Healthcare Burden Among Patients with Graves' Disease: A Targeted Literature Review

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BACKGROUND

- Graves' disease (GD) is a systemic autoimmune disorder, and the most common cause of hyperthyroidism.[1,2]
- GD treatment options have generally remained unchanged for 75 years, and include antithyroid drugs (ATD; most commonly methimazole), radioactive iodine (RAI), and thyroidectomy.[1,3,4]
- ATD are typically recommended as the first-line treatment for GD.[1,2] However, not all patients with GD have an adequate response to ATD therapy; for those who do, relapse is common.[1,5]

OBJECTIVES

- To assess the scientific literature and evaluate the burden of GD, focusing on Graves' hyperthyroidism, including clinical, humanistic, and treatment-related aspects.

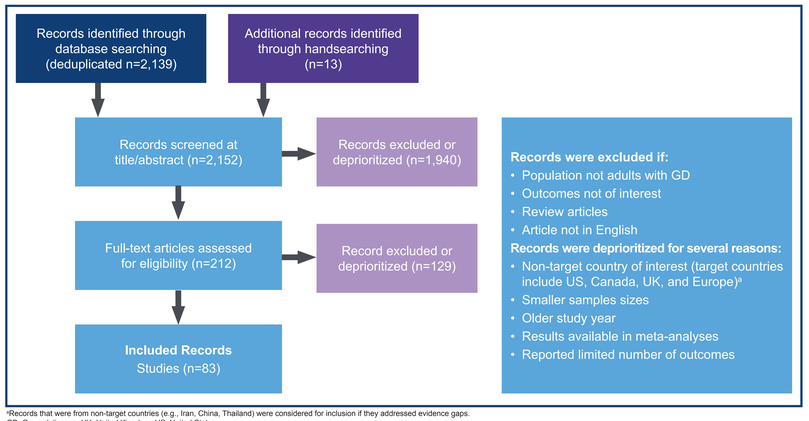
METHODS

- This analysis included a targeted review of scientific literature published from January 1, 2019 through August 2, 2024.
  - Literature searches were conducted in Embase, Medline, the Cochrane Library, and Econlit using a pre-defined search strategy designed to identify articles on disease burden, treatments, and guidelines associated with GD.
  - The focus of the literature review was on the United States (US), Canada, and Europe, including the United Kingdom. Records for other countries were considered for inclusion if they addressed key evidence gaps.
- Supplemental searches were performed to identify health technology assessments, primary sources from review papers found in the literature review, and relevant conference abstracts published from January 1, 2021 to August 2, 2024.
- Records of interest included observational studies, interventional trials, guidelines, and meta-analyses.
- One independent reviewer screened all records-first as title/abstracts, then as full texts. A second independent reviewer performed a quality control check of 10% of the records.
  - The following conferences were searched: American Thyroid Association, British Thyroid Foundation, European Thyroid Association, and ISPOR.

RESULTS

- From 2,152 unique records evaluated, 83 articles or conference abstracts were included (**Figure 1**).

Figure 1. Attrition of source materials



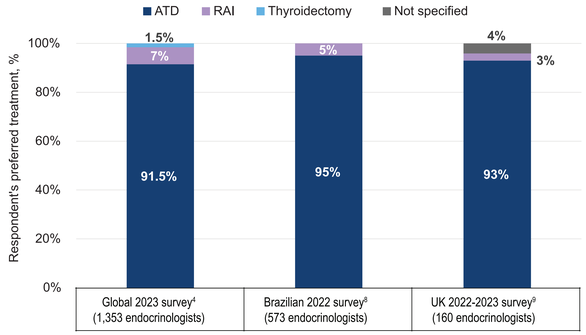
[a]Records that were from non-target countries (e.g., Iran, China, Thailand) were considered for inclusion if they addressed evidence gaps.
GD, Graves' disease; UK, United Kingdom; US, United States.

