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THE ENIGMA OF PERSISTENT SYMPTOMS IN HYPOTHYROID PATIENTS TREATED WITH LEVOTHYROXINE: A NARRATIVE REVIEW

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4 **THE ENIGMA OF PERSISTENT SYMPTOMS IN HYPOTHYROID PATIENTS**
5 **TREATED WITH LEVOTHYROXINE: A NARRATIVE REVIEW**
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8 **Short running title:** Persistent symptoms in hypothyroidism
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Summary

A significant minority of patients with hypothyroidism report persistent symptoms despite achieving normal thyroid biochemistry after levothyroxine (L-T4) replacement. Four principal lines of thinking, which are not mutually exclusive, may explain this enigma. The “low tissue liothyronine hypothesis” emphasises the potential imperfections of L-T4 replacement therapy, that may lead to hypothyroidism in some tissues like the brain, while others (for example hypothalamus) are euthyroid. The “Somatic Symptom and Related Disorders hypothesis” draws attention to an incidental coexistence of a diagnosis of Somatic Symptom and Related Disorders in patients with treated hypothyroidism. The “autoimmune neuroinflammation hypothesis”, highlights the potential consequences of inflammatory mediators due to thyroid autoimmunity (the commonest cause of hypothyroidism) on the brain. The “comorbidities and psychosocial hypothesis” implicates a variety of physical and psychosocial factors that have been noted to be associated with a diagnosis of hypothyroidism, which may be primarily the cause of persistent complaints. Over the past twenty years a great deal of time and effort has been expended pursuing the “low tissue liothyronine hypothesis”, which has failed to yield results that translate to patient benefits. This has skewed the balance in clinical practice, in favour of pursuing answers relating to L-T4 and liothyronine combination treatment, while the alternative explanations have been downplayed and potentially useful interventions have been given insufficient attention.

Key words: hypothyroidism, thyroxine, liothyronine, quality of life

Word count: 3,445

References: 73

Introduction

Overt hypothyroidism [raised serum thyroid stimulating hormone (TSH) associated with low serum free thyroxine (FT4)], and subclinical hypothyroidism (raised TSH with normal serum FT4) affect 2-10% of the population ¹. Autoimmunity is the cause of hypothyroidism in about 80% of cases ¹. While in most patients treatment with levothyroxine (L-T4) restores health, 10-15% of patients do not regain their well-being after apparently adequate treatment with L-T4. ²⁻⁴ Persistent symptoms are non-specific and include fatigue, weight gain and mood changes ^{1,5}. Such symptoms may lead to multiple medical consultations, patient requests for inappropriate investigations, and dissatisfaction with treatment ⁵⁻⁷. Given the high prevalence of hypothyroidism, this loss of well-being in a significant fraction of patients causes considerable socio-economic burden ⁸ and clinical management can be difficult and frustrating both for patients and clinicians ⁷. The underlying causes for persistent symptoms are unclear. Here, we outline four major hypotheses which are not mutually exclusive and review the available evidence. We also identify areas of uncertainty that are worthy of future research.

Pathophysiology of persistent symptoms in levothyroxine-treated patients

There are four explanations for persistent symptoms: (a) deficiency in tissue concentrations of liothyronine (T3), (b) Somatic Symptoms and Related Disorders (SSRD), (c) autoimmune neuroinflammation and (d) other physical and psychosocial comorbidities.

