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Title: Medically not yet explained symptoms (MNYES) in patients with hypothyroidism: a perspective

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Key words: Hypothyroidism; quality of life; thyroxine; liothyronine; questionnaire studies

Word count: 4000, **References:** 87

Illustrations: figures 2, tables 1, boxes 3

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Abbreviations:

E-MPATHY; E-Mode Patient self-Assessment of THYroid therapy

CBT; cognitive behavioral therapy

DSM-5; diagnostic and statistical manual of mental disorders

DTE; desiccated thyroid extract

HRQoL; health related quality of life

LT3; liothyronine

LT4; levothyroxine

MNYES; medically not yet explained symptoms

MUS; medically unexplained symptoms

PHQ15; patient health questionnaire 15

PCP; primary care physicians

SSD; somatic symptom disorder

THESIS; Treatment of Hypothyroidism in Europe by Specialists. An International Survey

Competing interests:

LH, PP, EVN, EP have received honoraria from IBSA Biochimique SA. LH reports receiving honoraria from Merck and Berlin-Chemie. CFC and APW report no competing interests.

Author roles:

LH and PP conceptualized the article. CFC, PP and LH wrote the first draft. Each coauthor added parts from their perspective. LH, CFC and PP compiled the final draft. All authors agreed on the final draft.

ABSTRACT

Persistent symptoms are common in the general population and more so in people with hypothyroidism. When unexplained and brought to medical attention, they can be referred to as Medically Not Yet Explained Symptoms (MNYES), a term preferred to other descriptors by patients, caregivers and experts. MNYES may be neglected by endocrinologists or misattributed to hypothyroidism. Awareness of MNYES opens up more effective and less harmful interventions than costly over-investigations, and over-treatment with thyroid hormones. The role of the endocrinologist is to recognize and acknowledge that MNYES may be underlying the patients' presentation, communicate effectively with the patient and others involved in their care, apply a 'two-track approach' in management by paying equal attention to physical and psychosocial contributors, and collaborate with other relevant health professionals. Categorization of patients into levels of risk for symptom deterioration helps in selecting suitable therapies. Effective management of MNYES demands time, training, expertise and resources.

INTRODUCTION

An excess of 10-15% of patients treated with levothyroxine (LT4) experience unexplained persistent symptoms despite achieving biochemical euthyroidism[1], compared to people without hypothyroidism. Experimental evidence from animal and some human studies has led to the hypothesis that LT4 treatment alone does not always restore normal tissue levels of tri-iodothyronine (T3) and symptoms can persist, despite normalization of serum TSH[2]. Strategies aimed at restoring tissue T3 levels by using combination therapy of LT4 with liothyronine (LT3)[3] or desiccated thyroid extract (DTE), have been tested extensively. To date several randomized controlled trials have shown no superiority of LT3-containing treatments over LT4 monotherapy using a variety of patient-reported outcomes[1,4]. Proponents of the 'low tissue T3 hypothesis' have re-focused their attention to subgroups of patients with specific profiles and treatment with slow-release LT3 formulations[5]. New data will be forthcoming over the next few years and are awaited with interest. In the meantime, there is a need to broaden our understanding of persistent symptoms in people treated with LT4.

The clinical profile of people who are treated with LT4 today is vastly different to the 'textbook cases' of hypothyroidism of the last millennium. Studies conducted over the past 10 years show that 6-30% of individuals who are started on LT4 by primary care physicians (PCP) do not have hypothyroidism, for whom deprescription of LT4 should be considered, while 60% have subclinical hypothyroidism[6-8]. Recent evidence shows that unselected patients with untreated subclinical hypothyroidism are no more symptomatic than the background population[9]. Consequently, improvements in symptoms following LT4 treatment cannot be expected when there is little or no perturbation of thyroid function, which seems to be the case for most patients currently being treated with LT4. Thus, the population of patients who are treated with thyroid hormones is highly heterogeneous, and once established on thyroid hormone replacement, judgement on attribution of persistent symptoms becomes difficult. In this context, the fact that recent evidence from the USA suggests that only 8% of patients started on LT4[7] have overt hypothyroidism supports the view that initiation of LT4 treatment in such patients is inappropriate. Lowering the biochemical threshold for initiating thyroid hormone treatment increases the prevalence of treated patients without resolution of presenting symptoms; such misattribution inevitably results in

dissatisfaction[1]. Serum TSH is under strong genetic control[10] and influenced by many variables[11]. It follows that age-adjusted reference ranges for serum TSH and awareness of the transient effects of non-thyroidal illness on thyroid function tests may reduce inappropriate LT4 therapy. The above reasoning leads to the conclusion that the 'low tissue T3 hypothesis' is unlikely to be relevant for many patients treated with LT4 presenting to endocrinologists with persistent symptoms. It follows that other avenues need to be explored as causes or contributors to persistent symptoms. In this respect it is relevant and well documented that hypothyroidism is bi-directionally associated with somatic[12] and psychiatric morbidity[13], and early retirement[14]. In addition, several other factors (unrelated to choice of thyroid hormone replacement), can potentially drive patient dissatisfaction and contribute to persistent symptoms (Table 1).

