BIBLIOTHECA ALEXANDRINA
مكتبة الإسكندرية

100 years of thyroxine, what is the future?

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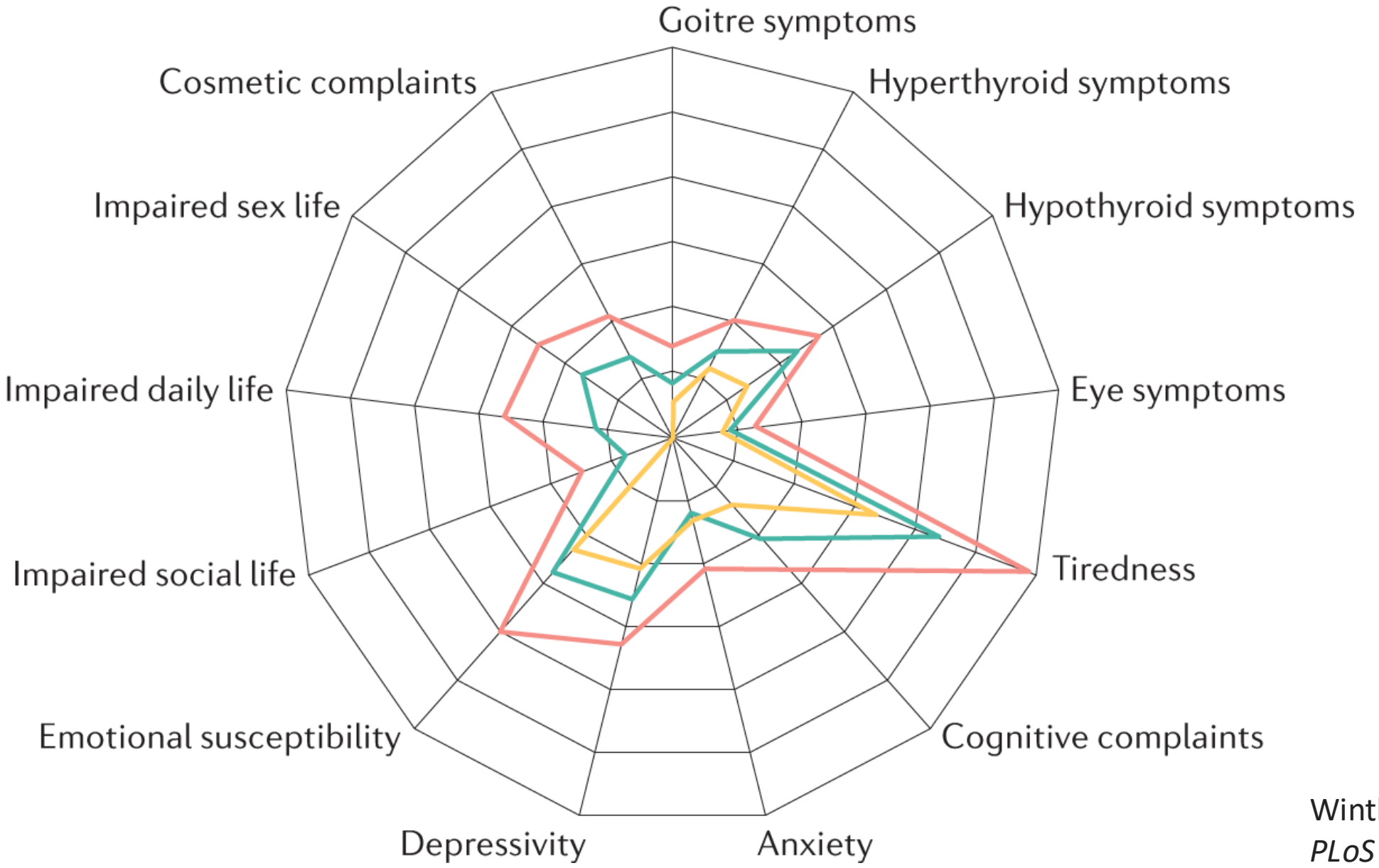
ARE YOU SATISFIED WITH THE CURRENT MANAGEMENT OF HYPOTHYROIDISM?

هل أنت راضٍ عن العلاج الحالي لقصور الغدة الدرقية؟



Winther, K. H. et al.
PLoS ONE **11** (2016).

Radar plot showing patient-related outcome using ThyPRO, at baseline (red) and 6 months after starting LT4 autoimmune hypothyroidism (green), compared with normative data (yellow).

THYROID
Volume 17, Number 7, 2007

DOI: 10.1089/thy.2007.0069

Which Domains of Thyroid-Related Quality of Life Are Most Relevant? Patients and Clinicians Provide Complementary Perspectives

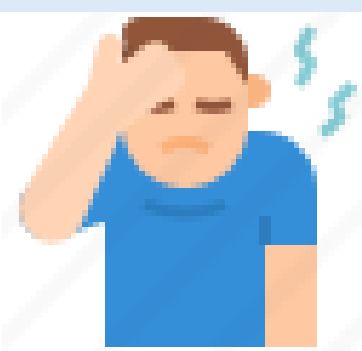
Torquil Watt,[1,2] Laszlo Hegedüs,[3] Åse Krogh Rasmussen,[1] Mogens Groenvold,[2] Steen Joop Bonnema,[3] Jakob Bue Bjorner,[4] and Ulla Feldt-Rasmussen[1]

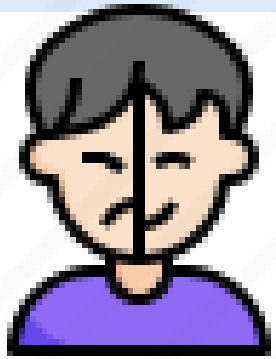
The relevance of 138 thyroid disease–related issues was rated during interviews. For each issue, three relevance measures were obtained: a diagnosis-specific patient rating, a diagnosis-specific expert rating, and a combined overall patient=expert rating. The 75 most relevant issues overall and the 15 most relevant issues in each patient category were selected.

