

ORIGINAL ARTICLE

Thyroid

Liothyronine (LT3) prescribing in England: Are cost constraints inhibiting guideline implementation?

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Abstract

Background: Primary hypothyroidism affects about 3% of the general population in Europe. In most cases people with hypothyroidism are treated with levothyroxine. In the context of the 2023 British Thyroid Association guidance and the 2020 Competitions and Marketing Authority (CMA) ruling, we examined prescribing data for levothyroxine, Natural desiccated thyroid (NDT) and liothyronine by dose, regarding changes over the years 2016–2022.

Design: Monthly primary care prescribing data for each British National Formulary code were analysed for levothyroxine, liothyronine and NDT.

Patients and Measurements: The rolling 12-month total/average of cost or prescribing volume was used to identify the moment of change. Results included number of prescriptions, the actual costs, and the cost/prescription/mcg of drug.

Results: Liothyronine: In 2016 94% of the total 74,500 prescriptions were of the 20 mcg dose. In 2020 the percentage prescribed in the 5 mcg and 10 mcg doses started to increase so that by 2022 each reached nearly 27% of total liothyronine prescribing. The average cost/prescription in 2016 of 20 mcg was £404/prescription and this fell by 80% to £101 in 2022; while the 10 mcg cost of £348/prescription fell by only 35% to £255 and the 5 mcg cost of £355/prescription fell by 38% to £242/prescription. The total prescriptions of liothyronine in 2016 were 74,605, falling by 30% up to 2019 when they started to grow again - most recently at 60,990–15% lower than the 2016 figure, with the result that total costs fell by 70% to £9 m/year.

Conclusions: Liothyronine costs fell after the CMA ruling but remain orders of magnitude higher than for levothyroxine. The remaining 0.2% of patients with liothyronine treated hypothyroidism are still absorbing 16% of medication costs. The lower liothyronine 5mcg and 10 mcg doses as recommended by BTA are 240% the costs of the 20 mcg dose. Thus, following latest BTA guidance which recommends the lower liothyronine doses still incurs substantial additional costs vs the prescribing liothyronine in the no longer recommended treatment regime. High drug price continues to impact clinical decisions, potentially limiting liothyronine

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therapy availability to a considerable number of patients who could benefit from this treatment.

KEYWORDS

guidelines, hypothyroidism, levothyroxine, liothyronine, natural desiccated thyroid, prescribing costs

1 | INTRODUCTION

Primary hypothyroidism affects 3% of the general population in Europe,¹ and consistent with this, 1.7 million patients are registered on the 2022 primary care hypothyroidism quality and outcomes framework register in England.² The majority are treated with Levothyroxine (LT4) alone as recommended by expert societies and remain satisfied with their treatment, but up to 10%–15% of individuals report persistent symptoms and an impaired quality of life (QoL), despite serum free thyroxine (FT4) and thyroid stimulating hormone (TSH) levels within the laboratory reference range.³ A proportion of these individuals on LT4 monotherapy are prescribed liothyronine (LT3 -L-triiodothyronine) in combination with LT4 and occasionally as monotherapy by their physicians (both GPs and hospital doctors). Some prefer natural desiccated thyroid (NDT), which is an extract of pig or bovine thyroid containing a combination of LT4 and LT3.⁴

We previously reported how large price increases had reduced the prescription of LT3 between 2012 and 2020.⁵ The annual cost was maximal in 2015–2016 and amounted to an increase on average from £550 to £3000 per individual patient.⁶ NHS spending on Liothyronine tablets increased from around £600,000 per year before the manufacturers started their price optimisation strategy to more than £30 million, despite prescribing volumes remaining largely stable. Price increases were not driven by any meaningful innovation or investment and manufacturing costs did not change materially at the time of de-branding or afterwards. This exploited a loophole in the regulation of drug prices as prices of unbranded generic drugs were unregulated in the UK. Whereas the profits made from branded drugs were generally constrained by regulation, the assumption was that, once patents have expired and competitors become free to enter with generic versions of a drug, competition would prevent suppliers from setting high prices for those drugs. This period is often referred to as the 'third phase of the product lifecycle'. The UK Competition and Market Authority (CMA) investigated this price rise in 2016 and found that the price paid by the NHS in England for each LT3 prescription increased 1605% from £15 to £258.⁷ These findings were published, and the suppliers of LT3 at these enhanced prices were fined £101 million. Before that ruling the prices of LT3 had already fallen significantly as we have reported.⁶