Here, we focus on a neglected cause of persistent physical symptoms in people treated for hypothyroidism[15], which we refer to as Medically Not Yet Explained Symptoms (MNYES)[16], also known as Medically Unexplained Symptoms (MUS), Persistent Physical Symptoms, functional symptoms, or somatization[17,18] (Box 1). MNYES is a term that was coined, from the perspective of patients, caregivers and clinicians, in a priority setting partnership following the James Lind Alliance approach that laid down priorities for research in this domain in 2022[16]. MNYES was meant to indicate that although some insights might exist, our understanding is still incomplete and involves biological, psychological and social factors. The prevalence of MNYES with and without somatic comorbidity in the general population is 5.9%[19]. In primary care, prevalence rates range from 1.5% to 11% depending on whether or not the criteria are restrictive[20,21].

INSIGHTS FROM RECENT SURVEYS

Patient surveys

Lived experiences are a valuable and complementary to understanding the impact of disease and the effects of treatments[22]. In hypothyroidism, a notable paradox is the wealth of individual patient testimonies of the 'miraculously' transformative value of LT3-containing treatments[23] contrasting with negative evidence from randomized controlled trials[1]. Large patient surveys show that while patients on LT3-containing treatments report better outcomes than those treated with LT4 monotherapy,

symptoms and impaired quality of life generally persist[24,25]. There are several possible explanations for the dissonance between real life patient experiences with LT3-containing treatments and randomized controlled trials: (a) those who participate in surveys may be more representative of patients whose tissue levels of T3 are not restored by LT4, than those enrolled in clinical trials; (b) people who are successful in finding a physician prepared to prescribe T3-containing treatments, may also receive more support and compassion from peers and from their physician, than those who remain on LT4 treatment; (c) in real life, patients treated with LT3-containing therapies are often over-medicated[23], which for some patients may enhance their sense of well-being[26].

Data from E-MPATHY (E-Mode Patient self-Assessment of THYroid therapy), a patient survey with 3,915 patient responses from 68 countries, have recently been published[27]. This examined somatization, assessed using a validated questionnaire, in treated patients with hypothyroidism. Somatization was present in 59% of participants compared to 7% of an age and sex-matched normative population sample, and was associated with the attribution of persistent symptoms to the hypothyroidism (Fig. 1), dissatisfaction, negative impact on daily living, anxiety and depression[27]. Contrary to social media, LT4 treatment was associated with a better impact on everyday living than other thyroid treatments. Another striking finding was a large geographical effect, with particularly high somatization rates in North and Western European and North American countries compared to other regions.

E-MPATHY also explored type D personality (a vulnerability factor for general psychological distress) in people with hypothyroidism and found a prevalence of 54.2% and associations with somatization and dissatisfaction[28].

Despite the limitations of patient surveys, the high prevalence of somatization, misattribution of symptoms to hypothyroidism, and the association between somatization and type D personality with dissatisfaction with treatment, provide novel insights into MNYES among patients with hypothyroidism.

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Clinician surveys

Recent surveys (acronym THESIS) of the views of nearly 6,000 thyroid experts on the treatment of hypothyroidism, conducted in 28 European countries[29-50], Latin

America[51] and Australia[52] showed that over 98% recommended LT4 alone as the initial treatment for hypothyroid individuals. This concords with international guidelines[53,54]. The main causes of persistent symptoms were thought by thyroid experts to be psychosocial, comorbidities, and unrealistic patient expectations whereas 'inability of LT4 to restore tissue euthyroidism' was rated as least important (Fig 2), yet 40% of thyroid experts would prescribe combination treatment for patients with persistent symptoms. These findings highlight the need for better understanding of MNYES in biochemically euthyroid patients and the potential role of non-pharmacological interventions.