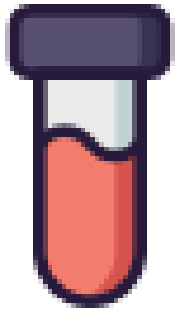
Watt, T., et al. (2007). Thyroid® **17**(7): 647-654.

10%-15% of patients do not regain their well-being after adequate treatment with L-T4

Persistent symptoms ➔ non-specific







Perros, P., et al. (2023). "The enigma of persistent symptoms in hypothyroid patients treated with levothyroxine: A narrative review." Clin Endocrinol (Oxf) **98**(4): 461-468.

Hypothyroidism	*P*	*E*
Most relevant to patients only		
Being slow*	1	*
Bags under the eyes*	4	*
Getting upset*	9	*
Palpitations	10	91
Globulus sensation	11	46
Dyspnea	13	63
Clearing throat often*	14	*

Hypothyroidism	*P*	*E*
Most relevant to both patients and experts		
General fatigue	2	1
Cold intolerance	3	11
Physical fatigue	5	6
Hypersomnia	6	4
Weight increase	7	9
Weight dissatisfaction	8	13
Mental fatigue	12	5
Constipation	15	3

Hypothyroidism	*P*	*E*
Most relevant to experts only		
Impaired memory	16	2
Limit daily activities	53	7
Hoarseness	76	8
Difficulty concentrating	24	10
Depression	33	12
Dry skin	46	14
Attention problems	31	15

Watt, T., et al. (2007). "Which Domains of Thyroid-Related Quality of Life Are Most Relevant? Patients and Clinicians Provide Complementary Perspectives." Thyroid® 17(7): 647-654.

Historical Evolution of Treatment

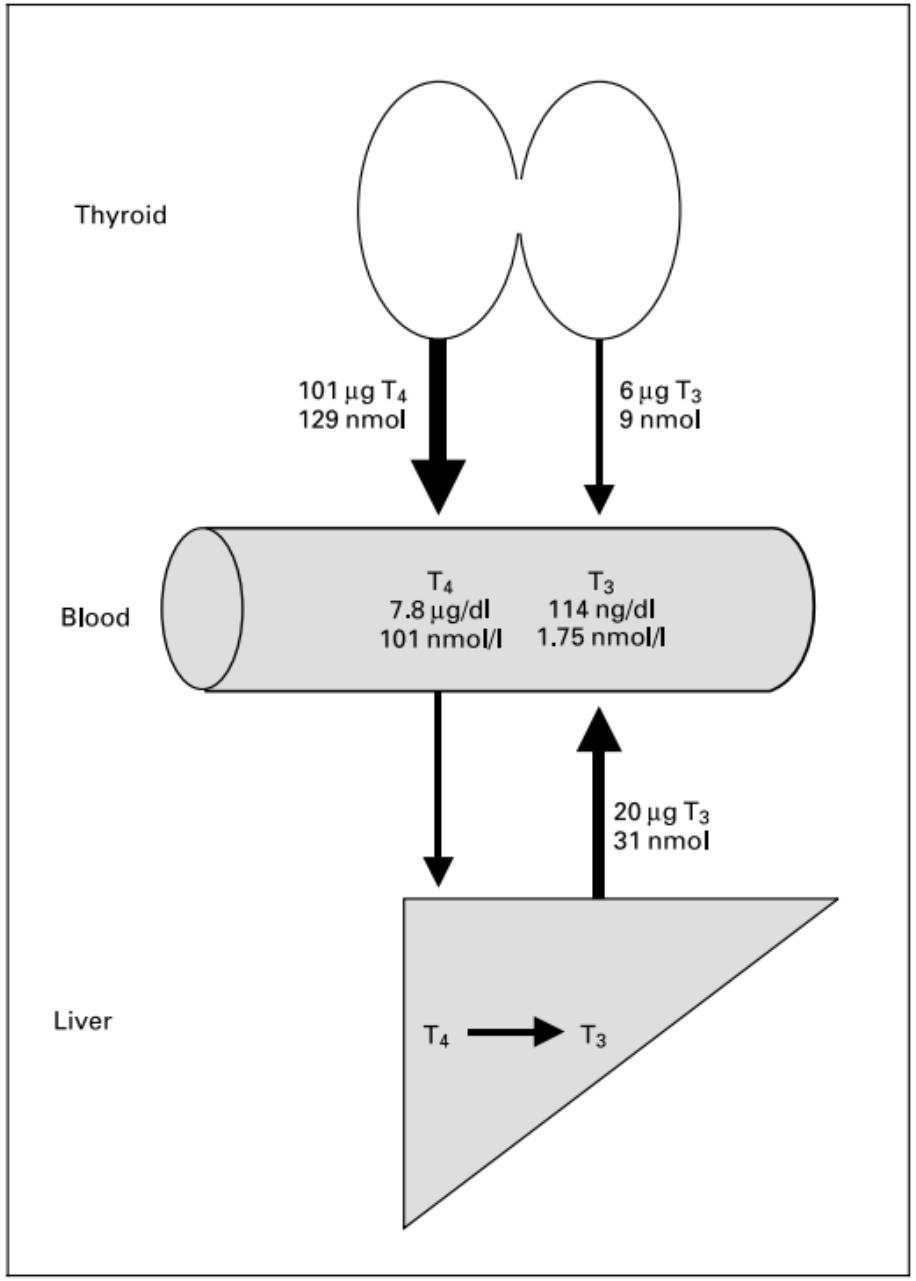


Fig. 1. Daily production rates of thyroid hormone in healthy adults weighing 70 kg.

Wiersinga, W. M. (2004). "Thyroid Hormone Replacement Therapy." Hormone Research **56**(Suppl. 1): 74-81.

- 1884: Moritz Schiff demonstrated thyroidectomy effects in animals could be diminished by implanting additional thyroid tissue.

