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LETTER

The efficacy of Li in bipolar disorder

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Dear editor

The efficacy of lithium (Li) for acute mania and as prophylaxis against recurrent episodes of mania in bipolar disorder has been well established, with the minimum effective Li serum concentration for acute mania in the range of 0.6–1.2 mEq/L, although lower maintenance concentrations can prove effective in some patients.[1–5]

Thyroid disorders are also associated with alterations in mood, and patients with hypothyroidism may present with depression and cognitive dysfunction,[6–8] while patients with hyperthyroidism may present with anxiety, depression, mood lability,[7,9] and manic symptoms.[10] However, considering that overt hyperthyroidism is uncommon in bipolar disorder, with a prevalence ≤2% across different studies,[11,12] this has been largely attributed to lithium,[13] with rates varying from 0 to 47% (average of about 10%) among patients on long-term treatment with lithium.[13–16]

Due to this association between thyroid disease and mood disorders (including bipolar disorder), an evaluation of thyroid function is made by psychiatrists before the diagnosis of any depressive or manic events and regularly evaluated during Li treatment. Furthermore, thyroid dysfunction is more common in patients with rapid cycling bipolar disorder or mixed states.[17] In addition, levothyroxine treatment may decrease the severity and frequency of manic and depressive episodes,[18] and patients with hyperthyroidism may also be associated with long-term mood disturbances.[19]

In this way, there are currently enough data about effects of Li on the thyroid, making it clear that Li affects the thyroid gland of all patients in a dose-dependent manner, with greater or lesser intensity.[20,21] The levels of free thyroxine (FT4) have been used as a secondary surrogate marker, added to Li plasma levels, for Therapeutic Drug Monitoring of Li.[22]

Thus, taking into account the changes that Li produces on the thyroid gland, and its relation to depressive and/or manic symptoms, it is evident that to give maximum validity to any current clinical study concerning the therapeutic and/or pharmacological activities of Li, the following should be considered: the initial and final thyroid status of patients; the use of equi-effective doses of Li with FT4 values in the range 1.0–1.1 mEq/L;[22] stratification of patients according to thyroid activity. In this manner, we will avoid bias, caused by the activity of the thyroid gland, in depressive and/or manic symptoms present in bipolar patients (with or without Li treatment) under study.

In conclusion, there are methodological hurdles still to be overcome in the standardization of clinical study design in bipolar disorder, with thyroid gland

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abnormalities being one of the principal areas of variability, documented among patients with bipolar disorder, as well as patients on Lithium treatments.

Disclosure

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