MEDICALLY NOT YET EXPLAINED SYMPTOMS

MNYES can develop in the context of known medical conditions, or in the absence of comorbidities[55]. MNYES are symptoms that can occur widely and be transient in people experiencing stress. MNYES *per se* are not a mental condition. However, they can be associated with depressive and anxiety disorders[56]. In some cases, MNYES can be associated with high levels of distress and disability, sufficient to cross the diagnostic threshold for mental disorder [57]. The distress related to somatic symptoms, which lies at the core of MNYES, is classified as Somatic Symptom Disorder (SSD) in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5[58] corresponding to Bodily distress disorders, Code 6C20 in ICD-11[59]), and defined as : "… based on a bodily symptom and significant symptom distress with excessive thoughts, feelings, or behaviors related to the somatic symptoms or associated health concerns, as manifested by at least one of the following: (a) disproportionate and persistent thoughts about the seriousness of one's symptoms; (b) persistently high level of anxiety about health or symptoms; (c) excessive time and energy devoted to these symptoms or health concerns"[58].

MNYES account for up to 30% of consultations in various medical specialties [60,61]. The most frequent symptoms are fatigue, pain and dizziness[62]. Typically, patients fear there is an underlying undetected illness, and this drives them to seek a diagnosis. They often feel they are not taken seriously, although care may have been taken to explain their condition in depth[63]. People with MNYES do not 'make up' their

symptoms, nor do they deliberately attempt to deceive health professionals. Current understanding of the etiology of MNYES suggests that a complex interaction of physical, psychological and social factors are at play, leading to an exaggerated perception of unpleasant symptoms[64].

MNYES AND HYPOTHYROIDISM

MNYES has not been studied specifically in patients with hypothyroidism, but symptoms such as fatigue, weight gain and mood changes are frequent in both conditions [65,66]. Such symptoms may lead to multiple medical consultations, patient requests for inappropriate investigations and dissatisfaction with treatment, which are behaviors that signal distress [2,24,25]. Extrapolating from what is known about MNYES in general, it can be assumed that at least 20% - 30% of patients with hypothyroidism presenting to PCPs or endocrine services are likely to have MNYES[61,67]. In a study of patients presenting to PCPs with persistent MNYES, 86% were found to have either a comorbid depressive or anxiety disorder or SSD[68], which is likely to apply to patients presenting to endocrinology. In the context of MNYES and hypothyroidism, it is of interest that the prevalence of depression, associated with an increased suicide risk ,[69,70] and anxiety disorder, has been found to be higher than expected and in concordance with non-hypothyroid populations.[13,71]

MANAGEMENT OF MNYES

The questions that the physician needs to address when confronted with a patient who complains of unexplained symptoms are: (a) could the symptoms be due to an underlying, as yet undiagnosed physical illness, or to a known comorbidity that is treated suboptimally? (b) are the symptoms manifestations of an underlying psychiatric disorder (depression, anxiety or SSD)? To answer these questions, the physician is required to perform a thorough assessment and initiate additional investigations as necessary. This responsibility befalls largely on PCPs who have a central and established role[72, 73] and are the usual first port of call by patients.

An evidence-based guideline for MNYES that applies to primary care as well as higher tiers, has been published[74]. The guideline underscores three important principles in the management of MNYES:

a) ***Two-track management approach:*** the clinician needs to be aware and vigilant for potential somatic causes for the symptoms, while at the same time broadening the agenda to explore psychosocial issues. The two-track approach helps to make a judgment as to which contributor is primarily responsible for the patient's symptoms. The prognosis of MNYES can be adversely affected by protracted diagnostic procedures, multiple expert opinions and prolonged treatment-optimizing attempts. The two-track management approach ensures that psychosocial aspects of the patient's care are not neglected and are addressed in parallel.

b) ***Patient profiles for levels of risk:*** these are defined in Box 2 and help to identify patients at risk of a disabling and deteriorating course and developing persistent MNYES. Taking patient profiles into account can guide physicians to choosing the best treatment at an appropriate risk level and setting.

c) ***Roles of different professionals:*** the care of patients with MNYES sometimes requires the involvement of several key health professionals (outlined broadly in Box 2), although this depends on the health care system in operation). It is imperative that an identified clinician (obvious to both patient and other professionals involved) takes overall responsibility for the care of the patient and acts as coordinator at any one time during the patient journey.

Patients with MNYES usually have three equally important expectations from their physician: (a) to be listened, taken seriously and be understood that their symptoms are real; (b) to be reassured (assuming that is appropriate) that there is no underlying serious disease; (c) to receive an explanation for their symptoms, which is rational, scientifically sound, convincing, and makes sense to them. To achieve these goals PCPs may need access to specialist advice and psychiatric consultation to help diagnose and if necessary treat any somatic and / or psychiatric comorbidity. Such an approach has been shown to be effective for MNYES in primary care[68,75].