- Late 19th Century: Bettencourt and Serrano attempted human thyroid transplantation (unsuccessful due to patient death).

1891: George Murray successfully treated myxedema with sheep thyroid extract injections.

- In 1891, he introduced the successful treatment of myxedema, with **injections** of sheep thyroid extract, the first instance of hormone replacement therapy

Desiccated (Dry) thyroid extract

- In 1892, Fox, Mac Kenzie, and Vermeulen independently discovered that orally administered dried extracts of animal thyroid glands (from sheep, cattle, and pork) significantly improved hypothyroidism symptoms.
- The extract was prepared by cleaning, drying, and powdering the thyroid glands after removing fat and connective tissue.

How were hypothyroid patients monitored in the past on desiccated thyroid extracts

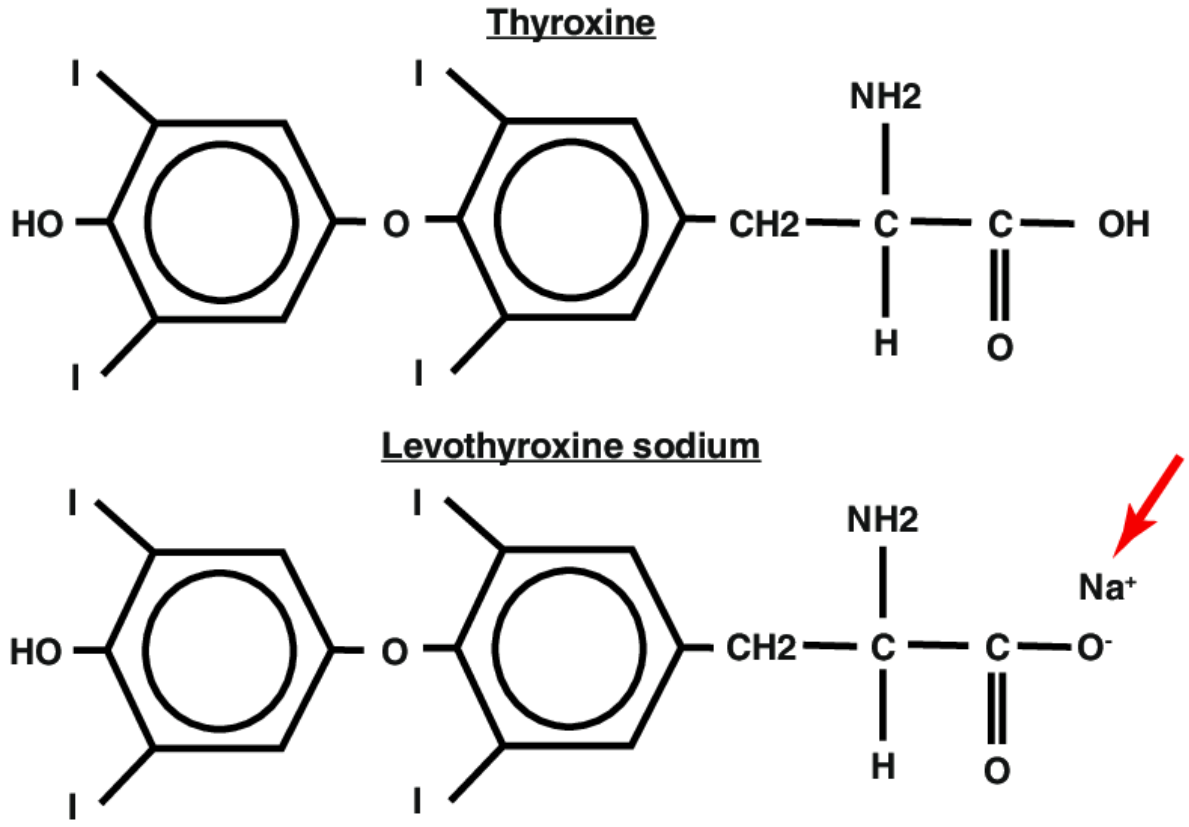
1. Symptom Observation
2. Physical Examination
3. Basal Metabolic Rate

Problems with desiccated thyroid extracts

1. Inconsistent ratio of T4 : T3 Levels
2. Limited Customization
3. Risk of Overmedication
4. Variability in Potency

1926: Barger and Harington synthesized thyroxine.

In **1949** the sodium salt of LT4 was synthesized



1970s Shift to L-T4 Monotherapy:

Key Drivers:

- Discovery of peripheral T4-to-T3 conversion (proving T4 alone could restore T3 levels).
- Development of TSH radioimmunoassay, enabling precise dosing to normalize TSH.
- Resulted in reduced dosing (from 200–500 mcg/day to 100–150 mcg/day) and fewer adverse effects.

What do the guidelines say?

1a. Is levothyroxine monotherapy considered to be the standard of care for hypothyroidism?

- **RECOMMENDATION**

  Levothyroxine is recommended as the preparation of choice for the treatment of hypothyroidism due to its efficacy in resolving the symptoms of hypothyroidism, long-term experience of its benefits, favorable side effect profile, ease of administration, good intestinal absorption, long serum half-life, and low cost.

  Strong recommendation. Moderate quality evidence.