The “low tissue liothyronine hypothesis”

L-T4 has to be converted to T3 to be biologically active ¹. The goal of treatment with L-T4 is to relieve the symptoms of hypothyroidism by restoring thyroid biochemistry ⁹. The “low tissue liothyronine hypothesis” proposes that persistent symptoms are due to failure to achieve normal tissue levels of T3 in some patients treated with L-T4. This arises due to differences between the hypothalamus and other tissues in type 2 deiodinase (DIO2) sensitivity to circulating serum T4 ¹. Low serum T3 concentrations may result in low intracellular T3 levels and therefore hypothyroidism

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3 at tissue level of some organs, including the brain. This in turn can cause persistent
4 symptoms. The reason why only a minority of patients suffer from these complaints
5 may be explained by variations in individual susceptibilities dictated by genetic
6 predisposition. Therefore, patients with persistent symptoms may require
7 replacement with both L-T4 and liothyronine (L-T3) in formulations and doses that
8 reproduce physiological tissue levels of thyroid hormones. A further consideration is
9 that serum TSH is genetically regulated ¹⁰ and can be influenced by personal habits
10 such as cigarette smoking ¹¹. Therefore, it has been argued that the target serum
11 TSH in hypothyroid patients may need to be individualised, although studies
12 investigating “fine-tuning” the dose of L-T4 have shown no differences in patient
13 outcomes ^{12,13}.

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23 The “low tissue liothyronine hypothesis” is conceptually sound, mechanistically
24 plausible and widely quoted ^{1,14,15}. The best evidence for hypothyroidism at cellular
25 level comes from rodents. Experimental work in the mid-1990’s by Escobar-Morreale
26 and colleagues demonstrated wide differences in the ability of different tissues to
27 maintain normal tissue T3 concentrations at different doses of administered L-T4,
28 with cerebral cortex and brown fat being best at sustaining normal T3 tissue levels,
29 while muscle, liver and spleen were least able to do so ¹⁶. The same researchers
30 demonstrated that combination of L-T4 and L-T3 treatment in thyroidectomised rats
31 restored normal tissue levels of T3 ¹⁶. More recently it was shown that normalisation
32 of tissue levels of T3 and activation of T3-regulated genes in brain required a
33 continuous supply of both L-T4 and L-T3, which could not be achieved with L-T4 or
34 orally administered combination treatment with L-T4 and L-T3 (L-T4+L-T3) ¹⁷.

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44 The occurrence of residual symptoms in L-T4-treated patients have been explored in
45 some populations. Saravanan et al ³ recruited 397 L-T4-treated patients from
46 general practice records and 551 age and sex-matched controls. Questionnaires
47 testing psychological well-being and hypothyroid symptoms were used. Patients had
48 significantly worse scores than controls. Wekking et al ² assessed neurocognitive
49 function and symptoms of 141 L-T4-treated patients and compared them with
50 reference values. Patients with hypothyroidism performed worse than controls.
51 Panicker et al ⁴ assessed anxiety and depression in 1,546 female L-T4-treated
52 patients and compared them with a large population of mainly women controls.
53 There was an excess of depression and anxiety symptoms in patients, which

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3 persisted after correction for serum TSH. All three studies assumed that biochemical
4 assessments on a single occasion reflected long-term control of hypothyroidism.

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6 Peterson and colleagues ⁵ performed an online survey which included 12,146
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8 hypothyroid patients mainly from the US. The average self-rated satisfaction score
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10 was 5 out of a maximum of 10.

