Effects of psychotropic medications on thyroid function

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Ms. L, age 53, presents to an inpatient psychiatric unit with depression, difficulty concentrating, fatigue, cognitive blunting, loss of appetite, increased alcohol intake, and recent suicidal ideation. Her symptoms began 3 months ago and gradually worsened. Her medical and psychiatric history is significant for hypertension, fibromyalgia, and chronic pain (back and neck), major depressive disorder (MDD; recurrent, severe), and generalized anxiety disorder (GAD). Ms. L's current medication regimen includes lisinopril, 40 mg daily; fluoxetine, 60 mg daily; mirtazapine, 30 mg at bedtime; gabapentin, 300 mg twice daily; alprazolam, 0.5 mg twice daily as needed for anxiety; and oral docusate, 100 mg twice daily as needed. Her blood pressure is 124/85 mm Hg, heart rate is 66 beats per minute, and an electrocardiogram is normal. Laboratory workup reveals a potassium level of 4.4 mEq/L, blood urea nitrogen level of 20 mg/dL, serum creatinine level of 0.8 mg/dL, estimated creatinine clearance of 89.6 mL/min, free triiodothyronine (T3) levels of 2.7 pg/mL, thyroid-stimulating hormone (TSH) level of 7.68 mIU/L, free thyroxine (T4) level of 1.3 ng/dL, and blood ethanol level <10 mg/dL. In addition to the symptoms Ms. L initially described, a review of systems reveals word-finding difficulty, cold intolerance, constipation, hair loss, brittle nails, and dry skin.

To target Ms. L's MDD, GAD, fibromyalgia, and chronic pain, fluoxetine, 60 mg daily is cross titrated beginning on Day 1 to duloxetine, 60 mg twice daily, over 4 days. Mirtazapine is decreased on Day 3 to 7.5 mg at bedtime to target Ms. L's sleep and appetite. Due to the presence of several symptoms associated with hypothyroidism and a slightly elevated TSH level, on Day 6 we initiate adjunctive levothyroxine, 50 mcg daily each morning to target symptomatic subclinical hypothyroidism, and to potentially augment the other medications prescribed to address Ms. L's MDD.

continued

Practice Points

- **Thyroid dysfunction can occur as a consequence of psychotropic therapy**. Hypothyroidism occurs more frequently than hyperthyroidism.
- **Patients who are at risk for or have a history of thyroid dysfunction** should be carefully monitored throughout their treatment with psychotropics.
- **Thyroid replacement therapy should be pursued** when patients meet diagnostic criteria for hypothyroidism or have symptomatic subclinical hypothyroidism; evaluating for thyroid symptoms is paramount and should be routinely done.
- **Psychotropic regimen changes to reduce thyroid impairment** can be considered based on the patient's history and clinical status.

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Table

Considerations for modifying psychotropic therapy based on the presence of thyroid dysfunction[a]

If a patient develops symptomatic thyroid dysfunction while taking one of the following psychotropics	Consider switching to one of the following alternatives
Lithium	Valproic acid Carbamazepine
Phenothiazines (ie, chlorpromazine, fluphenazine, thioridazine), haloperidol, or loxapine	Other first-generation antipsychotics Second-generation antipsychotics Consider avoiding amisulpride, quetiapine, clozapine, aripiprazole, and possibly risperidone
Tricyclic antidepressants	Non-tricyclic antidepressants • Selective serotonin reuptake inhibitors • Serotonin-norepinephrine reuptake inhibitors • Mirtazapine • Bupropion

[a]If a patient is stable on a specific psychotropic regimen and modifying therapy would be detrimental, consider continuing therapy and initiating thyroid replacement therapy

Source: Reference 1

Clinical Point

Thyroid function should be routinely assessed in patients treated with antipsychotics

Thyroid hormone function is a complex physiological process controlled through the hypothalamic-pituitary-thyroid (HPT) axis. Psychotropic medications can impact thyroid hormone function and contribute to aberrations in thyroid physiology.[1] Because patients with mental illness may require multiple psychotropic medications, it is imperative to understand the potential effects of these agents.

Antidepressants can induce hypothyroidism along multiple points of hormonal synthesis and iodine utilization. Tricyclic antidepressants have been implicated in the development of drug-iodide complexes, thus reducing biologically active iodine.[2] Tricyclic antidepressants also can bind thyroid peroxidase, an enzyme necessary in the production of T4 and T3, altering hormonal production, resulting in a hypothyroid state.[1] Non-tricyclic antidepressants (ie, selective serotonin reuptake inhibitors [SSRIs] and non-SSRIs [including serotonin-norepinephrine reuptake inhibitors and mirtazapine]) have also been implicated in thyroid dysfunction. Selective serotonin reuptake inhibitors have the propensity to induce hypothyroidism through inhibition of thyroid hormones T4 and T3.[1,3] This inhibition is not always seen with concurrent reductions in TSH levels. Conversely, non-SSRIs can influence thyroid hormone levels with great variation, leading to thyroid hormone levels that are increased, decreased, or unchanged.[1] Patients with a history of thyroid dysfunction should receive close thyroid function monitoring, especially while taking antidepressants.