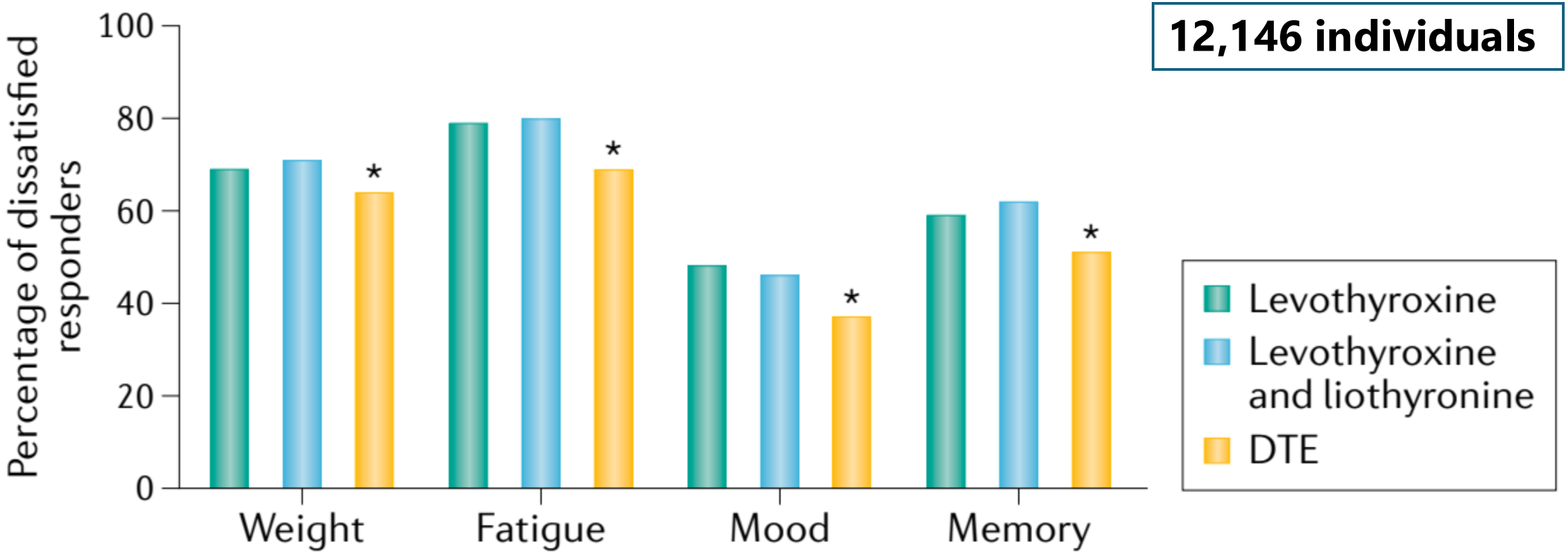
Jonklaas, J., et al. (2014). "Guidelines for the treatment of hypothyroidism" Thyroid **24**(12): 1670-1751.

Debates on Combination Therapy (T4 + T3)

- **Mixed Evidence**: Some trials show symptom improvement with desiccated thyroid or synthetic T4+T3, but results are inconsistent.
- **Challenges:**
  - Difficulty maintaining stable T3 levels due to its short half-life.
  - Risk of thyrotoxicosis (e.g., palpitations, angina).

An Online Survey of Hypothyroid Patients Demonstrates Prominent Dissatisfaction

12,146 individuals

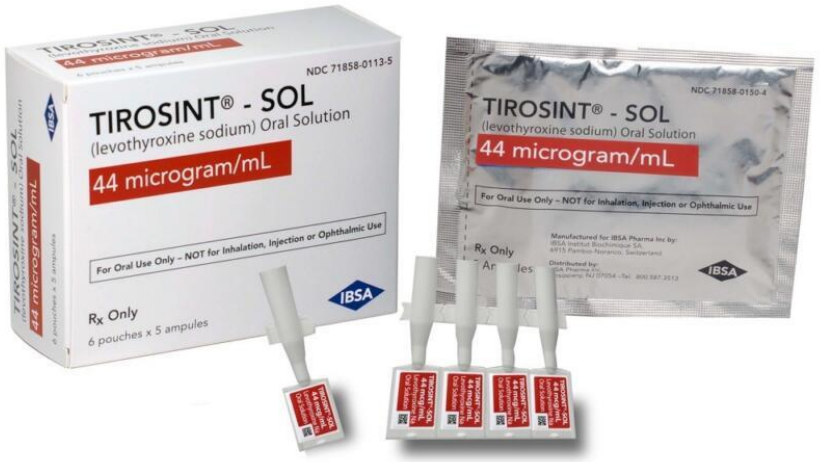


(Peterson, Cappola et al. 2018)

New Formulations to Improve Absorption:

Liquid L-T4 solutions:

- Bypass dissolution needs, faster absorption.
- Can be taken with food without affecting hormone levels, improving compliance.
- Effective for patients with gastric pH issues (e.g., post-bariatric surgery, H. pylori infection).



Virili C, Trimboli P, Centanni M. Novel thyroxine formulations: a further step toward precision medicine. Endocrine. 2019;66(1):87-94

Softgel capsules:

- Protect L-T4 from pH variations and drug interactions.
- Early studies suggest efficacy in malabsorption scenarios, but more research needed

Virili C, Trimboli P, Centanni M. Novel thyroxine formulations: a further step toward precision medicine. Endocrine. 2019;66(1):87-94

Thyromimetics

What are thyromimetics?

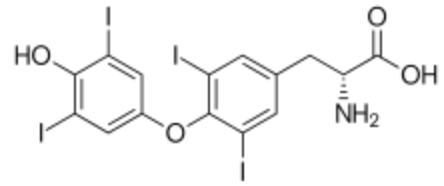
Thyromimetics are compounds which **activate** the nuclear thyroid hormone receptor.

Chemical structure similar to T3 with **changes** specifically targeting the thyroid hormone receptor α or β.

Some have been modified to target the **liver** specifically.

Sinha RA, Bruinstroop E, Yen PM. Actions of thyroid hormones and thyromimetics on the liver. Nat Rev Gastroenterol Hepatol. 2024.

