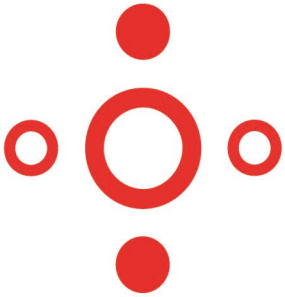
Grŵp Strategaeth Meddyginiaethau Cymru Gyfan
All Wales Medicines Strategy Group



Medicines identified as low value for prescribing in NHS Wales

July 2026

This document has been prepared by the All Wales Prescribing Advisory Group (AWPAG) with support from the All Wales Therapeutics and Toxicology Centre (AWTTC), and has subsequently been endorsed by the All Wales Medicines Strategy Group (AWMSG).

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1.0 Introduction

The purpose of this document is to provide an update to the previously published Medicines identified as low value for prescribing in NHS Wales guidance, supporting the effective use of resources within NHS Wales. This document provides advice to prescribers and health boards in Wales, with the aim of reducing the use of medicines* that should not be prescribed.

Value-based healthcare has been defined as "*the equitable, sustainable and transparent use of the available resources to achieve better outcomes and experiences for every person*"[1]. A key part of value-based healthcare is the optimum positioning of medicines to support pathways of care[2]. Value-based healthcare can be considered as a comprehensive concept built upon four value pillars (Table 1)[3].

Table 1. Definitions of the four value pillars of value-based healthcare

Value pillar	Definition
Technical	The achievement of best possible outcomes with available resources.
Allocative	The equitable resource distribution across all patient groups.
Personal	The appropriate care to achieve patients' personal goals.
Societal	The contribution of healthcare to social participation and connectedness.

The All Wales Medicines Strategy Group (AWMSG) endorsed Medicines identified as low value for prescribing in NHS Wales guidance, comprising three papers, has shown that when there is a nationally agreed criteria for targeting usage of medicines, significant change can be achieved. The focus of this work has been to decrease the prescribing of specified medicines in primary care. In 2022 the low value for prescribing work was incorporated within the AWMSG endorsed Value-based prescribing programme.

As well as providing recommendations, this document also details both general and specific exemptions to recommendations. However, it will be for health boards† to interpret the advice and determine how it is best implemented; this will include determining the circumstances in which these medicines should or should not be prescribed. In certain circumstances prescribing of these medicines might be initiated outside of the primary care setting. Therefore, organisations may be required to review all prescribing of these medicines. Each organisation will need to make decisions on local implementation individually, ensuring that they consider their legal duties to advance equality and reduce health inequalities.

Prescribers are expected to have due regard for this advice when deciding whether or not to prescribe these medicines. However, the guidance contained herein does not remove the clinical discretion of the prescriber in accordance with their professional duties.

* As most items included within the low value for prescribing guidance are medicines this is the term chosen for use throughout this document.
† Where reference is made to health boards, the recommendations may in certain circumstances also be relevant to the Velindre University NHS Trust.

2.0 Background

The All Wales Medicines Strategy Group's (AWMSG) role within NHS Wales is to ensure there is equitable access to the most clinically effective and cost-effective medicines. The Value-based prescribing programme aims to deliver meaningful change in the use of medicines and resources for patients within Wales. By having endorsed this programme AWMSG supports organisations to:

- increase the quality of care for patients
- fulfil the clinician's obligation to provide healthcare that is based on evidence of clinical effectiveness and cost-effectiveness
- optimise the use of selected medicines
- support the principles of prudent, and value-based, healthcare.

In 2024–2025, prescribing expenditure in NHS Wales totalled £1.32 billion[*]. This represented approximately 12% of the total Welsh Government budget for Health and Social Services[†4]. Between 2018–2019 and 2024–2025 total prescribing expenditure increased by approximately 45%[*]. As set out in the NHS Wales Planning Framework 2024–2027, the Value and Sustainability Board has a specific workstream focused on medicines management which was informed partly by AWMSG's low value for prescribing guidance. A reduction in interventions considered to be "low-value" has been identified as an area within which a consistent and significant impact must be made[5]. Although the primary aim of AWMSG's low value for prescribing guidance is not to deliver direct financial savings, it is intended to promote a safer and more efficient use of resources. A more prudent and value-based approach to the use of specified medicines considered not suitable for prescribing may, in turn, support wider financial incentives. The medicines management workstream, now led by the NHS Directors of Pharmacy Peer group through its Delivery Assurance Group for Value and Sustainability, support this review for potential inclusion within future workstream activity.

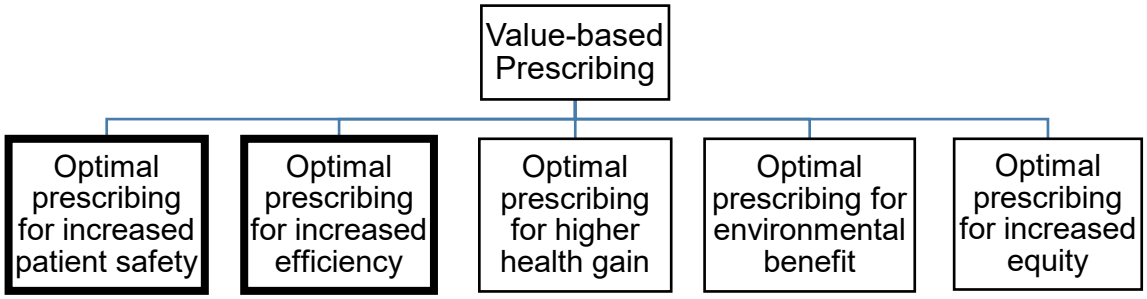
The low value for prescribing series has produced three guidance papers. The first low value for prescribing paper was endorsed by AWMSG in October 2017, with a second paper following in December 2018[6,7]. The third paper was endorsed by AWMSG in February 2020[8]. The proximity of the final endorsement to the COVID-19 pandemic resulted in delayed work for actioning the recommendations within the third paper, whilst available resources were prioritised to support the pandemic response. Active monitoring of health board performance in relation to these recommendations commenced in April 2021.

In developing this updated document, the previously included medicines have been reviewed for their continued suitability. A task and finish group was convened to support the review which comprised of medicines management representatives from all health boards. The group deliberated whether medicines should be removed from the active recommendations. The group also reviewed which value-based prescribing domain each medicine should be considered within and gave input into which had the greatest need for an extensive updated evidence review of the available literature. These outputs have been given due consideration and oversight by the All Wales Prescribing Advisory Group (AWPAG).

[*] Combined calculation of primary care and secondary/tertiary care spends using data from NHS Wales Shared Services Partnership and Digital Health and Care Wales. Rebates, and income from the Voluntary Scheme for Pricing Access and Growth (VPAG), are excluded.
[†] This calculation does not include capital allocation or annually managed expenditure.

Where medicines have been determined suitable for “retirement” they have been removed from the active recommendations list. Data will continue to be available for “retired” medicines to enable monitoring for any increases in usage. The recommendations within the document have all received an evidence review (except for blood glucose monitoring strips) and update to their expenditure figures. These medicines have been categorised within specific domains according to the Value-based prescribing programme[9]. Figure 1 provides the overarching structure of the Value-based prescribing programme domains, with those relevant to low value for prescribing highlighted. Appendix 1 provides a categorisation of the low value medicines within the relevant domains.

Figure 1. Value-based prescribing programme overarching structure with low value for prescribing domains highlighted*



Future work will consider whether additional medicines should be included. These may be medicines that are no longer preferred options within established prescribing pathways. Ongoing review of prescribing choices is essential to ensure effectiveness, efficiency and safety. There may also be opportunities to align deprescribing activity with medicines for which increased prescribing would be clinically advantageous, through complementary guidance within other domains of the Value-based prescribing programme.

Health board access to the advice contained within this document will enable a more equitable process for making decisions about organisational policies for prescribing. Each health board will need to make decisions on local implementation individually, ensuring they take into account their legal duties to both advance equality and reduce health inequalities. The NHS Directors of Pharmacy Delivery Assurance Group for Value and Sustainability may adopt some or all of the recommendations as future work which would provide a nationally governed approach to support implementation.

3.0 Recommendations

The aim of this document is to set out relevant recommendations for medicines considered to be low value, supported with a review of the evidence base and updated expenditure data. This is to provide further support in reducing the use of medicines where more cost-effective alternatives exist, where clinical effectiveness is limited, or, where use may possibly pose a risk of harm to patients.

The efficiency domain is populated based on the rationale that medicines are either of low clinical effectiveness or where more cost-effective alternatives are available.

* More detailed descriptions of these domains are provided within the Value-based prescribing strategy paper.