In clinical practice, physicians are primarily influenced by guidelines from expert societies such as the British Thyroid Association (BTA), who recommend the careful addition of LT3 using lower doses than the historical 20 mcg dose (whole or split) in the above subjects who have persistent symptoms with reduced QoL. The BTA have in

their recent guidelines recommended the introduction of 5–10 mcg of LT3 (given twice daily) on a trial basis under expert supervision.⁸ It is however important that any price differential does not act to disincentivize prescribing of the doses now recommended. There is increasing evidence that combination therapy is increasing in the USA⁹ where NDT remains popular with patients. However, physicians are also cognisant of, and invariably do consider cost constraints when deciding to prescribe medications.

We re-evaluate prescribing data and related costs for LT4, LT3 and NDT between 2016 and 2022 in light of the recent BTA recommendations which advocate the lower LT3 doses when LT3 is indicated, and the CMA judgement in 2020.

2 | MATERIALS AND METHODS

Primary care monthly English prescribing data¹⁰ were collected from 2016 to 2022. The data included all prescribed and dispensed medicines by British National Formulary (BNF) Chapter, Chemical Substance and Presentation for each General Practitioner (GP) Practice. The specific data were extracted for the British National Formulary (BNF) Subsection 6.2.1 Thyroid Hormones, which includes specific data for Levothyroxine sodium (0602010V0), Levothyroxine sodium and liothyronine (0602010Z0) and Liothyronine sodium together (0602010M0) (NDT) (<https://www.nice.org.uk/bnf-uk-only>).

(a) We used the following definitions in our calculations -

- Prescriptions (items) - the total number of times that the medicine on prescription forms that were prescribed and dispensed is referred to here as prescriptions
- Total Quantity - the total quantity of a medicine prescribed and dispensed for each BNF Presentation. This is calculated by multiplying Quantity by Items
- 'Net ingredient cost' of the items = drug, normally based on the price given in the Drug Tariff or published wholesale prices
- 'Actual cost' of the drug, that accounts for the national average discount and some payments to dispensers
- ADQ usage - average daily quantity (ADQ)¹¹ is the typical daily dose of a medication, prescribed to adult patients by GP Practices. The ADQ for Levothyroxine has been determined at 100 mcg/day and Liothyronine at 40 mcg/day. It is worth noting that Liothyronine is most often used in conjunction with Levothyroxine and so doses are titrated so full ADQ may not be appropriate.

- (b) Calculations - We calculated the total prescriptions, actual costs, and ADQ based patients on therapy in England for each calendar year for each medication dose and formulation as tablets both in total and by dose size. The actual costs/prescriptions were calculated by dividing the total annual cost by the total annual prescription.
- (c) Difference in prescription rates - The 2016 value was taken as 100% and the annual values thereafter were shown as a percentage of the 2016 value.

All data are publicly available and can be made available on appropriate request.

3 | RESULTS

3.1 | Change in cost and prescribing trends for LT4, LT3 and NDT

Our analyses comparing 2016 to 2022 indicate the following (Table 1 and Figure 1A,B,C)

- (1) Total number of prescriptions - The number of LT4 prescriptions increased but there was a significant reduction in the number of LT3 and NDT prescriptions; LT3 increased again from 2020, while NDT prescriptions continued to fall. In 2016, 94% of

TABLE 1 Thyroid hormone prescribing 2016–2022.

