

# Remission of classic rapid cycling bipolar disorder with levothyroxine augmentation therapy in a male patient having clinical hypothyroidism

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**Abstract:** The literature suggests that patients with bipolar disorder, particularly females, have greater vulnerability to rapid cycling features. Levothyroxine therapy might be potentially useful to attenuate mood instability in this patient group. In contrast, reports on male patients remain limited and controversial. Herein, we report a 32-year-old male patient who had bipolar I disorder for 12 years who developed a breakthrough rapid cycling course and first-onset clinical hypothyroidism at the age of 31 years during lithium therapy. After levothyroxine augmentation therapy was introduced, the patient had remission from the rapid cycling illness course along with normalization of serum levels of free T4 and thyroid stimulating hormone in the subsequent year. This observation suggested that investigation of both levothyroxine pharmacology and thyroid pathology in male patients with rapid cycling bipolar disorder might be of much value.

**Keywords:** mood disorder, therapy, thyroid hormone

## Introduction

According to the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), rapid cycling bipolar disorder is defined as the presence of at least four mood episodes within a 12-month period that meet the criteria for hypomania, mania, or a major depressive episode.<sup>1</sup> Significantly, the prevalence rate of the rapid cycling subtype of bipolar disorder ranges from 25% to 43% in the current literature.<sup>2</sup> Furthermore, patients with rapid cycling bipolar disorder are at an increased risk for poor treatment response, a longer course of illness, and greater morbidity and mortality.<sup>2</sup> Nevertheless, the exact pathophysiology of rapid cycling bipolar disorder is still not clearly understood, and the current options for effective treatment remain limited.

Thyroid pathology has long been a subject of investigation in rapid cycling bipolar disorder. Evidence has indicated that levothyroxine therapy might be a potentially useful treatment to reduce mood instability in this group of patients,<sup>3-8</sup> however, most responsive cases in the literature were females and the responses were independent of thyroid status. We present the case of a 32-year-old male who developed a breakthrough rapid cycling course and first-onset clinical hypothyroidism at the age of 31 years while receiving lithium therapy. After levothyroxine augmentation therapy was given, the patient showed significant improvement in the course of rapid cycling and abnormal thyroid function over the following year.

## Case report

Mr A was a 32-year-old male patient with the first onset of a depressive episode and suicide attempt at the age of 20 years. When he was 22 years old, he had his first manic

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episode and consequently received a DSM-IV diagnosis of bipolar 1 disorder. Despite a good response to lithium 600 mg, valproic acid 1,200 mg, and risperidone 2 mg per day, Mr A did not take medication regularly after each period of acute treatment. In the subsequent 5 years, he was hospitalized an average of two times each year for the acute treatment of manic or depressive episodes. During depressive episodes, therapy of lithium but not antidepressant was provided. Lamotrigine was used briefly for a depressive episode at the age of 26 years and discontinued because a subsequent manic episode occurred. Thyroid function tests showed subclinical hypothyroidism (serum free T4: 1.03 ng/dL, referential range: 0.7–2.3 ng/dL; thyroid-stimulating hormone [TSH]: 6.36  $\mu$ IU/mL, referential range: 0.4–5.0  $\mu$ IU/mL) only once during acute treatment for mania with lithium 600 mg and valproic acid 1,700 mg per day at age 28 years.

Mr A received the maintenance therapy of bipolar disorder in the daycare unit from the age of 28 years. After 2-year treatment with valproic acid 1,500 mg per day, lithium 600 mg per day, and long-acting injectable risperidone 25 mg every 2 weeks, Mr A had more regular medication adherence and remained in remission of bipolar disorder between the ages of 28 and 30 years. By the age of 30 years, lithium and risperidone were discontinued due to intolerable hand tremors. Quetiapine 400 mg per day was subsequently combined with valproic acid 1,500 mg per day for maintenance therapy. The follow-up thyroid function test between the ages of 28 and 30 years did not show abnormalities. In addition, Mr A did not have evidence of physical diseases or substance abuse during the period of psychiatric treatment. His first-degree family did not report any history of psychiatric or thyroid morbidities.

At age 31 years, Mr A had a breakthrough manic episode while on maintenance therapy of valproic acid 1,500 mg and quetiapine 400 mg per day. Lithium 900 mg per day was added (serum lithium level: 0.85 mEq/L); however, a classic rapid cycling course of illness occurred over the following year (mania for 3 months, depression for 2 months, mania for 5 months, and depression) despite the combination therapy of lithium, valproic acid, and various antipsychotics at adequate dosage for sufficient duration. During each of these episodes, serum levels of free T4 and TSH were measured. The exam during the second depressive episode of the course of rapid cycling illness showed clinical hypothyroidism (serum free T4: 0.6 ng/dL; TSH: 11.5  $\mu$ IU/mL) for the first time in his life. Investigations for anti-thyroid peroxidase antibodies and anti-thyroglobulin antibodies were negative. A thyroid sonogram revealed diffuse goiters. Because of the clinical

hypothyroidism and thyroid goiters, levothyroxine 50  $\mu$ g per day was administered in addition to the psychopharmacotherapeutic regimen of lithium 900 mg, lamotrigine 50 mg, and clozapine 100 mg per day. The major depressive episode went into remission over the following 3 months. Serum levels of free T4 and TSH then returned to normal, at 1.1 ng/dL and 3.8  $\mu$ IU/mL, respectively. Mr A maintained the therapeutic regimen and remained in remission from the rapid cycling illness for the subsequent year. No intolerable adverse effect was noted.