The safety domain is populated with medicines which have a recognised potential risk of harm from their use. For medicines already included within the low value for prescribing guidance the following determinations have been made:

- Low value for prescribing medicines to be actively monitored within the safety domain are – co-proxamol, chloral hydrate, minocycline, and paracetamol/tramadol combination products.
- Low value for prescribing medicines to be actively monitored within the efficiency domain are – oxycodone/naloxone combination products, perindopril arginine, rubefacients, probiotics, ascorbic acid, alimemazine, blood glucose testing strips, liothyronine including desiccated thyroid extracts (e.g. Armour Thyroid), and omega-3 fatty acid compounds.
- Low value for prescribing medicines to no longer be actively monitored are – tadalafil, aliskiren, ketovite, selenium, silk garments and doxazosin modified release tablets.
- Low value for prescribing medicines to be temporarily removed from the active recommendations while further work relating to the implementation of the recommendations is considered – lidocaine 5% plasters.

Medicines removed from the active recommendation list are still considered to be of low value and data for their use will continue to be available for monitoring purposes. Should usage start to increase, their reintroduction to the active monitoring list will be considered.

Medicines discontinued from the active recommendations were identified primarily due to a decrease in use since their original inclusion within the recommendations and are as such now considered to not offer any significant efficiency gain. Tadalafil is an exception to this where usage has increased since it was first included within the recommendations. However, the rationale for its inclusion changed following its loss of patent and subsequent overall price reduction. In 2018 an addendum was added to the relevant recommendation monograph to indicate that health boards may wish to prioritise other medicines. Doxazosin modified release tablets have been removed as, due to changing prices, it is no longer a useful efficiency recommendation. No medicines included on a safety basis have been removed from the active recommendations as these potentially apply to all use, irrespective of the magnitude of use across Wales.

The 2024–2025 NHS Wales expenditure for each of the medicines are provided within Appendix 2. Appendix 3 provides a breakdown of the primary care expenditure for 2024–2025 by health board. Appendix 4 provides the primary care expenditure per 1,000 patients for each health board in 2024–2025. These figures do not necessarily represent potential savings, as the deprescribing of these medicines may require alternatives to be prescribed.

All health boards will be expected to action this advice and put mechanisms in place to ensure these areas are reviewed, with direction given by Medical Directors working with their Directors of Pharmacy. Where necessary, medicines management teams should work closely together with relevant specialist teams to ensure patients identified as part of these recommendations are supported appropriately. These recommendations are focused on primary care prescribing as per the previous papers. However, it is recognised that in certain circumstances prescribing in primary care can be initiated within the secondary care setting. Whilst our current data does not allow us to report when this may be the case Appendix 5 provides the

expenditure values for medicines showing usage data within the secondary care datasets in 2024–2025.

Resources to help support the implementation of these recommendations are detailed in Appendix 6. A new dashboard hosted within the Server for Prescribing Information Reporting and Analysis (SPIRA), accessible to all users who are on the NHS Wales network, provides more detailed analysis for the usage of medicines identified within the low value for prescribing guidance. This will be made available following endorsement of this guidance by AWMSG.

All medicines continuing within the active recommendations have had an evidence review (except for blood glucose monitoring strips). These are provided in Appendix 7. The evidence supports the recommendations and exemptions as detailed within the individual medicine monographs. Where appropriate, the Specialist Pharmacy Service (SPS)* and PrescQIPP†, as well as other resources, have been used to provide further support to the recommendations.

In accordance with these recommendations, these medicines should not be initiated or prescribed for new patients unless explicitly permitted within the recommendations or included under the specified patient exemptions. All patients currently receiving these medicines should be subject to review, and where appropriate, switched to an alternative treatment option. If a medicine is prescribed in secondary care with the intention that prescribing will continue in primary care, the reasons for the prescribing decision should be clearly communicated to the primary care prescriber when requesting continuation of treatment.

Table 2 lists the medicines identified as low value for prescribing, with accompanying rationale, recommendations and exemptions where relevant.

* The specialist pharmacy service is a national organisation commissioned by NHS England to support NHS organisations with expert advice, guidance and resources on medicines.
† PrescQIPP is an NHS funded, not-for-profit organisation supporting quality, optimised prescribing for patients.

Table 2. Medicines identified as low value for prescribing within NHS Wales and not recommended for prescribing

Recommendation rationale	Value-based Prescribing domain	NHS Wales primary care expenditure 2024–2025
Co-proxamol	**Safety**	**£29,801**

Rationale:
Co-proxamol was withdrawn in 2005 on the advice of the Medicines and Healthcare products Regulatory Agency (MHRA) Committee on Safety of Medicines. This withdrawal was phased over a two-year period to allow alternative regimens to be prescribed. A joint Health Professional Letter was published in 2017 by the Chief Medical Officer and Chief Pharmaceutical Officer in Welsh Government as a reminder to health boards and prescribers to urgently review all co-proxamol prescriptions to allow alternative regimens to be prescribed. Advice highlighted within this letter includes:

- There is no robust evidence that co-proxamol is more effective than paracetamol alone in either chronic or acute use.
- No patient group has been identified in which the risk/benefit ratio favours using co-proxamol.
- The fatal dose of co-proxamol is relatively low and can be potentiated by alcohol and other central nervous system depressants.
- Death from co-proxamol overdose occurs rapidly; the risk of dying after co-proxamol overdose is 2.3 times that for tricyclic antidepressants, 10 times that for co-codamol or co-dydramol, and 28.1 times that for paracetamol.
- Co-proxamol is an unlicensed medicine.

It is estimated that the withdrawal of co-proxamol from the UK has saved around 300 to 400 lives each year from self-poisoning, around a fifth of which were accidental[10].

A search of the evidence was carried out in January 2026; at the time of publication, no significant relevant evidence has been published since 2017 which would challenge the existing recommendation.

Recommendation:
Within NHS Wales it is recommended that co-proxamol is not prescribed.

- All patients currently receiving prescriptions for co-proxamol should be urgently reviewed with the intention of switching patients to alternative, safer treatments.

Patient exemptions:
No patient exemptions identified.

Table 2 (continued). Medicines identified as low value for prescribing within NHS Wales and not recommended for prescribing

Recommendation rationale	Value-based Prescribing domain	NHS Wales primary care expenditure 2024–2025
Liothyronine including desiccated thyroid extracts (e.g. Armour Thyroid)	**Efficiency**	**£548,678**

Rationale:
Levothyroxine is the oral thyroid hormone of choice as it is cost effective, suitable for once daily dosing due to its long half-life and provides stable and physiological quantities of thyroid hormones for patients requiring replacement. It is licensed for the control of hypothyroidism, congenital hypothyroidism in infants, acquired hypothyroidism in children and juvenile myxoedema. Liothyronine is not recommended for prescribing as it has a much shorter half-life and steady-state levels cannot be maintained with once daily dosing[11].

Desiccated thyroid extracts (DTE) comprise a combination of levothyroxine (T4) and liothyronine (T3) and are unlicensed for use in the UK. Prescribing of DTE should not be initiated in primary care. Existing prescribing should be reviewed by an NHS endocrinologist and, where clinically appropriate, switching to levothyroxine should be considered. Recognised brands of DTE available in the UK include Armour Thyroid, NatureThroid, WP Thyroid, NP Thyroid and ERFA Thyroid[12].

A search of the evidence was carried out in October 2025; 5 systematic reviews, 6 guidelines and 1 economic evaluation were identified and are described in more detail in their respective appendices (Appendix 7.1.1, Appendix 7.1.3 and Appendix 7.1.4). A follow-up search for DTE was carried out in December 2025; 2 systematic reviews were identified and are also described in more detail in the appendix (Appendix 7.1.2).

National Institute for Health and Care Excellence (NICE) NG145 (2023) advise not routinely offering liothyronine (either alone or in combination with levothyroxine) for primary hypothyroidism[13]. A Joint British Thyroid Association and Society for Endocrinology Consensus Statement (2023) recommends that most patients should be treated with levothyroxine alone, however outlines investigations and/or levothyroxine adjustments to make before considering a trial of liothyronine (as combination therapy). The lack of clinical benefit evidenced in numerous clinical trials is acknowledged alongside the benefit experienced by some receiving liothyronine treatment[14].

At the time of publication, no significant relevant evidence has been published since 2017 which would challenge the existing recommendation.

Recommendation[15]:
Within NHS Wales it is recommended that liothyronine is not prescribed. All patients currently receiving prescriptions for liothyronine should be subject to review, and where appropriate, switched to an alternative treatment option. This includes:

- Patients with hypothyroidism who are currently receiving either liothyronine monotherapy, or liothyronine and levothyroxine combination therapy.
  - Continued use of liothyronine should be assessed with the intention to switch to levothyroxine monotherapy where clinically appropriate. In some cases, a retrospective review of the original diagnosis of hypothyroidism may be necessary. Arrangements should be made for switching to be undertaken by a consultant NHS endocrinologist, or by a General Practitioner with consultant NHS endocrinologist support. Patients who are currently obtaining supplies via private prescription or who are self-funding should not be offered NHS prescribing unless they meet the criteria in this guidance. The consultant NHS endocrinologist must specifically define the reason if any patient currently taking liothyronine should not undergo a trial titration to levothyroxine monotherapy, and this must be communicated to the General Practitioner.
- Patients with resistant depression who are currently receiving either liothyronine monotherapy, or liothyronine and levothyroxine combination therapy.
  - Continued use of liothyronine should be reviewed by a consultant NHS psychiatrist, who should consider switching to an alternative treatment where clinically appropriate, or to levothyroxine monotherapy where hypothyroidism is diagnosed. Patients continuing to receive liothyronine should be overseen by a consultant NHS psychiatrist.
- The prescribing of unlicensed liothyronine or of thyroid extracts (e.g. Armour thyroid, ERFA Thyroid), plus compound thyroid hormones, iodine containing preparations or dietary supplementation is not supported.