Role of endocrinologists in managing MNYES

The role of the endocrinologist is to recognize that MNYES may be underlying the patients' presentation, communicate effectively with the patient and others involved in their care, comply with the two-track management approach and collaborate with other relevant health professionals. When MNYES is suspected, appropriate referrals should follow to either the PCP or psychiatry depending on the type and severity of symptoms and distress, and on configuration of local services.

The majority of endocrinologists are not trained in managing patients with MNYES and therefore the central role of the PCP should be maintained while patients are followed up. Some clinician behaviors and attitudes are unhelpful, can exacerbate the difficulties that patients with MNYES face, are commonly displayed by endocrinologists[24,25,76], and should be avoided. They include not listening to patients, being dismissive, disbelieving or disinterested, lacking compassion, being unable to provide coherent explanations and saying or implying that the patient's symptoms are 'all in the mind'.

In relation to the three levels of risk described in Box 2, the role of the endocrinologist is outlined below, subject to local provisions and resources. Box 3 summarizes suggested steps in the management of patients with MNYES and hypothyroidism.

Over the whole process of management of patients with MNYES and hypothyroidism, in all settings and throughout the patient journey, a two-track diagnostic process should be followed that explores somatic and psychiatric aspects. Treatments should address both physical and psychological aspects of the patient's health. Most will be dealt with at primary care level (low-risk); an estimated 15% at hospital level by the endocrinologist (moderate risk); and an estimated 1% jointly by endocrinologist and psychiatrist, ideally and if no time constraints exist (high-risk)[75].

Level 1: Low risk for persistence, deterioration and disability– collaboration with the PCP

The majority of patients with MNYES fall in this category, which can be their first presentation of symptoms. MNYES is likely to be transient and management is as described in Box 2. The endocrinologist may be asked to provide an opinion as to whether there is an as yet unknown underlying endocrine diagnosis. The role of the endocrinologist therefore is peripheral and usually limited to collaborating with the PCP (who should coordinate the care of the patient) by providing an expert opinion. Patients in this category benefit from education and appropriate management of their expectations.

Level 2: Moderate risk for persistence, deterioration and disability

This category includes patients whose symptoms are not transient, or have comorbid psychiatric and / or somatic conditions. If MNYES is suspected in a patient with an established diagnosis of hypothyroidism, an endocrine opinion may be needed to ensure that the treatment of hypothyroidism is optimal. Such referrals to endocrinology are common. A typical example is a patient presenting with subclinical hypothyroidism who has been treated with LT4, remains symptomatic, has normal thyroid biochemistry, is dissatisfied, and believes that the treatment received so far is suboptimal. Such patients are often perceived by physicians as being "difficult"[77,78], and are more likely to have SSD, anxiety or depression (67% versus 35%). The endocrinologist's principal role is to treat the endocrine comorbidity. When symptoms seem to be related to stress and lifestyle, this should be explained to the patient and that the PCP is the appropriate professional for management of their symptoms. Collaboration between endocrinologist and PCP is essential. The role of coordinator of care is best allocated to one or the other professional on a case by case basis, depending on the complexity of the endocrinological condition. It is sometimes necessary to involve a psychiatrist for assessment and further management of mental health conditions.

A careful assessment of the patients' symptoms, their evolution, and adverse personal circumstances is often revealing. Exclusion of other endocrine and medical diagnoses is warranted, if not already achieved. Here the two-track approach should be followed by the endocrinologist, exploring potential psychosocial causes of the symptoms as follows. The endocrinologist should acknowledge that the patients'

symptoms are real. Listening to patients' concerns and an empathic approach by the endocrinologist are themselves therapeutic[78]. This requires evaluating cautiously any potential cause of dissatisfaction with treatment due to problems relating to general health, family life, social and working environment. Questions about medication adherence should be addressed without implying blame.

Following clinical assessment and any necessary additional investigations, endocrinologists should communicate their findings in a language that is easily understood by patients and allow further discussion and answer questions that may arise. Factual information should be supported with printed material or recommending appropriate websites and a plan should be formulated and agreed upon. When the endocrine assessment concludes that MNYES is the principal contributor to patients' symptoms, the care of MNYES can be handed back to the patients' PCP.

The approach described above often demands several endocrine appointments and may generate resource conflicts, which will need to be addressed. It can be helpful to monitor progress, especially for patients that may otherwise feel abandoned, but this should not duplicate or antagonize the role of the PCP. Evaluation forms are available on the internet and can be edited to align with the health service situation[79].

