BURDEN OF ORAL LEVOTHYROXINE THERAPY: A SYSTEMATIC LITERATURE REVIEW OF VARIABILITY, TREATMENT COMPLEXITY, AND QUALITY OF LIFE IMPACT

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INTRODUCTION

Despite widespread use of oral levothyroxine (LT4), many patients with hypothyroidism experience persistent symptoms and impaired quality of life. Evidence suggests that maintaining stable thyroid-stimulating hormone (TSH) control in routine practice is challenging.[1-3] Oral LT4 absorption is influenced by multiple factors, including food intake, drug interactions, gastrointestinal conditions and adherence, contributing to variability in treatment exposure. This variability may result in TSH fluctuations, frequent dose adjustments, and ongoing management burden.[2,4]

Current clinical guidelines primarily emphasize dose titration to achieve target TSH levels but provide limited guidance on managing variability over time.[5,6] This review aimed to characterize the burden associated with oral LT4 therapy and identify key factors contributing to variability in treatment response.

OBJECTIVES

This systematic literature review (SLR) aimed to:

- Assess the burden of oral LT4 therapy and its impact on quality of life (QoL) among patients experiencing adherence constraints and LT4 absorption challenges
- Characterize optimization, absorption, and lifestyle burdens that hinder stable TSH control with oral LT4 treatment
- Evaluate how these factors collectively impact consistency of biochemical control over time

METHODS

- This SLR followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist and identified peer-reviewed manuscripts and conference abstracts published in English from January 2010 to October 2025 in PubMed and Embase **(Figure 1)**
- Identified articles were uploaded to an artificial intelligence (AI)-enhanced platform used to facilitate the SLR process*; duplicates across the databases were removed in the platform
- Title/abstract screening was conducted per the defined population, intervention, comparator, outcomes, and study design (PICOS) criteria by one human researcher in parallel with one AI screener providing reviewer-level decisions; adjudication was performed by an independent human researcher
- The validated AI screening platform was initially trained using 50 adjudicated screening decisions and 10 inclusions before activation and continued to improve its performance through subsequent screening. The remainder of the title/abstract screenings were conducted with one human and one AI screener that provided reviewer-level decisions, with adjudication by another independent human
- After screening, full texts were retrieved and screened by two independent human reviewers, facilitated via the AI platform
- A prioritization rubric was then applied using an AI screener and reviewed by a human researcher for detailed data extraction to identify high-priority publications that focused on populations taking oral LT4 for hypothyroidism and explicitly discussed the burden of daily oral LT4 as a central focus in their objectives and/or analyses. Most high-priority publications were clinical trials/studies **(Figure 2)**

** AI-enhanced platform utilized for the SLR was Nested Knowledge*

Figure 1: PRISMA Flow Diagram of Study Selection

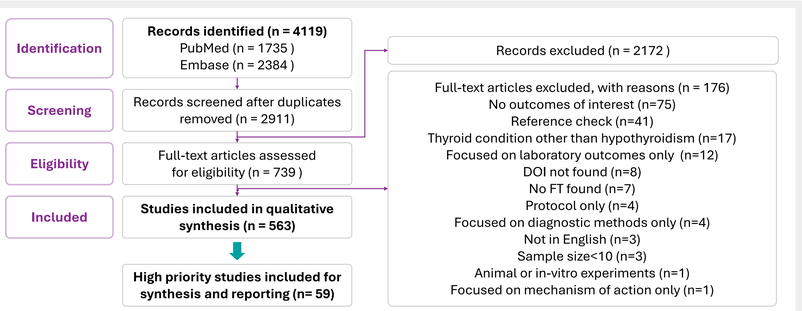


Figure 2: Distribution of High Priority Publications by Study Type (N=59)

RESULTS

- The SLR identified 563 publications meeting PICOS criteria, with 59 high-priority studies focused on oral LT4 burden. Evidence converged across three non-mutually exclusive domains: Optimization Burden (n=19), Absorption Burden (n=39), and Lifestyle Burden (n=40) **(Figure 3)**.
- Across these domains, findings consistently demonstrated multiple interacting sources of variability in treatment exposure and response, including dose adjustments, TSH fluctuations, and external influences on absorption and adherence. These factors collectively contribute to challenges in maintaining stable biochemical control over time.

OPTIMIZATION BURDEN

Key Findings Daily oral LT4 is associated with repeated dose adjustments, laboratory monitoring, and clinical visits, often driven by variability in absorption and adherence. Some studies suggest that switching from tablets to non-tablet formulations may improve control in some patients **(Table 1).**

Table 1: Optimization Burden Key Findings

Theme	Key Findings	References
Dose Adjustments	**Frequent LT4 adjustments were common in real-world practice, especially in patients with GI comorbidities or interacting drugs**, with ~31–40% of LT4-treated patients reported to have ≥1 dose/formulation change in the prior 12 months, and almost half of those with adjustments having ≥2 changes over 24 months	McMillan (2016), Ernst (2017b)
	Repeated LT4 dose adjustments **substantially increased healthcare costs** (~160% increase) and **lost productivity** (i.e., compared to patients without dose adjustments, patients with ≥3 changes had 86% higher lost-productivity cost)	Ernst (2017b)
Formulation Switches	**Difficult-to-control patients experienced frequent dose changes on tablets, but switching to gel caps reduced titration burden** as mean dose adjustments fell from 1.61 to 0.73 per patient after switching from tablets to gel caps (~55% reduction)	Ernst (2017a)
	For patients with GI disorders, switching from tablets to gel caps or liquid formulations improved symptom control in ~62% and ~70% of patients, respectively	Ernst (2017a), Henderson (2024)
	When gastric pH–related factors drove instability, replacing tablets with liquid/soft-gel formulations could restore control without further dose escalation	Vita (2014), Sachmechi (2023)