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12 There are some weaknesses of the “low tissue liothyronine hypothesis”. The excess
13 prevalence of persistent symptoms in L-T4-treated patients compared to controls
14 have not been recapitulated in studies from Asia or in children and adolescents ^{18,19}.
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16 Also, studies show that following an episode of hypothyroidism, recovery of some
17 symptoms may be delayed by 6 months or more after normalisation of TSH ^{20,21}. A
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19 recent study reported on 6,138 patients who had been on L-T4 for at least one year
20 and had their serum TSH measured on two separate occasions 25-28 weeks apart
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22 ²². Of those patients who had a normal TSH at baseline, 19% had a TSH outside the
23 normal range at follow-up (11% hypothyroid and 8% hyperthyroid). Based on such
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25 data, there is a high probability that some participants in the three studies
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27 highlighting persistent symptoms ²⁻⁴ had experienced episodes of thyroid dysfunction
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29 in the preceding 6 months (despite normal TSH recorded at the time of the study). In
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31 other words, some patients with persistent symptoms may indeed have poorly
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33 controlled hypothyroidism despite a normal serum TSH if only measured at a single
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35 time point.
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39 Several studies have examined the relationship between serum TSH and free T3
40 (FT3) concentrations in L-T4-treated patients. In keeping with the “low tissue
41
42 liothyronine hypothesis”, some have shown a lower FT3 concentration in L-T4-
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44 treated patients than controls²³, although in one of the studies that showed an
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46 excess of residual symptoms in patients with hypothyroidism and normal TSH, the
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48 serum FT3 concentration was normal ². Other published cross-sectional data also
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50 indicate that serum FT3 levels do not correlate with cognitive function, well-being ^{3,23}
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52 or quality of life (QoL) ²⁴ in L-T4-treated patients. Furthermore, in a prospective
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54 study, patients with a previous diagnosis of thyroid cancer on TSH-suppressive L-T4
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56 therapy who transitioned to normal serum TSH concentrations did not experience
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58 any negative somatic or neurocognitive symptoms, despite a reduction in serum FT3
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60 concentrations ²⁵.

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3 Two small human studies have implicated genetic variants of the MCT10 thyroid
4 hormone transporter and the DIO2 genes^{26,27} in determining patient reported
5 responses to L-T4+L-T3. However, these are preliminary data which require
6 confirmation and the same DIO2 polymorphism had no association with serum
7 thyroid hormones, QoL and cognitive function in either a large healthy population or
8 in hypothyroid patients²⁸.
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14 The increased prevalence of persistent symptoms in L-T4-treated patients described
15 above²⁻⁵ triggered an extensive research effort evaluating whether such patients
16 might benefit from combination treatment with L-T4+L-T3. To date 15 randomised
17 controlled trials have been published studying L-T4+L-T3 compared to L-T4 alone²⁹
18 using patient reported outcomes as endpoints (general and health-related QoL,
19 mental health). In the three largest studies (total number of participants 939) there
20 were no differences³⁰⁻³². Two studies reported improved outcomes in patients
21 treated with L-T4+L-T3. The first³³ was small (n=33), a large proportion of patients
22 had thyroid cancer and the mean dose of L-T4 was high (175 mcg daily) reflecting an
23 atypical patient population. The other study included more patients (n=59), but used
24 a large and potentially unphysiological dose of T3 (20 mcg daily)³⁴. Two recent
25 systematic reviews^{35,36} and a meta-analysis³⁷ evaluating fourteen randomised
26 controlled trials concluded that L-T4+L-T3 and desiccated thyroid extract (DTE),
27 which has a significantly higher T3:T4 ratio than that produced by humans, were no
28 different to L-T4 alone in terms of QoL, neurocognitive function and somatic
29 symptoms.
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42 T3 has a short half-life and its use gives rise to unphysiological peaks and troughs,
43 therefore it is plausible that “slow-release” T3 formulations may yield different results.
44 Other shortcomings in study design of the previous trials on combination treatment
45 have been highlighted³⁸ and include variable T4/T3 ratios, duration of treatment,
46 outcome measures and other methodological problems, calling for further studies. It
47 is of some interest that online surveys of hypothyroid patients indicate that 20-40% of
48 patients are dissatisfied with their treatment and about 50% have poor QoL, with little
49 difference between patients on L-T4, combination treatment, DTE or L-T3 alone^{5,7}.
50 Based on available evidence, it can be inferred that combination treatment with L-
51 T4+L-T3 is ineffective, or that the effect size is minor and / or that the proportion of
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3 patients that benefit is small. In contrast to L-T4, long-term safety data on L-T4+L-T3
4 treatments are limited, **though what is available is reassuring** ³⁹.