Treatment patterns

- ATD use has been increasing, whereas RAI therapy and surgery (thyroidectomy) use has been decreasing in the past two decades[6,7],
  - Based on a US-based claims database analysis (first-line ATD use increased from <50% of patients in 2005 to >65% of patients in 2014),[6] and on a Thai retrospective cohort study (first-line ATD use increased from 55.4% of patients during 1985 to 1994 to 83.4% of patients during 2015 to 2019).[7]
- More than 90% of endocrinologists preferred ATD as first-line treatment for GD,[4,8,9]
  - Based on survey studies conducted from 2022 to 2023 (**Figure 2**).
- Evidence also suggests that patients prefer ATD over surgery or RA,[10]
  - Based on results of a Dutch discrete choice experiment, which demonstrated that patients with GD (n=286) had significant ($P \leq 0.05$) negative preferences toward surgery (β coefficient = -1.35) and RAI (β coefficient= -1.04) compared with ATD.[10]

RESULTS

Figure 2. Endocrinologist-preferred first-line treatment for GD

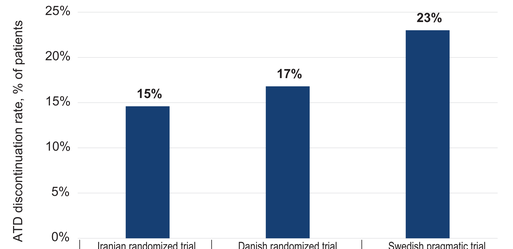


ATD, antithyroid drug; GD, Graves' disease; RAI, radioactive iodine; UK, United Kingdom.

Clinical burden

- Despite the increased use of ATDs for first-line GD treatment, ATDs are not sufficiently effective or tolerable for all GD patients.
  - A reported 15% to 23% of patients with GD were unable to complete an initial treatment course of ATD in clinical trials due to several reasons-including adverse reactions or insufficient control of hyperthyroidism (**Figure 3**),[11-13]
  - Additional evidence showed that, among those who are able to complete a course of first-line ATD therapy, a reported 47% to 76% experienced a relapse of hyperthyroidism after cessation of therapy, and that all patients will eventually relapse within 10 years of ATD withdrawal (**Figure 4**),[5,7,14-17]
  - Subclinical hyperthyroidism (a condition characterized by suppressed thyroid-stimulating hormone and associated with poor outcomes) was observed in approximately 7% to 27% of patients treated with ATD ± levothyroxine in a real-world setting,[18] and in up to 10.8% of patients treated with ATD in clinical trials.[19,20]
- The risk of all-cause mortality was significantly higher among treated patients with GD (N=4,189 [ATD: n=3,094; RAI: n=829; thyroidectomy: n=266]), compared with matched controls (N=16,756), in a nationwide retrospective survey conducted in Wales between January 1, 1998 and December 31, 2013 (adjusted hazard ratio=1.23 [95% CI: 1.06 to 1.42]; P=0.033).[21]
- Compared with healthy controls, patients with GD had a significantly increased risk of developing other conditions (e.g., major cardiovascular events and heart failure, diabetes, depression, and dementia).[21-26]

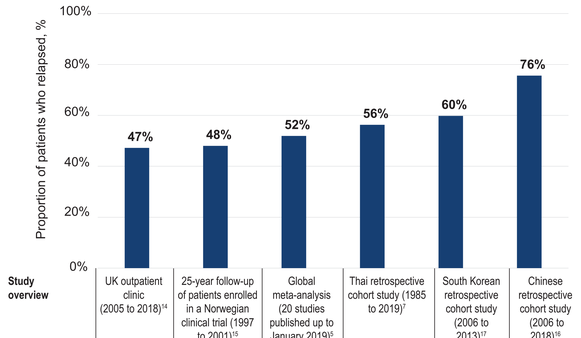
Figure 3. Patients who were unable to complete a coure of ATD therapy within clinical trials



Study overview	Iranian randomized trial (2001 to 2017)[11]	Danish randomized trial (2007 to 2011)[12]	Swedish pragmatic trial (2003 to 2013)[13]
GD patients assigned to ATD treatment, N	302	208	774
Reasons why patients were unable to complete course of ATD therapy	Did not complete initial ATD course due to side effects (n=12), relapse of hyperthyroidism (n=12), insufficient control of hyperthyroidism (n=6), lost to follow-up (n=11), and hypothyroidism (n=3)	Did not complete initial ATD course due to lack of compliance (n=15), development of orbitopathy (n =7), moving out of the area (n=4), ADR (n=4), comorbidities (n=3), pregnancy (n=1), and suspicion of thyroid cancer (n=1)	Changed ATD course due to adverse reactions, development or worsening of TAO, persistent or high levels of TRAb, patient wishes, or desired pregnancy