Note: Full citations can be accessed through the QR code

ABSORPTION BURDEN

Key Findings Oral LT4 tablets create chronic absorption burden for patients because the oral tablets are highly sensitive to food, meal timing, GI comorbidities, bariatric surgery, and common co-medications (e.g., PPI/calcium) **(Table 2).**

Table 2: Absorption Burden Key Findings

Theme	Key Findings	References
Food-Drug and Drug-Drug Interactions	**Meal timing and fasting window requirements (e.g., breakfast vs bedtime, Ramadan) are major, recurrent drivers of absorption-linked burden** as ~50% of patients felt burdened by postponing breakfast and ~25% choosing to omit breakfast entirely	Willems (2024), Perez (2013), Bolk (2010)
	Interacting drugs and supplements are commonly co-used with LT4 and substantially compromise LT4 absorption. It was reported that ~68% of patients frequently consumed foods/beverages known to cause LT4 malabsorption and 34% used co-medication, of which ~62% interfered with LT4 absorption	McMillan (2016), Willems (2024)
GI Conditions	**Gastritis, GERD, celiac and other GI diseases are consistently linked to malabsorption, unstable TSH and higher treatment burden,** with one survey reporting 47% of patients having at least one GI comorbidity	Ernst (2017b), McMillan (2016)

Note: Full citations can be accessed through the QR code

LIFESTYLE BURDEN

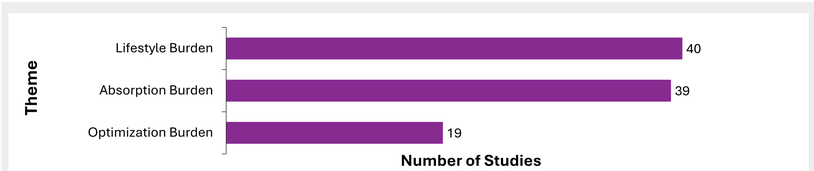
Key Findings Daily oral LT4 administration is disruptive to the lifestyle of patients, especially in the morning, limiting adherence to medications **(Table 3).**

Table 3: Lifestyle Burden Key Findings

Theme	Key Findings	References
Impact of Routine Complexity / Restriction on Adherence	Patients with hypothyroidism are **not fully adherent to their medications**, with ~42% of patients exhibiting low adherence. **Daily routine complexities and restrictions of daily oral LT4 were reported to be difficult** to maintain by patients	Topaloğlu (2021), Juch (2016), Cappelli (2018), Akin (2018)

Note: Full citations can be accessed through the QR code

*Figure 3: Distribution of High Priority Publications by Theme**

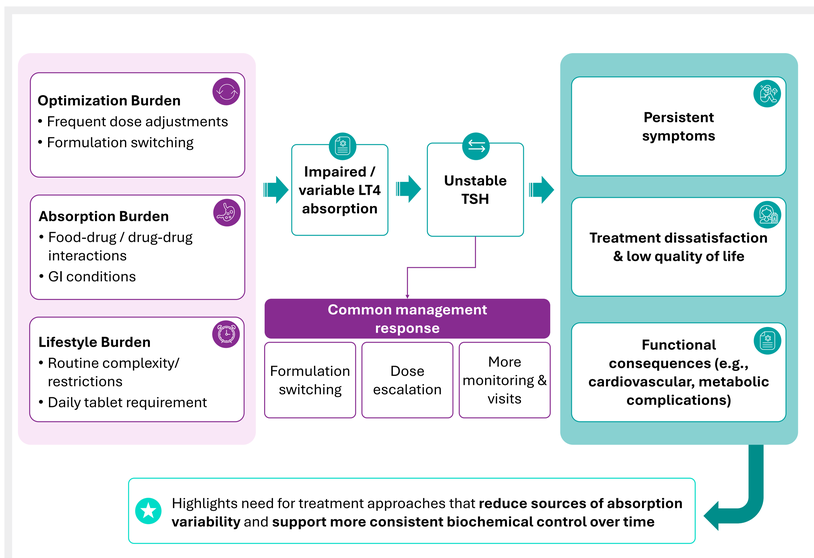


** Study themes non-mutually exclusive across the 59 publications*

DISCUSSION AND CONCLUSIONS

- Findings across optimization, absorption, and lifestyle domains demonstrate that oral LT4 therapy is associated with multiple, interacting sources of variability in treatment exposure and response **(Figure 4).**
- These include factors affecting absorption (e.g., food, drug interactions, gastrointestinal conditions), adherence challenges, and clinical management practices such as dose adjustments and monitoring frequency.
- Together, these factors may contribute to variability in thyroid hormone levels and challenges in maintaining consistent TSH control over time.
- Variability in biochemical control may be associated with persistent symptoms, treatment dissatisfaction, and reduced quality of life, as well as potential downstream clinical consequences reported in some studies.
- Current management approaches primarily focus on dose titration but may not fully address these sources of variability.
- These findings suggest that variability in treatment response is a systemic feature of oral LT4 therapy rather than an isolated patient-level issue.
- Addressing variability in treatment exposure may represent an important opportunity to improve long-term management of hypothyroidism.

Figure 4: Conceptual Model: Drivers of Variability in Oral LT4 Therapy and Impact on Biochemical Control



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