Thyroid

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Clinical Outcomes After Discontinuation of Thyroid Hormone Replacement - A Systematic Review and Meta-Analysis

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ABSTRACT

***Background*:** Levothyroxine (LT4) is one of the most commonly prescribed medications. Although considered a life-long replacement therapy, LT4 therapy can be discontinued for some patients. This study aims to: 1) review the evidence on clinical outcomes of patients undergoing thyroid hormone replacement discontinuation, 2) identify the predictors of successful discontinuation, and 3) systematically appraise frameworks used for deprescribing thyroid hormone.

Methods: We searched multiple bibliographic databases including Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily, Ovid Embase, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus, from inception to February 2020 for studies in which thyroid hormone replacement was discontinued. Clinical outcomes assessed included: proportion of patients that remained euthyroid or needed to restart thyroid hormone replacement after discontinuation and frequency of clinical symptoms of hypothyroidism and adverse effects. We also evaluated predictors for discontinuation and deprescribing frameworks. Reviewers (FJKT, NB, NSO, SM) evaluated studies for inclusion, extracted data and assessed methodological quality independently and in duplicate.

***Results*:** Seventeen observational studies at moderate to high risk of bias met inclusion criteria, including a total of 1,105 patients (87% women) with an age range of 5-81 years. Approximately a third of patients undergoing LT4 discontinuation remained euthyroid at follow-up (34.1%, 95% CI: 21.2% - 47.0%, I^2 97.5%). Sub-group analysis showed that patients with a previous diagnosis of overt hypothyroidism were less likely to remain euthyroid (11.8%, 95% CI: 4.0%- 23.2%, I^2 90.3%) than patients with a prior diagnosis of subclinical hypothyroidism (35.6%, 95% CI: 8.2%- 62.9%, I^2 93.5%). No study followed a framework for systematically deprescribing LT4.

***Conclusions*:** Low quality evidence suggests that up to a third of patients remained euthyroid after LT4 discontinuation, with a higher proportion of patients with an initial diagnosis of subclinical hypothyroidism remaining euthyroid than patients with an initial diagnosis of overt hypothyroidism. A deprescribing framework focusing on adequate selection of patients for deprescribing LT4 and a systematic process is warranted to guide clinicians in re-evaluating the need for LT4 in their patients.

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INTRODUCTION

Thyroid hormone medications may be prepared synthetically or be derived from animal sources and contain thyroxine (T4), triiodothyronine (T3), or both. These medications are used to restore thyroid hormone levels in patients with hypothyroidism.(1) Levothyroxine (LT4), a synthetic form of T4, is the second-most prescribed drug in the U.S. The global market for the treatment of thyroid disorders, dominated by hypothyroidism, was valued at $2,057 million in 2017, and is estimated to reach $2,771 million by 2025 at a compound annual growth rate of 3.8% from 2018 to 2025.(2,3) Although many factors likely play a role in the extensive prescription of LT4, an increase in the treatment of subclinical hypothyroidism (SCH) is a contributing factor.(4)

SCH is a common biochemical diagnosis, which affects ~10% of adults(5) and is accompanied by either nonspecific symptoms (2/3 of cases) or no symptoms at all.(5,6) Once thyroid hormone replacement is started, 9 in 10 patients with SCH continue thyroid hormone therapy indefinitely.(7) Although the benefits of LT4 use for patients with overt hypothyroidism (OH) are clear, no benefits have been demonstrated with respect to quality of life or thyroid-related symptoms for patients with SCH.(7–11) Observational studies have shown an association of untreated SCH with increased mortality,(12,13) but randomized trials have not found that LT4 therapy decreases the risk of death.(9) In addition to the treatment burden associated with thyroid hormones use, approximately 50% of patients older than 65 years who take thyroid hormones develop iatrogenic hyperthyroidism, increasing their risk for arrhythmias, angina pectoris, bone loss, and fractures.(14–16) After an extensive review of the available evidence, a guideline panel recently concluded that almost all adults with SCH do not benefit from thyroid hormone treatment.(17) Thus, many patients currently on LT4 may not experience any significant benefit, while being exposed to its potential harms.

Deprescribing refers to the “thoughtful and systematic process of identifying problematic medications and either reducing the dose or stopping these medications in a manner that is safe, effective, and helps patients maximize their wellness and goals of care.”(18) Deprescribing has been shown to reduce potentially inappropriate or

unnecessary medications (19,20) and may be successful and effective in selected classes of drugs.(21) Deprescribing LT4 has the potential to reduce medication burden and avoid LT4 adverse effects. The goal of this study was to summarize the clinical outcomes of patients for whom thyroid hormone replacement was discontinued, identify the predictors of successful discontinuation, and evaluate the frameworks used to deprescribe thyroid hormone replacement.

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METHODS

We conducted a systematic review of academic databases and meta-analysis of included studies. This review follows the recommendations of the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA).(22)

Eligibility criteria

We sought randomized controlled trials and observational studies that included patients on thyroid hormone replacement (regardless of the indication for therapy) who underwent treatment discontinuation, with no restrictions in terms of participants' age or type of hormone replacement (LT4, liothyronine, thyroid extracts, combination therapy). Studies reporting on the following were included: 1) thyroid function assessment after discontinuation of thyroid hormone replacement, 2) predictors and procedures related to thyroid hormone discontinuation, 3) the frequency of symptoms or adverse events as a result of thyroid hormone discontinuation, and/or 4) description of a framework for thyroid hormone discontinuation. We excluded studies of patients undergoing thyroid hormone withdrawal in preparation for radioactive iodine treatment, patients whose indication for therapy was central or congenital hypothyroidism, postpartum thyroiditis or thyroid cancer, and patients exposed to recent interventions that could affect thyroid hormone requirements (e.g., bariatric surgery). Finally, we excluded studies with inadequate information to determine eligibility and those for which there was no response from the authors seeking that information.

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Data sources and search strategies

An experienced librarian (LCH) designed and performed a comprehensive search which ran from database inception through February 27, 2020. **Appendix 1** describes the included databases, the search terms and how they were combined. The search excluded animal studies, had no language limits, and used controlled vocabulary supplemented with keywords. The reference list of the included studies was reviewed to identify any additional relevant studies.

Study selection

The search results were uploaded into the systematic review software DistillerSR (Evidence Partners, Ottawa, Canada). Reviewers working independently and in duplicate reviewed all abstracts and titles for inclusion. After abstract screening and retrieval of potentially eligible studies, the full text publications were assessed for eligibility. Duplicate studies were excluded. The kappa statistic for full text screening was 0.77. Disagreements were resolved by consensus.