Dextro-Thyroxine

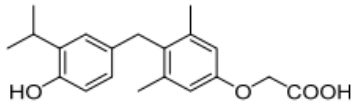
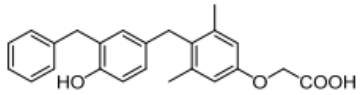
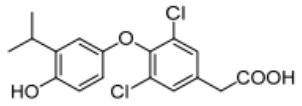
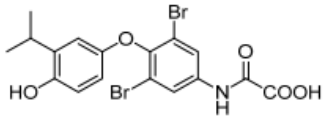
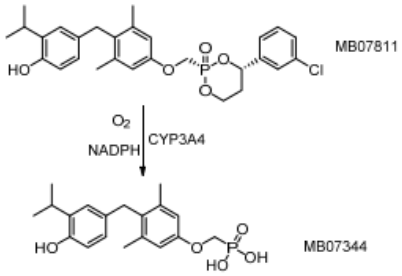
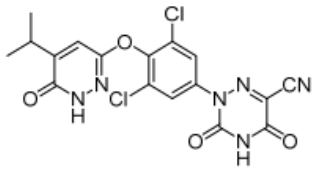


- Synthetic thyroid hormone used to lower cholesterol levels
- Discontinued due to cardiac side effects

T2

- Potential benefits in metabolism and weight management.
- It has some direct thyroid hormone activity
- However, its use as a supplement is still under investigation.
- More studies are needed to fully understand its safety and efficacy

Table 1. Summary of synthetic thyromimetics.

Compounds	Structure	Beneficial Effects	Deleterious Effects	Clinical Trials
Sobetirome (GC-1)		(1) 10-fold lower affinity of TRα (2) Reducing cholesterol level (3) Inhibiting HCC development (4) Liver regeneration	Fasting blood sugar and insulin resistance	Ending in phase I
GC-24		(1) 40-fold higher affinity of TRβ (2) Lower insulin sensitivity	(1) Low sensitivity for activated-TRβ (2) No hepatic targeting	——
KB-141		(1) Metabolic enhancement (2) Weight loss	——	——
Eprotirome (KB2115)		(1) Reducing triglycerides level markedly (2) Liver targeting (3) Liver regeneration	(1) Increasing fasting blood insulin (2) Adverse effects on dogs' cartilage of withdrawal	Ending in phase III
M07811 (VK2809) /MB07344		(1) Reducing cholesterol and triglycerides level (2) Inhibiting hepatic steatosis (3) Promoting hepatocyte proliferation	——	Phase II ongoing
Resmetirom (MGL-3196)		(1) Reducing cholesterol and triglycerides level (2) Inhibiting hepatic steatosis and fibrosis (3) Reducing hepatic fat markedly (4) Heart protection	——	Phase III ongoing

Thyroid hormone receptor agonist

Cardiac arrhythmias and increased mortality

Osteoporosis and Fractures

Table 1 | Completed and ongoing clinical trials of thyromimetics in MASLD and MASH

Compound	Indication	Primary outcome	Timeline	Adverse effects
VK2809 (VOYAGE, phase IIb) NCT04173065 (ref. 160)	Biopsy-confirmed MASH (n=229)	12-week reduction in liver fat content	Completed; 52-week biopsy data awaited	NA
Resmetirom (MGL3196) (MAESTRO-NAFLD-1 phase III)	MASLD (LSM >5.5 kPa and CAP >280 dB) (n=972)	Week 52 TEAEs (not significant)	Published[141]; open-label extension (NAFLD-OLE)	Main TEAEs diarrhoea, nausea; TSH= and FT3=, FT4↓ (100 and 80 mg resmetirom per day)
Resmetirom (MGL3196) (MAESTRO-NASH phase III)	MASH (fibrosis stage F1B–F2–F3) (n=966)	Week 52 MASH resolution (P<0.001) fibrosis improvement (P<0.001)	Published[131]; 54-month ongoing clinical outcomes study	No increased heart rate, no changes in BMD TSH= (100 mg resmetirom per day) ↓ (80 mg resmetirom per day) FT3=, FT4↓ (100 and 80 mg resmetirom per day)
Resmetirom (MGL3196) (MAESTRO-NASH OUTCOMES phase III) NCT05500222 (ref. 161)	MASH cirrhosis (well compensated) (n=700)	Progression to decompensated cirrhosis	Ongoing	NA
TERN-501 (DUET phase IIa+FXR agonist) NCT05415722 (ref. 162)	Presumed MASH (biopsy and/or imaging) (n=162)	12 weeks Reduction in liver fat content	Completed	NA
HSK31679 (phase II) NCT06168383 (ref. 163)	Biopsy-proven MASH (F2–F3) (n=180)	52 weeks MASH resolution	Ongoing	NA
ALG-055009 (HERALD phase IIa) NCT06342947 (ref. 164)	MASH non-cirrhotic (n=100)	12 weeks Reduction in liver fat content	Ongoing	NA

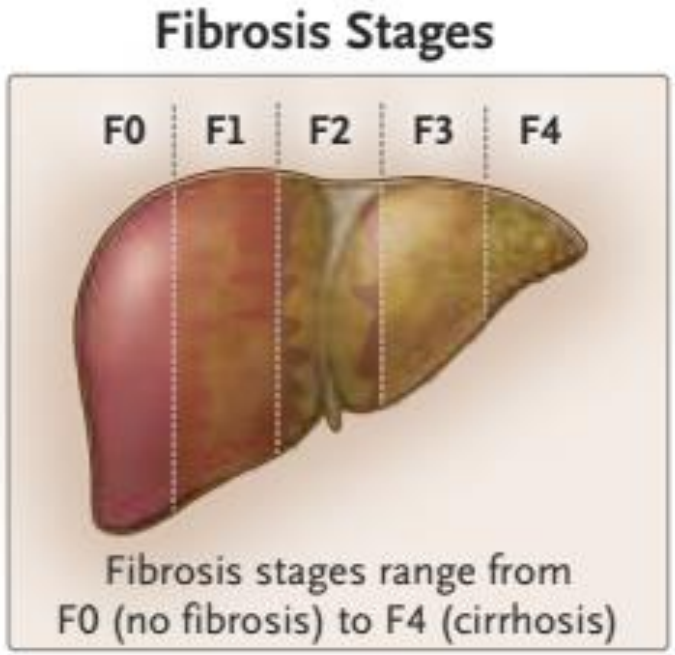
BMD, bone mineral density; CAP, controlled attenuation parameter (with FibroScan); FT3, free triiodothyronine; FT4, free thyroxine; FXR, farnesoid X receptor; LSM, liver stiffness measurement (with FibroScan); MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated liver disease; NA, not applicable; NAFLD, non-alcoholic steatohepatitis; TEAE, treatment-emergent adverse events; TSH, thyroid-stimulating hormone.

