Thyroid hormone treatment for lithium-induced thyroid dysfunction in mood disorder

I read with interest the article by Joffe[1] about thyroxine (T4) supplementation for lithium-induced subclinical and clinical hypothyroidism in patients with bipolar disorder. Given the paucity of clinical guidelines in this area, I would like to discuss 4 important issues related to thyroid hormone supplementation for lithium-induced thyroid dysfunction.

First, growing literature suggests that triiodothyronine (T3) and T4 may have differential augmenting effects in mood disorders. T3 augmentation may potentiate antidepressants[2] and may be beneficial for patients with treatment-resistant depression and hypothyroidism who were also receiving T4.[3] T4 appears to be effective in augmenting the effects of mood stabilizers in patients with bipolar disorder.[4] Although T4, rather than T3 supplementation, has been recommended for hypothyroidism because T4 produces steadier hormone levels,[5] the efficacy of T3 in the treatment of hypothyroidism has also been well documented.[6] Taking into account the differential augmenting effects of T3 and T4 and the efficacy of T3 in the treatment of hypothyroidism, T3 supplementation may be preferable for lithium-induced hypothyroidism in patients with unipolar depression and T4 in patients with bipolar disorder.

Second, when T4 supplementation is considered for modest elevations above the normal range of thyroid stimulating hormone (TSH) in a symptomatic bipolar patient with lithium-associated hypothyroidism, careful titration of T4 dosage is required to prevent suppression of TSH below the normal range and subclinical hyperthyroidism from developing.

Third, T4 prophylactic supplementation can be considered for a patient with symptomatic rapid cycling bipolar disorder with a mildly elevated TSH level associated with lithium treatment. Further, T4 suppressive therapy can be used with caution even if TSH levels correspond to the upper limit of normal range during lithium therapy. Since there are no clinical guidelines regarding a safe lower threshold for TSH concentration in TSH-suppressive therapy, levels should be kept within the lower part of normal range.

Fourth, although the effects of T4 on clinically significant bone loss in post- or pre-menopausal women receiving TSH-suppressive T4 are controversial,[7,8] regular bone mineral density assessments and prophylactic calcium treatment should be carefully considered during T4 supplementation in post-menopausal women with bipolar disorder. Given the risk of lithium-induced hyperparathyroidism in some patients, parathyroid function should be assessed before calcium supplementation is initiated.

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Competing interests: Dr. Ramasubbu has served on the advisory board of Eli Lilly.

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Manic-switch induced by fluvoxamine in abstinent pure methamphetamine abusers

On a global level, methamphetamine (MAP) is typically abused in combination with other drugs of addiction. However, in Japan, many MAP abusers use the drug alone.[1] The depressive state caused by MAP, generally seen during the withdrawal period, generally disappears within several days.[2,3] However, in cases where the depressive symptoms persist, treatment with antidepressants, including the tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs), may be nec-

essary. Antidepressants can elicit manic or hypomanic episodes in patients with unipolar depression,[4] but to our knowledge, there are no reports of this with respect to stimulants users. We describe 2 abstinent MAP patients (neither abused other drugs) who developed mania after taking fluvoxamine for persistent depressive symptoms.

Ms. A, a 23-year-old married woman, started abusing MAP by intravenous injection twice a week or more at age 16. There was no significant premorbid depression before MAP use began or genetic vulnerability to depression. She married at age 20, but did not stop using MAP. She stopped taking MAP at age 23 when her family noticed her abuse, but then began to develop MAP abstinence symptoms, such as depressive moods and insomnia.

She was admitted to our hospital 21 days after the last use of MAP. MAP was not detected in the urine. The woman complained of severe depressive mood, insomnia, inertia and loss of appetite. We prescribed fluvoxamine (150 mg/d) and brotizolam as needed (0.5 mg/d). Thirteen days after treatment was initiated, she began to show a manic state with elevated mood, talkativeness and increased activity. Because these symptoms lasted for 10 days, we discontinued fluvoxamine treatment, and her manic symptoms readily dissipated. The patient became euthymic and was discharged from the hospital 3 months after admission.

Ms. B, a 22-year-old single woman with no premorbid depression before using MAP or genetic vulnerability to depression, started abusing MAP at age 17, and abused MAP once or twice a week for 4 years. She stopped taking MAP at age 21 when her family noticed her abuse. She began to exhibit MAP abstinence symptoms (i.e., low mood, listlessness and insomnia) and was admitted to our hospital 23 days after she last used MAP. MAP was not detected in her urine. We started to treat her symptoms with fluvoxamine (100 mg/d) and brotizolam as needed (0.5 mg/d). Her depressive symptoms disappeared in several days, but 2 weeks after treatment with fluvoxamine was instituted, she became manic, exhibiting talkativeness and aggressiveness with grandiose ideation. When fluvoxamine was discontinued, her manic state subsided within several days. The woman was discharged from the hospital 3 months after admission.

Some studies suggest that one of the acute abstinent symptoms after MAP abuse is a depressive state.[2,3] Generally, the depressive state peaks 48–72 hours after the last dose and resolves completely within a week.[2] Thus, our cases where the depressive state persisted for 3 weeks or longer are considered unusual. Indeed, in our hospital in the last 5 years, we have seen only 5 cases where MAP-induced depressive symptoms persisted. To our knowledge, this is the first report of an antidepressant causing a manic switch in abstinent MAP abusers with depressive symptoms.

We cannot explain this phenomenon at present. The induction of mania or hypomania by SSRIs such as fluvoxamine may depend on the dose used.[4] However, in our cases, manic switch occurred using standard dosages. Studies in laboratory animals indicate that repeated MAP administration can produce long-lasting depletion of brain serotonin (5-HT) and dopamine (DA).[5] Therefore, it is possible that the sudden increase in serotonin levels produced by fluvoxamine's blockade of the serotonin transporter may induce the manic switch in these patients.[6] Given the well-described 5-HT/DA interactions in the brain, the SSRI-induced mania may also involve DA. This explanation is highly speculative however, and it is not known whether manic switch in MAP users with depression is specific to SSRIs such as fluvoxamine or not.

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