YEAR	2016	2017	2018	2019	2020	2021	2022
000 items (prescriptions)							
Levothyroxine	30,785	31,484	32,157	31,224	32,847	33,196	33,429
Liothyronine	74.9	67.9	61.1	52.0	55.4	58.0	61.2
NDT (LT4 + LT3)	4.3	4.0	3.5	2.9	2.8	2.7	2.4
Actual_cost £,000							
Levothyroxine	£90,504	£81,273	£62,644	£59,307	£67,055	£64,517	£52,439
Liothyronine	£30,034	£27,627	£23,645	£16,418	£13,623	£11,421	£9029
NDT (LT4 + LT3)	£885	£1114	£1040	£976	£1049	£1033	£1049
000 patient years based on DDD							
Levothyroxine	1270	1286	1309	1263	1330	1342	1353
Liothyronine	9.8	8.6	7.6	6.5	6.6	6.6	6.7
NDT (LT4 + LT3)	0.52	0.47	0.42	0.35	0.33	0.29	0.27
Actual cost/prescription							
Levothyroxine	£3.1	£2.8	£2.1	£2.0	£2.2	£2.1	£1.6
Liothyronine	£433.1	£439.1	£417.0	£340.4	£264.4	£211.3	£157.8
NDT (LT4 + LT3)	£223.6	£302.5	£324.0	£362.1	£398.7	£416.7	£470.3
Practices prescribing							
Levothyroxine	8531	8352	8100	7849	7719	7398	7395
Liothyronine	4343	4008	3611	3270	3103	3095	3156
NDT (LT4 + LT3)	539	509	449	391	353	322	291
Total items (000 prescriptions)	30,864	31,556	32,222	31,279	32,905	33,257	33,492,
Total actual cost £,000						£121,424	£110,015
£87,330	£76,701	£81,729	£76,972	£62,518			
Total patient years based on DDD = Defined daily dose, 000	1281	1296	1317	1270	1337	1349	1360
Total actual cost/prescription	£4.2	£3.7	£2.9	£2.6	£2.6	£2.5	£2.0
Total practices prescribing	8533	8354	8103	7851	7722	7399	7396