Data collection and management

Reviewers working independently and in duplicate using a standardized form collected the following from eligible studies: 1) baseline clinical features: age, type of hypothyroidism (etiology), degree of hypothyroidism/thyroid status (euthyroid, subclinical, overt), type of hormone replacement, sex, thyroid hormone replacement dose at withdrawal, treatment duration, goiter presence, family history of thyroid disease, thyroid antibody positivity (thyroid peroxidase and/or thyroglobulin antibody), thyroid gland heterogeneity on ultrasound, and body mass index, 2) TSH and free T4 levels at baseline and after withdrawal, 3) clinical outcomes and predictors [thyroid status after withdrawal (e.g., euthyroid), thyroid hormone levels after withdrawal, symptoms and side effects during follow up] and 4) features of deprescribing strategies. We extracted TSH and/or free T4 levels cut-offs used to define euthyroidism, SCH and OH, as well as definitions for goiter and thyroid gland heterogeneity.

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Risk of bias assessment

Reviewers working independently and in duplicate used the Newcastle-Ottawa risk of bias tool for observational studies to evaluate the methodological quality of included studies.(23) This tool determines the comparability of cohorts, their representativeness, and the ascertainment of exposure and outcomes. Disagreements were resolved by consensus.

Author contact

To reduce reporting bias, we contacted the authors of studies in which clarification or more information was needed to determine eligibility or to complete analysis. Four of the seven contacted authors replied.(24–27)

Meta-analysis and subgroup analysis

A random effects meta-analysis was conducted to evaluate the percentage of patients who were euthyroid at follow-up and those who needed to restart thyroid hormone replacement after thyroid hormone discontinuation (OpenMeta Analyst, Brown University Evidence-Based Practice Center). We performed subgroup analyses according to type of hypothyroidism and age group. Similarly, we evaluated the mean differences in TSH measurements before and after thyroid hormone discontinuation. Inconsistency was assessed using I^2 statistic, with values >75% indicative of high inconsistency not due to chance.(28)

RESULTS

Study identification

We identified 2,673 potentially eligible studies;17 observational studies including patients undergoing discontinuation of thyroid hormone replacement therapy were deemed eligible.(24–27,29–41) **Figure 1** describes the study selection process.

Study characteristics

Table 1 summarizes the characteristics of the included studies. Sixteen studies evaluated thyroid hormone status categorically (e.g., proportion of euthyroid patients after discontinuation), eight evaluated thyroid hormone status numerically (e.g., TSH levels) and four evaluated clinical symptoms. Four studies evaluated children and adolescents, three studies evaluated mixed populations (children, adolescents and adults), and ten studies evaluated adults. The etiology and degree of hypothyroidism was also variable, including autoimmune and idiopathic, and SCH and OH. In addition, some studies included patients that were euthyroid at baseline (time of initial diagnosis). **Table 2** summarizes patient characteristics.

In fourteen studies, thyroid hormone replacement therapy consisted of LT4. Ohsawa et al. studied an LT4 and a liothyronine group; Krugman et al. studied patients on variable regimens (LT4/liothyronine combination, LT4, and thyroid extract); and in the study by Nikolai et al., the type of thyroid hormone replacement was unspecified.(29,30,34) Three studies discontinued therapy following a tapering regimen. Tapering regimens included: discontinuing therapy within 2 weeks, first halving dose at week one and discontinuing the remaining dose at week two (26); halving LT4 dose successively every 4 weeks until a dose ≤12.5 mcg/day was reached and therapy was then discontinued (27); or either halving dose and eliminating remaining dose in two months or by 25 mcg reductions until discontinuation.(34)

No study formally used the term deprescribing when referring to the process of discontinuing thyroid hormone replacement therapy, and none described a systematic process of deprescribing thyroid hormone in clinical practice.

Study quality

We judged the observational studies to be at moderate to high risk of bias on the basis of representativeness of the exposed cohort (most were a selected group of users), lack of blinding and lack of assessment of cofounders (**Supplemental Table 1**).

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Meta-analysis

Proportion of patients that remained euthyroid

Sixteen studies evaluated the proportion of patients that remained euthyroid after LT4 discontinuation (**Figure 2)**. A total of 1,092 patients were included and the time of outcome assessment ranged from 10 days to a median follow up of 5 years. Most studies (N=10) included adults only or participants with no description of the degree of hypothyroidism and/or a mix of overt/subclinical/euthyroid patients (N=9). **Table 3** describes the proportion of patients with euthyroidism according to the indication for LT4 therapy. The definitions for euthyroidism for each study are summarized in **Supplemental Table 2**.

When all studies were included, the pooled estimate for euthyroidism at follow-up was 34.1% (95% CI: 21.2%, 47.0%, I^2 97.5%). The pooled estimate for euthyroidism was lower for those with OH 11.8% (95% CI: 4.0%, 23.2%, I^2 90.3%) and for adults 32.2% (95% CI: 16.0%, 48.3%, I^2 97.5%). **Figure 3** shows the results of this meta-analysis.

Proportion of patients that reinitiated thyroid hormone treatment

Nine studies evaluated the percentage of patients in which LT4 was restarted during follow up. A total of 843 patients were included and the time of outcome assessment ranged from 3 weeks to a median of 5 years. The criteria for reinitiating LT4 therapy varied across studies. Most studies reinitiated treatment when laboratory evidence of SCH was present, applying different TSH thresholds for treatment between 4.5 to 10 mIU/L or above the reference value.

When all studies were included, the pooled estimate for restarting LT4 during follow up was 62.5% (95% CI: 45.5%, 79.5%, I^2 96.9%). The pooled estimate for patients with OH was higher, 87.2% (95% CI: 76.0%, 98.4%, I^2 86.3%). **Figure 4** shows the results of this meta-analysis.

TSH changes at follow up

In four studies (27,31,36,40) the mean TSH values before and after LT4 withdrawal were available. Three of the studies included adults. Two studies included patients with SCH and two with OH. Time of outcome assessment ranged from one week to five years of median follow up. The mean TSH difference (increase) was 9.4 mIU/L (95% CI: 5.0, 12.8, I^2 97.4%).

Predictors for developing hypothyroidism after LT4 withdrawal

Data regarding predictors for the development of hypothyroidism after LT4 withdrawal were insufficient for meta-analysis, however statistically significant predictors are summarized in **Table 4**.