7 Guidance from professional organisations on L-T4+L-T3 is variable. The American
8 Thyroid Association contends that there is insufficient evidence for use of L-T4+L-T3
9 in routine practice “*outside a formal clinical trial or N-of-1 trial*” ⁹. The European
10 Thyroid Association guideline suggests that “*T4+T3 combination therapy might be*
11 *considered as an experimental approach in compliant levothyroxine-treated*
12 *hypothyroid patients who have persistent complaints despite serum TSH values*
13 *within the reference range*”. They add that treatment should be carefully titrated and
14 monitored by accredited internists/endocrinologists ¹⁵. The British and Italian Thyroid
15 Associations ^{40,41} have adopted a similar approach to the European guidelines.
16 Despite these recommendations, evidence suggests widespread prescribing of L-T3
17 and desiccated thyroid extract by non-accredited physicians, frequent purchasing of
18 L-T3 without prescriptions, and adjustment of dose by patients based on self-
19 evaluation of symptoms from day to day ^{6,7,42}.

32 33 **The “Somatic Symptom and Related Disorders Hypothesis”**

35 SSRD is a classification described in the Diagnostic and Statistical Manual of Mental
36 Disorders (DSM-5) ⁴³, which refers to persistent bodily symptoms associated with
37 significant functional impairment, psychological distress and high healthcare costs. It
38 occurs in up to 40% of primary care patients ⁴⁴. SSRD is the successor of the
39 classification “*somatoform disorders*” in the DSM-4, that only pertained to medically
40 unexplained symptoms. In SSRD, the distress can concern bodily symptoms in the
41 context of a chronic medical condition, such as hypothyroidism, or medically
42 unexplained symptoms (MUS). A key difference in the classification of SSRD over
43 MUS is that SSRD can occur in patients with known medical conditions and might
44 explain the distress of patients suffering from overt and subclinical hypothyroidism.
45 SSRD can be accompanied by anxiety or depressive disorders, and first
46 presentations with severe distress about physical symptoms can be a masked
47 expression of these; SSRD can also be distress about physical symptoms as
48 standalone phenomenon without psychiatric comorbidity, which makes it important to
49 explore such possible comorbidities in the diagnostic phase.
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3 The possibility that hypothyroid patients with persistent symptoms may merely
4 represent an expected overlap of two common but independent conditions was
5 proposed several years ago ⁴⁵. The “somatic symptom and related disorders
6 hypothesis” proposes that patients with SSRD have multiple medical consultations
7 and inevitably thyroid function tests are ordered. Based upon an *a priori* chance and
8 the high underlying prevalence of both disorders, approximately 10% of patients with
9 a SSRD may also have thyroid dysfunction, usually subclinical hypothyroidism. If
10 patient and doctor assume that the symptoms are due to hypothyroidism, L-T4 is
11 prescribed but will not be followed by symptom resolution if the actual diagnosis is
12 SSRD. Any benefits tend to be minor and transient, leading to escalation of the dose
13 of L-T4, without consistent symptomatic improvement. The patient can react to this
14 in several ways, including sustained treatment-seeking behaviour. L-T4 is declared
15 ineffective by the patient who, having consulted blogs and patient forums, may then
16 seek treatment with L-T4+L-T3 or DTE. The patient may encounter resistance from
17 the doctor to prescribe these treatments leading to consultations with several
18 specialists or alternative practitioners or purchasing L-T3 or DTE online. **The
19 difficulty that patients experience accessing their “desired” treatment may also
20 increase the perception of a benefit of treatment when they receive it, although
21 symptoms usually persist ^{5,7}. Frustration and dissatisfaction ensue and are
22 perpetuated by the absence of effective treatment directed at the underlying cause of
23 the symptoms.**

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40 The evidence in favour of the “SSRD hypothesis” is circumstantial. Healthcare-
41 seeking behaviour (defined as “any action or inaction undertaken by individuals who
42 perceive themselves to have a health problem or to be ill for the purpose of finding
43 an appropriate remedy”) ⁴⁶, may contribute to the increase of thyroid function test
44 requests ^{47,48} in the general population. Healthcare-seeking behaviour is suggested
45 by a study which showed that patients with psychological morbidity are more likely to
46 have thyroid function tests than a control population ⁴⁹, although alternatively it may
47 reflect a tendency for general practitioners wishing to rule out hypothyroidism as the
48 cause of symptoms of suspected anxiety or depression that may also occur in the
49 context of SSRD.

