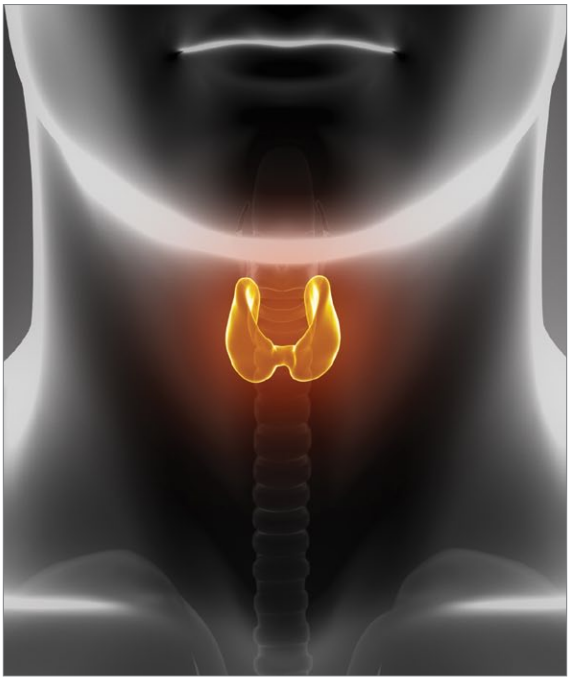
Treating thyroid disorders and depression: 3 case studies

Recognizing clinical nuances can improve screening and treatment of both disorders



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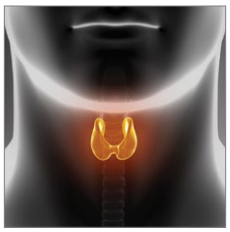
Many endocrine disorders can manifest as depression, including relatively rare disorders such as Cushing's syndrome (hypercortisolism) or Conn's syndrome (primary hyperaldosteronism) as well as common ones such as diabetes mellitus. Most clinicians do not routinely screen for adrenal disorders when evaluating depressed patients because the yield is low, but do screen for thyroid disease because these disorders often mimic depression. The following 3 cases from my practice illustrate some nuances of screening and treating depressed patients with suspected thyroid abnormalities.

CASE 1

Feeling 'like an 80-year-old'

Ms. A, age 25, has a gastrointestinal stromal tumor (GIST) and states that she feels "like an 80-year-old woman." She is sore all over with facial swelling, abdominal cramping, and fatigue. This feeling has worsened since she started chemotherapy with sunitinib for the GIST. Her Patient Health Questionnaire-9 (PHQ-9) score is 14 out of 27, indicating moderate depression. As part of a workup for her depression, what general laboratory tests would be most helpful?

Because Ms. A is of menstruating age, check hemoglobin/hematocrit levels to evaluate for anemia. Monitoring electrolytes would allow you to assess for hypernatremia/hyponatremia, hyperkalemia/hypokalemia, and impaired renal function, all of which could cause depressive symptoms. Depending on Ms. A's habitus or risk of metabolic syndrome, a fasting blood glucose or hemoglobin A1C test to screen for diabetes mellitus might be valuable because



Thyroid disorders

Clinical Point

The American Thyroid Association recommends thyroid dysfunction screening after age 35, with a recheck every 5 years

Table 1

Hypothyroidism symptoms

Psychiatric overlap
Fatigue
Hypersomnolence
Cognitive impairment (forgetfulness)
Difficulty concentrating or learning
Weight gain or fluid retention
Somatic signs and symptoms
Dry, itchy skin
Brittle hair and nails
Constipation
Myalgias
Heavy and/or irregular menstrual cycle
Increased rate of miscarriage
Sensitivity to cold

depression may be associated with diabetes.[1] A1C is a preferred primary screening test for diabetes (≥6.5% constitutes a positive screen) based on revised clinical practice recommendations of the American Diabetes Association. A1C is available as an office-based test that requires just a drop of blood from a finger prick and does not require a fasting blood sample or a full laboratory analysis.

A popular test for a workup of depression is serum 25-hydroxyvitamin D [25(OH)D] (vitamin D), particularly for patients who live in areas with limited exposure to ultraviolet B radiation from sunlight.[2] In a study of older adults, vitamin D levels were 14% lower in patients with minor depression and 14% lower in patients with major depressive disorder compared with controls. This study suggests that depression severity is associated with decreased serum vitamin D levels,[3] but the association between depression and vitamin D insufficiency and deficiency is unknown. Checking sex hormones also may be helpful depending on the patient's symptoms, because testosterone deficiency in men and dehydroepiandrosterone deficiency in women can have a direct impact on a patient's libido and overall sense of well-being. If repleted, improved levels of sex hormones can lead to a dramatic improvement in mood as well.