Symptoms and adverse events after LT4 withdrawal

Four studies evaluated the development of symptoms after LT4 withdrawal. In two studies, no patients developed symptoms; Livadas et al. reported no changes in quality of life after LT4 discontinuation; (24) Wasniewska et al. found no clinical signs or symptoms of hypothyroidism.(36) Two studies reported development of symptoms after LT4 withdrawal; Comtois et al. reported fatigue in 15.2% of patients, however whether these patients became hypothyroid was not reported.(32) Takasu et al. reported “symptoms of hypothyroidism” in 71.4% of patients, all of whom were biochemically hypothyroid.(35) These four studies relied on self-reporting and none included a systematic assessment of symptoms. Rizzolo et al. assessed eight hypothyroidism-related symptoms at baseline and 21 days after thyroid hormone discontinuation, but included patient populations not meeting our inclusion criteria (e.g., subtotal thyroidectomy), thus are not reported here.(41) Reporting on the development of symptoms after abrupt versus tapered LT4 discontinuation was unavailable.

Three studies evaluated adverse events after LT4 withdrawal. Livadas et al. reported no “adverse events”(24) and Radetti et al. found no adverse effects on growth, lipid profile, glucose homeostasis and the development or worsening of goiter.(26) Carlwe et al.

reported intolerable fatigue in one participant (7.7%) who dropped out with unknown thyroid function status.(40)

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DISCUSSION

We performed a systematic review and meta-analysis to summarize the available evidence on clinical outcomes after thyroid hormone discontinuation that could guide LT4 deprescription in clinical practice. We found that 34% of patients remained euthyroid at follow up when including all studies; with a lower proportion (12%) for patients initially diagnosed with OH. Similarly, most patients (63%) were restarted on thyroid hormone replacement, although different criteria, including the development of SCH, were used to restart therapy. Moreover, heterogenous echogenicity on thyroid ultrasound, elevated TSH ≥ 8-9 mIU/L, and presence of thyroid antibodies were negatively associated with the rate of euthyroidism after thyroid hormone discontinuation in individual studies. Data pertinent to patient-centered outcomes (adverse effects, development of symptoms) were scarce. No study reported a systematic process/framework for deprescribing LT4. These findings suggest that deprescribing LT4 could be successful for carefully selected patients and highlight the need for studies at low risk of bias that include evaluation of patient important outcomes.

Despite decades-old controversies related to treatment thresholds for SCH, current guidelines (1,17,42) do not recommend the continuous evaluation of the need for thyroid hormone replacement therapy. However, in clinical practice, patients may be overtreated with LT4 if therapy is initiated without a well-documented hypothyroidism diagnosis, if clinicians start therapy based solely on the non-specific symptoms of hypothyroidism, and depending on thresholds used to start treatment for SCH.(7,24,43)

The term deprescribing usually refers to the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes. Therefore, deprescribing is a more complex process than just stopping a medication.(44–46) This systematic process, starts with an accurate evaluation of the medication list, followed by identification of potentially inappropriate medications, collaboration between patients and clinicians to decide if

deprescribing would be appropriate and establishing a supportive plan to safely deprescribe the medication.(44,45) Shared decision making is fundamental for a successful deprescribing intervention, as patients are more likely to consider deprescription if they: 1) understand why the medication is inappropriate, 2) have their concerns related to stopping the medication addressed and 3) understand the deprescribing plan and feel supported by the clinical team. Deprescribing conversations should focus on raising awareness about alternatives, discussing the risks and benefits of deprescribing and understanding the patient's preferences.(44,47)

The rationale, indications and a proposed process for deprescribing LT4 are summarized in **Figure 5**. Briefly, LT4 deprescribing is reasonable in patients for whom the benefits of treatment do not outweigh the risks. This could be the case for patients diagnosed with SCH based on a single TSH measurement or for whom LT4 was started as part of a therapeutic trial and was never discontinued despite the lack of clinical improvement.(4,48) As summarized in Figure 5, there is a strong rationale to consider LT4 discontinuation and preliminary clinical evidence guiding patient selection and process to deprescribe LT4.

After patients and physicians decide to deprescribe LT4, a plan for discontinuation and follow up should be made. The likelihood of developing symptoms while using an abrupt versus tapering discontinuation regimen has yet to be elucidated. Once LT4 has been discontinued, it might be reasonable to follow up patient's symptoms and thyroid function tests every 4-6-weeks (49) and less frequently after 6 months of follow up if the patient remains clinically and biochemically euthyroid. The patient-physician discussion should also delineate what criteria would merit LT4 re-initiation.

Though research on deprescribing is increasing, data on deprescribing thyroid hormone are scarce.(50) Available studies have evaluated changes in thyroid function status or the need to re-prescribe thyroid hormone replacement; however, long-term effects and patient-centered outcomes are yet to be determined. Future studies should consider measuring quality of life, adverse drug withdrawal events and reduction in cardiovascular or bone health events.(50,51) Non-inferiority study designs may be helpful

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to evaluate deprescribing interventions.(50,52) This design was developed from the need to evaluate similar efficacy as compared to the established treatment while offering greater safety, convenience, or lower cost. Although these trial designs may be more complex than those used to establish superiority, they can help determine that an intervention is not worse than the control treatment.(53) Therefore, the use of non-inferiority study designs evaluating the absence of change in clinical status after medication withdrawal has been proposed in the development of deprescribing trials.(50) Studies focusing on the process of deprescribing (e.g., selection of patients, conversation about deprescribing and deprescribing plan) are needed to support safe and likely beneficial deprescribing of LT4 in practice. Furthermore, the field will need to develop and test multi-level strategies for deprescribing that are context-specific but feasible, cost-effective, adaptable, and generalizable across settings. Such strategies will need to specifically target the unique barriers to deprescribing of thyroid hormone therapy. Future research should investigate potential unintended negative consequences of deprescribing for patients, clinicians, and healthcare systems.

Incomplete searching and arbitrary study selection represent potential limitations of systematic reviews. However, the rigorous and comprehensive nature of our overlapping search strategies with a medical librarian's input minimize the possibility that we missed studies that could have substantially changed the inferences drawn from this study.(54) The risk of reporting bias is high, particularly when the body of evidence is based on small observational studies. We attempted to decrease the chances of reporting bias by contacting authors.(55) Although it would have been clinically meaningful to evaluate the effects of important patient characteristics on thyroid function after LT4 withdrawal (e.g., thyroid autoimmunity status) or perform subgroup analysis according to time of follow-up, this was not possible due to insufficient data. Due to their uncontrolled and observational nature, and the lack of adjustment for confounders, the included studies were at moderate- to high-risk of bias. In addition, the meta-analysis results showed high heterogeneity and imprecision. Studies included patients with variable characteristics limiting the direct application of the results to specific patients. In all, low quality evidence suggests that deprescribing LT4 could be successful, but patient selection is important.