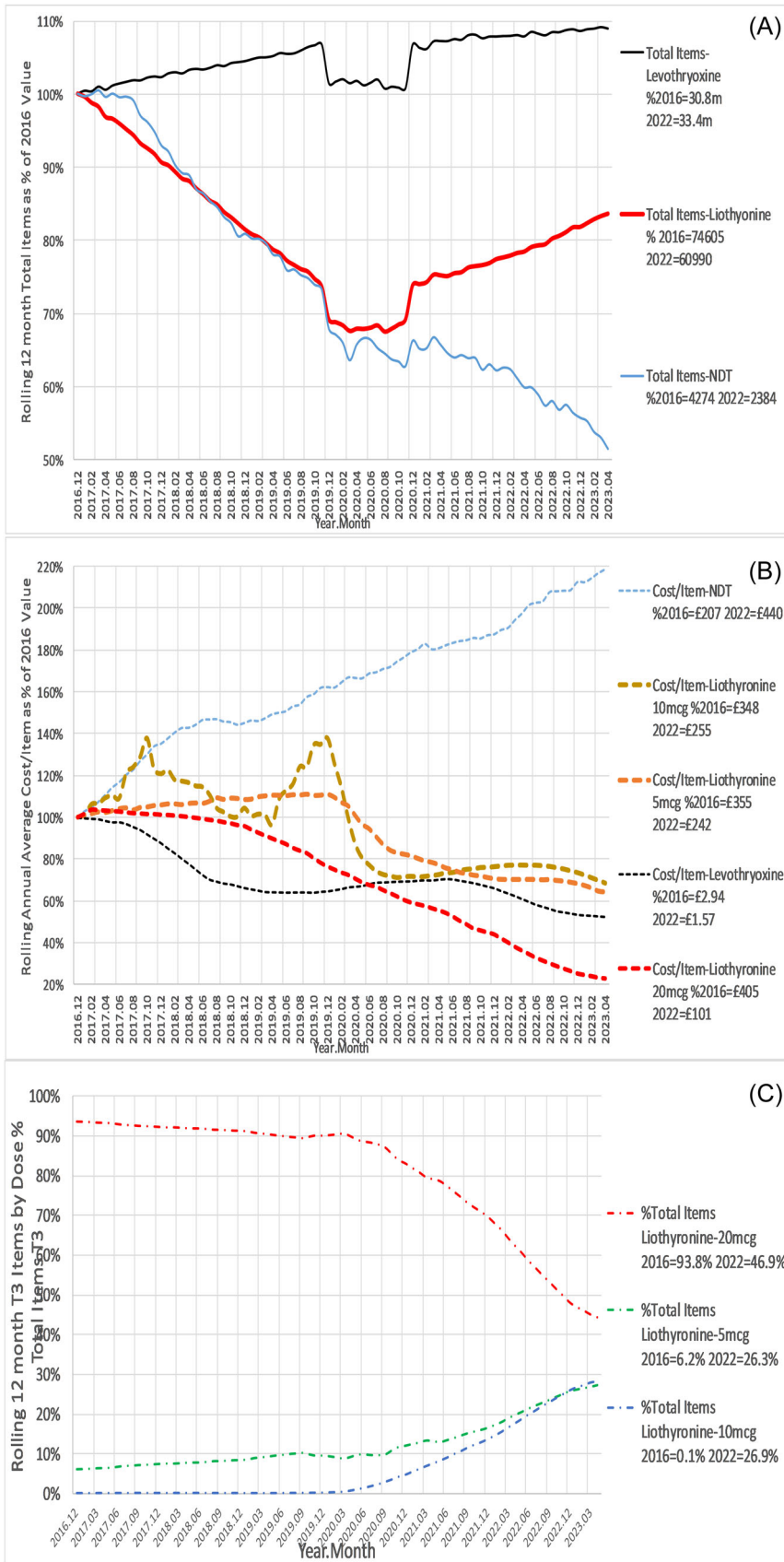


FIGURE 1 (A–C) Monthly rolling annual (total items) for thyroid medication as % 2016 Values (A) Total items/prescriptions levothyroxine, liothyronine, NDT. (B) Average costs/prescription. (C) Percentage of total liothyronine prescriptions by dose. [Color figure can be viewed at wileyonlinelibrary.com]

prescriptions were for 20 mcg tablets; but in 2022, only 46.9% were for 20 mcg (Table 2, Supplementary Table and Figure 1A,C). By 2022 prescriptions for LT3 5 mcg had risen to 26.3% of LT3 items and for LT3 10 mcg to 26.9% of LT3 items.

- (2) GP practices issuing prescriptions for LT3 - The number of GP practices issuing prescriptions for LT3 fell by 27% between 2016 and 2022 from 4343 to 3156. The total number of prescriptions is shown for NDT by way of comparison (Table 2).
- (3) Total annual cost of each prescription -There was a significant reduction in the annual cost of LT4 and LT3 (total) prescriptions between 2016 and 2022, but the cost for NDT increased progressively each year. The reduction of cost for LT3 was much greater for its 20 mcg strength tablets (80%) compared to its 10 mcg (35%) and 5 mcg (38%) tablets. However, the cost of NDT increased significantly (Figure 1B).
- (4) Total annual cost of prescriptions - There was a significant reduction in the annual cost of LT4 and LT3 (total) prescriptions from 2016 until 2022, with fluctuations in the total annual cost of NDT as item price increased while total number of prescriptions fell (Table 2).

In 2016, 94% of prescriptions were for 20 mcg tablets; but in 2022, only 47% of prescriptions were for the 20 mcg strength (Table 2, Supplementary Table and Figure 1C). The number of GP practices issuing prescriptions for LT3 fell by 27% between 2016 and 2022 from 4343 to 3156. The total number of prescriptions is shown for NDT by way of comparison.

4 | DISCUSSION

We have demonstrated a significant reduction in the price of LT3 (both in individual prescription prices and total annual costs) from 2016 onwards which is likely a result of the CMA investigation quoted above. Price reductions in LT3 began in 2016 showing a downward trend between then and 2022, although the prices remain significantly above the tablet costs in other European countries.⁶

It is important to point out however, that the major price reduction in LT3 has been in its 20-mcg strength tablet (80% reduction from 2016), leading to a significant cost differential with the current costs of 10 and 5 mcg tablets (Table 2 and Figure 1B) which are approximately 252% and 239% respectively the cost of the 20-mcg tablet. The 20 mcg tablet (not recommended in current expert society guidelines) is therefore cheaper to prescribe than the two recommended strengths imposing cost constraints on the prescriber—the BTA 2023 guidance⁸ very clearly recommends the lower doses of LT3. This places clinicians in an invidious position as the BTA recommends a daily dose of 5–10 mcg twice each day in those prescribed LT3⁸—the 20 mcg tablet is not ideal therefore for clinical use. Individual clinicians may therefore reconsider their decisions to commence LT3 therapy as the cost of the doses recommended for a trial of LT3 are significantly greater compared to the cost of the higher dose. This may disadvantage patients who may miss out on genuine benefit from a trial of combination therapy with LT4 and LT3 purely based on cost constraints (the majority of these individuals being women). During this same period 2016 to 2022, (a) the cost of LT4 (per prescription and total cost per year) reduced significantly despite an increase in the number of prescriptions, and (b) the price of NDT has increased despite a reduction in the number prescribed (Table 1 and Figure 1A). NDT is only prescribed to a very small proportion of people with hypothyroidism. Therefore it is possible that the price point for NDT can be elevated without resulting in a significant decrease in prescribing. NDT is not a licensed medication in the UK. In North America it has the status of being recognised as safe and effective' or 'grandfathered'.