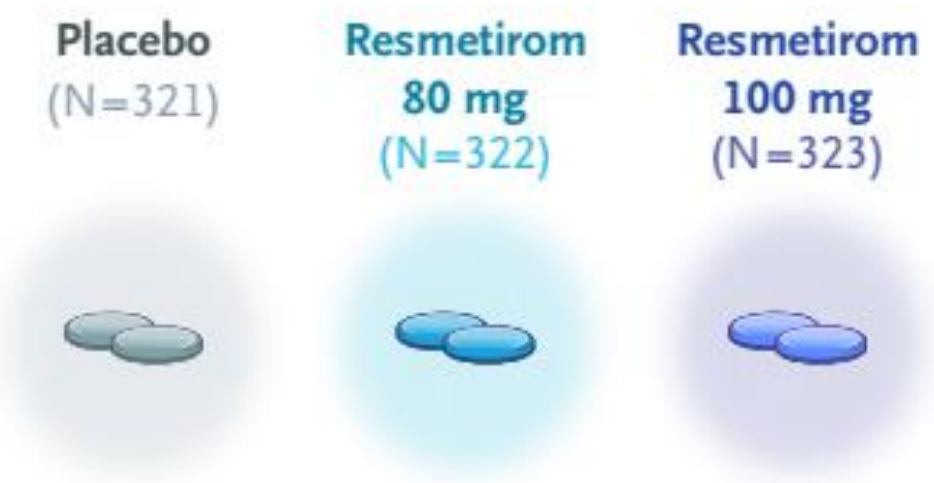
Sinha RA, Bruinstroop E, Yen PM. Actions of thyroid hormones and thyromimetics on the liver. Nat Rev Gastroenterol Hepatol. 2024.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 8, 2024 VOL. 390 NO. 6