Although these limitations could not be overcome methodologically, our review exhibited important strengths including synthesis of the totality of the available evidence following a predetermined protocol, with reproducible judgements about study selection and quality and focused analyses assessing the effects of LT4 discontinuation, which has not been performed previously.(56)

In summary, low quality evidence suggests that up to a third of patients remained euthyroid after LT4 discontinuation, with a higher proportion of patients with an initial diagnosis of SCH remaining euthyroid than patients with an initial diagnosis of OH. Data regarding patient-centered outcomes remain sparse. Nonetheless, for some patients deprescribing LT4 is likely reasonable. Patients and physicians can use this information when discussing if discontinuation of LT4 is a reasonable consideration.

Author Contribution Statement

NSO, JPB, and SM conceived and designed the study with input from all the co-authors. LCH designed and performed the literature search with input from NSO and SM. NB, FJKT, NSO, and SM carried out the data collection and statistical analysis, with input from JPB. All co-authors contributed to critical appraisal and review of the results and the manuscript. All authors reviewed and agreed on the final version of the manuscript.

Author Disclosure Statement

The authors have nothing to disclose. No competing financial interests exist.

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Figure legends

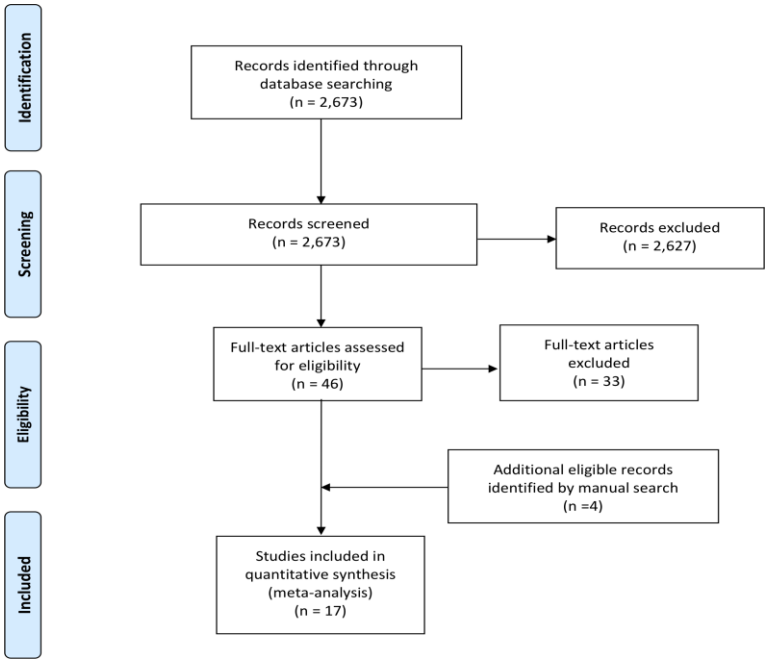

Figure 1. PRISMA Flow Diagram

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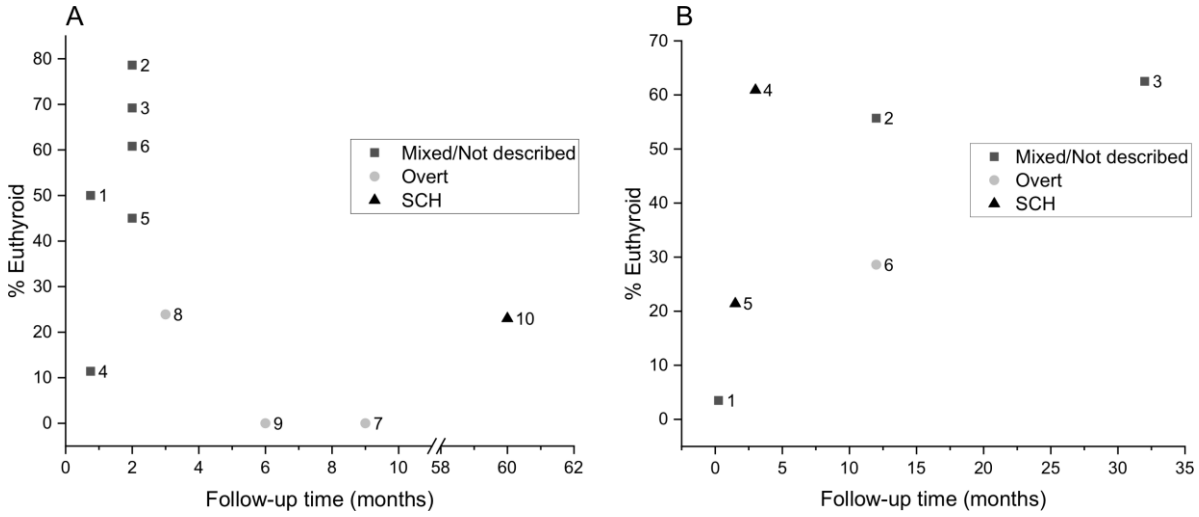

Figure 2A. Percentage of euthyroid adult patients by type of hypothyroidism and follow-up time. (1) Rizzolo 1986 (2) Krugman 1975 (3) Ohsawa 1981 (4) Comtois 1995 (5) Rieu 1994 (6) Livadas 2018 (7) Höfling 2013 (8) Takasu 1990 (9) Nikolai 1989 (10) Rosario 2016

Figure 2B. Percentage of euthyroid patients by type of hypothyroidism and follow-up time in studies with mixed patient age groups (children, adolescents and adults). (1) Battelino 1994 (2) Radetti 2017 (3) Sklar 1986 (4) Wasniewska 2012 (5) Fava 2009 (6) Takasu 1992. SCH, subclinical hypothyroidism; Overt, overt hypothyroidism