ADR, adverse drug reaction; ATD, antithyroid drug; GD, Graves' disease; TAO, thyroid-associated ophthalmology; TRAb, thyrotropin receptor antibody

Figure 4. Proportion of patients experiencing relapse after ATD withdrawal



Study overview	UK outpatient clinic (2005 to 2018)[14]	25-year follow-up of patients enrolled in a Norwegian clinical trial (1997 to 2001)[15]	Global meta-analysis (20 studies published up to January 2019)[5]	Thai retrospective cohort study (1985 to 2019)[7]	South Korean retrospective cohort study (2006 to 2013)[17]	Chinese retrospective cohort study (2006 to 2018)[16]
GD patients, N	276	182	3,242	2,763	908	6,385
Duration of ATD treatment	Median: 13 months (IQR: 12−16)	Not reported	Not reported	Not reported	Median: 23.3 months (SD: 17.4)	Not reported
Follow-up after ATD withdrawal	Median: 41 months (IQR: 13-74)	2 years	≥12 months	Median: 36 months (IQR: 12-84)	1 year	Median: 90 months

ATD, antithyroid drug; GD, Graves' disease; IQR, interquartile range; UK, United Kingdom.

Humanistic burden

- Three studies demonstrated impaired health-related quality of life (HRQoL) among patients with GD compared with controls, including patients treated with ATD, RAI, or thyroidectomy (**Table 1**).[15,24,27,28]

Table 1. Summary of HRQoL among patients with GD compared with controls

Study Overview	GD Patients, N	Key Findings
Swedish pragmatic trial (2003 to 2013) [27,28]	1,186	• Significantly worse HRQoL among patients with GD, including treated patients, compared with controls on several SF-36 domains and on most ThyPRO domains.
Swedish prospective, longitudinal, case-controlled study (2011 to 2019)[24,25]	65	• Significantly worse fatigue among patients with GD compared with controls, as measured by the Mental Fatigue Scale • Significantly worse anxiety and depression among patients with GD compared with controls, including patients treated with 15 months of ATD, as measured by the Comprehensive Psychopathological Rating Scale.
Norwegian randomized trial evaluating ATD treatment (1997 to 2001); retrospective follow-up performed 25 years after trial completion[15]	156	• Significantly worse physical symptoms among patients with GD treated only with ATDs (n=49) compared with controls, as measured by the ThyPRO. • Significantly worse HRQoL among patients with GD with hypothyroidism (n=87), either spontaneously or after ablative treatment, compared with controls on most ThyPRO domains.

ATD, antithyroid drug; GD, Graves' disease; HRQoL, health-related quality of life; PRO, patient-reported outcomes; SF-36, 36-item Short-Form Health Status; ThyPRO, Thyroid-Related Patient-Reported Outcome.

CONCLUSIONS

- **Management of GD has evolved over the past two decades with a preference for ATD as first-line therapy and an aversion to use of ablative treatments**
- **A subset of patients with GD are unable to complete an initial course of ATD, due to several reasons, including adverse reactions or insufficient control of hyperthyroidism.**
- **Among patients who achieve euthyroidism after an initial course of ATDs, many will subsequently relapse. Evidence suggests that all patients will eventually relapse within 10 years of ATD withdrawal.**
- **Patients with GD experience substantial clinical and humanistic disease burden, including increased risks of mortality and comorbidity, that current treatment options do not adequately address.**
- **Further evaluation based on robust, long-term, real-world evidence studies are needed to understand the long-term impact of GD and care needs throughout a patient's lifetime.**

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DISCLOSURES

LAMW and **KT** are employees of Immunovant, Inc. **EM**, **SR**, and **SN** are employees of PPD™ Evidera™ Health Economics & Market Access, Thermo Fisher Scientific. **NA** was an employee of Immunovant, Inc., at the time this work was carried out.

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