup>24</sup>

Research into the cause of HD's neuropsychiatric symptoms has focused on abnormalities in frontostriatal brain circuitry.<sup>25</sup> Depressive symptoms might respond to any class of antidepressant.

**Wilson's disease**—caused by copper accumulation in the liver and basal ganglia—is characterized by degenerative changes in the brain, liver disease, and golden-brown or green Kayser-Fleischer rings in the cornea.

**Signs and symptoms.** Hepatic symptoms include hepatomegaly, hepatitis, and cirrhosis. Psychiatric symptoms—which include personality changes, depression, irritability, and psychosis—may occur alone or concurrent with neurologic symptoms such as tremor or dystonia.<sup>26</sup> Neuropsychiatric symptoms—the initial presentation in up to one-third of Wilson's disease patients—may respond to anticopper therapies.<sup>26</sup>

**Multiple sclerosis (MS).** Up to 50% of MS patients experience depression, although it is unclear if symptoms are caused by the disease or the impact of having a progressive chronic illness.

## Clinical Point

Depressive symptoms may be the clinical presentation of a simple or complex partial seizure

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**Signs and symptoms.** MS may cause weakness, visual loss, incontinence, paresthesias, and speech disturbances. MS symptoms such as fatigue, insomnia, and poor concentration overlap with DSM-IV-TR criteria for major depression. Depressive symptoms may worsen during disease flare-ups and with advanced neurologic disease.<sup>27</sup> Irritability, discouragement, and a sense of frustration are more common than low self-esteem and guilt.<sup>28</sup>

Depression may be more prevalent in MS patients with brain lesions compared with those with spinal cord lesions.<sup>29</sup> Imaging studies indicate that depressed MS patients are more likely to have hyperintense lesions in the left inferior frontal regions of the brain and greater atrophy of the left anterior temporal region,<sup>30</sup> indicating that the disease may play a role in depressive symptoms.

**Parkinson's disease (PD).** Nearly one-half of PD patients experience depression, which recent research suggests is related to neuroanatomic degeneration and not a reaction to having the illness.<sup>31</sup>

**Signs and symptoms.** Because PD can present with sleep disturbances, bradykinesia, restricted range of facial expression, and apathy, it initially might be mistaken for a depressive disorder.

**Other neurologic disorders.** Depression in Alzheimer's disease typically involves prominent anhedonia, irritability, apathy, and anxiety, rather than suicidal ideation and guilt.<sup>32</sup> In traumatic brain injury, the most common psychiatric disturbance is a depressive syndrome resembling endogenous depression.<sup>32</sup> Progressive supranuclear palsy—a degenerative disorder of the basal ganglia, brainstem, and cerebellar nuclei—is associated with cognitive impairments and personality changes and may present as depression.<sup>33</sup>

## Infectious disease

**Human immunodeficiency virus (HIV).** Depression affects 22% to 45% of HIV patients, particularly women, homosexual men, intravenous drug users, and patients

**Table 3**

## Medications that may be linked to depressive symptoms

### Antiepileptic drugs

Primidone, tiagabine, vigabatrin, felbamate, levetiracetam, topiramate, and phenytoin may cause depression,<sup>1</sup> and phenobarbital may cause depression associated with suicidal ideation<sup>2</sup>

### Beta-blockers

Recent randomized studies indicate these drugs do not carry a higher risk of depression, contrary to earlier accepted wisdom

### Corticosteroids

Depressive symptoms may occur after initial corticosteroid administration, with long-term use, or with drug discontinuation<sup>3</sup>

### Interferon alfa

Depression rates of nearly 50% have been reported.<sup>4</sup> Depressive symptoms seem to be related to dose and duration of treatment and may take several weeks to develop

### Interferon beta

Initial studies raised concern about an increased risk of depression and suicide, but a review of 16 studies did not detect an increased risk of depression<sup>5</sup>