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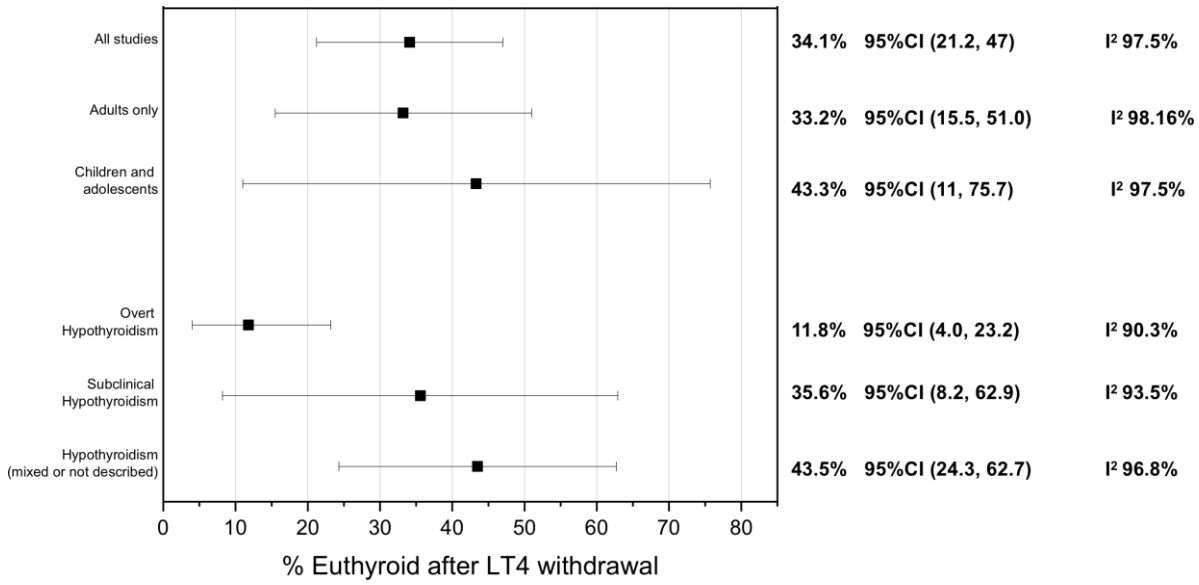

Figure 3. Meta-analysis of euthyroidism (%) after levothyroxine (LT4) discontinuation including all studies and subgroup analysis by degree of hypothyroidism and age of participants

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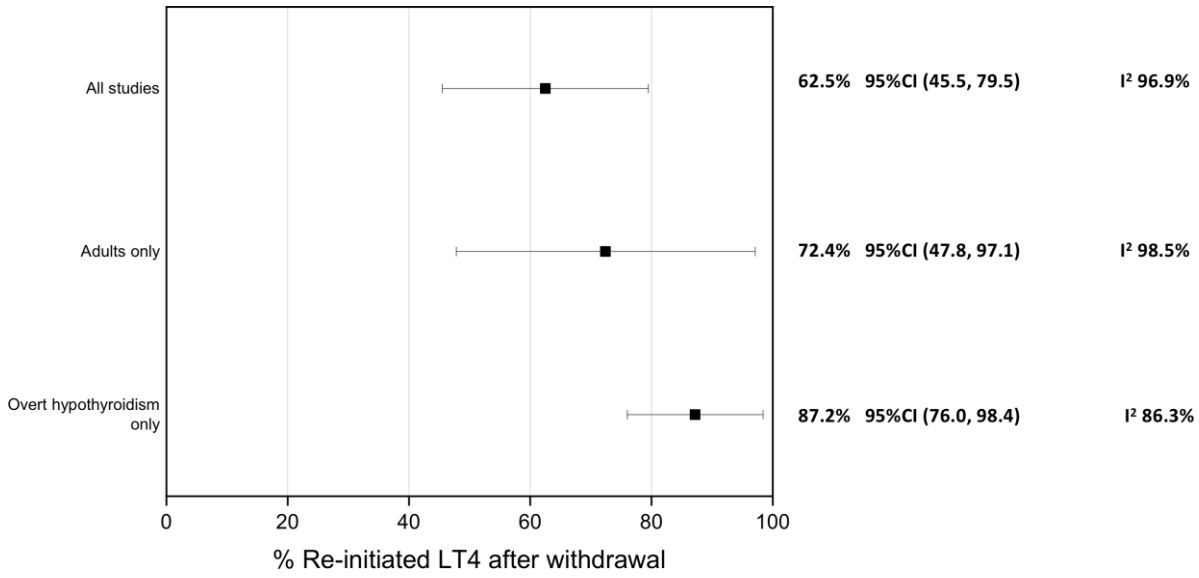

Figure 4. Meta-analysis of re-initiation of levothyroxine (LT4) (% X axis), including all studies and subgroup analysis according to degree of hypothyroidism and age of participants

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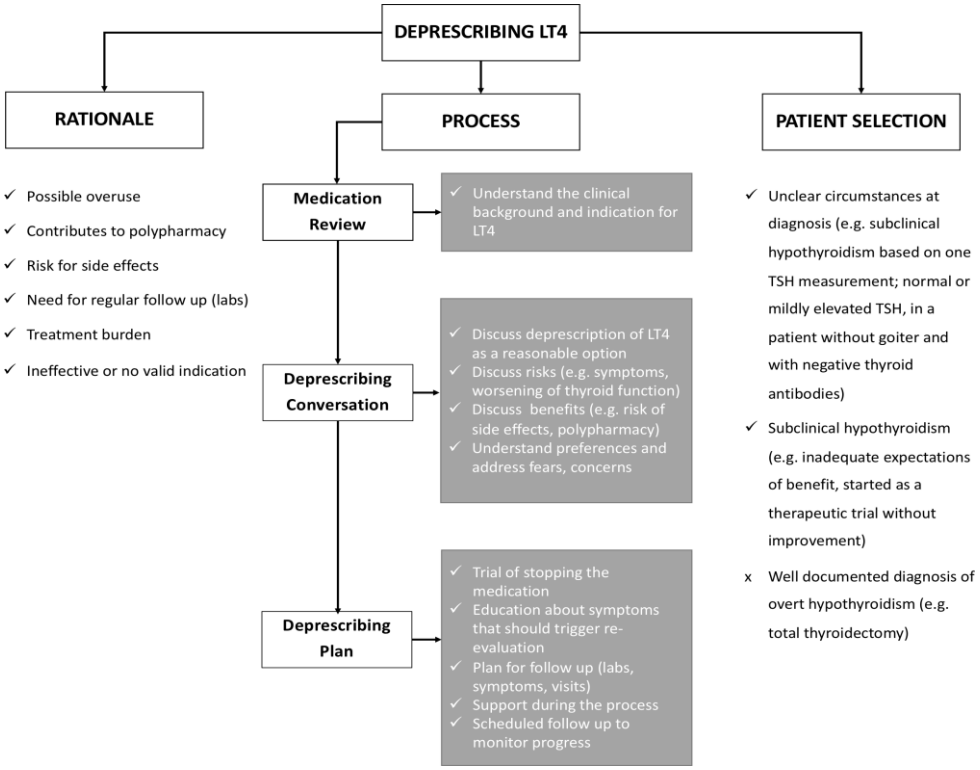