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58 A study of women from a general population sample found no association between
59 subclinical hypothyroidism when identified by screening with impaired well-being ⁵⁰,

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3 indicating that subclinical hypothyroidism is not itself associated with symptoms and
4 healthcare-seeking. Similar findings were noted in another study in patients with
5 overt hypothyroidism identified by screening ⁵¹, in contrast to patients with previously
6 known overt hypothyroidism who reported impaired self-rated health. The authors
7 suggested that diagnostic labelling may have a negative impact on self-perception of
8 health. However, assuming that only patients with symptoms would seek diagnosis
9 and treatment, the diagnostic labelling could follow the experience of symptoms and
10 hence may not explain the perception of health *per se*. An older Korean population of
11 people with untreated overt hypothyroidism identified by screening had a better QoL
12 than euthyroid controls, thus introducing possibilities of demographic and cultural
13 variables being of some importance ⁵².

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23 In keeping with experience of cognitive behaviour therapy (CBT) in non-hypothyroid
24 patients, a randomised controlled trial of CBT in 96 L-T4-treated women showed
25 significant improvements after 12 group sessions in emotional health, energy, and
26 general health ⁵³. A collaborative care model combining training with psychiatric
27 consultation in a general practice setting was found to be effective in the treatment of
28 patients presenting themselves with persistent medically unexplained symptoms.
29 The majority (86%) of whom were diagnosed with an underlying and until the
30 consultation undetected depressive or anxiety disorder ⁵⁴. Patients responded well to
31 an intervention focusing on exploration and explanation of the physical symptoms
32 and the proposal of a treatment plan taking biological aspects and psychiatric
33 comorbidity into account. In that study 4.9% of the patients suffered from
34 hypothyroidism, which suggests that such an intervention might be a useful
35 treatment model for persistent symptoms in both overt and subclinical
36 hypothyroidism ⁵⁴. It can secure a classification of SSRD and support the general
37 practitioner or endocrinologist providing treatment.

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49 To summarise, the “Somatic Symptom and Related Disorders Hypothesis” describes
50 how patients with subclinical and overt hypothyroidism can feel distress leading to
51 persistent healthcare-seeking behaviour. Uncertainties about choice and
52 effectiveness of treatment and psychiatric and somatic comorbidities may be
53 additional contributions. This calls for a comprehensive clinical approach taking
54 these knowledge gaps into account.
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“Autoimmune neuroinflammation” hypothesis

It has been suggested that inflammation resulting from an autoimmune disease may be causally related to persistent symptoms⁵⁵. This is supported by observational studies showing that patients with thyroid autoantibodies had more symptoms, poorer QoL and more anxiety and depression than controls^{56,57}, although the largest study⁵⁸ comprising more than 30,000 subjects failed to demonstrate such associations. However, this remains a plausible hypothesis and is in keeping with a recent randomised controlled trial of 147 patients with autoimmune thyroiditis⁵⁹. Patients with persistent symptoms and high anti-thyroid peroxidase (TPO) antibodies, who had a normal serum TSH on L-T4 treatment were randomised to total thyroidectomy or no treatment. General health and fatigue scores improved impressively following total thyroidectomy, which persisted at 18 months and was accompanied by a decline in anti-TPO antibodies⁵⁹. Post-operative morbidity included infection (4.1%), permanent hypoparathyroidism (4.1%), and recurrent laryngeal nerve injury (5.5%). This study needs to be confirmed before its findings can be applied to clinical practice, given its lack of a double-blinded control and invasive nature. Selenium supplementation in autoimmune thyroiditis has been shown to lead to reduction in anti-TPO antibodies⁶⁰ and is currently under investigation in a randomised controlled trial using a thyroid disease-specific thyroid QoL (ThyPRO) instrument⁶¹, **however selenium supplementation has not been shown to alter the course of autoimmune thyroid diseases.**⁶²

