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Optimal prescribing of levothyroxine for underactive thyroid gland treatment

Submission date
23/06/2022

Recruitment status
No longer recruiting

Registration date
18/10/2022

Overall study status
Completed

Last Edited
31/12/2024

Condition category
Nutritional, Metabolic, Endocrine

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Levothyroxine is the third most commonly prescribed medication in the UK and at 4 pence per 100-µg tablet is amongst the cheapest. The general assumption has been that when patients are prescribed levothyroxine for a diagnosis of hypothyroidism (thyroid underactivity), the treatment is life-long. However, the commonest cause of hypothyroidism is Hashimoto's (autoimmune) thyroiditis, which may result in a variable degree of mild hypothyroidism or even have a relapsing/remitting course in some patients. In addition, levels in the blood of thyroid stimulating hormone (TSH) may rise for a short period following any 'non-thyroidal illness' and this physiological phenomenon may easily be mistaken for mild hypothyroidism in someone who doesn't feel well following an intercurrent infection or other health issues. Therefore, guidelines suggest observing such patients for 3 to 6 months to see if the elevation of TSH is persistent and then considering a trial of levothyroxine treatment in younger patients with compatible hypothyroid symptoms. Unfortunately, not all short-duration, variable or mild hypothyroidism is recognised as such, leading to overtreatment.

Recent evidence both from the US and the UK suggests that many patients with only mildly abnormal or even normal thyroid blood tests are being prescribed levothyroxine in primary care settings. A complementary meta-analysis of 11 studies showed that if levothyroxine therapy is withdrawn, 30-50% of patients remain euthyroid (with normal TSH levels). Thus, overprescribing levothyroxine is a potentially detrimental situation, not only because of wasted resources in medication prescriptions and monitoring blood tests but also because out-of-range thyroid tests are found in around 50% of people taking levothyroxine, which are associated with several undesirable health outcomes, including fractures, heart problems and increased mortality. Because levothyroxine is taken by around 3 million people in the UK, overprescribing could be adversely affecting the health of around half a million people. This study aims to address how this important public health issue can be best addressed.

Who can participate?
Patients identified from GP databases as taking levothyroxine for more than 6 months

What does the study involve?
Patients will be asked to temporarily stop taking their levothyroxine for 6 weeks. Thyroid blood

tests will be done at the end of 6 weeks and quality of life will be measured at the start and end of the study. Patients will be asked what they thought about stopping their medication, how they felt during the period off levothyroxine and whether they would recommend trying off thyroid medications to a friend. After 6 weeks, patients will have the option of staying on medication if they prefer, but if their thyroid tests are suitable, they will be offered the chance to remain off levothyroxine.

What are the possible benefits and risks of participating?
Benefits and risks not provided at time of registration

Where is the study run from?
Newcastle University (UK)

When is the study starting and how long is it expected to run for?
December 2021 to December 2024

Who is funding the study?
Newcastle University (Policy) (UK)

Who is the main contact?
Dr Simon Pearce
simon.pearce@ncl.ac.uk

Contact information

Type(s)
Principal Investigator

Contact name
Prof Simon Pearce

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
313119

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
10156, IRAS 313119, CPMS 52796

Study information

Scientific Title
Optimal prescribing of levothyroxine study (OPAL)

Acronym
OPAL

Study objectives
A proportion of patients taking levothyroxine medication without documented overt hypothyroidism or serum thyroid-stimulating hormone (TSH) >10 mU/l will be able to discontinue thyroid hormone replacement with no detriment to health

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 01/06/2022, West of Scotland 4 (Research Ethics, Ward 11, Dykebar Hospital, Grahamston Road, Paisley, Scotland, PA2 7DE, United Kingdom; +44 (0)141 314 0213; WoSREC4@ggc.scot.nhs.uk), ref: 22/WS/0067

Study design
Single-group 6-week temporary-withdrawal interventional study

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
GP practice

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Hypothyroidism

Interventions

Withdrawal of levothyroxine from patients taking levothyroxine medication without documented overt hypothyroidism or serum thyroid-stimulating hormone (TSH) >10 mU/l

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Levothyroxine

Primary outcome measure
1. Serum thyroid stimulating hormone levels measured using chemiluminescent assay at 6 weeks after levothyroxine treatment withdrawal
2. Serum free thyroxine (FT4) levels measured using chemiluminescent assay at 6 weeks after levothyroxine treatment withdrawal

Secondary outcome measures
1. Change from baseline in quality of life measured using thyroid-specific patient-reported outcome 39-item (ThyPRO-39) scoring at 6 weeks after levothyroxine treatment withdrawal
2. Proportion of recruitments versus patients invited at the start of the study measured using signed consent forms versus letters of invitation sent
3. Friends and family test measured using a subjective questionnaire at end of the study
4. Multivariate analysis of baseline demographics (sex, age), thyroid clinical features (prior TSH, duration of LT4 treatment) and biochemical parameters at 6 weeks (TSH, FT4)
5. Serum TSH measurements measured using electronic health records over 1 year
6. Number of levothyroxine prescriptions measured using electronic health records over 1 year

Overall study start date
01/12/2021

Completion date
06/12/2024

Eligibility

Key inclusion criteria
1. Patients taking levothyroxine for more than 6 months
2. Aged 18 years and over
3. No documented serum TSH ≥10 mU/l recorded in electronic health records
4. Pregnancy, breastfeeding or with a plan for pregnancy within 6 months
5. No history of thyroidectomy, pituitary disease or thyroid cancer
6. No active ischaemic heart disease, arrhythmia or other condition that in the opinion of the principal investigator would render the withdrawal of thyroid hormone unsafe
7. No dementia, active psychotic or serious mental health condition
8. Ability to give written informed consent

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
130

Total final enrolment
102

Key exclusion criteria
Does not meet the inclusion criteria

Date of first enrolment
20/06/2022

Date of final enrolment
01/11/2024

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Forest Hall Medical Group
Station Road
Forest Hall
Newcastle upon Tyne
United Kingdom
NE12 9BQ

Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust

Sponsor details

Regent Point
Newcastle upon Tyne
England
United Kingdom
NE3 3HD
+44 (0)191 2825789
tnu-tr.sponsormanagement@nhs.net

Sponsor type
Hospital/treatment centre

Website
http://www.newcastle-hospitals.org.uk/

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
University/education

Funder Name
Newcastle University

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Universities (academic only)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
1. Report to Newcastle University policy team
2. Planned publication in a high-impact peer-reviewed journal

Intention to publish date
01/01/2026

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are/will be available upon request from Dr Simon Pearce, simon.pearce@ncl.ac.uk. These anonymised data will be made available to bona fide researchers following an initial publication.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet			27/06/2022	No	Yes
HRA research summary			28/06/2023	No	No