Figure 5. Algorithm for approaching levothyroxine (LT4) deprescribing; TSH, thyroid stimulating hormone

Table 1. Characteristics of studies included in the systematic review

Author (reference)	*Year*	*Country*	*Age Group*	*Etiology of Hypothyroidism*	*Degree of Hypothyroidism*	*Outcomes*	*Follow-up time (months)*
Wasniewska	2012	Italy	Children Adolescents	Idiopathic	Subclinical	Clinical Symptoms Thyroid Hormone Status Categorical Thyroid Hormone Status Numerical	3
Battelino	1994	Slovenia	Children Adolescents	Autoimmune	Mixed	Thyroid Hormone Status Categorical	0.33
Radetti	2017	Italy	Children Adolescents	Autoimmune	Mixed	Thyroid Hormone Status Categorical Thyroid Hormone	12 months 2, 6,

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						Status Numerical Need to restart thyroid replacement	12, 24
Sklar	1986	USA	Children Adolescents	Autoimmune	Euthyroid Subclinical Overt	Thyroid Hormone Status Categorical	variable (28-36)
Fava	2009	Italy	Children Adolescents Adults	Autoimmune	Subclinical	Thyroid hormone status categorical	1.3
Takasu	1992	Japan	Children Adolescents Adults	Autoimmune	Overt	Clinical Symptoms Thyroid Hormone Status Categorical	12
Takasu	1990	Japan	Adults	Autoimmune	Overt	Thyroid Hormone Status Categorical	3

Carlwe	2013	Sweden	Adults	No description	Overt	Thyroid Hormone Status Numerical	0.25
Rizzolo	1986	USA	Adults	No description	No description	Thyroid Hormone Status Categorical	0.75
Krugman	1975	USA	Adults	Mixed	No description	Thyroid Hormone Status Categorical	2
Rosario	2016	Brazil	Adults	Mixed	Subclinical	Thyroid Hormone Status Categorical Thyroid Hormone Status Numerical	24-120 Median: 60
Ohsawa	1981	Japan	Adults	Autoimmune	No description	Thyroid Hormone Status Categorical Thyroid Hormone	2

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						Status Numerical	
Comtois	1995	Canada	Adults	Autoimmune	Mixed	Thyroid Hormone Status Categorical Thyroid Hormone Status Numerical	0.75
Höfling	2013	Brazil	Adults	Autoimmune	Overt	Thyroid Hormone Status Categorical Thyroid Hormone Status Numerical	9 1
Rieu	1994	France	Adults	Autoimmune	Euthyroid Hypothyroid	Thyroid Hormone Status Categorical	2
Livadas	2018	Greece	Adults	Other (Mixed)	No description	Clinical Symptoms Thyroid	1.5-2

						Hormone Status Categoric al Thyroid Hormone Status Numerical	
Nikolai	198 9	USA	Adults	Primary	Overt	Thyroid Hormone Status Categoric al	6 12 36

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Table 2. Patient characteristics of the studies included in the systematic review

Study	*Sample size (N)*	*Age (years)*	*Women (%)*	*Were all patients euthyroid at LT4 discontinuation*	*LT4 dose at discontinuation (mcg/day)*	*Treatment duration (years)*	*Thyroid Antibodies TPO and/or anti-TG Ab (%)*	*Goiter (%)*	*Heterogeneous gland (%)*	*Family history of thyroid disease (%)*
Children & Adolescents										
Sklar 1986	17	-	-	Unclear		Median 2.2	-	100	-	-
Battelino 1994	29	Mean 14.9 Range 8.5-19.7	79	Yes	-	-	-	-	-	-
Wasniewska 2012	69	9.4 (4.0)	75.4	Yes	-	2	7.2[a]	0	7.2	-
Radetti 2017	149	-	82.6	No	-	4.1 (2.6) Range 1-12	100	-	100	47.7

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Children, Adolescents & Adults										
Takasu 1990	92	Range 14-68	90.2	Yes	-	Mean 3.8 Range 1-8	100	100	-	-
Takasu 1992	21	31 [12-72] *	85.7	Yes	-	Range 1.5-7	-	33.3	-	-
Fava 2009	14	18 [8-26] *	78.6	Yes	1.26 (0.3)†	6.4 [2.8-12.4] *	-	42.9	100	21.4
Adults										
Krugman 1975	14	Range 17-68	71	Unknown	-	Range 0.4-22	-	21.4	-	-
Ohsawa 1981	24	-	100	Unknown	LT4: 200 LT3: 50	Range 0.1-5	-	100	-	-
Rizzolo 1986	22	-	-	Unknown	-	-	-	-	-	-
Nikolai 1989	49	Mean 52 Range 23-81	79.6	Unclear	-	Range 0.5-3	-	38.8	-	-
Rieu	20	-	-	Yes	-	1	-	100	-	-

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1994										
Comtois 1995	79	39 (13) Range 17-64	91	Yes	110 (30) Range 50-150	1	-	55.7	-	44
Carlwe 2013	13	Mean 43 Range 28-60	92	Yes	109 [75–162)]	-	-	-	-	-
Höfling 2013	20	42.1 (11.6)	100	Yes	Mean 90.00 CI (70.87–109.13)	4.52 (3.47)	90[a] 80[b]	25	100	-
Rosario 2016	182	42 [19-63] *	100	Yes	Range 25-100 Range 0.3-1.5[†]	3 [2-6.8]*	55[a]	-	23.1	-
Livadas 2018	291	48 (16.4)	84	Yes	0.92 (0.42) [†]	Mean 8.1 Range 1-37	58	0	62	63

LT4, levothyroxine; LT3, liothyronine; TPO antibody, Thyroid Peroxidase Antibody; Anti-TG Ab, anti-thyroglobulin antibody

Results are mean (SD) unless otherwise indicated. * Results are median [range];† Results are mcg/kg/day; [a] TPO antibody only; [b] anti-TG Ab only

Table 3: Percent of euthyroid patients after thyroid hormone discontinuation by prior indication for therapy