### Isotretinoin

Although initial studies did not show an association between isotretinoin and depression and suicide, 24 reports of depression and more than 170 cases of isotretinoin-associated suicide have been reported.<sup>6</sup> In many patients, depressive symptoms resolved when the medication was discontinued, and several case studies reported depression recurrence with medication rechallenge

### Varenicline and bupropion

Postmarketing cases have described neuropsychiatric symptoms including depression and suicidal ideation with these antismoking agents, prompting changes in the drugs' prescribing information. Many of the cases reflect new-onset depressed mood, suicidal ideation, and changes in emotion and behavior within days to weeks of initiating treatment. Patients with pre-existing psychiatric illness may experience worsening of symptoms<sup>7</sup>

with a history of depression.<sup>34</sup> The cause of depression in HIV infection is unclear because studies are complicated by factors such as:

## Clinical Point

In multiple sclerosis patients, irritability, discouragement, and a sense of frustration are more common than low self-esteem and guilt

Table 4

## Clinical symptoms of hyperparathyroidism

Physical	Psychiatric
Kidney stones	Poor sleep
Headache	Anhedonia
Gastroesophageal reflux disease	Decreased concentration
Palpitations	Irritability
Aching bones	Decreased libido
Increased blood pressure	

### Clinical Point

Exposure to ticks, cranial nerve involvement, arthralgias, memory deficits, and psychotic depression may suggest Lyme disease

- social stigma and isolation associated with HIV
- side effects (such as fatigue) of anti-retroviral medications
- comorbid opportunistic CNS infections, such as tuberculosis or cryptococcal meningitis
- the virus itself, which is known to affect the brain.<sup>35</sup>

Certain sociodemographic factors are associated with depression in HIV patients, but Gibbie et al<sup>36</sup> found that CD4 count and viral load are not. This suggests that HIV does not directly cause depression, although research is ongoing. Comorbid substance dependence and AIDS-related dementia can complicate the clinical picture.

The depressive syndrome in patients with HIV typically does not precede the diagnosis of HIV. Diagnosing depression in HIV patients—regardless of the cause—is crucial because of its effect on quality of life, productivity, medication adherence, and mortality.<sup>37</sup>

**West Nile virus.** Among the one-third of patients who report new-onset depression after West Nile infection, 75% experience mild-to-severe depression as measured on a depression scale.<sup>38</sup> Studies of depression in West Nile virus infection are complicated by recall bias, illness-related disability, and fatigue that interferes with psychiatric assessment. Similar to HIV, a depression diagnosis typically is made following a known West Nile virus infection.

**Lyme disease.** More than one-third of patients diagnosed with post-Lyme syndrome—chronic symptoms that persist after antibiotic treatment—will have depression during their lifetime.<sup>39</sup> One report that attempted to determine a causal relationship between Lyme disease and depression found a similar lifetime incidence of depression in those with Lyme disease and in the general population. Even so, the incidence of depression doubled in this sample after the onset of Lyme disease. Studies of this relationship are confounded by other effects of Lyme disease, small numbers of subjects, and recall bias.

**Signs and symptoms.** Exposure to ticks, cranial nerve involvement, arthralgias, memory deficits, and psychotic depression may suggest Lyme disease.

**Creutzfeldt-Jakob disease** is a rare prion disease that can be genetic, spontaneous, or acquired via contaminated beef, corneal transplants, or dural transplants. Patients may present with cognitive impairment, fatigue, emotional lability, and depression.

**Signs and symptoms** include changes in the brain seen on an MRI, rapid physical and mental decline, and myoclonus and ataxia signs that occur late in the disease. Depression caused by this incurable disease often fails to respond to treatment.

**Neurosyphilis** patients may experience personality changes, irritability, psychosis, and decreased self-care, which may be interpreted as anhedonia or depressed mood.