Level 3: High risk for unfavorable course, chronicity and disability

Patients in this category tend to have multiple cormorbid conditions, have experienced difficulties in patient-doctor relationships, are dissatisfied with their treatment and care and have often sought several specialist consultations relating to their symptoms. In complex cases, which occur in an estimated 1% of medical outpatients, a multidisciplinary consultation involving endocrinology and psychiatry specialists can be helpful to address diagnosis and management.[80] If a longer or more intensive follow up by the endocrinologist is necessary (e.g. when multiple changes in treatment for hypothyroidism and close monitoring are required, or when the severity of MNYES affects adherence with treatment for the hypothyroidism) joint follow-up consultations with a psychiatrist can be highly effective and can reduce the risk of iatrogenic harm[74]. Also, discussion of the patient-doctor relationship and how

to deal with it by the endocrinologist in peer group intervision or so-called Balint groups[81] can be helpful. In rare cases, specialist psychiatric multidisciplinary treatment will be needed in a specialized mental health ward. In that case, the endocrinologist can act as a consultant to the psychiatrist who provides treatment.

ETHICAL PERSPECTIVES

The paradigm of MNYES poses ethical challenges. While physicians should do their best to improve patients' wellbeing, including consideration of LT3 treatment, uncertainties about safety are equally important. Patients who request LT3 may argue that they prioritize quality of life over longevity. Reluctance by clinicians to prescribe LT3 may be discriminatory and drive patients who can afford it to seek LT3 via private practitioners or purchase it online at considerable cost and without medical supervision.

Thyroid hormones are increasingly prescribed for euthyroid people with 'hypothyroid-like symptoms' by PCPs,[6,7] and a significant proportion of thyroid specialists prescribe LT3 for patients with persistent, unexplained symptoms, despite believing that the underlying causes are psychosocial or due to unrealistic patient expectations[50]. The principle of non-maleficence is highly relevant in this context[82].

Optimal and ethically sound management requires time above all: (a) informing patients of the evidence about symptom causation, (b) making them aware of all therapeutic options (pharmacological, psychological, lifestyle) and the evidence base for and against different approaches, (c) acknowledging and exploring uncertainties and (d) guiding them to solutions that are most beneficial, least harmful, respectful of their autonomy and just. When faced with conflict, negotiation is preferable to alienation and involvement of another independent expert may be necessary.

CONSEQUENCES OF DISREGARDING MNYES

MNYES is common in the background population, as is hypothyroidism, especially when it is subclinical[6]. The occurrence of MNYES in treated hypothyroidism is therefore frequent and requires recognition, but is often overlooked.

In overburdened public health care systems, short of necessary sensitivity, time and empathy required for the management of MNYES, there are several consequences. Firstly, over-investigation prolongs uncertainty and anxiety, is costly, and can delay treatment. Secondly, patients' misconceptions and unrealistic expectations are reinforced by offering LT4 to those who cannot expect any improvement, without adequate consideration of unrelated causes for persistent symptoms and dissatisfaction. Thirdly, pressure from some patient organizations, supported by internet blogs and practitioners in the private and alternative sector, supports and endorses the use of LT3 and DTE. In the short-term this may lead to improvement in well-being due to over-treatment[26]. However, underestimation of the risk of patient or physician-caused over-treatment may lead in the long-term to excess morbidity and mortality[12,13,83].

COMMENTARY

The increased use of LT4 in euthyroid or mildly hypothyroid patients, and the controversy over the role of combination treatment in patients with hypothyroidism who experience persistent symptoms, has created a new and complex landscape. There are at least three important factors that complicate this area of thyroidology: (a) thyroid specialists receive little or no training in managing MNYES but are increasingly called upon to use their expertise for patients with unexplained symptoms. Judging by the high level of dissatisfaction expressed in patient surveys about endocrinologists[24,25,76], it can be concluded that their contribution is not appreciated by many patients; (b) over-treatment with thyroid hormones, particularly with LT3, may diminish the perception of MNYES at the expense of exposing patients to the risks of thyrotoxicosis;[26] (c) guidelines issued by authoritative professional organizations have delivered ambiguous messages on the management of patients with hypothyroidism and persistent symptoms. The European Thyroid Association guidelines published in 2012 state that "*combination therapy might be considered as an experimental approach in compliant L-T4-treated hypothyroid*