“Other physical and psychosocial comorbidities” hypothesis

Several other factors that affect well-being are associated with hypothyroidism. Whether these relationships are causative remains unclear.

Physical comorbidities

Undiagnosed diseases such as other autoimmune diseases, deficiencies in vitamins and iron, sleep apnoea, chronic infection, and a long list of other diagnoses can potentially present with non-specific symptoms that may be wrongly attributed to hypothyroidism¹⁴. Symptoms arising from known comorbidities may also add to the burden of persistent symptoms. An increased prevalence of comorbidities in patients with hypothyroidism and persistent symptoms was reported by Saravanan et al³.

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3 This association has been confirmed by other investigators and is bidirectional.
4 Somatic morbidity ⁶³ is increased in those subsequently diagnosed with
5 hypothyroidism, but the diagnosis of hypothyroidism also increases the subsequent
6 likelihood of further diagnoses ^{3,8,23}. Patients who have other comorbidities are more
7 likely to be investigated for hypothyroidism ⁴⁹, thus introducing a bias in favour of
8 clustering of chronic symptoms and a diagnosis of hypothyroidism.
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13 ***Psychiatric comorbidities***

15 Hypothyroid patients are more likely to suffer from psychiatric illness ^{49,64}. A
16 multicenter European study in patients with Major Depressive Disorder found a
17 prevalence rate for comorbid hypothyroidism of 13.2% ⁶⁵. Patients with this
18 comorbidity were more likely to be older, female, and suffering from more severe
19 depression including psychotic symptoms, and from comorbid chronic somatic
20 conditions such as cardiovascular disorders. They needed treatment with a
21 combination of psychotropic medication including augmentation of
22 psychopharmacological drugs, especially with antipsychotics, mood stabilisers and
23 pregabalin to achieve treatment response ⁶⁵.
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31 ***Chronic medication***

32 Patients who receive chronic medications have been shown to have compromised
33 physical, social and psychological well-being ⁶⁶. L-T4-treated patients were shown to
34 be more likely to be prescribed statins, beta-blockers, analgesics antidepressants
35 and a variety of other drugs compared to controls ^{3,23}. Patients treated with L-T4
36 tablets are advised to avoid food and drink (other than plain water) and some other
37 commonly used medications for a minimum of 30 minutes after ingestion of L-T4.
38 These restrictions may have a negative impact on patients' wellbeing. The
39 absorption of some formulations of L-T4 seem not to be affected by food, drinks or other
40 medications ⁶⁷, however there are no robust data on the effects of different L-T4
41 formulations on QoL.
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49 ***Physical inactivity***

51 Small studies have shown that exercise training improved the QoL and fatigue
52 perception in patients with L-T4-treated subclinical and overt hypothyroidism ^{68,69}.
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55 ***Obesity***

56 Obesity is a common complaint in patients with L-T4-treated hypothyroidism and is
57 associated with poor QoL ^{5,24}. Obesity is also associated with a mildly serum
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3 elevated serum TSH, which occasionally leads to improper diagnosis of subclinical
4 hypothyroidism and L-T4 administration ⁷⁰.