Antipsychotics have a proclivity to induce hypothyroidism by means similar to antidepressants via hormonal manipulation and immunogenicity. Phenothiazines impact thyroid function through hormonal activation and degradation, and induction of autoimmunity.[1] Autoimmunity may develop by means of antibody production or antigen immunization through the major histocompatibility complex.[2] Other first-generation antipsychotics (FGAs) (eg, haloperidol and loxapine) are known to antagonize dopamine receptors in the tuberoinfundibular pathway, resulting in increased prolactin levels. Hyperprolactinemia may result in increased TSH levels through HPT axis

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activation.[1] Additionally, FGAs can induce an immunogenic effect through production of antithyroid antibodies.[1] Similar to FGAs, second-generation antipsychotics (SGAs) can increase TSH levels through hyperprolactinemia. Further research focused on SGAs is needed to determine how profound this effect may be.

The ***Table***[1] (***page 62***) outlines considerations for modifying psychotropic therapy based on the presence of concurrent thyroid dysfunction. Thyroid function should be routinely assessed in patients treated with antipsychotics.

Mood stabilizers are capable of altering thyroid function and inducing a hypothyroid state. Lithium has been implicated in both hypothyroidism and hyperthyroidism due to its inhibition of hormonal secretion, and toxicity to thyroid cells with chronic use, respectively.[1,4] Hypothyroidism can develop shortly after initiating lithium; women tend to have a greater predilection for thyroid dysfunction than men.[1] Carbamazepine (CBZ) can reduce thyroid hormone levels without having a direct effect on TSH or thyroid dysfunction.[1] As with lithium, women tend to be more susceptible to this effect. Valproic acid (VPA) has been shown to either increase, decrease, or have no impact on thyroid hormone levels, with little effect on TSH.[1] When VPA is given in combination with CBZ, significant reductions in thyroid levels with a concurrent increase in TSH can occur.[1] In patients with preexisting thyroid dysfunction, the combination of VPA and CBZ should be used with caution.

CASE CONTINUED

By Day 8, Ms. L reports less fatigue, clearer thinking, improved concentration, and less pain. She also no longer reports suicidal ideation, and demonstrates improved appetite and mood. She is discharged on Day 9 of her hospitalization.

The treatment team refers Ms. L for outpatient follow-up in 4 weeks, with a goal TSH level <3.0. Unfortunately, the effects of levothyroxine on Ms. L's TSH level could not be determined during her hospital stay, and she has not returned to the facility since the initial presentation.

Related Resources

- Cojić M, Cvejanov-Kezunović L. Subclinical hypothyroidism – whether and when to start treatment? Open Access Maced J Med Sci. 2017;5(7):1042-1046.
- Garber JR, Cobin RH, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Thyroid. 2012;22(12):1200-1235.
- Iosifescu DV. 'Supercharge' antidepressants by adding thyroid hormones. Current Psychiatry. 2006;5(7):15-20,25.

Drug Brand Names

Alprazolam • Xanax
Aripiprazole • Abilify
Bupropion • Wellbutrin
Carbamazepine • Carbatrol, Tegretol
Chlorpromazine • Thorazine
Clozapine • Clozaril
Duloxetine • Cymbalta
Fluoxetine • Prozac
Fluphenazine • Prolixin
Gabapentin • Neurontin
Haloperidol • Haldol
Levothyroxine • Synthroid
Lisinopril • Prinivil, Zestril
Lithium • Eskalith, Lithobid
Loxapine • Loxitane
Mirtazapine • Remeron
Quetiapine • Seroquel
Risperidone • Risperdal
Thioridazine • Mellaril
Valproic acid • Depakote

Thyroid function and mood

Ms. L's case illustrates how thyroid function, pain, cognition, and mood may be interconnected. It is important to address all potential underlying comorbidities and establish appropriate outpatient care and follow-up so that patients may experience a more robust recovery. Further, this case highlights the importance of ruling out other potential medical causes of MDD during the initial diagnosis, and during times of recurrence or relapse, especially when a recent stressor, medication changes, or medication nonadherence cannot be identified as potential contributors.

Clinical Point

Lithium has been implicated in both hypothyroidism and hyperthyroidism

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