patients who have persistent complaints despite serum TSH values within the reference range"[84]. The American Thyroid Association guidelines published in 2014 used the cryptic phrase: "*there is currently insufficient evidence to support the routine use of a trial of a combination of levothyroxine and liothyronine therapy outside a formal clinical trial or N-of-1 trial*"[53], which has been interpreted as both an endorsement and disapproval of combination treatment. The UK NICE guidelines published in 2019 state "*do not routinely offer liothyronine for primary hypothyroidism, either alone or in combination with levothyroxine*".[54] Some of the guidelines cited above were produced more than a decade ago, however the lack of willingness to face up to MNYES in hypothyroidism seems to be perpetuated in a recent review by experts with the title "approach to hypothyroid patients with persistent symptoms", where MNYS is not even acknowledged as an entity and all attention is focused on combination treatment[85]. The discrepancy between physician opinion about causation of persistent symptoms and their actions, so clearly demonstrated by THESIS[29-52], is probably related to the so far inadequate messages in professional guidelines. Furthermore, no guideline has addressed how to resolve the common scenario faced by endocrinologists of patients who have an initial improvement in their symptoms upon the introduction of LT3, but the benefit wanes following which the patient requests a higher dose of LT3 and the cycle is repeated until iatrogenic thyrotoxicosis becomes a serious concern. It is hoped that the eagerly awaited updated ATA guidelines will bridge this gap.

CONCLUSIONS

MNYES is often overlooked in the management of symptomatic patients with treated hypothyroidism. A two-track somatic and psychosocial management approach should be followed throughout the patient journey. Assigning levels of risk for deterioration and disability is helpful in selecting appropriate treatments. Good communication between clinicians and patients and close collaborations between different healthcare professionals involved in the care of patients are crucial. Endocrinologists play an important role in the care of such patients. Research focusing on how to deliver supportive care for patients with MNYES in a cost-effective way is needed. Based on experience with MNYES in the primary care

setting, and the effectiveness of psychiatric input in this patient group[68,75], pilot studies and clinical trials to develop and evaluate psychiatric and lifestyle interventions in hypothyroid patients would be warranted to explore feasibility, effectiveness and cost-effectiveness upon which evidence-based guidance for endocrinologists can be developed.

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TABLES

TABLE 1

Possible causes and contributors to dissatisfaction with treatment and care by patients with hypothyroidism

Clinical care

Quality of healthcare does not meet patient expectations

-healthcare system-related

-healthcare professional-related

Treatment

Perceived lack of efficacy

Perceived side effects

Burden of having to take medication

Burden of having a diagnosis of a chronic disease

Burden of long-term monitoring

Blood tests

Changes in dose of thyroid medication

Patient misattribution of symptoms

Other organic illnesses

Mental / psychological disorders

Adverse social circumstances

Medically not yet explained symptoms

FIGURE LEGENDS

Fig. 1:

Attribution of persistent symptoms by E-MPATHY respondents to hypothyroidism or its treatment. Respondents were asked to indicate if they attributed the symptom to the hypothyroidism or its treatment, another condition or its medication, aging, lifestyle, short-term illness or other. Data are shown for those respondents with (black bars) and without (white bars) probable somatic symptom disorder. Derived from Perros P, Nagy EV, Papini E, et al. Hypothyroidism and Somatization: Results from E-Mode Patient Self-Assessment of Thyroid Therapy, a Cross-Sectional, International Online Patient Survey. Thyroid. Aug 2023;33(8):927-939. doi:10.1089/thy.2022.0641, with publisher's permission (reference [27]).

Fig. 2:

Specialists' (n=4163) opinion on the cause of persistent symptoms in LT4 treated biochemically euthyroid patients. The values show the percentage of survey respondents who have agreed (responses "agree" and "strongly agree" combined) that the given factor contributes to the persistent symptoms (based on references [29-48]).