Patient exemptions:
This recommendation does not apply in the following circumstances:

- Post thyroidectomy in thyroid cancer patients. Prescribing in thyroid and parathyroid cancer should only be addressed by specialists in secondary/tertiary care.
- Thyroid cancer, where liothyronine is prescribed for use as an adjuvant to radioactive iodine treatment. This should only be addressed by specialists in secondary/tertiary care. Thyroid cancer patients who have completed their treatment usually need to take levothyroxine for life and should be managed in the same way as patients with hypothyroidism.
- In rare situations, where patients with hypothyroidism experience continuing symptoms whilst on levothyroxine (that have a material impact upon normal day-to-day function), and other potential causes have been investigated and eliminated, a 3-month trial with additional liothyronine may occasionally be appropriate. This is only to be initiated by a consultant NHS endocrinologist. Following this trial the consultant NHS endocrinologist will advise on the need for ongoing liothyronine. Many endocrinologists may not agree that a trial of levothyroxine/liothyronine combination therapy is warranted in these circumstances and their clinical judgement is valid given the current understanding of the science and evidence of the treatments.

Table 2 (continued). Medicines identified as low value for prescribing within NHS Wales and not recommended for prescribing

Recommendation rationale	Value-based Prescribing domain	NHS Wales primary care expenditure 2024–2025
Omega-3 fatty acid compounds	**Efficiency**	**£408,558**

Rationale:
Omega-3 fatty acid compounds (omega-3 FAs) are essential fatty acids which can be obtained from the diet. They are licensed for adjunct to diet and statin therapy in type IIb or type III hypertriglyceridemia and to diet in type IV hypertriglyceridemia (severe hypertriglyceridemia).

A search of the evidence was carried out in January 2026; 10 Cochrane systematic reviews and 2 economic evaluations were identified and are described in more detail in their respective appendices (Appendix 7.2.1 and Appendix 7.2.3).

A PrescQIPP bulletin (343)[16] from 2024 on omega-3 FAs and other fish oils aligns with NICE guidance (e.g. TA805) and makes a number of recommendations:

- do not initiate new patients on omega-3 FAs and other fish oils in primary care, except for icosapent ethyl (an ethyl ester of eicosapentaenoic acid [EPA], a long chain omega-3 FA) which is recommended as an option for reducing the risk of cardiovascular (CV) events in adults[17]
- deprescribe omega-3 FAs for existing patients, except for icosapent ethyl in line with NICE TA805
- if omega-3 FAs have either been prescribed for specialist indications or recommended by specialist lipid clinic, refer patients back to specialists for review
- if appropriate, patients prescribed omega-3 FAs with statins for reducing the risk of CV events with raised triglycerides should be switched to icosapent ethyl in line with NICE TA805

Indications for which omega-3 FAs should not be initiated and for which patients should be referred back to specialists for review, as referenced by both PrescQIPP (343) and NICE include:

- Prevention of CV disease (NG238)
- Prevention of another myocardial infarction (NG185)
- Familial hypercholesterolaemia (CG71)
- Non-alcoholic fatty liver disease (NAFLD) (NG49)
- Multiple sclerosis (NG220)
- Management of sleep problems in autistic children and young people (CG170)
- Schizophrenia (ESUOM19)

Detailed recommendations for patients prescribed warfarin who stop taking omega-3 FAs (e.g. these patients are advised to inform their anticoagulant clinic of the change) are also outlined, in addition to highlighting a dose dependent increased risk of atrial fibrillation in patients with established cardiovascular disease (CVD) or cardiovascular (CV) risk factors when taking omega-3 FAs (compared to placebo). If atrial fibrillation develops, omega-3 FA supplementation should be permanently discontinued[16].

At the time of publication, no significant relevant evidence has been published since 2017 which would challenge the existing recommendation. Icosapent ethyl is excluded from the 'Omega-3 FA' basket of medicines.

Recommendation:
Within NHS Wales it is recommended that omega-3 fatty acid compounds are not prescribed.

- All patients currently receiving prescriptions for omega 3 FAs should be subject to review and, where appropriate, switched to an alternative treatment option.

Patient exemptions:
This recommendation does not apply to:

- Patients using omega-3 fatty acid compounds who have severe hypertriglyceridaemia (type IIb, type III or type IV hypertriglyceridaemia).
- Prescribing icosapent ethyl in line with NICE TA805, as an option for reducing the risk of CV events in adults.

Table 2 (continued). Medicines identified as low value for prescribing within NHS Wales and not recommended for prescribing

Recommendation rationale	Value-based Prescribing domain	NHS Wales primary care expenditure 2024–2025
Oxycodone and naloxone combination products	**Efficiency**	**£132,833**
Rationale: Oxycodone and naloxone combination products are licensed for the treatment of severe pain, which can be adequately managed only with opioid analgesics. Targinact® is also licensed for second line symptomatic treatment of patients with severe to very severe idiopathic restless legs syndrome after failure of dopaminergic therapy. The opioid antagonist naloxone is added to counteract opioid-induced constipation by blocking the action of oxycodone at opioid receptors locally in the gut. Opioid-induced constipation is a common side effect of opioid treatment during palliative care, it typically worsens as doses increase. A search of the evidence was carried out in January 2026. At the time of publication, no significant relevant evidence has been published since 2018 which would challenge the existing recommendation. **Recommendation:** Within NHS Wales it is recommended that oxycodone and naloxone combination products are not prescribed. • All patients currently receiving prescriptions for oxycodone and naloxone combination products should be subject to review and, where appropriate, switched to an alternative treatment option. **Patient exemptions:** In exceptional circumstances, if there is a need for an oxycodone and naloxone combination product to be prescribed, this should be in a cooperation arrangement with a multi-disciplinary team and/or healthcare professional experienced in pain management.		

Table 2 (continued). Medicines identified as low value for prescribing within NHS Wales and not recommended for prescribing

Recommendation rationale	Value-based Prescribing domain	NHS Wales primary care expenditure 2024–2025
Rubefacients (excluding NSAIDs and capsaicin cream)	**Efficiency**	**£117,780**
Rationale: Rubefacients are topical preparations that cause irritation and reddening of the skin due to increased blood flow. They are used to relieve pain in various musculoskeletal conditions and are available on prescription and in over-the-counter remedies[18]. Rubefacients act by counter-irritation. Pain, whether superficial or deep-seated, is relieved by any method that itself produces irritation of the skin. Topical rubefacient preparations may contain nicotinate and salicylate compounds, essential oils, capsicum, and camphor. A search of the evidence was carried out in January 2026. At the time of publication, no relevant evidence has been published since 2020 which would challenge the existing recommendation. **Recommendation:** Within NHS Wales it is recommended that rubefacients are not prescribed. • All patients currently receiving prescriptions for rubefacients should be subject to review and, where appropriate, switched to an alternative treatment option. **Patient exemptions:** No patient exemptions identified.		

Table 2 (continued). Medicines identified as low value for prescribing within NHS Wales and not recommended for prescribing

Recommendation rationale	Value-based Prescribing domain	NHS Wales primary care expenditure 2024–2025
Probiotics	**Efficiency**	**£25,060**
Rationale: Probiotics are live micro-organisms that, when administered in adequate amounts, confer a health benefit on the host[19]. Probiotics are not licensed as medicines. The Advisory Committee on Borderline Substances reviewed the probiotic products VSL#3® and Vivomixx™ in 2019 and concluded that the evidence available did not sufficiently demonstrate that the products are clinically effective[20]. A search of the evidence was carried out in January 2026 with a focus on Cochrane systematic reviews, the results of which are described in more detail in the appendix (Appendix 7.4). At the time of publication, no significant relevant evidence has been published since 2020 which would challenge the existing recommendation. All patients prescribed probiotics should be discontinued where clinically appropriate due to there being insufficient evidence for their use[21]. With respect to safety, there are concerns around their potential to disrupt the gut microbiome, to transfer antibiotic resistance genes or to cause serious adverse effects, particularly in patients who are immunocompromised already. **Recommendation:** Within NHS Wales it is recommended that probiotics are not prescribed. • All patients currently receiving prescriptions for probiotics should be subject to review and, where appropriate, switched to an alternative treatment option. **Patient exemptions:** No patient exemptions identified.		