Population	**Study**	**Indication for treatment**	**N**	**% Euthyroid**
Children and adolescents	Battelino 1994	Autoimmune hypothyroidism (overt or subclinical)	29	3.5
	Wasniewska 2012	Idiopathic SCH	69	60.9
	Radetti 2017	Autoimmune hypothyroidism (overt or subclinical)	149	55.7
	Sklar 1986	Autoimmune euthyroid Autoimmune SCH Autoimmune overt hypothyroidism	8 4 5	88 65 20
Children, adolescents, and adults	Fava 2009	Autoimmune hypothyroidism (overt or subclinical)	14	21.4
	Takasu 1990	Autoimmune overt hypothyroidism	92	23.9
	Takasu 1992	Autoimmune overt hypothyroidism	21	28.6
Adults	Rizzolo 1986	Hypothyroidism: clinical diagnosis without adequate laboratory confirmation Hypothyroidism: diagnosis based on laboratory tests Hypothyroidism: diagnosis based on symptoms and the presence of goiter	7 7 8	86 14 50
	Comtois 1995	Autoimmune hypothyroidism (overt or subclinical)	79	11
	Krugman 1975	Overt hypothyroidism Goiter Hashimoto's thyroiditis Nontoxic nodular goiter	10 1 2 1	70 100 100 100

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	Rieu 1994	Euthyroid Goitrous Hashimoto's disease Autoimmune overt hypothyroidism	9 11	100 0
	Ohsawa 1981	Euthyroid Hashimoto's thyroiditis	13 11	69 55[a]
	Livadas 2018	Presence of thyroid nodules but not on suppression therapy Unknown reason for LT4 supplementation or no evidence of past thyroid dysfunction provided Therapy initiated post pregnancy without reassessment Hashimoto's thyroiditis or hypothyroidism-like or related symptoms	96 78 15 102	63.5* 46.2* 73.3* 67.6*
	Nikolai 1989	Overt hypothyroidism	49	0
	Höfling 2013	Autoimmune overt hypothyroidism	20	0
	Rosario 2016	SCH with presence of TPO Ab with or without goiter, symptoms of hypothyroidism, dyslipidemia, depression, infertility or unknown reasons	182	23

SCH, subclinical hypothyroidism; LT3, liothyronine; LT4, levothyroxine; TPO Ab, Thyroid Peroxidase Antibody

[a] % euthyroid after LT3 discontinuation; * % hypothyroid (overt/subclinical) was reported for subgroups and % euthyroid was derived from this report

Table 4: Predictors for development of euthyroidism and hypothyroidism after thyroid hormone discontinuation

Population	*Predictors for euthyroidism*
Adults	Positive family history of thyroid disease (Comtois 1995)
Children and adolescents	TSH at diagnosis < 10 mIU/L (Radetti 2017)
Population	*Predictors for hypothyroidism*
Adults	Heterogeneous thyroid on ultrasound (Livadas 2018)
	TPO Ab and ultrasound with diffuse hypoechogenicity (Rosario 2016)
	TSH ≥ 8 mIU/L at diagnosis (Rosario 2016)
Children and adolescents	Baseline TSH > 9 mIU/L (Wasniewska 2012)
	Age at diagnosis (younger) (Radetti 2017)
	Anti-TG Ab at diagnosis (Radetti 2017)
	Age at withdrawal (younger) (Radetti 2017)
	TPO Ab level at withdrawal (Radetti 2017)
	Goiter at thyroid hormone withdrawal (Radetti 2017)

Anti-TG Ab, Anti Thyroglobulin Antibody; TPO Ab, Thyroid Peroxidase Antibody

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Appendix 1. Actual Search Strategies

Ovid

Database(s): **Ovid MEDLINE(R) 1946 to Present and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) Daily, EBM Reviews - Cochrane Central Register of Controlled Trials** January 2020**, EBM Reviews - Cochrane Database of Systematic Reviews** 2005 to February 27, 2020**, Embase** 1974 to 2020 February 27

Search Strategy:

#	Searches
1	exp Hypothyroidism/
2	(hypothyr* or "hypo-thyr" or myxedema or hypothyreoidism or hypothyreosis or hypothyroidea or hypothyroidosis or hypothyrosis or (thyro* adj (deficien* or insufficien*)) or SCH).mp.
3	1 or 2
4	(sublinic* or "sub-clinic*" or suppressed or underactiv* or "under-activ" or mild* or moderate or "short-term" or borderline or "10 mIU/L" or "<10 mIU/l").mp.
5	3 and 4
6	"subclinical hypothyroidism"/
7	5 or 6
8	exp Thyroiditis/
9	Hashimoto Disease/
10	(hashimoto* or thyroiditis).mp.
11	or/7-10
12	exp Thyroid Hormones/
13	(thyroid* adj1 (hormon* or extracts or "combination therapy")).mp.
14	exp Thyrotropin/
15	(thyrotropin* or thyreotropin* or thyrotrophin* or thyretropin* or tsh or thyrogen*).mp.

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16	(thyroxin* or tyroxin* or thyronin* or triiodothyronin* or diiodothyronin* or calcitonin* or dextrothyroxin* or monoiodotyrosin*).mp.
17	("L-triiodothyronin*" or "L-thyroxin*" or "L-thyronin*").mp.
18	("L-T3" or LT3 or "L-T4" or LT4 or FT3 or "F-T3" or "F-T4" or FT4).mp.
19	(levothroid* or levothyroid* or levothyrox* or levothyroxin* or laevothyrox* or "levo thyrox*" or levoxin* or levoxyl or novothyral or novothyrox or liothyronin* or liotrix or thyrolar or "armour thyroid" or "nature-throid*" or elthyron* or westhyroid* or oroxine or synthroid or synthrox or thyrax or soloxine or tiroidine or unithroid or berlthyrox or dexnon or eferox or eltroxin or eltroxine or euthyrox or eutirox or cytomel).mp.
20	"Hormone Replacement Therapy"/ or hormone substitution/
21	((replac* or substitut*) adj3 hormon*).mp.
22	or/12-21
23	(overus* or deprescrib* or deprecription* or de-prescrib* or de-precription* or discontinu* or "de-escalate*" or withhold* or withdraw* or titrat* or taper* or cessation).mp.
24	((benefit* or beneficial or "re-evaluat*" or reevaluat* or interrupt* or halt* or stop* or paus* or reintroduc* or "re-introduc*") adj2 (treatment or therapy)).ti.
25	((progress* or overt or "natural history" or positive or persistence or persistent or prognosis or prognostic or ultrasound) adj6 ("antithyroperoxidase antibodies" or tpo* or "thyroid peroxidase antibod*" or hypothyroid* or SCH or "chronic thyroiditis" or "TSH < or = 10 mIU/L" or ">10 mIU/L*" or sublinic* or "sub-clinic*" or suppressed or underactiv* or "under-activ" or mild* or disease)).mp.
26	Disease Progression/ or *disease exacerbation/
27	Predictive Value of Tests/ or *predictive value/
28	Prognosis/
29	or/23-28
30	11 and 22 and 29
31	"Iodine Radioisotopes"/