A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis





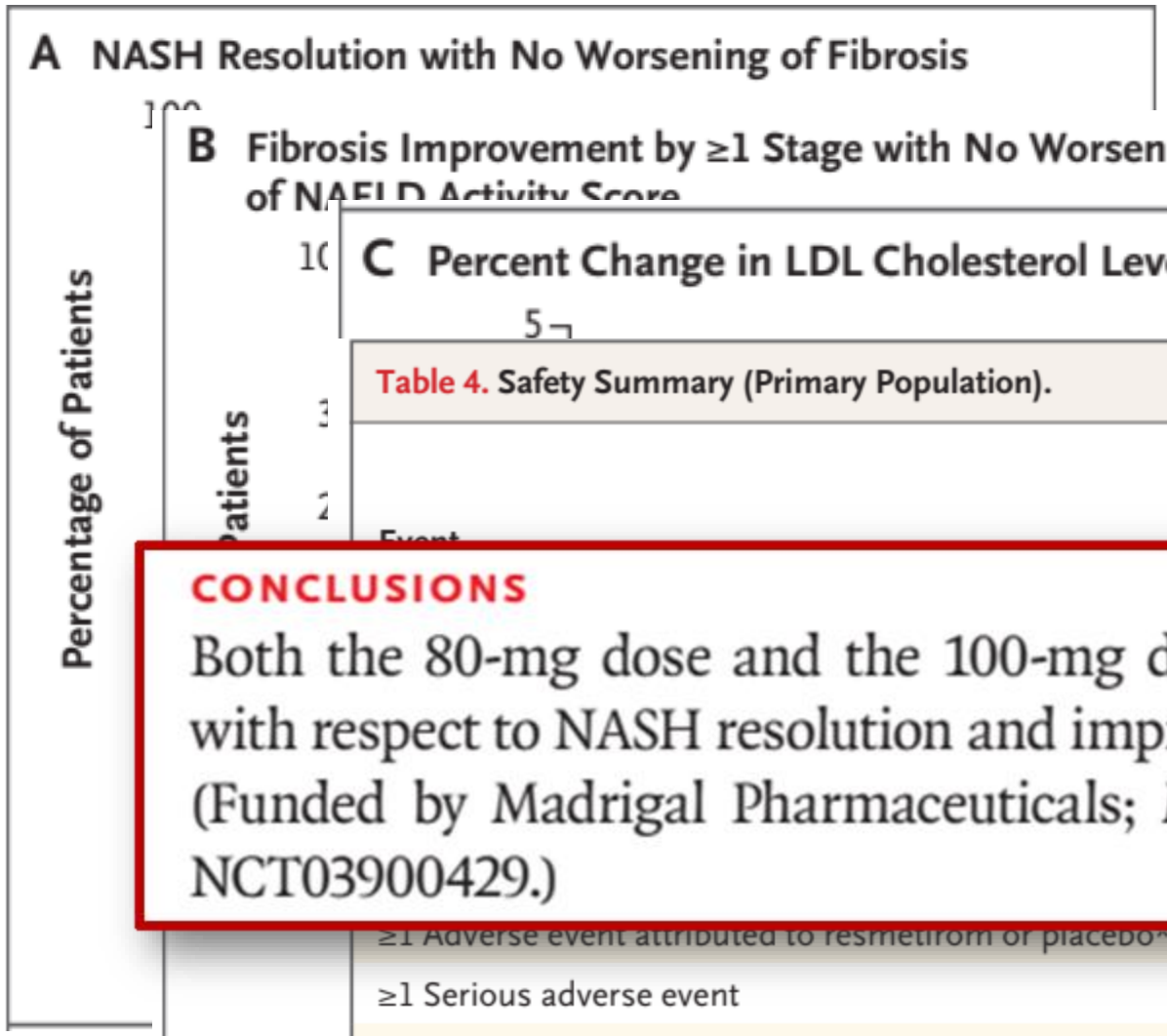
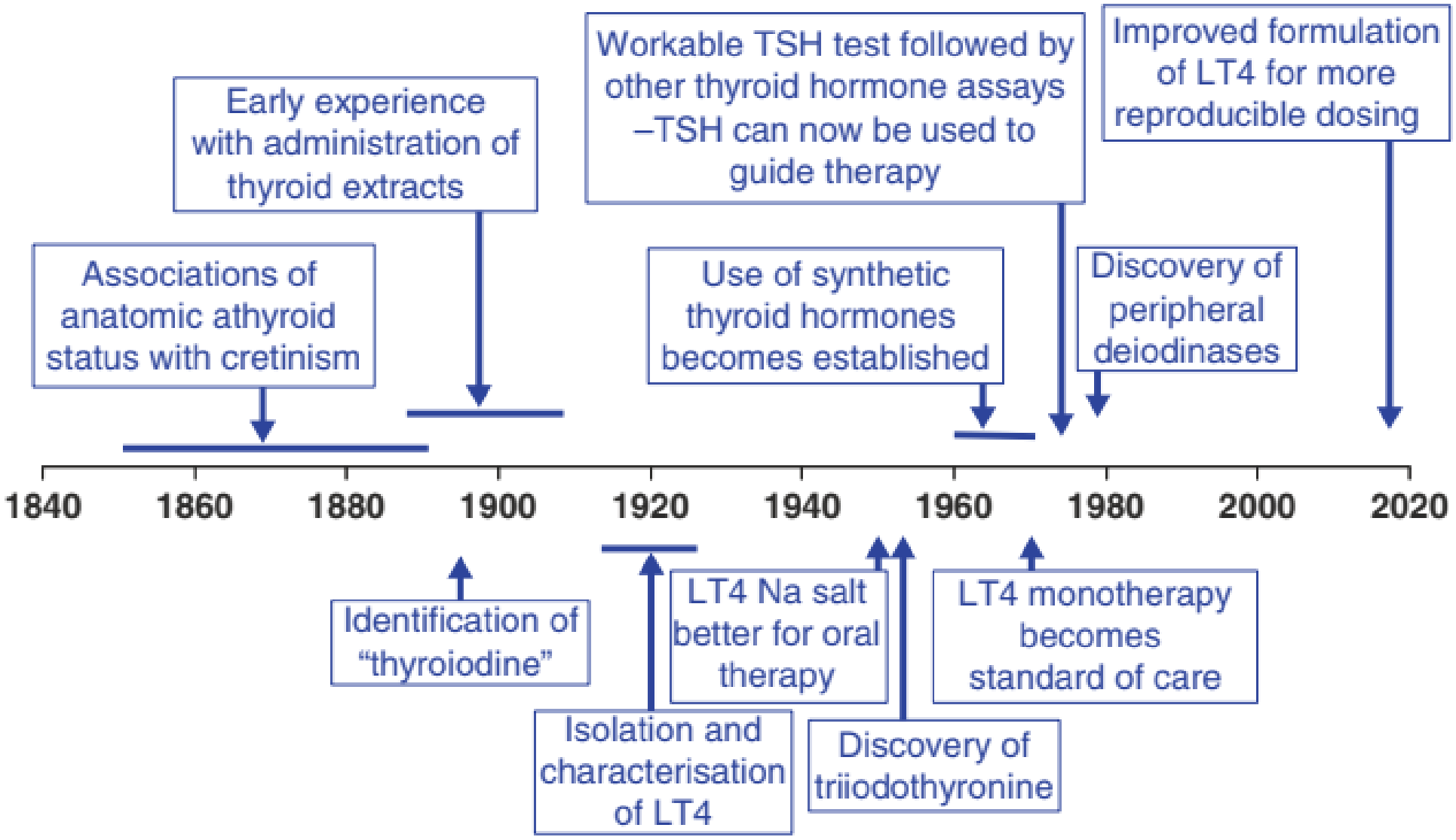


Table 4. Safety Summary (Primary Population).

Event	Resmetirom, 80 mg (N=322)	Resmetirom, 100 mg (N=323)	Placebo (N=321)
≥1 Adverse event attributed to resmetirom or placebo*	124 (38.5)	134 (41.5)	88 (27.4)
≥1 Serious adverse event	35 (10.9)	41 (12.7)	37 (11.5)
≥1 Serious adverse event attributed to resmetirom or placebo*	2 (0.6)	0	1 (0.3)