Figure 1

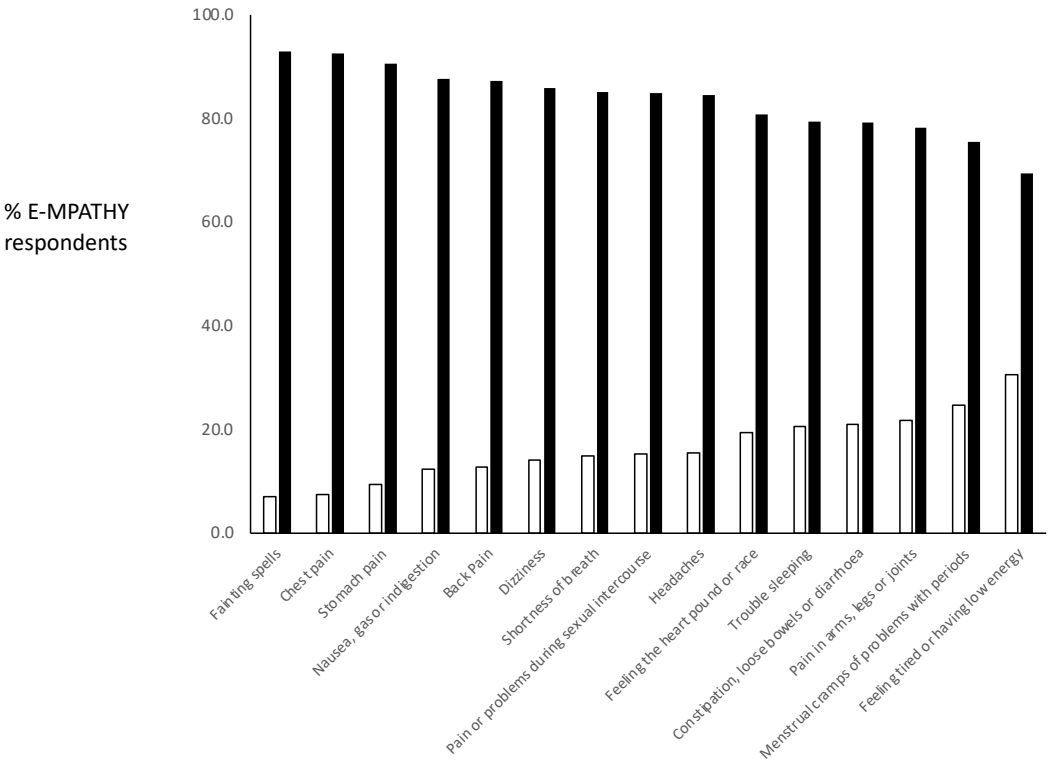
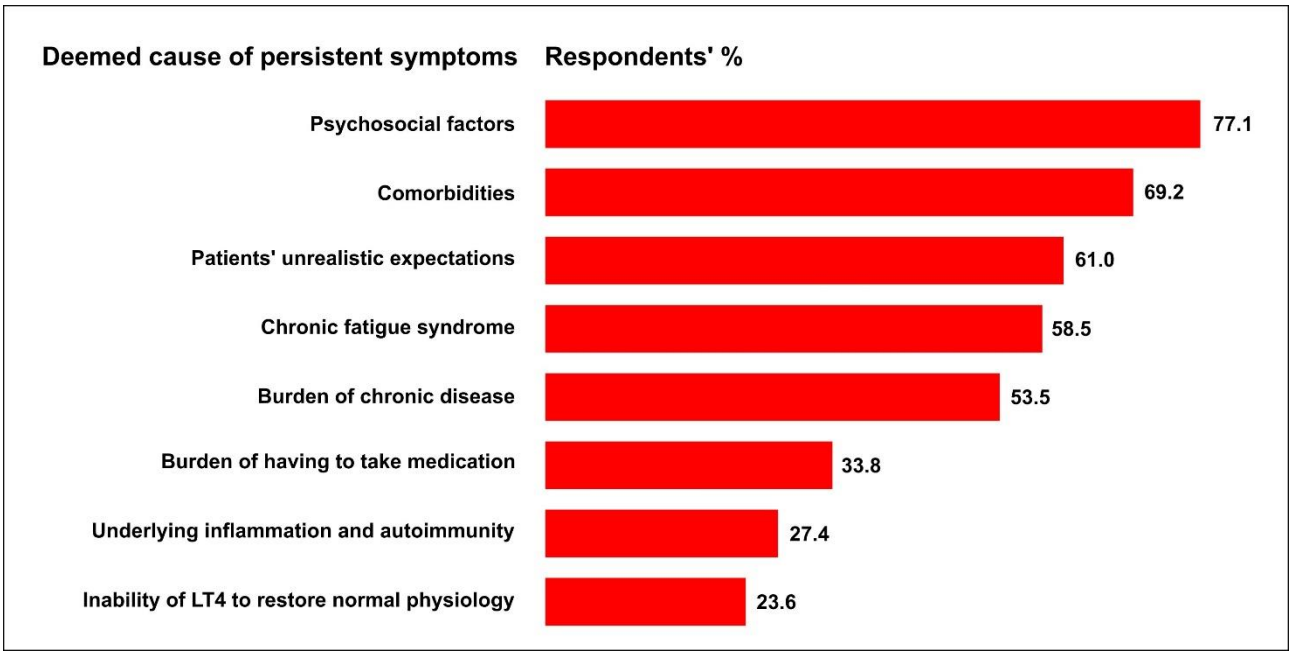

% E-MPATHY respondents
100.0
80.0
60.0
40.0
20.0
0.0
Fainting spells
Chest pain
Stomach pain
Nausea, gas or indigestion
Back Pain
Dizziness
Shortness of breath
Pain or problems during sexual intercourse
Headaches
Feeling the heart pound or race
Trouble sleeping
Constipation, loose bowels or diarrhoea
Pain in arms, legs or joints
Menstrual cramps or problems with periods
Feeling tired or having low energy