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32	iodine.mp.
33	31 or 32
34	30 not 33
35	34 not ((case* adj3 report*).ti,ab,hw,kw. or case report/)
36	35 not (metaanalysis or "meta analysis" or systematic or review).ti.
37	36 not ((exp animals/ or exp nonhuman/) not exp humans/)
38	remove duplicates from 37

SCOPUS

1	(hypothyr* or "hypo-thyr" or myxedema or hypothyreoidism or hypothyreosis or hypothyroidea or hypothyroidosis or hypothyrosis or (thyro* w/1 (deficien* or insufficien*)) or SCH)
2	(sublinic* or "sub-clinic*" or suppressed or underactiv* or "under-activ" or mild* or moderate or "short-term" or borderline or "10 mIU/L" or "<10 mIU/l")
3	1 and 2
4	(hashimoto* or thyroiditis)
5	3 or 4
6	TITLE-ABS-KEY ((thyroid* W/1 (hormon* OR extracts OR "combination therapy")))
7	TITLE-ABS-KEY ((thyrotropin* OR thyreotropin* OR thyrotrophin* OR thyretropin* OR tsh OR thyrogen*))
8	TITLE (("L-T3" OR lt3 OR "L-T4" OR lt4 OR ft3 OR "F-T3" OR "F-T4" OR ft4))
9	TITLE-ABS-KEY (levothroid* OR levothyroid* OR levothyrox* OR levothyroxin* OR laevothyrox* OR "levo thyrox*" OR levoxin* OR levoxyl OR novothyral OR novothyrox OR liothyronin* OR liotrix OR thyrolar OR "armour thyroid" OR "nature-throid*" OR elthyron* OR westhyroid* OR oroxine OR synthroid OR synthrox OR thyrax OR soloxine OR tiroidine OR unithroid OR berlthyrox OR dexnon OR eferox OR eltroxin OR eltroxine OR euthyrox OR eutirox OR cytomel)
10	TITLE-ABS-KEY ((replac* OR substitut*) W/1 hormon*)

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11	TITLE-ABS-KEY (thyroxin* OR tyroxin* OR thyronin* OR triiodothyronin* OR diiodothyronin* OR calcitonin* OR dextrothyroxin* OR monoiodotyrosin*)
12	TITLE-ABS-KEY ("L-triiodothyronin*" OR "L-thyroxin*" OR "L-thyronin*")
13	6 or 7 or 8 or 9 or 10 or 11 or 12
14	TITLE-ABS-KEY (overus* OR deprescrib* OR deprecription* OR de-prescrib* OR de-precription* OR discontinu* OR "de-escalate*" OR withhold* OR withdraw* OR titrat* OR taper* OR cessation)
15	TITLE ((benefit* OR beneficial OR "re-evaluat*" OR reevaluat* OR interrupt* OR halt* OR stop* OR paus* OR reintroduc* OR "re-introduc*") W/2 (treatment OR therapy))
16	TITLE-ABS-KEY ((progress* OR overt OR "natural history" OR positive OR persistence OR persistent OR prognosis OR prognostic OR ultrasound) W/3 ("antithyroperoxidase antibodies" OR tpo* OR "thyroid peroxidase antibod*" OR hypothyroid* OR sch OR "chronic thyroiditis" OR "TSH < or = 10 mIU/L" OR ">10 mIU/L*" OR sublinic* OR "sub-clinic*" OR suppressed OR underactiv* OR "under-activ" OR mild* OR disease))
17	14 or 15 or 16
18	5 and 13 and 17
19	TITLE (iodine)
20	18 not 19
21	TITLE-ABS-KEY (case* W/3 report*)
22	TITLE (metaanalysis OR "meta analysis" OR systematic OR review)
23	21 or 22
24	20 not 23
25	INDEX(embase) OR INDEX(medline) OR PMID(0* OR 1* OR 2* OR 3* OR 4* OR 5* OR 6* OR 7* OR 8* OR 9*)
26	24 not 25
27	DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh) OR DOCTYPE(ch)
28	26 not 27

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29	(TITLE-ABS-KEY ((alpaca OR alpacas OR amphibian OR amphibians OR animal OR animals OR antelope OR armadillo OR armadillos OR avian OR baboon OR baboons OR beagle OR beagles OR bee OR bees OR bird OR birds OR bison OR bovine OR buffalo OR buffaloes OR buffalos OR "c elegans" OR "Caenorhabditis elegans" OR camel OR camels OR canine OR canines OR carp OR cats OR cattle OR chick OR chicken OR chickens OR chicks OR chimp OR chimpanze OR chimpanzees OR chimps OR cow OR cows OR "D melanogaster" OR "dairy calf" OR "dairy calves" OR deer OR dog OR dogs OR donkey OR donkeys OR drosophila OR "Drosophila melanogaster" OR duck OR duckling OR ducklings OR ducks OR equid OR equids OR equine OR equines OR feline OR felines OR ferret OR ferrets OR finch OR finches OR fish OR flatworm OR flatworms OR fox OR foxes OR frog OR frogs OR "fruit flies" OR "fruit fly" OR "G mellonella" OR "Galleria mellonella" OR geese OR gerbil OR gerbils OR goat OR goats OR goose OR gorilla OR gorillas OR hamster OR hamsters OR hare OR hares OR heifer OR heifers OR horse OR horses OR insect OR insects OR jellyfish OR kangaroo OR kangaroos OR kitten OR kittens OR lagomorph OR lagomorphs OR lamb OR lambs OR llama OR llamas OR macaque OR macaques OR macaw OR macaws OR marmoset OR marmosets OR mice OR minipig OR minipigs OR mink OR minks OR monkey OR monkeys OR mouse OR mule OR mules OR nematode OR nematodes OR octopus OR octopuses OR orangutan OR "orang-utan" OR orangutans OR "orang-utans" OR oxen OR parrot OR parrots OR pig OR pigeon OR pigeons OR piglet OR piglets OR pigs OR porcine OR primate OR primates OR quail OR rabbit OR rabbits OR rat OR rats OR reptile OR reptiles OR rodent OR rodents OR ruminant OR ruminants OR salmon OR sheep OR shrimp OR slug OR slugs OR swine OR tamarin OR tamarins OR toad OR toads OR trout OR urchin OR urchins OR vole OR voles OR waxworm OR waxworms OR worm OR worms OR xenopus OR "zebra fish" OR zebrafish) AND NOT (human OR humans OR patient OR patients)))
30	28 not 29

Thyroid
Clinical Outcomes After Discontinuation of Thyroid Hormone Replacement - A Systematic Review and Meta-Analysis (DOI: 10.1089/thy.2020.0679)