Rev Psiquiatr Salud Ment (Barc.). 2019;12(3):199–200

Revista de Psiquiatría y Salud Mental

www.elsevier.es/saludmental

LETTER TO THE EDITOR

Levothyroxine treatment for persistent cognitive symptoms in major depression☆

Tratamiento con levotiroxina de los síntomas cognitivos persistentes en depresión mayor

Dear Editor,

Patients with major depression, including both unipolar forms and also depressive episodes of bipolar disorder, may present with persistent cognitive symptoms even in stages of remission or euthymia,[1] which has a negative impact on their quality of life and how they function. Although it has routinely been suggested that cognitive symptoms associated with depression improve once the depressive episode has been recovered from, it is now known that cognitive deficits may exist in different areas of memory, concentration, executive functions and information processing speed, and may be present regardless of the state of mind. Since effective precognitive interventions in major depression are rare, this could be an area of interest for testing whether drugs which are already on the market with beneficial effects on cognition in other clinical conditions could play a precognitive role in patients with major depression with persistent cognitive symptoms.

In this regard, thyroid hormones could be considered a potential therapeutic option. Thyroid hormones are necessary for the development of the central nervous system and also perform actions in the adult brain.[2] One of these actions is that of modulating the proliferation of neuronal precursors, with affects migration, differentiation and formation of neuronal synapses, and also the development and differentiation from glial cells.[2] There is also a distribution of receptors for thyroid hormones in regions of the brain which are essential for cognitive skills, including the prefrontal cortex and the hippocampus, and it would therefore be plausible for thyroid hormones to play a major role in neurocognition. In fact, patients with hypothyroidism present cognitive changes in the form of attention deficit, verbal memory and work, visual perception and executive functions, which improve with the introduction of Levothyroxine (L-T4).[3] These changes may also exist in patients with subclinical hypothyroidism, although a meta-analysis shows that these changes are visible in patients under 75 years of age.[4]

Thyroid hormones, together with other biomarkers such as hormones related to the hypothalamic-pituitary-adrenalin axis or inflammatory factors,[5] could play a role in the aetiopathogenesis of major depression. Furthermore, treatment with triiodothyronine (T3) is considered a standard strengthening strategy for improving depressive symptoms in resistant depression,[6] but studies show that enhancement with L-T4 would also be an effective strategy.[7] Several studies have shown that the addition of T3 could improve cognitive performance in patients with bipolar disorder who receive lithium, or that it could even mitigate the negative cognitive effects of electroconvulsive therapy in patients with affective disorders.[8] However, the addition of thyroid hormones as a cognitive enhancer is not a strategy which is usually used in clinical practice.

The decision to initiate specific replacement therapy in subclinical hypothyroidism is standard practice when TSH is above 10 mUI/L, although it may be considered in some cases with TSH figures between the upper limit of normality (usually considered to be 4.12 mUI/L) and 10 mUI/L, especially if there is positivity for anti-thyroid antibodies, pregnancy, in a child or teenage population or where there is concomitant cardiovascular risk.[9] There is a lack of consensus regarding the use of L-T4 in patients with TSH between 4.12 and 10 mUI/L. National clinical guidelines[10] and international[9] ones recommend assessing the addition of L-T4 if symptoms are suggestive of hypothyroidism. In fact the clinical guideline of the thyroid disease workgroup from the Spanish Society of Endocrinology and Nutrition (SEEN) indicates that, in patients with subclinical hypothyroidism and TSh concentrations between 4.5 and 10 mUI/L who present with symptoms of hypothyroidism, a therapeutic trial could be considered with L-T4 for several months and with monitoring of the evolution of symptoms so as to decide whether to continue or discontinue treatment depending on response.

The problem with regard to taking decisions on the possible addition of this treatment in patients with major depression is that many of the symptoms of hypothyroidism (depressive mood, asthenia, cognitive complaints) overlap with the actual symptoms of depression, which makes the decision more complex in patients with major depression and comorbid subclinical hypothyroidism. Given the high

☆ Please cite this article as: Labad J, Soria V, Armario A, Monreal JA. Tratamiento con levotiroxina de los síntomas cognitivos persistentes en depresión mayor. Rev Psiquiatr Salud Ment (Barc). 2019. https://doi.org/10.1016/j.rpsm.2019.02.002

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prevalence of subclinical hypothyroidism in patients with major depression (20% in resistant major depression[11]), in those cases which present with cognitive symptoms a therapeutic analysis could be undertaken so as to assess whether their cognitive aspect would improve with the addition of L-T4. Although this therapeutic strategy could be carried out in normal clinical practice following some of the recommendations for the clinical guidelines,[10] it is particularly important that clinical researchers carry out prospective studies to assess whether this therapeutic strategy is effective as procognitive treatment in patients with major depression and subclinical hypothyroidism. This awareness would lead to the extension of the therapeutic arsenal of psychiatrists to better treat the persistent cognitive symptoms in unipolar and bipolar major depression.

Financing

Javier Labad received an Intensification of Research Activities (SLT006/17/00012) from the Department of Health of the Generalitat de Catalunya during 2018 and 2019.

Conflict of interests

The authors have no conflict of interest to declare regarding this manuscript.

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18 January 2019