## Discussion

This 32-year-old male carried a diagnosis of bipolar 1 disorder for 12 years. A breakthrough rapid cycling course and concurrent clinical hypothyroidism first occurred in the eleventh year of his illness despite combination treatment with various mood stabilizers and antipsychotics. Levothyroxine augmentation therapy markedly attenuated the mood instability and corrected the thyroid dysfunction. This case suggested that the pathophysiology of rapid cycling bipolar illness involves thyroid dysregulation in the subgroup of patients whose bipolar mood symptoms respond well to the administration of levothyroxine.

Previous reports have suggested that more than half of the patients with refractory rapid cycling disorder were clinically responsive to levothyroxine therapy.<sup>3–8</sup> Notably, this treatment response was independent of clinical thyroid status despite evidence from another study showing that hypothyroidism was associated with rapid cycling in bipolar disorder.<sup>9</sup> In these reports about levothyroxine therapy for rapid cycling bipolar disorder, responsive patients were most likely to be female. On the other hand, male patients with rapid cycling bipolar disorder were under-investigated, and the efficacy of levothyroxine therapy for these cases was controversial. Bauer and Whybrow reported successful thyroxine treatment of a male patient whose bipolar rapid cycling course began and resolved after changes in thyroid status.<sup>5</sup> Positive results of thyroxine therapy were also observed in two other male cases reported by Bauer and Whybrow and by Weeston and Constantino.<sup>6,7</sup> Conversely, Stancer and Persad reported only a transitory response to levothyroxine treatment in two male patients with rapid cycling bipolar disorder.<sup>3</sup> We report a male patient with classic rapid cycling bipolar disorder and coexisting thyroid pathology who responded well to levothyroxine therapy. This finding supported that understanding thyroid pathophysiology is relevant in male patients with rapid cycling bipolar disorder and levothyroxine efficacy.

A mechanism for the association between thyroid dysfunction and rapid cycling bipolar disorder has not been fully elucidated. Early evidence suggested that hypothyroidism decreases noradrenergic turnover rates and results in hypersensitivity of the  $\beta$ -adrenergic receptors. This hypersensitivity, in turn, leads to a rapid switch to mania, particularly when antidepressants that block the effects of norepinephrine reuptake are coadministered.<sup>10,11</sup> Furthermore, emerging investigations have indicated that thyroid hormones are important regulators of the periodicity of the biological clocks underlying bipolar disorder.<sup>12,13</sup> Impairment in self-regulation of the hypothalamic–pituitary–thyroid axis may therefore contribute to the pathological oscillations of the catecholamine systems in rapid cycling bipolar disorder.<sup>14</sup>

In our case, we could not totally exclude the possibility that the hypothyroidism was associated with lithium therapy. Although the hypothyroidism in our rapid cycling bipolar patient was mild, we provided levothyroxine to him since levothyroxine therapy concurrent with lithium treatment is recommended in rapid cycling bipolar cases having thyroid goiters or clinical hypothyroidism.<sup>15</sup> The positive result in our patient supported this recommended strategy. In contrast to previous reports about lithium-related hypothyroidism,<sup>15</sup> our patient was distinct in being male, aged below 50 years, and with no family history of thyroid diseases or thyroid autoantibodies. Moreover, antidepressants were not given to our patient during major depressive episodes since antidepressants might trigger rapid cycling in bipolar disorder.<sup>2</sup> Levothyroxine augmentation therapy therefore warrants further investigation in depressed patients with rapid cycling bipolar disorder and concurrent hypothyroidism.

Emerging evidence also suggests that combined treatment with clozapine and lamotrigine might be useful for treatment-resistant rapid cycling bipolar disorder.<sup>16,17</sup> In our patient, we provided levothyroxine augmentation therapy 1 week after the initiation of clozapine therapy and 2 weeks before the initiation of lamotrigine. Consequently, we should also consider the possibility that this remission was due to this combination. Historically, one of our patient's episodes of depression switched to mania during lamotrigine therapy when he was 26 years old. Therefore, the present treatment response might also have been due to the addition of levothyroxine rather than to the combination of clozapine and lamotrigine. However, this hypothesis cannot be examined at this point because of clinically ethical reasons.

## Conclusion

Levothyroxine augmentation therapy improved mood instability and thyroid dysfunction in our male patient with rapid cycling bipolar disorder and concurrent hypothyroidism. This observation suggested that further investigation of both levothyroxine pharmacology and thyroid pathology in male patients with rapid cycling bipolar disorder is indicated.

## Disclosure

The authors report no conflicts of interest in this work.

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