Table 2 (continued). Medicines identified as low value for prescribing within NHS Wales and not recommended for prescribing

Recommendation rationale	Value-based Prescribing domain	NHS Wales primary care expenditure 2024–2025
Ascorbic acid (Vitamin C)	**Efficiency**	**£211,632**
Rationale: Ascorbic acid (vitamin C) is licensed for the treatment and prevention of scurvy (as a result of vitamin C deficiency). As Vitamin C cannot be stored in the body, it is recommended that people meet their daily requirements through their diet[22]. A search of the evidence was carried out in January 2026; the results of which are described in more detail in the appendix (Appendix 7.5). At the time of publication, no significant relevant evidence has been published since 2020 which would challenge the existing recommendation. **Recommendation:** Within NHS Wales it is recommended that ascorbic acid is not prescribed. • All patients currently receiving prescriptions for ascorbic acid should be subject to review and, where appropriate, switched to an alternative treatment option. **Patient exemptions:** This recommendation does not apply to: • Medically diagnosed deficiency, including for those patients who may have a lifelong or chronic condition or have undergone surgery that results in malabsorption. However, continuing need should be reviewed on a regular basis. • Use of ascorbic acid to prevent and/or treat scurvy.		

Table 2 (continued). Medicines identified as low value for prescribing within NHS Wales and not recommended for prescribing

Recommendation rationale	Value-based Prescribing domain	NHS Wales primary care expenditure 2024–2025
Paracetamol and tramadol combination products	**Safety**	**£44,556**

Rationale:
The UK's Advisory Council on the Misuse of Drugs (ACMD) highlighted tramadol safety concerns in 2013 which led to the reclassification of tramadol, and its combination products, as Schedule 3 controlled drugs in 2014[23]. Since then, the number of deaths involving tramadol in Wales has fluctuated annually, with nine deaths reported in 2024[24]. Tramadol's unique pharmacological profile increases the risk of the adverse effects seen in overdose. Concerns remain regarding its potential for abuse, misuse and diversion. AWMSG's *Tramadol Educational Resources* advises prescribing tramadol only:

- where it is clearly indicated (for both acute and chronic pain) if it improves pain and function
- if first-line opioids (e.g. codeine, co-codamol) are not effective or are not appropriate and/or tolerated[23].

The combination product offers no significant effectiveness or safety advantages over individual products prescribed separately. The British National Formulary (BNF) states that compound analgesic preparations (such as the paracetamol and tramadol combination product) "*reduce the scope for effective titration of the individual components in the management of pain of varying intensity*"[25]. There are different strengths of tramadol (37.5 mg) and paracetamol (325 mg) in the combination product compared to commonly available individual preparations of tramadol (50 mg) and paracetamol (500 mg), with the combination product containing a subtherapeutic dose of paracetamol. Whilst paracetamol and tramadol combination products are not captured within the tramadol National Prescribing Indicator 2025-2028 (NPI) basket, safety concerns around the use of tramadol also apply to the combination product[26].

Finally, paracetamol and tramadol combination products are also more expensive than purchasing the individual components as separate products[27].Due to this combination of factors, paracetamol and tramadol combination products should not be prescribed.

A search of the evidence was carried out in January 2026; the results of which are described in more detail in the appendix (Appendix 7.6). At the time of publication, no significant relevant evidence has been published since 2018 which would challenge the existing recommendation.

Recommendation:
Within NHS Wales it is recommended that paracetamol and tramadol combination products are not prescribed.

- All patients currently receiving prescriptions for paracetamol and tramadol combination products should be subject to review and, where appropriate, switched to an alternative treatment option.

Patient exemptions:
No patient exemptions identified.

Table 2 (continued). Medicines identified as low value for prescribing within NHS Wales and not recommended for prescribing

Recommendation rationale	Value-based Prescribing domain	NHS Wales primary care expenditure 2024–2025
Chloral hydrate	**Safety**	**£247,957**

Rationale:
Chloral hydrate is licensed for the short-term treatment of severe insomnia in adults which is interfering with normal daily life and where other therapies have failed; as an adjunct to non-pharmacological therapies. Following an MHRA drug safety update on the use of chloral hydrate in 2021, the paediatric indication was further restricted to only children and adolescents (aged 2 years and above) with a suspected or definite neurodevelopmental disorder where the benefits of short-term use outweigh any potential risk. Treatment should be for the shortest duration possible, not exceeding 2 weeks, and its use should be under the supervision of a medical specialist[28]. Chloral hydrate is classified within the BNF as being less suitable for prescribing in insomnia[25]. It has a narrow therapeutic index, no reversal agent, can result in re-sedation and has been associated with patient fatalities[29].

A search of the evidence was carried out in February 2026. At the time of publication, no significant relevant evidence has been published since 2020 which would challenge the existing recommendation.

A position statement on the off-label use of chloral hydrate in the management of intrusive movement and motor disorder in children and young people was prepared by the Neonatal and Paediatric Pharmacist Group (NPPG), in conjunction with the British Paediatric Neurology Association (BPNA) and British Academy of Childhood Disability (BACD), in response to the MHRA DSU and published in November 2024. The statement describes specific situations for which use of chloral hydrate in children and young people with movement disorders may be appropriate. It advises using the lowest effective dose, at the lowest frequency and for the shortest timeframe possible with the need for ongoing use regularly assessed and documented[30].

Recommendation:
Within NHS Wales it is recommended that chloral hydrate is not prescribed.

- All patients currently receiving prescriptions for chloral hydrate should be subject to review and, where appropriate, switched to an alternative treatment option.

Patient exemptions:
Chloral hydrate must be initiated by a specialist, or in conjunction with a specialist, undertaken in a cooperation arrangement with a multidisciplinary team and/or other healthcare professional. Chloral hydrate is only indicated for short-term treatment (2 weeks).

Table 2 (continued). Medicines identified as low value for prescribing within NHS Wales and not recommended for prescribing

Recommendation rationale	Value-based Prescribing domain	NHS Wales primary care expenditure 2024–2025
Minocycline for acne	**Safety**	**£8,642**

Rationale:
Minocycline is a tetracycline antibiotic that is licensed for the treatment of acne. The AWMSG endorsed primary care antimicrobial guidelines (last updated March 2026) do not recommend minocycline for acne vulgaris[31].

There are various safety risks associated with the use of minocycline. The British National Formulary states that minocycline is less suitable for prescribing when compared with other tetracyclines, as it is associated with a greater risk of lupus-erythematosus-like syndrome and it sometimes causes irreversible pigmentation. It is also associated with hepatotoxicity and use for greater than six months requires monitoring every three months for this[25]. The evidence does not support the claim that the extended-release preparations are safer than the standard release preparations for the treatment of acne with minocycline[32].

A search of the evidence was carried out in February 2026; the results of which are described in more detail in the appendix (Appendix 7.7). At the time of publication, no significant relevant evidence has been published since 2020 which would challenge the existing recommendation.

Recommendation:
Within NHS Wales it is recommended that minocycline is not prescribed.

- All patients currently receiving prescriptions for minocycline should be subject to review and, where appropriate, switched to an alternative treatment option.

Patient exemptions:
No patient exemptions identified.

Table 2 (continued). Medicines identified as low value for prescribing within NHS Wales and not recommended for prescribing

Recommendation rationale	Value-based Prescribing domain	NHS Wales primary care expenditure 2024–2025
Perindopril arginine	**Efficiency**	**£37,438**
Rationale: Perindopril is an angiotensin-converting-enzyme (ACE) inhibitor used in heart failure, hypertension, and prophylaxis of cardiovascular events for people with a history of myocardial infarction and/or revascularisation. Perindopril arginine is equivalent to perindopril erbumine with respect to pharmacokinetics, efficacy and safety; it was developed for increased stability in extreme climates (e.g. Australia) and a longer shelf-life[33,34]. For these reasons, perindopril arginine is significantly more expensive than perindopril erbumine[27]. Due to the significant extra costs associated with the perindopril arginine, and perindopril erbumine being readily available, perindopril arginine should not be routinely prescribed. A 2.5 mg dose of perindopril arginine is equivalent to a 2 mg dose of perindopril tert-butylamine (erbumine). A search of the evidence was carried out in February 2026. At the time of publication, no relevant evidence has been published since 2018. **Recommendation:** Within NHS Wales it is recommended that perindopril arginine is not prescribed. • All patients currently receiving prescriptions for perindopril arginine should be subject to review and, where appropriate, switched to an alternative treatment option. **Patient exemptions:** No patient exemptions identified.		

