Lithium side-effects and predictors of hypothyroidism in patients with bipolar disorder: sex differences
C. Henry

To cite this version:


HAL Id: hal-02679656
https://hal.inrae.fr/hal-02679656
Submitted on 31 May 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Copyright
Lithium side-effects and predictors of hypothyroidism in patients with bipolar disorder: sex differences

Chantal Henry, MD, PhD

Service Universitaire de Psychiatrie, CH Charles Perrens and INSERM U-394, Neurobiologie Intégrative, Bordeaux, France.

Objective: To determine the prevalence of the side effects of lithium therapy and possible predictors of hypothyroidism in women and men with bipolar disorder. Method: Twenty-two men and 38 women with bipolar disorder and taking lithium for at least 1 year, were interviewed about lithium side effects using a list of the most commonly reported symptoms. Results: The complaint most frequently reported was polyuria–polydipsia syndrome, which affected 36 (60%) of 60 patients. More men than women reported tremor (54% v. 26%, \(p < 0.05\)), but weight gain during the first year of treatment was more frequent in women than men (47% v. 18%, \(p < 0.05\)), as was the development of clinical hypothyroidism (37% v. 9%, \(p < 0.05\)). Weight gain during the first year of treatment (and not sex) was the only significant predictor of hypothyroidism. Conclusion: Weight gain during the first year of lithium treatment, in the absence of biological evidence of subclinical hypothyroidism, was the most predictive and, possibly, the first sign of hypothyroidism.
Introduction

Lithium, a mainstay in the treatment of bipolar disorder, has been reported to induce adverse effects in 35%–93% of patients who take it, and these adverse events often lead to noncompliance. To optimize lithium treatment, it is therefore important to be aware of these effects. The “antithyroid” effect of lithium is one of the most common side effects, but little is known of the factors that predispose patients to develop hypothyroidism during treatment. A recent study showed that the main risk factor was being female (prevalence of 14% in women v. 4.5% in men). Women also seemed to be at highest risk during the first 2 years of lithium treatment, and the prevalence was highest for women starting treatment over the age of 50 years. Another study showed that patients with first-degree relatives affected by thyroid disease experienced an earlier onset of lithium-induced hypothyroidism. It has been suggested that even mild thyroid dysfunction may be associated with impaired cognition, mood and response to psychotropic medication; it is therefore important to define subjects at high risk for developing hypothyroidism so that they can be followed with particular attention.

With the exception of hypothyroidism, differences between the sexes in lithium side effects have not been systematically studied. Thus, the purpose of this study was to assess the side effects of lithium treatment as a function of sex and to identify factors that are predictive of developing hypothyroidism.

Methods

The study population consisted of 22 men and 38 women outpatients with bipolar disorder, type I. All patients provided informed written consent for participation. Patients were screened for diagnosis using the French version of the “Diagnosis Interview for Genetic Studies,” a clinical interview constructed for the assessment of major mood and psychotic disorders and their spectrum conditions. We then used a list of the 15 symptoms most frequently reported in the literature and the Vidal dictionary (used by most practitioners in France) to interview patients who had been taking lithium for at least 1 year about side effects they had experienced (Table 1).

The clinical severity and biochemical abnormalities associated with hypothyroidism vary greatly. We therefore took into account only overt hypothyroidism for which patients were taking thyroid supplementation.

Chi-square tests were used to assess differences between men and women in terms of side effects. If the sample size was too small to perform the chi-square test, a p value for Fisher’s exact test was calculated. However, only those groups of a size appropriate for statistical analysis were compared. To investigate the relation between hypothyroidism and risk factors, a linear regression was performed with age, sex, duration of treatment and weight gain as putative predictive factors.

Results

The mean age of the 22 men (36.7%) and 38 women (63.3%) with bipolar disorder, type I, was 41.3 (standard deviation [SD] 12.8, range 19–75) years. At the time of the interview, the mean duration of lithium treatment was 6.9 (SD 6.5, range 1–26) years, and mean blood lithium concentration was 0.74 (SD 0.11, range 0.6–1) mmol/L. Lithium treatment improved the symptoms in all patients; only 8 received other concomitant medication.

The complaint most frequently reported in the side-effects interview was polyuria–polydipsia syndrome, which affected 36 (60%) of 60 patients (Table 2). It is difficult to assess increases in fluid intake accurately without a 24-hour urine volume measurement, but we asked patients if they needed to get up during the night to drink, urinate or both, and 36 (60%) of the 60 patients said they had to since beginning lithium treatment. However, creatinine levels of these patients were in the normal range.

Hypothyroidism (for which thyroid supplementation was required) was observed in 16 (27%) of the 60 patients, and 9 of these had a goiter. The mean time between the start of lithium treatment and diagnosis of thyroid dysfunction was 7 (SD 4.53, range 1–14) years.