Figure 2



BOXES

BOX 1

Definitions of terms used in this review in relation to persistent symptoms

Somatic: describing, relating to, or arising in the body rather than from the mind[86]

Somatization: the tendency to experience and communicate somatic distress in response to psychosocial stress and to seek medical help for it [17,18]

Medically Unexplained Symptoms: symptoms for which adequate examination does not reveal sufficiently explanatory structural or other specified pathology[87]

Persistent Physical Symptoms: somatic symptoms that last for at least 6 months and cause significant suffering to the patient[15]

Somatic Symptom Disorders: bodily symptom and significant symptom distress with excessive thoughts, feelings, or behaviors related to the somatic symptoms or associated health concerns, as manifested by at least one of the following: (a) disproportionate and persistent thoughts about the seriousness of one's symptoms; (b) persistently high level of anxiety about health or symptoms; (c) excessive time and energy devoted to these symptoms or health concerns

Medically Not Yet Explained Symptoms: an alternative term to medically unexplained symptoms, persistent physical symptoms and somatization. MNYES is meant to indicate that although some insights might exist, our understanding of the symptoms is still incomplete and involves biological, psychological and social factors [16].

BOX 2: Collaborative care management of MNYES based on risk profiles

Level 1: Low risk for persistence, deterioration and disability

Low risk patients have transient MNYES that may be associated with stressors that are as yet unexplored. They need reassurance by the Primary Care Practitioner, (if necessary confirmed by specialist opinion), that their remaining symptoms should not be a cause for concern but can be treated in other ways. A referral for Cognitive Behavioral Treatment (CBT) can support the patient to avoid entering a cycle of excessive investigation, repetitive health care usage and worsening anxiety. The aim should be to limit referrals to other specialties and avoid iatrogenic harm, and this should be explained to the patient who needs to understand that over-investigation is not in their interests.

Level 2: Moderate risk, psychiatric comorbidity

Moderate risk patients often suffer from psychiatric or other comorbidity mostly comorbid depressive and anxiety disorder; although their presentation may be concerning in terms of disease burden, treatment of those conditions with antidepressant medication and CBT can greatly improve their symptoms. Follow up to see if this approach improves the patient's well-being can be delivered by the PCP.

The PCP follows a two-track diagnostic approach, exercising awareness and vigilance for potential somatic causes for the symptoms, while at the same time broadening the agenda to explore psychosocial issues. In this way a judgement can be reached as to which comorbidity might be the principal contributor to the patient's symptoms. Access to specialist advice including psychiatric consultation to optimize treatment of physical comorbidities, manage psychiatric comorbidity, and explain the causes of symptoms, treatment options and prognosis to the patient, can be helpful and is desirable. Such an approach has been shown to be effective for MNYES in primary care[63, 64, 65]

Level 3: high risk for persistence, deterioration and disability

High-risk patients often have long term Somatic Symptom Disorder and a perturbed patient-doctor relationship with their PCP; for this group, specialist mental health treatment is necessary.

BOX 3: Summary of actions that may be necessary in the evaluation of patients with hypothyroidism with persistent symptoms

Initial assessment

- Verification of diagnosis of hypothyroidism and consideration of deprescription in patients inappropriately treated with thyroid hormones
- Evaluation of previous and present level of control of hypothyroidism
- Evaluation of current symptoms
- Documentation of known comorbidities and consideration of potential for optimizing treatment of comorbidities
- Clear communication with patient about outcome of first assessment, explanation / interpretation of findings
- Plans, explanations and agreement with patient for next steps, if deemed appropriate
- Reassurance for patient, if appropriate
- If a psychiatric diagnosis seems likely (depression / anxiety, Somatic Symptom Disorder) help should be sought through the primary care physician (PCP) route
- Further endocrine follow-up may not be necessary if patient concerns have been addressed and further investigations are unnecessary
- Outcome of consultation clearly communicated to PCP and patient

Exclusions and optimization

- Exclude other previously unknown contributing diagnoses (if appropriate)
- Optimize thyroid treatment (if necessary)

- Optimize treatment of other comorbidities (if necessary; may require referral to other medical specialties)

Consideration of MNYES

- Evaluate all the accumulated information generated thus far and consider whether the diagnosis of MNYES is likely
- Clinical judgement in favor of no further investigations for very rare causes of persistent symptoms on the basis of patient's best interests.
- Communicate findings, assessment and expert opinion to the patient, explaining that MNYES need to be explored further
- Answer questions, explore patient concerns
- Communicate findings and opinion to PCP and request that PCP takes over management of MNYES
- Consider endocrine follow-up if appropriate

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