Table 2 (continued). Medicines identified as low value for prescribing within NHS Wales and not recommended for prescribing

Recommendation rationale	Value-based Prescribing domain	NHS Wales primary care expenditure 2024–2025
Alimemazine	**Efficiency**	**£206,640**
Rationale: Alimemazine is a sedating antihistamine licensed for management of urticaria and pruritus in adults and children aged 3 years and over, and also for pre-medication as a sedative before general anaesthesia in children aged 2-7 years. It comes in oral solution, syrup and tablet form (with different forms being more appropriate for different indications). Alimemazine may be more sedating than the alternative first generation antihistamine chlorphenamine which is a more cost-effective option[25]. Pricing from the February 2026 online Drug Tariff states that a box of 28 tablets of alimemazine costs £48.77, compared to 28 tablets of chlorphenamine costing just 78p[27]. A search of the evidence was carried out in February 2026. At the time of publication, no relevant evidence has been published since 2018. **Recommendation:** Within NHS Wales it is recommended that alimemazine is not prescribed. • All patients currently receiving prescriptions for alimemazine should be subject to review and, where appropriate, switched to an alternative treatment option. **Patient exemptions:** As a premedication to anaesthesia in children 2 to 6 years old.		

Table 2 (continued). Medicines identified as low value for prescribing within NHS Wales and not recommended for prescribing

Recommendation rationale	Value-based Prescribing domain	NHS Wales primary care expenditure 2024–2025
Blood glucose testing strips	**Efficiency**	**£5,100,790**
Rationale: The intention of this recommendation is not for patients to be deprescribed blood glucose testing strips or not initiated on them. It is intended to encourage health boards and prescribers to consider more cost-effective alternatives (ideally those below £10 per 50 strips) as the price of strips is not influenced by strip effectiveness. An evidence search was not carried out for this reason. As of February 2026, there are currently 75 different types of blood glucose testing strips available in the UK. They range in price from £4.95 to £16.41 per 50 strips, therefore promoting use of more cost-effective testing strips first line will enable savings to be made whilst not affecting patient care[27]. The SPIRA low value for prescribing dashboard provides detailed analysis for the usage of blood glucose testing strips in primary care. Rationalising the number of readily available meters and testing strips also facilitates improved education of healthcare professionals in their use, who in turn can better assist patients with their testing. NICE guidance NG28 (last updated February 2026) outlines specific criteria for when self-monitoring of blood glucose may be suitable in patients with type 2 diabetes[35]. **Recommendation:** Within NHS Wales it is recommended that blood glucose monitoring strips costing greater than £10 per 50 strips are not prescribed. • All patients with type 2 diabetes currently receiving prescriptions for blood glucose monitoring strips costing greater than £10 per 50 strips should be subject to review and, where appropriate, switched to an option costing less than £10 per 50 strips. **Patient exemptions:** No patient exemptions identified.		

References

1. Hurst L, Mahtani K, Pluddemann A et al. Defining value-based healthcare in the NHS. 2019. Available at: https://www.cebm.ox.ac.uk/resources/reports/defining-value-based-healthcare-in-the-nhs. Accessed Feb 2026.
2. Welsh Value in Health Centre. Welsh Value in Health Centre: our strategy to 2024. 2021. Available at: https://vbhc.nhs.wales/about-us/our-strategy/?msclkid=6681947ba5e511ec90c9c1cc6bed530e. Accessed Feb 2026.
3. European Commission. Expert Panel on effective ways of investing in Health (EXPH). Defining Value in "Value-based Healthcare". 2019. Available at: https://op.europa.eu/en/publication-detail/-/publication/beaebce1-ac29-11e9-9d01-01aa75ed71a1/language-en. Accessed Feb 2026.
4. Welsh Government. Final Budget 2024 to 2025. 2024. Available at: https://www.gov.wales/final-budget-2024-2025. Accessed Feb 2026.
5. Welsh Government. NHS Wales planning framework 2024 to 2027. 2024. Available at: https://www.gov.wales/nhs-wales-planning-framework-2024-2027. Accessed Feb 2026.
6. All Wales Medicines Strategy Group. Medicines Identified as Low Priority for Funding in NHS Wales - Paper 1. Nov 2019. Available at: https://awttc.nhs.wales/medicines-optimisation-and-safety/medicines-optimisation-guidance-resources-and-data/prescribing-guidance/items-identified-as-low-value-for-prescribing-in-nhs-wales/. Accessed Feb 2026.
7. All Wales Medicines Strategy Group. Medicines Identified as Low Priority for Funding in NHS Wales - Paper 2. Sep 2022. Available at: https://awttc.nhs.wales/medicines-optimisation-and-safety/medicines-optimisation-guidance-resources-and-data/prescribing-guidance/items-identified-as-low-value-for-prescribing-in-nhs-wales/. Accessed Feb 2026.
8. All Wales Medicines Strategy Group. Medicines Identified as Low Priority for Funding in NHS Wales - Paper 3. Mar 2022. Available at: https://awttc.nhs.wales/medicines-optimisation-and-safety/medicines-optimisation-guidance-resources-and-data/prescribing-guidance/items-identified-as-low-value-for-prescribing-in-nhs-wales/. Accessed Feb 2026.
9. All Wales Medicines Strategy Group. Value-based prescribing – Strategy. Jun 2022. Available at: https://awttc.nhs.wales/medicines-optimisation-and-safety/medicines-optimisation-guidance-resources-and-data/value-based-prescribing/value-based-prescribing-strategy/. Accessed Feb 2026.
10. Medicines and Healthcare products Regulatory Agency. Drug Safety Update. (Dextro)propoxyphene: new studies confirm cardiac risks. 2014. Available at: https://www.gov.uk/drug-safety-update/-dextro-propoxyphene-new-studies-confirm-cardiac-risks. Accessed Jan 2026.
11. PrescQIPP. Liothyronine bulletin (314). 2023. Available at: https://www.prescqipp.info/our-resources/bulletins/bulletin-314-liothyronine/. Accessed Nov 2025.
12. Specialist Pharmacy Service. Avoid prescribing desiccated (natural) thyroid extract. 2026. Available at: https://www.sps.nhs.uk/articles/avoid-prescribing-desiccated-natural-thyroid-extract/. Accessed Jan 2026.
13. National Institute for Health and Care Excellence. NG145 Thyroid disease: assessment and management. 2023. Available at: www.nice.org.uk/guidance/ng145 Accessed Nov 2025.

14. Ahluwalia R, Baldeweg SE, Boelaert K et al. Use of liothyronine (T3) in hypothyroidism: Joint British Thyroid Association/Society for endocrinology consensus statement. *Clinical Endocrinology.* 2023;99(2):206–216. Accessed Nov 2025.
15. NHS England. Liothyronine – advice for prescribers. 2023. Available at: https://www.england.nhs.uk/long-read/liothyronine-advice-for-prescribers/. Accessed Nov 2025.
16. PrescQIPP. Omega-3 fatty acid compounds and other fish oils (343). 2024. Available at: https://www.prescqipp.info/our-resources/bulletins/bulletin-343-omega-3-fatty-acid-compounds-and-other-fish-oils/. Accessed Jan 2026.
17. National Institute for Health and Care Excellence. TA805 Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides. 2022. Available at: https://www.nice.org.uk/guidance/ta805. Accessed Jan 2026.
18. Derry S, Matthews P, Wiffen P et al. Salicylate-containing rubefacients for acute and chronic musculoskeletal pain in adults. *Cochrane Database of Systematic Reviews.* 2014 Accessed Jan 2026.
19. Hill C, Guarner F, Reid G et al. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nature Reviews Gastroenterology & Hepatology.* 2014;11:506–514. Accessed Jan 2026.
20. UK Medicines Information. Probiotics VSL#3 and Vivomixx have been removed from the Drug Tariff, following review by Advisory Committee on Borderline Substances (ACBS). 2019. Available at: https://www.medicinesresources.nhs.uk/en/Medicines-Awareness/Guidance-and-Advice/Drug-Prescribing/Probiotics-VSL3-and-Vivomixx-have-been-removed-from-the-Drug-Tariff-following-review-by-Advisory-Committee-on-Borderline-Substances-ACBS-/. Accessed Jan 2026.
21. PrescQIPP. Probiotics bulletin (262). 2020. Available at: https://www.prescqipp.info/our-resources/bulletins/bulletin-262-probiotics/. Accessed Jan 2026.
22. NHS website. Vitamin C. 2020. Available at: https://www.nhs.uk/conditions/vitamins-and-minerals/vitamin-c/. Accessed Jan 2026.
23. All Wales Medicines Strategy Group. Tramadol educational resources. Sep 2021. Available at: https://awttc.nhs.wales/medicines-optimisation-and-safety/medicines-optimisation-guidance-resources-and-data/prescribing-guidance/tramadol-educational-resources-2021-review/. Accessed Jan 2026.
24. Office for National Statistics. Deaths related to drug poisoning by selected substances, England and Wales. 2026. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathsrelatedtodrugpoisoningbyselectedsubstances. Accessed Jun 2026.
25. BMJ Group and the Royal Pharmaceutical Society. British National Formulary. 2026. Available at: https://www.medicinescomplete.com/mc/bnf/current/. Accessed Jan 2026.
26. All Wales Medicines Strategy Group. National Prescribing Indicators 2025-2028. Dec 2024. Available at: https://awttc.nhs.wales/medicines-optimisation-and-safety/medicines-optimisation-guidance-resources-and-data/national-prescribing-indicators/national-prescribing-indicators-2025-2028/. Accessed Jan 2026.

