

Short Communication

Advisory Caution Message on Retail Packaging of Levothyroxine and Its Significance in the Treatment of Hypothyroidism

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Levothyroxine is extensively used for overt hypothyroidism. Most of the time, it is also prescribed by general practitioners in developing countries for subclinical hypothyroidism at the initial stages, despite adequate recommendations for the treatment, causing the manifestation of new health disorders. Therefore, it is opined that an advisory caution message should be inscribed on the retail packaging of Levothyroxine to give an indication to the non-endocrinologist general practitioner about the correct treatment protocol and to make the patient aware as well.

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Thyroid hormones are critical for regulating various body functions, and their malfunctioning could cause a variety of diseases. Hypothyroidism is a widespread, common endocrine disorder that results from reduced activity of the thyroid gland, which causes a deficient production of thyroid hormones. In developed countries, the incidence of subclinical hypothyroidism is approximately 8% in women and 3% in men [1]. The global thyroid disorder market was valued at \$2,057 million in 2017 and is estimated to reach \$2,771 million by 2025, at a Compounded Annual Growth Rate (CAGR) of 3.8% between 2018 and 2025 [2]. The most prevalent treatment for hypothyroidism is supplementation with a synthetic thyroid hormone called levothyroxine. In the USA alone, levothyroxine has been a top-selling drug since 2016, prescribed to over 114 million people, retaining the number one position among the top 300 drugs in 2019 [3]. In India, every third person suffers from hypothyroidism [4], and the immediate line of treatment

is levothyroxine for overt or subclinical hypothyroidism (SCH) even if the patient does not show any symptoms like tiredness, muscle aches, constipation, dry skin, weight gain, slow heartbeat, or sensitivity to cold. The usual dosage of levothyroxine ranges from 25 µg to 300 µg per day for an adult, with an initial dose at a rate of 1.6 µg/kg of body weight. During the treatment of chronic subclinical hypothyroidism patients in India, most of the consulting general medical practitioners (GPs) kept on increasing levothyroxine doses to an upper limit of 300 µg/day or even more, up to 500 µg/day in some isolated cases, to keep TSH within the standard pathological limits, irrespective of the T3 and T4 levels. More strangely, the treatment is governed by the pathological test for TSH alone, whereas it has been found that, in some isolated cases, T3 and/or T4 go beyond the recommended limits while TSH remains within recommended limits. Furthermore, most GPs developed the false belief that, once started, levothyroxine cannot be discontinued.

Thyroid disorders in the initial stages are not life-threatening and remain asymptomatic over a long period. High-quality treatment for thyroid disorders in developing or underdeveloped countries is limited to certain metropolitan pockets due to the dismal availability of practicing endocrinologists. In such a scenario, GPs handle most of the thyroid disorder cases. We can't expect every GP to be knowledgeable in all domains of medicine. They acquire most of their practicing knowledge from the marketing executives of pharmaceutical companies. Indeed, they don't get the time to update their knowledge in state-of-the-art research and development (R&D) in advanced medicine. It is surprising to note that many practicing GPs at reasonably good multi-specialty hospitals have limited awareness of thyroid disorders, especially subclinical hyperthyroidism (SCH). They prescribe levothyroxine at the moment when the level of the Thyroid Stimulating Hormone (TSH) approaches the upper recommended limit of 5.0 mIU/L, despite the fact that enough literature is available on the initiation of SCH treatment ^{[5][6]}. Levothyroxine reduces TSH levels in SCH as long as it is taken continuously, providing patients with satisfactory numbers. Once the administration of levothyroxine is started, its dosage progressively increases, along with the burden of manifestation of other morbidities such as cardiovascular disease, tremors, weight gain/loss, headache, vomiting, diarrhoea, change in appetite, hair loss, skin dryness, joint pains, leg cramps, changes in the menstrual cycle, and mood swings, of which the patient is unaware, and which the patient accepts on account of their advancing age.

In my more than four decades of general practice, I have come across patients with the following chronic complaints:

- weight gain or loss

- chronic headache
- persistent vomiting
- remittent fever
- changes in the menstrual cycle
- sensitivity to heat
- dryness of hair and hair loss
- premature joint pain, and
- leg cramps

who had been on levothyroxine or its variants like Eltroxin and Thyroxin for more than a decade at high doses such as 50 mcg to 350 mcg. Moreover, despite such high doses, the TSH level was still beyond the upper limit. A nominal increase in the level of TSH occurring when T3/T4 remain within the recommended pathological limits can be comfortably managed with physical exercises coupled with suitable medication for a limited time.

Nowadays, most patients and their caretakers have better awareness about medicines on account of increased literacy and the ready availability of the Internet. Most of them look for an “Expiry Date” before going for any medicine. In view of the recommendations ^{[5][6]} for treatment for SCH and to mitigate various side effects of excessive or unwarranted use of levothyroxine, it is opined that an “Advisory Caution” message needs to be inscribed on the retail packaging of levothyroxine. It will educate GPs to update their knowledge and would be helpful in the correct treatment of hypothyroidism. Furthermore, the patient can also cross-reference his treatment with laboratory results and flag the discrepancy to their GP, if any.

The suggested format for an “Advisory Caution” may be as below, in one or more of the most popular native languages – e.g., for India, it could be written in the widely spoken English and Hindi languages, like in the following format:

| English | Hindi |
|---|---|
| Caution: Not recommended for patients with normal T3/T4 and TSH below 10mIU/L | चेतावनी: उन रोगियों के लिए उचित नहीं जिनका T3/T4 सामान्य और TSH 10mIU/L से कम है। |

Inscription of such an advisory caution on the drug's leaflet alone may not serve the purpose, because invariably the majority of patients feel that the leaflet is meant just for practicing doctors. However, such an "Advisory Caution" could significantly help in healthcare, and reduce the burden of new morbidities due to side reactions to levothyroxine.

Conflict of interest

None.

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Declarations

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