Men presented tremor more frequently than did women (54% v. 26%, p < 0.05), but weight gain was more frequent in women than in men (47% v. 18%, p < 0.05) as was hypothyroidism (37% v. 9%, p < 0.05). Dermatological effects also were more frequent in women (16% v. 9%), but this difference was not statistically significant.

We carried out a linear regression with hypothyroidism as the dependent variable and age, sex, duration of treatment and weight gain as independent variables. The only independent variable that was significant for predicting hypothyroidism was weight gain (> 5 kg) in
the first year of treatment ($b = 0.38, t = 2.7, p < 0.01$), and there was a trend for age ($b = 0.008, t = 1.7, p < 0.09$).

**Discussion**

In this study, the side effects of lithium differed between men and women; men were more likely to experience tremor, whereas women were more likely to gain weight and develop clinical hypothyroidism. Moreover, the factor most predictive of hypothyroidism was weight gain during the first year of treatment (weight gain was not due to subclinical hypothyroidism).

As reported by others, our patients frequently experienced polyuria–polydipsia syndrome. In addition, there were more dermatological effects reported by women than men; although not statistically significant, this result is consistent with the findings of Sarantidis and Waters.

We observed overt hypothyroidism in 27% of the patients in our sample. This is higher than the 8% to 20% reported in other studies. There may be several reasons for this. First, definitions of clinical and subclinical hypothyroidism may differ between studies. Indeed, hypothyroidism is a graded phenomenon with various degrees of clinical severity and biochemical abnormalities. Patients with overt hypothyroidism have abnormally low free thyroxin levels and high

<table>
<thead>
<tr>
<th>Table 1: Questionnaire about potential side effects of lithium treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>When did you start this treatment? (to be filled in only if the subject has received lithium treatment for at least 6 months)  __________________________________</td>
</tr>
<tr>
<td>Since you began this treatment, have you experienced any of the following:</td>
</tr>
<tr>
<td>Gastrointestinal symptoms?</td>
</tr>
<tr>
<td>If yes, please specify: nausea, vomiting, diarrhea?  __________________________</td>
</tr>
<tr>
<td>Impairment in psychic functioning?</td>
</tr>
<tr>
<td>If yes, please specify: sleepiness, lethargy?  __________________________</td>
</tr>
<tr>
<td>Neurologic symptoms?</td>
</tr>
<tr>
<td>If yes, please specify: tremor, dizziness?  __________________________________</td>
</tr>
<tr>
<td>Muscular symptoms, such as muscle weakness?  ________________________________</td>
</tr>
<tr>
<td>Weight gain?</td>
</tr>
</tbody>
</table>
| If yes, please specify: Weight before treatment:  ______________  
  Current weight:  ______________ |
| Did you receive any other medication during this period? |
| If yes, which?  ______________________________________________________ |
| Thyroid problems? |
| If yes, please specify:  
  Goiter alone? Date and circumstances of diagnosis:  ___________________  
  Hypothyroidism? With associated goiter? Date and circumstances of diagnosis:  ___________________  
  Has this hypothyroidism required hormonal substitution treatment?  __________  
  If yes, since when?  __________________ |
| Hyperthyroidism?  __________________ |
| Abnormal blood test results? If yes, please specify  ____________________ |
| An increase in fluid intake and the need to urinate during the day? |
| If yes, how many liters of fluid do you drink each day?  ______________  
  Do you need to get up during the night to drink or urinate?  ______________ |
| Dermatologic effects? |
| If yes, please specify: acne, psoriasis:  ____________________  
  Do these dermatologic effects require treatment?  __________________ |
| Sexual problems?  __________________ |
| Last serum lithium concentration measured on:  __________________ |

Henry
concentrations of thyroid stimulating hormone. In addition, overt hypothyroidism is usually, but not always, associated with symptoms. In our sample, we considered only those patients who required thyroid supplementation as having overt hypothyroidism. The hormone substitute was prescribed by another physician, independent of the psychiatrist.

Another possible explanation for the high incidence of hypothyroidism in our group, is the well-established observation that the rate of thyroid dysfunction is high in the southwest of France, particularly in the Pyrenees area where some of our patients lived.

Transbol et al suggested that the risk of developing lithium-induced hypothyroidism increases with the duration of treatment. The mean duration of lithium treatment for our sample was relatively long, at 6.9 years. However, in this study, the duration of treatment was not associated with an increase in the risk of developing hypothyroidism.

We investigated weight gain during the first year of treatment only because weight generally increases with age and because rapid weight gain is a symptom of hypothyroidism. People who rapidly gained weight at the beginning of lithium treatment seemed to have a higher risk of developing hypothyroidism.

Although more women than men developed hypothyroidism in our sample, the factor most predictive of hypothyroidism was not sex, but weight gain. This is the first study to consider this parameter as a predictor of hypothyroidism and suggests that psychiatrists should monitor body weight changes during treatment and consider thyroid dysfunction as a possible side effect of lithium if a patient starts to gain weight during treatment.

Competing interests: None declared.

References