27. NHS Business Services Authority. Drug Tariff. 2026. Available at: https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff. Accessed Jan 2026.
28. Medicines and Healthcare products Regulatory Agency. Chloral hydrate, cloral betaine (Welldorm): restriction of paediatric indication. 2021. Available at: https://www.gov.uk/drug-safety-update/chloral-hydrate-cloral-betaine-welldorm-restriction-of-paediatric-indication. Accessed Feb 2026.
29. Grissinger M. Chloral Hydrate: Is It Still Being Used? Are There Safer Alternatives?. *Pharmacy & Therpeutics.* 2019;44(8):444–445.
30. Neonatal and Paediatric Pharmacist Group (NPPG) in conjunction with the British Paediatric Neurology Association (BPNA) and British Academy of Childhood Disability (BACD). Off label use of Chloral Hydrate in the Management of Intrusive Movement and Motor Disorders in Children and Young People. Nov 2024. Available at: https://nppg.org.uk/chloral-hydrate/. Accessed Feb 2026.
31. All Wales Medicines Strategy Group. Primary care antimicrobial guidelines. Mar 2026. Available at: https://awttc.nhs.wales/medicines-optimisation-and-safety/medicines-optimisation-guidance-resources-and-data/prescribing-guidance/primary-care-antimicrobial-guidelines/. Accessed Feb 2026.
32. Garner SE, Eady A, Bennett C et al. Minocycline for acne vulgaris: efficacy and safety. *Cochrane Database of Systematic Reviews.* 2012 Accessed Feb 2026.
33. Kubler P. New drugs for old. *Australian Prescriber.* 2006;29:148–149. Accessed Feb 2026.
34. Telekjo E. Perindopril arginine: benefits of a new salt of the ACE inhibitor perindopril. *Current Medical Research and Opinion.* 2007;23(5):953–960. Accessed Feb 2026.
35. National Institute for Health and Care Excellence. NG28 Type 2 diabetes in adults: management. 2026. Available at: https://www.nice.org.uk/guidance/ng28. Accessed Feb 2026.
36. Bahl S, Taylor PN, Premawardhana LD et al. Risk of death and adverse effects in patients on Liothyronine: a multi-source systematic review and meta-analysis. *The Journal of clinical endocrinology and metabolism.* 2025;10(11):3278–3288. Accessed Nov 2025.
37. Vargas-Uricoechea H, and L. W. Combination Therapy vs. Monotherapy with LT4 for Persistent Symptoms of Hypothyroidism: A Systematic Review. *International journal of molecular sciences.* 2024;25(17) Accessed Nov 2025.
38. Nassar M, Hassan A, Ramadan S et al. Evaluating the effectiveness of combined T4 and T3 therapy or desiccated thyroid versus T4 monotherapy in hypothyroidism: a systematic review and meta-analysis. *BMC Endocrine Disorders.* 2024;24(90) Accessed Nov 2025.
39. Millan-Alanis JM, Gonzalez-Gonzalez JG, Flores-Rodriguez A et al. Benefits and Harms of Levothyroxine/L-Triiodothyronine Versus Levothyroxine Monotherapy for Adult Patients with Hypothyroidism: Systematic Review and Meta-Analysis. *Thyroid.* 2021;31(11):1613–1625. Accessed Nov 2025.
40. Akirov A, Fazelzad R, Ezzat S et al. A Systematic Review and Meta-Analysis of Patient Preferences for Combination Thyroid Hormone Treatment for Hypothyroidism. *Frontiers in Endocrinology.* 2020;10(477) Accessed Nov 2025.
41. Hoang TD, Olsen CH, Mai VQ et al. Desiccated thyroid extract compared with levothyroxine in the treatment of hypothyroidism: a randomized, double-blind,

crossover study. *The Journal of Clinical Endocrinology & Metabolism.* 2013;34(6) Accessed Dec 2025.
42. Shakir MKM, Brooks D, McAninch EA et al. Comparative Effectiveness of Levothyroxine, Desiccated Thyroid Extract, and Levothyroxine+Liothyronine in Hypothyroidism. *The Journal of Clinical Endocrinology & Metabolism.* 2021;106(11):e4400–e4413. Accessed Dec 2025.
43. Riis KR, Larsen CB, and SJ. B. Potential Risks and Benefits of Desiccated Thyroid Extract for the Treatment of Hypothyroidism: A Systematic Review. *Thyroid.* 2024;34:687–701.
44. British Medical Journal. Best Practice Primary Hypothyroidism guidance. 2025. Available at: https://bestpractice.bmj.com/topics/en-gb/535. Accessed Nov 2025.
45. Hughes DA, Skiadas K, Fitzsimmons D et al. Liothyronine for hypothyroidism: a candidate for disinvestment or in need of further research? A value of information analysis. *BMJ Open.* 2021;11(12) Accessed Nov 2025.
46. Heald AH, Premawardhana LD, Taylor PN et al. Liothyronine (LT3) prescribing in England: Are cost constraints inhibiting guideline implementation? *Clinical Endocrinology.* 2024;101(1):62–68. Accessed Nov 2025.
47. Competition Appeal Tribunal. Liothyronine (1419;1421-1422) - Judgment. Aug 2023. Available at: https://www.catribunal.org.uk/judgments/liothyronine-14191421-1422-judgment-8-aug-2023http://www.mims.co.uk/. Accessed Jan 2026.
48. Stedman M, Taylor P, Premawardhana L et al. Trends in costs and prescribing for liothyronine and levothyroxine in England and wales 2011-2020. *Clinical Endocrinology.* 2021;94(6):980–989. Accessed Nov 2025.
49. Stedman M, Taylor P, Premawardhana L et al. Liothyronine and levothyroxine prescribing in England: A comprehensive survey and evaluation. *International Journal of Clinical Practice.* 2021;75(9) Accessed Nov 2025.
50. Taylor PN, Razvi S, Muller I et al. Liothyronine cost and prescriptions in England. *The Lancet Diabetes & Endocrinology.* 2019;7(1):11–12. Accessed Nov 2025.
51. Abdelhamid AS, Brown TJ, Brainard JS et al. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. *Cochrane Database of Systematic Reviews.* 2020 Accessed Jan 2026.
52. Brignardello-Petersen R, and GH. G. Assessing the certainty of the evidence in systematic reviews: importance, process, and use. *American Journal of Epidemiology.* 2025;194(6):1681–1686. Accessed Jan 2026.
53. Middleton P, Gomersall JC, Gould JF et al. Omega-3 fatty acid addition during pregnancy. *Cochrane Database of Systematic reviews* 2018 Accessed Jan 2026.
54. Tam KW, Wu MY, Siddiqui FJ et al. Omega-3 fatty acids for dialysis vascular access outcomes in patients with chronic kidney disease. *Cochrane Database of Systematic Reviews.* 2018 Accessed Jan 2026.
55. Downie LE, Ng SM, Lindsley KB et al. Omega-3 and omega-6 polyunsaturated fatty acids for dry eye disease. *Cochrane Database of Systematic Reviews.* 2019 Accessed Jan 2026.
56. Watson H, and C. S. Omega-3 fatty acid supplementation for cystic fibrosis. *Cochrane Database of Systematic Reviews.* 2020 Accessed Jan 2026.
57. Appleton KM, Voyias PD, Sallis HM et al. Omega-3 fatty acids for depression in adults. *Cochrane Database of Systematic Reviews.* 2021 Accessed Jan 2026.