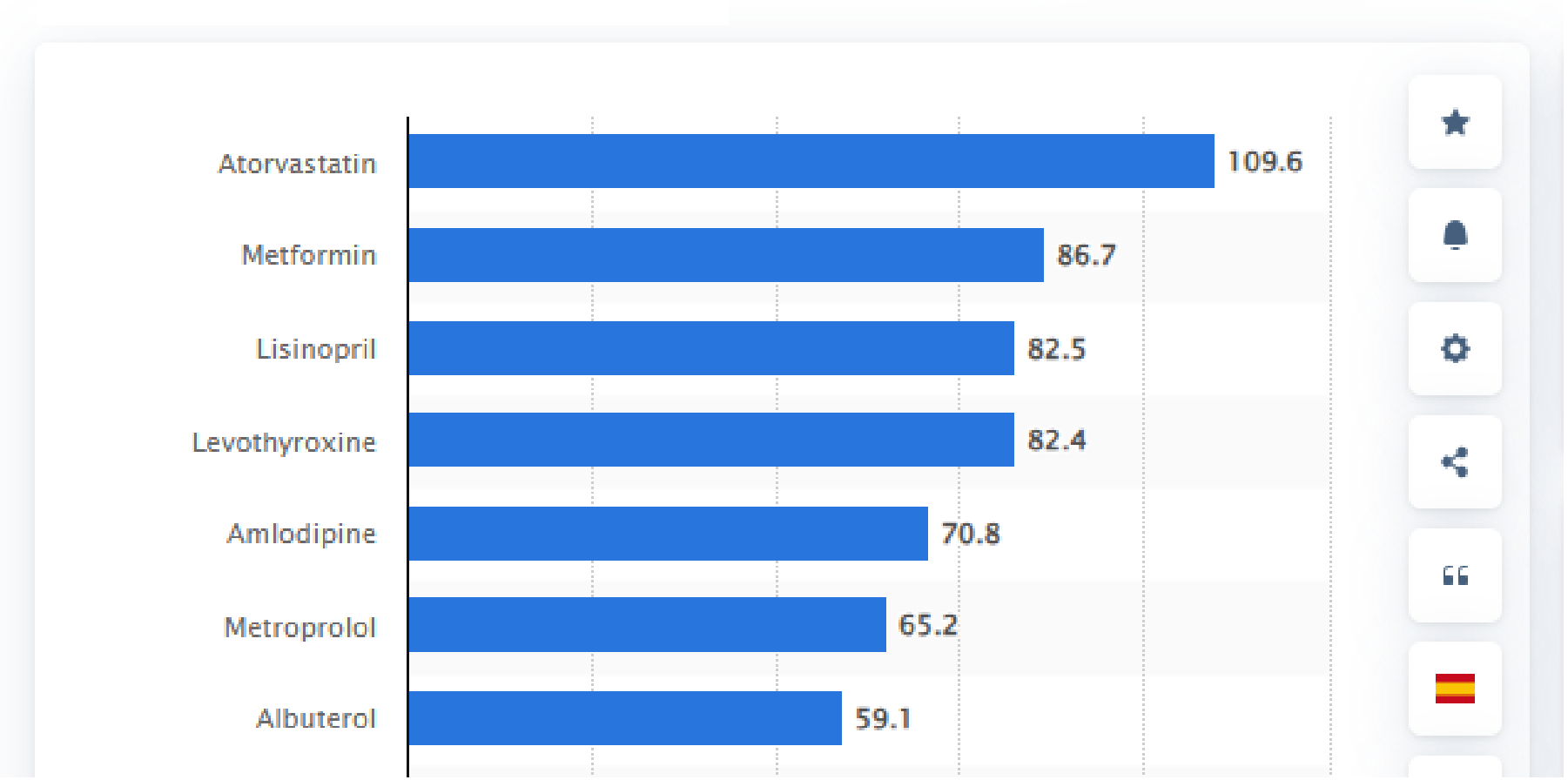
CONCLUSIONS

Both the 80-mg dose and the 100-mg dose of resmetirom were superior to placebo with respect to NASH resolution and improvement in liver fibrosis by at least one stage. (Funded by Madrigal Pharmaceuticals; MAESTRO-NASH ClinicalTrials.gov number, NCT03900429.)


Associations of anatomic athyroid status with cretinism
Early experience with administration of thyroid extracts
Workable TSH test followed by other thyroid hormone assays –TSH can now be used to guide therapy
Improved formulation of LT4 for more reproducible dosing
Use of synthetic thyroid hormones becomes established
Discovery of peripheral deiodinases
1840
1860
1880
1900
1920
1940
1960
1980
2000
2020
Identification of "thyroiodine"
Isolation and characterisation of LT4
LT4 Na salt better for oral therapy
Discovery of triiodothyronine
LT4 monotherapy becomes standard of care

Economic Impacts

Leading 20 U.S. pharma products by total prescriptions in 2022 *(in millions)*



Levothyroxine overuse: time for an about face?

Lancet Diabetes Endocrinol 2016

Published Online
October 28, 2016
http://dx.doi.org/10.1016/
S2213-8587(16)30276-5

In the UK, about 25% of the adult population are estimated to have their thyroid function measured every year.

Additionally, people in the UK with TSH <10 mIU/L were prescribed levothyroxine 1·3 times more in 2009 than in 2001,

31% of treated patients in this cohort had a TSH <10 mIU/L or less, normal T4 and no symptoms of hypothyroidism or abnormal CV risk factors

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S2213-8587(16)30276-5

LT4 3-month cost to patients in the USA from $4 to $100

Synthroid, with 21·5 million annual prescriptions, is the leading prescribed brand-name medication in the USA, with revenues greater than **US$1 billion** annually

Levothyroxine overuse: time for an about face?

Lancet Diabetes Endocrinol 2016

Published Online
October 28, 2016
http://dx.doi.org/10.1016/
S2213-8587(16)30276-5

In the UK, the annual amount of thyroid replacement therapy has tripled from 1998 to 2007 and the cost per day increased from less then **£5000 to more than £40 000**.

In assessments of the economic effects of current practice, the costs to patients and other payers of thyroid testing, clinical follow-up of abnormal test results, clinical visits, and possible lifelong monitoring, follow-up, and levothyroxine use must be taken into account.

Cost-of-Illness Trends Associated with Thyroid Disease in Korea

Results: The cost-of-illness of thyroid disease in Korea was estimated at 224.2 billion won in 2002, 303.4 billion won in 2004, 400.3 billion won in 2006, 570.4 billion won in 2008, and 762.2 billion won in 2010. For example, the cost-of-illness of thyroid disease in 2010 was 3.4 times greater compared to 2002. The direct cost of the total cost-of-illness was 69.7%, which accounted for the highest proportion of costs. Cost-of-illness for individuals between the ages of 30 and 50 accounted for the greatest share of costs.

Conclusion: The cost-of-illness of thyroid disease was relatively large in economically active age groups, and demonstrated a very rapid growth rate compared to other major diseases in Korea. Therefore, we suggest nationwide recognition of the importance of prevention and management of thyroid disease and prioritization of the management of thyroid disease among current and future health promotion policies in Korea.