Because more than one-half of the estimated 27 million Americans with hyperthyroidism or hypothyroidism are undiagnosed, the American Thyroid Association recommends universal screening for thyroid dysfunction after age 35, with a recheck every 5 years.[4] However, checking serum thyroid-stimulating hormone (TSH) levels this often may not be cost-effective. Typically, I do not follow this recommendation when assessing or treating asymptomatic individuals, but Ms. A has symptoms of hypothyroidism (***Table 1***) and is taking a medication—sunitinib—thought to be associated with hypothyroidism.[5] Her serum TSH was very high (110 mIU/L; range 0.28 to 5.00) and her serum free T4 (FT4) was low (0.5 ng/dL; range 0.7 to 1.8). These values were consistent with overt hypothyroidism, defined as low FT4 and elevated TSH levels. This is in contrast to subclinical hypothyroidism (SH), which is defined as having an elevated serum TSH with normal thyroid hormone (T3 and T4) levels. SH presents in 5% of young patients (age <45) and increasingly is being diagnoses in older patients (age >55), who are most likely to suffer adverse effects in mood or cognition.[6]

CASE 1 CONTINUED

A classic case

Ms. A is started on a full levothyroxine replacement dose of 1.6 µg/kg/d. For hypothyroid patients who do not have cardiac symptoms, weight-based replacement is thought to be safe and more convenient than starting with a low dose and titrating up.[7] Ms. A responds quickly. At 6-week follow-up—the recommended time interval for repeat thyroid lab testing after initiating thyroid replacement—her depressive symptoms are markedly improved and her PHQ-9 score is 6, indicating mild depression.

CASE 2

Chronic pain, low mood, and fatigue

Ms. B, age 62, has fibromyalgia and chronic back pain. She takes cyclobenzaprine, 5 mg 2 to 3 times daily, and oxycodone, 40 mg/d, and describes mild depressive symptoms when she presents for routine follow-up. Most of her complaints are related to chronic pain, but

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she has a history of low mood and fatigue. She says she was prescribed levothyroxine, but is unable to remember if she stopped taking it because of financial constraints or laboratory/clinical improvement. Her neurologist recently checked her serum TSH, which was elevated at 8.1 mIU/L. Is it best to restart thyroid replacement or wait 6 weeks and recheck her thyroid panel?

Mild SH typically is defined as TSH between 4.5 and 10 mIU/L. In contrast, TSH between 10 and 20 mIU/L is considered severe SH. Because Ms. B did not have prominent new symptoms, I felt it was reasonable to wait the recommended 6 weeks before rechecking her thyroid function. At follow-up, Ms. B's TSH was 4.64 mIU/L and her FT4 was normal: 0.7 ng/dL. Thyroid replacement was not indicated because she did not have obvious symptoms and treating SH does not impact overall mood and cognition until TSH is ≥10 mIU/L.[8,9]

CASE 2 CONTINUED

Prominent symptoms emerge

Ms. B returns several months later. Another clinician prescribed duloxetine, titrated from 30 mg to 60 mg, for worsening fibromyalgia. Her depressive symptoms are more prominent at this visit, and her PHQ-9 score has risen from 7 to 14, indicating moderate depression. She says previously she failed or poorly tolerated several antidepressants—fluoxetine, sertraline, and citalopram—but was hoping for a pharmacologic adjustment. Most evidence-based augmentation algorithms for treating major depression start with adding a second "traditional" antidepressant such as bupropion, then move to lithium, second-generation antipsychotics, or lamotrigine.[10] But what about thyroid hormone augmentation?

Thyroid hormone often is on the lower rungs of depression treatment algorithms despite Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial data. The data suggest triiodothyronine's (T3) lower side effect burden and ease of use may offer an advantage over lithium augmentation for depressed patients who have failed several medication trials.[11] Liothyronine sodium (triiodothyronine) is a relatively benign medication with potential for augmentation when started at 25 to 50 mcg/d concurrently with antidepressants such as sertraline.[12] Unfortunately, most augmentation trials with T3 have been short-term—generally 4 to 8 weeks. In my practice, T3 has limited application; I use it mainly for patients with treatment-resistant depression who have failed several other treatments.

Lithium, the comparison medication to thyroid hormone in the third augmentation arm of the STAR*D trial, requires an annual check of thyroid function (TSH testing) to properly monitor for potential lithium-related hypothyroidism or thyroiditis. Hypothyroidism, for which thyroid replacement is required, with lithium therapy is common, affecting 8% to 27% of patients.[13] Patients who rapidly gain weight at the beginning of lithium treatment seem to have a higher risk of developing hypothyroidism.[13] However, the risk

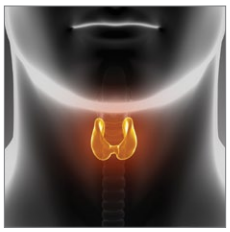
Table 2

Hyperthyroidism symptoms

Psychiatric overlap
Decrease or increase in appetite
Insomnia
Fatigue
Mood instability
Irritability
Anxiety, nervousness
Somatic signs and symptoms
Frequent bowel movement, eg, diarrhea
Heart palpitations
Heat intolerance
Increased sweating
Light or missed menstrual periods, fertility problems
Muscle weakness
Shortness of breath
Sudden paralysis
Tremor, shakiness, dizziness
Vision changes
Weight loss or gain
Thinning of hair
Itching and hives
Possible increase in blood sugar