58. Alvarez Campano CG, Macleod MJ, Aucott L et al. Marine-derived n-3 fatty acids therapy for stroke. *Cochrane Database of Systematic Reviews.* 2022 Accessed Jan 2026.
59. Campisi SC, Zasowski C, Bradley-Ridout G et al. Omega-3 fatty acid supplementation for depression in children and adolescents. *Cochrane Database of Systematic Reviews.* 2024 Accessed Jan 2026.
60. Mohammady M, Brown T, Radmehr M et al. Omega-3 fatty acids for intermittent claudication. *Cochrane Database of Systematic Reviews.* 2024 Accessed Jan 2026.
61. Britten-Jones AC, Linstrom TA, Makrai E et al. Omega-3 fatty acid supplementation for distal symmetrical peripheral neuropathy in adults with diabetes mellitus. *Cochrane Database of Systematic Reviews.* 2025 Accessed Jan 2026.
62. Cao Z, Han K, Lu H et al. Paracetamol Combination Therapy for Back Pain and Osteoarthritis: A Systematic Review and Meta-Analyses. *Drugs.* 2024;84:953–967. Accessed Jan 2026.
63. Waitayangkoon P, Moon SJ, Ponnusamy JJT et al. Long-Term Safety Profiles of Macrolides and Tetracyclines: A Systematic Review and Meta-Analysis. *Journal of Clinical Pharmacology.* 2023;64(2):164–177. Accessed Feb 2026.
64. Wewege MA, Bagg MK, Jones MD et al. Comparative effectiveness and safety of analgesic medicines for adults with acute non-specific low back pain: systematic review and network meta-analysis. *British Medical Journal.* 2023;380 Accessed Jan 2026.
65. Buendia JA, Guerrero-Patino D, and A. Z. Cost-utility analysis of prenatal supplementation with long-chain n-3 fatty acids to reduce the incidence of wheezing and asthma in neonates. *The Journal of Asthma.* 2024;61(9):988–996. Accessed Jan 2026.
66. Bernasconi AA, Maki KC, and EA. F. Cost-Effectiveness of Long-Chain Omega-3 Supplementation for the Secondary Prevention of Cardiovascular Disease in the United States. *Value in Health* 2025;28(10):1481–1487. Accessed Jan 2026.
67. Gkegkes ID, Minis EE, and C. I. Oxycodone/naloxone in postoperative pain management of surgical patients. *Journal of Opioid Management.* 2018;14(1) Accessed Jan 2026.
68. Candy B, Jones L, Vickerstaff V et al. Mu-opioid antagonists for opioid-induced bowel dysfunction in people with cancer and people receiving palliative care. *Cochrane Database of Systematic Reviews.* 2022 Accessed Jan 2026.
69. Kistemaker KRJ, Sijani F, Brinkman DJ et al. Pharmacological prevention and treatment of opioid-induced constipation in cancer patients: A systematic review and meta-analysis. *Cancer Treatment Reviews.* 2024;125 Accessed Jan 2026.
70. Davidson SJ, Barrett HL, Price SA et al. Probiotics for preventing gestational diabetes. *Cochrane Database of Systematic Reviews.* 2021 Accessed Jan 2026.
71. Zhao Y, Rong Dong B, and Q. H. Probiotics for preventing acute upper respiratory tract infections. *Cochrane Database of Systematic Reviews.* 2022 Accessed Jan 2026.
72. Sharif S, Meader N, Oddie SJ et al. Probiotics to prevent necrotising enterocolitis in very preterm or very low birth weight infants. *Cochrane Database of Systematic Reviews.* 2023 Accessed Jan 2026.

73. Esmaeilinezhad Z, Ghosh NJ, Walsh CM et al. Probiotics for the prevention of Clostridioides difficile-associated diarrhea in adults and children. *Cochrane Database of Systematic Reviews.* 2025 Accessed Jan 2026.
74. Vasant DH, Paine PA, Black CJ et al. British Society of Gastroenterology guidelines on the management of irritable bowel syndrome . *Gut.* 2021;70(7):1214–1240. Accessed Jan 2026.
75. Buzatu R, Luca MM, and BA. B. Does Vitamin C Supplementation Provide a Protective Effect in Periodontal Health? A Systematic Review and Meta-Analysis. *International Journal of Molecular Sciences* 2024;25(16) Accessed Jan 2026.
76. Ruzijevaite G, Acaite E, and E. J. Therapeutic Impact of Ascorbic Acid on Oral and Periodontal Tissues: A Systematic Literature Review. *Medicina.* 2024;60(12) Accessed Jan 2026.
77. Hujoel PP, Kato T, Hujoel IA et al. Bleeding tendency and ascorbic acid requirements: systematic review and meta-analysis of clinical trials. *Nutrition Reviews.* 2021;79(9):964–975. Accessed Jan 2026.
78. Guan Y, Dai P, and H. W. Effects of vitamin C supplementation on essential hypertension: A systematic review and meta-analysis. *Medicine.* 2020;99(8) Accessed Jan 2026.
79. Namkhah Z, Ashtary-Larky D, and F. N. Does vitamin C supplementation exert profitable effects on serum lipid profile in patients with type 2 diabetes? A systematic review and dose-response meta-analysis. *Pharmacological Research.* 2021;169 Accessed Jan 2026.
80. Lbban E, Kwon K, Ashor A et al. Vitamin C supplementation showed greater effects on systolic blood pressure in hypertensive and diabetic patients: an updated systematic review and meta-analysis of randomised clinical trials. *International Journal of Food Sciences and Nutrition.* 2023;74(8):814–825. Accessed Jan 2026.
81. Lei T, Lu T, Yu H et al. Efficacy of Vitamin C Supplementation on Chronic Obstructive Pulmonary Disease (COPD): A Systematic Review and Meta-Analysis. *International Journal of Chronic Obstructive Pulmonary Disease* 2022;17:2201–2216. Accessed Jan 2026.
82. Pejcic AV, Petrovic NZ, Djordjic MD et al. Vitamin C Levels in Pregnant Women and the Efficacy of Vitamin C Supplements in Preventing Premature Rupture of Membranes: A Systematic Review and Meta-Analysis. *Balkan Medical Journal.* 2024;41(4):248–260. Accessed Jan 2026.
83. Otte JA, Chu G, Heran B et al. Tramadol (with or without acetaminophen) efficacy and harm. *Canadian Family Physician.* 2025;71(9):574–581. Accessed Jan 2026.
84. Armstrong AW, Hekmatjah J, and LH. K. Oral Tetracyclines and Acne: A Systematic Review for Dermatologists. *Journal of Drugs in Dermatology.* 2020;19(11):s6–s13. Accessed Feb 2026.
85. Jeppesen R, Christensen RHB, Pedersen EMJ et al. Efficacy and safety of anti-inflammatory agents in treatment of psychotic disorders - A comprehensive systematic review and meta-analysis. *Brain, Behavior & Immunity.* 2020;90:364–380. Accessed Feb 2026.
86. Joaquim AF, Daniel JW, Schroeder GD et al. Neuroprotective Agents as an Adjuvant Treatment in Patients With Acute Spinal Cord Injuries: A Qualitative Systematic Review of Randomized Trials. *Clinical Spine Surgery.* 2020;33(2):65–75. Accessed Feb 2026.

87. Strickland BA, Bakhsheshian J, Emmanuel B et al. Neuroprotective effect of minocycline against acute brain injury in clinical practice: A systematic review. *Journal of Clinical Neuroscience.* 2021;86:50–57. Accessed Feb 2026.
88. Jin XX, Wang X, Shan Y et al. Efficacy and safety of tetracyclines for pemphigoid: a systematic review and meta-analysis. *Archives of Dermatological Research.* 2021(2):191–201. Accessed Feb 2026.
89. Zhou K, Li CL, Zhang H et al. Minocycline in the eradication of Helicobacter pylori infection: A systematic review and meta-analysis. *World Journal of Gastroenterology.* 2024;30(17):2354–2368. Accessed Feb 2026.
90. Gilron I, Xiao MZX, Carley M et al. Glial-modulating agents for the treatment of pain: a systematic review. *Pain.* 2025;166(5):1030–1049. Accessed Feb 2026.
91. Ravindra D, Huang G, Hallett K et al. Antibiotic Exposure and Dental Health: A Systematic Review. *Pediatrics.* 2023;152(1) Accessed Feb 2026.
92. Steadman W, Brown Z, and Wall CJ. Minocycline black bone disease in arthroplasty: a systematic review. *Journal of Orthopaedic Surgery.* 2021;16 Accessed Feb 2026.

Appendix 1: Categorisation of low value for prescribing medicines within value-based prescribing programme domains

Table 3. Categorisation of low value for prescribing medicines within value-based prescribing programme domains

Optimal prescribing for increased patient safety	Optimal prescribing for increased efficiency
Co-proxamol	Omega-3 fatty acids
Chloral hydrate	Oxycodone/naloxone combination products
Minocycline	Perindopril arginine
Paracetamol/tramadol combination products	Rubefacients
	Probiotics
	Ascorbic acid
	Alimemazine
	Blood glucose testing strips
	Liothyronine
	Armour thyroid

Appendix 2: All Wales primary care expenditure (£) on the medicines identified as low value for prescribing in NHS Wales 2024–2025

Table 4. Primary care expenditure in NHS Wales on the medicines identified as low value for prescribing in 2024–2025

Low value medicine	NHS Wales primary care expenditure 2024-2025
Alimemazine	£206,640
Armour Thyroid	£93,290
Ascorbic acid	£211,632
Blood glucose testing strips	£5,100,790
Chloral hydrate	£247,957
Co-proxamol	£29,801
Liothyronine	£548,678
Minocycline	£8,642
Omega-3 fatty acid compounds	£408,558
Oxycodone/naloxone	£132,833
Paracetamol/tramadol	£44,556
Perindopril arginine	£37,438
Probiotics	£25,060
Rubefacients	£117,780