**Signs and symptoms.** Common physical signs include dysarthria, hyperreflexia, cognitive decline, hallucinations, tremor, tabes dorsalis, and Argyll Robertson pupils. Neurosyphilis is confirmed by positive venereal disease research laboratory test of cerebrospinal fluid and treated with high-dose penicillin. Consensus is lacking on the role of psychotropic medications for the management of psychiatric symptoms.<sup>40</sup>

**Hepatitis C** patients have a higher lifetime prevalence of major depression compared with controls.<sup>41</sup> Although evidence does

not support a causal link between hepatitis C infection and depression, anecdotal reports persist.<sup>42</sup> Studies of comorbid depression and hepatitis C are complicated by hepatic encephalopathy, fatigue, medication side effects, and social and economic factors associated with hepatitis C. Physical symptoms include decreased appetite, fatigue, fever, nausea, vomiting, abdominal pain, clay-colored stool, joint pain, and jaundice.

Interferon (IFN) treatment for chronic, active hepatitis C has been associated with increased depressive symptoms and suicidal behavior. In a study of 31 hepatitis C patients, 23% experienced depressive episodes concurrent with IFN alfa treatment.<sup>43</sup> Depressive symptoms seem to be related to dose and treatment duration and may take several weeks to develop.

## Malignancy

Cancer patients often report depressive symptoms, although a causal relationship between malignancy and depression remains unclear. Some evidence suggests that pancreatic cancer and paraneoplastic syndromes can cause depression. In a retrospective study, depression preceded a pancreatic cancer diagnosis more often than with other gastrointestinal or non-gastrointestinal cancers.<sup>44</sup> Typically, depression starts >1 year before the cancer is discovered. It is unclear, however, if the cancer leads to depression or depression predisposes a person to pancreatic cancer.

**Signs and symptoms.** New-onset depression, dramatic unintended weight loss, and predominant sleep disturbance warrant further evaluation for malignancy. In patients diagnosed with cancer, depressive symptoms may be caused by reactive depression, an acute stress reaction, or adjustment disorder with depressed mood.

Paraneoplastic syndromes can cause depression, behavior and personality changes, and memory deficits.<sup>45</sup> These syndromes are commonly found in breast, lung, and testicular cancer, all of which might not be discovered when psychiatric symptoms develop.<sup>46</sup>

The immune system's reaction to can-

cer produces antibodies that attack the nervous system. Diagnosis of the resulting limbic encephalitis thought to underlie psychiatric symptoms is by CSF-positive antibodies (anti-Yo antibodies, anti-Ma2 antibodies, or anti-Hu) and abnormalities in brain MRI. Psychiatric symptoms often improve when the underlying malignancy is treated.

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## Clinical Point

**Depressive symptoms related to interferon treatment for chronic, active hepatitis C infection may take several weeks to develop**

continued

## Clinical Point

Depression associated with pancreatic cancer typically starts >1 year before the cancer is discovered

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## Related Resources

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### Drug Brand Names

Bupropion • Wellbutrin, Zyban	Primidone • Mysoline
Felbamate • Felbatol	Propranolol • Inderal
Interferon alfa • Intron, Roferon	Tiagabine • Gabitril
Interferon beta • Avonex, Rebif	Topiramate • Topamax
Isotretinoin • Accutane	Verapamil • Isoptin
Levetiracetam • Keppra	Vigabatrin • Sabril
Phenytoin • Dilantin	Varenicline • Chantix

### Disclosures

Dr. Carroll reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

Dr. Rado receives research support from Eli Lilly and Company, Neuronetics, and Otsuka, and is a speaker for Eli Lilly and Company.

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## Bottom Line

Medical illness and treatments may cause depressive symptoms, including fatigue, insomnia, and dysphoria. Although screening for various medical conditions is not cost-effective or warranted for most patients, stay attuned to such possibilities—especially on follow-up visits and in treatment-resistant patients. Vigilance may decrease unnecessary treatment delays, allow effective depression treatment, and facilitate communication with other medical providers.