Clinical Point

The longer a patient has been treated with lithium, the greater the risk of developing lithium-induced hypothyroidism



Thyroid disorders

Related Resources

- National Women's Health Resource Center, Inc. Thyroid disorders. www.healthywomen.org/condition/thyroid-disorders.
- American Thyroid Association. www.thyroid.org.
- American Association of Clinical Endocrinologists. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. www.aace.com/files/hypo-hyper.pdf.

Drug Brand Names

Atenolol • Tenormin
Bupropion • Wellbutrin, Zyban
Citalopram • Celexa
Cyclobenzaprine • Flexeril
Divalproex ER • Depakote ER
Duloxetine • Cymbalta
Fluoxetine • Prozac
Lamotrigine • Lamictal
Levothyroxine • Levoxyl, Synthroid
Liothyronine sodium • Cytomel, Triostat
Lithium • Eskalith, Lithobid
Methimazole • Tapazole
Oxycodone • OxyContin
Paroxetine • Paxil
Sertraline • Zoloft
Sunitinib • Sutent

Disclosure

Dr. Raj is a speaker for AstraZeneca and Merck.

Clinical Point

Hypothyroidism is commonly associated with depressive symptoms, but hyperthyroidism also may present as depression

of developing lithium-induced hypothyroidism is tied to the length of treatment; the longer a patient has been treated with lithium, the greater the risk of developing lithium-induced hypothyroidism.

CASE 3

Unable to slow down

Mr. C, age 45, has a 20-year history of major depression controlled reasonably well with paroxetine, 40 mg. He presents with escalating anxiety, depression, and irritability. His wife is concerned about his overwhelming thoughts of death, especially because Mr. C's father committed suicide 30 years ago under similar circumstances. Mr. C has been tremulous for the past month and has not been sleeping well. He feels like he is "in constant motion" and unable to slow down. He screens in the "highly likely" range for bipolar disorder on the Bipolar Spectrum Diagnostic Scale[14] and is started on divalproex ER, 500 mg/d.

His thyroid function tests returns with a suppressed TSH of 0.03 mIU/L and an elevated FT4 of 3.26 ng/dL. Divalproex is discontinued and he is started on the beta blocker atenolol, 25 mg/d, to target his anxiety, tachycardia, and akathisia. TSH receptor antibody testing was positive, which, along with an abnormal radioactive iodine uptake scan, confirmed a diagnosis of Graves' disease. He receives methimazole, 20 mg/d, as a temporizing measure. An endocrinologist completes a radioactive iodine (I-131) ablation procedure on Mr. C, which resolves his mood and anxiety symptoms.

Although hypothyroidism commonly is associated with depressive symptoms, hyperthyroidism also may present as depression. Most cases of overt hyperthyroidism are directly referred to an endocrinologist because when treating disorders such as Graves' disease—the most common cause of hyperthyroidism, especially among women age 20 to 40—many nuclear medicine teams require the expert guidance of an endocrinologist before considering radioiodine ablation. Hyperthyroidism often is accompanied by psychiatric and somatic symptoms of an "overactive" nature (***Table 2, page 19***). However, older patients (age >65) with hyperthyroidism may develop apathetic hyperthyroidism, a subset that comprises approximately 10% to 15% of all hyperthyroidism cases in older adults.[15] Rather than becoming nervous, jittery, and restless, patients with apathetic hyperthyroidism are depressed, lethargic, and weak, and may develop proximal myopathy or cardiomyopathy. It is essential to differentiate apathetic hyperthyroidism from typical hyperthyroidism because accurately diagnosing and treating apathetic hyperthyroidism will improve outcomes.[15]

Bottom Line

Both hypothyroidism and hyperthyroidism can masquerade as depression. Checking thyroid-stimulating hormone levels can help narrow the diagnosis of patients who present with depressive symptoms. Triiodothyronine is an option in adjunctive depression treatment, even for patients with a normal thyroid; longer-term studies are needed to assess its efficacy and long-term safety.

Using beta blockers to treat hyperthyroidism can help control tachycardia or palpitations, tremulousness, and anxiety that often are inherent in hyperthyroidism. But can beta blockers induce depressive symptoms? A 1-year prospective Dutch study of patients who had survived a myocardial infarction did not find evidence that beta blockers induced depressive symptoms.[16] However, the long-term and high-dosage effects of beta blockers still are in question.[16] In Mr. C's case, beta blockers had only positive effects on his symptoms and did not exacerbate his depressive symptoms.

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Clinical Point

A 1-year study of patients who survived a myocardial infarction did not find evidence that beta blockers induced depressive symptoms