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Liothyronine prescribing in the UK has changed dramatically with widespread variation by clinical commissioning group and is strongly influenced by economic deprivation.

Peter N Taylor, Salman Razvi, Ilaria Muller, John Wass, Colin M Dayan, Krishna Chatterjee and Kristien Boelaert

Levothyroxine is commonly prescribed for hypothyroidism and its use is steadily increasing<sup>1</sup>. A subgroup of patients are dissatisfied on levothyroxine monotherapy<sup>2</sup> and in some clinical trials, patients demonstrated preference for a combination of thyroxine and liothyronine. With clinical trials not showing clear-cut superiority, combination thyroid hormone therapy remains controversial<sup>3</sup>. However, acknowledging limitations (small size, short duration, inconsistent dosage) of previous studies, specialist society guidance recognises that a trial of liothyronine may be appropriate in selected patients<sup>4</sup> and studies of genetic polymorphisms (e.g. Thr92AlaD2) may indicate specific patients to target. In 2016, the 28-day NHS cost of liothyronine increased dramatically from ~£4·50 to £258·19, resulting in widespread patient concern and media coverage<sup>5</sup>. Over this time the cost of levothyroxine has broadly remained unchanged. Clinicians are under increasing pressure to justify prescriptions and for many patients treatment has been discontinued or requires private sourcing. A parliamentary enquiry is ongoing. Given these changes in costs occurred uniquely in the NHS, these trends in T3 prescribing likely only apply to the UK.

We analysed NHS England open prescribing data<sup>6</sup>, between 01/08/2013 and 01/07/2018, sequentially examining the monthly number and cost of NHS liothyronine prescriptions for each clinical commissioning group (CCG N=195). CCGs are responsible for commissioning healthcare services in their local area. In August 2013, the median number of monthly liothyronine prescriptions per CCG was 22 (IQR 12-38) falling to 17 (IQR 10-30)  $p<0\cdot0001$  by July 2018. Most marked prescribing changes in early 2016 coincided with substantial rise in costs (**Figure 1**). The total monthly cost of liothyronine prescriptions in August 2013 was £758,975 and this rose almost ten-fold to £7,018,679 by July 2018, despite 122 CCGs prescribing less liothyronine.

Between August 2013 and July 2018, there was a median 37% reduction in the ratio of liothyronine prescriptions per 1,000 levothyroxine prescription nationwide, with a maximum 32-fold reduction in one CCG. Widespread variation by CCG is now apparent, with a 49-fold difference in liothyronine prescriptions per 1,000 levothyroxine prescriptions. Analysis of CCG demographics showed that for each quintile increase in economic deprivation there were 0·21SD (95%CI -0·31, -0·11)  $p<0\cdot001$  lower liothyronine prescriptions. An overview of current liothyronine prescribing by CCG is shown in **Supplementary Figure 1** with changes from 2013-2018 shown in **Supplementary Figure 2**.

Over this time period no major study or guideline has advocated a change in liothyronine prescribing. Thus, this substantial reduction in prescribing appears to have been largely driven by cost. Given the concerns raised by patients, this near 50-fold disparity between CCGs in prescribing liothyronine linked to deprivation status, is difficult to justify. Moreover, patients in more affluent areas may source liothyronine by private prescription, further exacerbating the inequality.

Overall, current pricing of liothyronine has markedly reduced its prescription, engendered widespread variability in patients' access to it and significantly increased its overall cost to the NHS. Furthermore patients may have turned to alternate sources of T3 such as Armour thyroid which contains a supraphysiologic ratio of T3:T4 and may have more adverse effects. Furthermore the rising cost of T3 may adversely impact its availability for patients with thyroid cancer undergoing radioactive iodine treatment. Our findings support the need for urgent measures to reduce liothyronine's NHS cost. Alternatively, if future, adequately-powered, randomised controlled trials strengthen the evidence-base for liothyronine therapy, this may identify the cost-benefit equation for its use.

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## Figure legends

### Figure 1A

**Total cost and number of liothyronine prescriptions per 1000 T4 prescriptions 2013-2018**

### Figure 1B

**Median number of liothyronine prescriptions per 1000 levothyroxine prescriptions by Index of Multiple Deprivation Quintile**

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#### Declaration of interests

The authors declare no competing interests.