Hypothyroidism affects approximately 2 million individuals in the UK,¹² but as many as 10% of treated individuals are dissatisfied with LT4 monotherapy because of persistent symptoms and a poor QoL.^{13–15} The reasons for this are complex and multifactorial and include the fact that some people may be started on LT4 when more time might have been given to monitor thyroid hormone status before moving to LT4 replacement.^{8,16} Expert societies recommend a trial of LT3 combination therapy in carefully selected such individuals under supervision.^{8,17} The number who are dissatisfied is likely to increase as the demand for LT4 treatment increases for reasons

TABLE 2 Change in the cost between 2016 and 2022 - for LT4, by tablet dose for LT3 and NDT.

Drug	Cost per prescription (Percentage change vs. 2016)		Total prescriptions (Percentage change vs. 2016)		Total cost/year £,000 (Percentage change vs. 2016)	
	2016	2022	2016	2022	2016	2022
LT4	£2.74	£1.47 (- 48%)	30.8 million	33.4 million (8%)	£90,504	£52,439 (-42%)
Total LT3**			74,500	60,999 (-18%)	£30,034	£9029 (- 70%)
20 mcg	£404	£101 (- 75%)				
10 mcg	£348	£255 (- 27%)				
5 mcg	£355	£242 (- 32%)				
NDT	£207	£440 (+113%)	4257	2384 (-44%)	£885	£1049 (18%)

**The total number of LT3 prescriptions decreased by 30% in 2019 and increased to its current level in 2022 (data not shown here).

discussed elsewhere.¹⁸⁻²⁰ This will potentially also increase the number considered for combination LT4 + LT3 therapy.

The current unmet need therefore is significant and is likely to increase in the future. It should also be noted that despite active discouragement of LT3 prescription in general practice, a significant number of them still do prescribe LT3 to their patients. The licensing situation around NDT²¹ combined with the increasing cost per item is clearly resulting in a trend to less prescribing of this year on year. A multi-level approach is under way in relation to research to determine whether there is plausibility to the additional prescription of liothyronine. However the price level for liothyronine or any similar preparations needs to be such as to be an affordable option for prescribers

There are limitations to our analysis—(a) these data do not capture hypothyroid individuals obtaining their LT3 through private prescription (b) the data pertains only to patients and general practices from England and therefore may not be representative of the other three nations of the United Kingdom. We accept that the 20 mcg LT3 tablet could be cut into half but this is certainly not ideal and in any event many people are now taking the 5 mcg LT3 dose

5 | CONCLUSIONS

In conclusion, despite recent reductions in the price of LT3, the price differential that exists between its tablet strengths may impact clinical decision making to the detriment of some of people with treated hypothyroidism who are dissatisfied with their LT4 monotherapy. This price differential needs to be reviewed again now and on a regular basis, to give individuals with levothyroxine unresponsiveness, the benefit of being considered for LT3 + LT4 in light of the recent expert clinical recommendations.

AUTHOR CONTRIBUTIONS

Premawardhana LD and Heald AH wrote the manuscript with data analysis by Stedman M. Premawardhana LD, Heald AH, Okosieme OE, Taylor PN, Dasha Depesina, Nadia Chaudhury, and Dayan CM contributed to and have approved the final version of the manuscript. Dayan CM, Premawardhana LD and Okosieme OE provided senior review.

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CONFLICTS OF INTEREST STATEMENT

All authors declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

DATA AVAILABILITY STATEMENT

The data that supports the findings of the study are publicly available.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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