6 ***Demographic factors***

8 A study of patients with hypothyroidism showed that hypothyroid symptoms at the
9 time of diagnosis were more prevalent in women than men ⁷¹. A hypothyroid patient
10 survey showed a positive correlation between older age and male gender, with
11 satisfaction with treatment and care ⁷, suggesting that demographic factors may
12 influence expressions of satisfaction.
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17 ***Socioeconomic factors***

18 Unemployment is associated with somatic symptoms in patients on L-T4 treatment
19 ⁷². Hypothyroidism predicted disability and loss of life-long earning, early retirement
20 and loss of labour market income ⁸. These studies suggest an association between
21 somatic symptoms in patients with treated hypothyroidism and adverse
22 socioeconomic parameters.
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27 ***Unrealistic patient expectations***

28 A recent survey of hypothyroid patients showed that unrealistic patient expectations
29 correlated with dissatisfaction ⁷.
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33 ***Poor patient experience with health professionals***

34 Poor experience with health professionals is frequently cited by dissatisfied
35 hypothyroid patients ^{5,7} and may be due to communication barriers. Areas of concern
36 include not being listened to by health professionals, long delays in diagnosis, lack of
37 information about diagnosis and treatment and being denied participation and
38 engagement in choice of investigations and treatments ^{5,7}.
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43 ***Misinformation***

44 Poor patient knowledge and misinformation about hypothyroidism and its treatment
45 have been shown to be barriers to positive patient outcomes ⁷³. Misinformation may
46 be further amplified by social media.
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51 **Future research questions**

52 Table 1 lists some research questions that arise as a result of considerations
53 covered in this review.
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57 **Conclusions**

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3 Interventions using L-T4+L-T3 have been disappointing and are unlikely to unlock
4 the persistent symptom enigma **for the majority of patients**, therefore other avenues
5 need to be explored. CBT, lifestyle changes, better management of patient
6 expectations, provision of good quality information and psychiatric consultation to
7 support the endocrinologist or general practitioner in delivering optimal care, are
8 interventions that merit further study.
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15 **Declarations of interest**

16 PP, EP, EN and LH have undertaken consultancy work for IBSA Group
17 Pharmaceuticals, Switzerland. CFC and APW have no conflicts of interest to declare.
18 IBSA has had no involvement in the preparation of the manuscript and neither IBSA
19 nor any other agency has supported this review financially.
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Table 1

Research questions pertaining to persistent symptoms in hypothyroid patients

- What is the relationship between persistent symptoms in hypothyroid patients and other causes such as Somatic Symptom and Related Disorders, and how can they be identified?
- Can persistent physical symptoms be traced before the onset of hypothyroidism?
- What is the socioeconomic cost of persistent symptoms in hypothyroid patients?
- What is the impact of better long-term control of hypothyroidism using intensive biochemical monitoring and levothyroxine adjustment?
- What is the natural history of persistent symptoms in hypothyroid patients?
- Is the phenomenon of persistent symptoms in hypothyroid patients found in parts of the world other than Western Europe, North America and Australia?
- How effective are formulations of L-T4 that can be taken with food and drink in hypothyroid patients with persistent symptoms?
- Is combination treatment with L-T4 with physiological doses of slow-release L-T3 more effective than L-T4 alone?
- How effective is treatment of obesity for persistent symptoms in hypothyroid patients?
- Is cognitive behaviour therapy effective for hypothyroid patients with persistent symptoms?
- Are exercise programmes effective for hypothyroid patients with persistent symptoms?

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- Can the total thyroidectomy study in patients with autoimmune thyroiditis be confirmed?
 - Can selenium supplementation and other immunomodulatory agents or thyroid remnant ablation with radioiodine (augmented by administration of recombinant human TSH) aimed to reducing thyroid autoantibodies improve persistent symptoms in patients with autoimmune thyroiditis?
 - Does personality play a role in the development of persistent symptoms in hypothyroid patients?
 - Can better information delivered to patients at the time of diagnosis of hypothyroidism prevent persistent symptoms?
 - Can better management of patients' expectations at the time of diagnosis of hypothyroidism prevent persistent symptoms?
 - Can psychiatric consultation in the management of hypothyroid with Somatic Symptom and Related Disorders lead to improved outcomes?