Appendix 3: Primary care expenditure (£) on the medicines identified as low value for prescribing in NHS Wales by health board in 2024–2025

Table 5. Primary care expenditure (£) on the medicines identified as low value for prescribing in NHS Wales per health board in 2024–2025

Low value medicine	Aneurin Bevan	Betsi Cadwaladr	Cardiff And Vale	Cwm Taf Morgannwg	Hywel Dda	Powys	Swansea Bay
Alimemazine	9,058	25,834	22,303	61,388	36,589	22,941	28,528
Armour Thyroid	11,827	7,469	22,975	3,882	4,761	23,470	18,908
Ascorbic acid	40,103	40,067	28,358	52,288	15,321	13,930	21,566
Blood glucose testing strips	1,060,127	1,306,886	688,066	702,490	602,590	260,138	480,493
Chloral hydrate	76,517	20,255	32,688	55,317	28,659	0	34,521
Co-proxamol	0	20,807	0	2,421	6,573	0	0
Liothyronine	112,862	76,160	110,399	56,499	108,656	20,173	63,930
Minocycline	1,942	961	521	1,246	2,582	328	1,062
Omega-3 fatty acid compounds	136,432	81,676	36,035	82,725	34,303	7,575	29,812
Oxycodone/naloxone	10,970	1,502	44,702	29,116	29,902	6,517	10,123
Paracetamol/ tramadol	6,460	14,835	6,120	9,645	5,025	1,211	1,260
Perindopril arginine	3,204	25,824	1,887	2,610	2,678	377	857
Probiotics	3,145	2,035	5,750	5,410	3,106	1,845	3,769
Rubefacients	16,789	34,504	10,656	29,159	14,605	3,901	8,166

Appendix 4: Primary care expenditure (£) per 1,000 patients on the medicines identified as low value for prescribing in NHS Wales by health board in 2024–2025

Table 6. Primary care expenditure (£) per 1,000 patients on the medicines identified as low value for prescribing in NHS Wales per health board in 2024–2025

Low value medicine	Aneurin Bevan	Betsi Cadwaladr	Cardiff And Vale	Cwm Taf Morgannwg	Hywel Dda	Powys	Swansea Bay
Alimemazine	14.38	36.14	41.22	130.23	91.17	161.68	71.01
Armour Thyroid	18.77	10.45	42.46	8.24	11.86	165.41	47.06
Ascorbic acid	63.66	56.06	52.41	110.93	38.18	98.18	53.68
Blood glucose testing strips	1,682.74	1,828.45	1,271.54	1,490.28	1,501.53	1,833.40	1,195.94
Chloral hydrate	121.46	28.34	60.41	117.35	71.41	0.00	85.92
Co-proxamol	0.00	29.11	0.00	5.14	16.38	0.00	0.00
Liothyronine	179.15	106.55	204.02	119.86	270.75	142.18	159.12
Minocycline	3.08	1.34	0.96	2.64	6.43	2.31	2.64
Omega-3 fatty acid compounds	216.56	114.27	66.59	175.50	85.48	53.39	74.20
Oxycodone/ naloxone	17.41	2.10	82.61	61.77	74.51	45.93	25.20
Paracetamol/ tramadol	10.25	20.76	11.31	20.46	12.52	8.53	3.14
Perindopril arginine	5.09	36.13	3.49	5.54	6.67	2.66	2.13
Probiotics	4.99	2.85	10.63	11.48	7.74	13.00	9.38
Rubefacients	26.65	48.27	19.69	61.86	36.39	27.49	20.33

Appendix 5: Secondary care expenditure (£) on the medicines identified as low value for prescribing in NHS Wales 2024–2025

Table 7. Secondary care expenditure (£) in 2024–2025 for the active recommendations basket*

Low value medicine	Spend 2024–2025
Alimemazine	£25,209
Armour Thyroid	£39,499
Ascorbic acid	£4,505
Chloral hydrate	£109,424
Co-proxamol	£9,253
Liothyronine	£99,976
Minocycline	£1,197
Omega-3 fatty acid compounds	£7,316
Oxycodone/naloxone	£5,180
Probiotics	£1,689

* Where medicines are showing a zero spend in the secondary care related data these have not been included within this table.

Appendix 6: Supporting information for implementation of the recommendations

1. **Co-proxamol**
   - Welsh Government: Health Professional Letter: Prescribing of co-proxamol

2. **Liothyronine**
   - Use of liothyronine (T3) in hypothyroidism: Joint British Thyroid Association/Society for endocrinology consensus statement
   - Specialist Pharmacy Service (SPS): Avoid prescribing desiccated (natural) thyroid extract
   - PrescQIPP bulletin 314: Liothyronine
   - NICE NG145: Thyroid disease: assessment and management
   - NHS England. Liothyronine – advice for prescribers

3. **Omega-3 fatty acid compounds**
   - PrescQIPP bulletin 343: Omega-3 fatty acid compounds and other fish oils

4. **Probiotics**
   - PrescQIPP bulletin 262: Probiotics
   - British Society of Gastroenterology guidelines on the management of irritable bowel syndrome
   - NICE CKS: Aphthous ulcer
   - NICE CKS: Dyspepsia - proven functional

5. **Paracetamol and tramadol combination products**
   - BNF Analgesics

6. **Chloral hydrate**
   - Chloral hydrate, cloral betaine (Welldorm): restriction of paediatric indication (Drug Safety Update)
   - BNF Chloral hydrate

7. **Minocycline**
   - NICE CKS: Acne vulgaris
   - Minocycline for acne vulgaris: efficacy and safety
   - Primary Care Dermatology Society guidelines Acne Primary Care Treatment Pathway
   - AWMSG: Primary care antimicrobial guidelines

8. **Alimemazine**
   - NICE CKS: Urticaria

9. **Blood glucose testing strips**
   - NICE NG28: Type 2 diabetes in adults: management

Appendix 7: Evidence summaries

Evidence summaries were undertaken for all items except blood glucose testing strips. Relevant evidence was sifted and summarised for all items except co-proxamol, chloral hydrate, perindopril arginine and alimemazine for which no relevant evidence was found.

7.1 Liothyronine including desiccated thyroid extracts (e.g. Armour Thyroid)

The All Wales Therapeutics & Toxicology Centre (AWTTC) undertook a scoping search on 13 October 2025 and a literature search on 20-21 October 2025 to find evidence for the use of liothyronine to treat hypothyroidism in adults (non-pregnant) and children. MEDLINE, Embase and the Cochrane Library were searched from 1 January 2017 until 20 October 2025 as well as key resources such as PrescQIPP and TRIP. The search strategies were designed using a combination of both indexing and free text terms and were restricted to English language publications. One search was restricted to secondary studies (e.g. systematic reviews), where reduction in symptoms and, separately, adverse events were the outcomes of interest. A separate search was restricted to economic evaluations and used an economic search filter provided by Canada's Drug Agency (described under 'Economic evaluations'). The reference lists of relevant reviews were hand-searched to extract and compare included studies. The full search strategy is available on request. Results from the literature search were sifted and screened by an AWTTC author. After de-duplication, 53 clinical studies were identified, 6 (systematic reviews with or without meta-analyses) were relevant by title, 5 of these were relevant by abstract and 3 of these were relevant by full text. Two additional systematic reviews were identified using TRIP. This evidence summary includes 5 systematic reviews and 6 guidelines, described below.

7.1.1 Clinical

All 5 systematic reviews included searches of Pubmed/MEDLINE, 4 used Embase and Web of Science, 3 used Cochrane databases, 2 used ClinicalTrials.gov and Scopus while the remaining resources were used within single studies, Clinical Study registry, the US Food and Drug Administration Adverse Reporting System (FAERS), MHRA Yellow Card Scheme, BIOSIS, Emcare and PsycInfo. Although different review questions were asked, the randomised controlled trials (RCTs) identified (n = 26) were similar across all five systematic reviews; four of the studies defined exclusively including RCTs, while the fifth review included reporting on case reports, cohort studies and pharmacovigilance databases (MHRA and FAERS), in addition to RCTs.

Bahl et al. (2025) reported 21 RCTs investigating combination therapy (liothyronine and levothyroxine) compared with levothyroxine monotherapy for hypothyroidism (including Hashimoto's thyroiditis and autoimmune thyroiditis, as per search strategy) in relation to liothyronine safety. Defined reporting outcomes included death, cardiovascular outcomes and adverse effects (AEs)/severe AEs. Authors undertook a meta-analysis of withdrawals due to adverse effects within RCTs finding no increase in AE related treatment discontinuation in combination therapy when compared with monotherapy. Analysis of Yellow Card reports and FAERS data indicated a similar AE profile for both liothyronine and levothyroxine[36].

Vargas-Uricoechea et al. (2024) reported 19 RCTs investigating combination therapy (liothyronine and levothyroxine) compared with levothyroxine monotherapy for

persistent symptoms of hypothyroidism (including primary and secondary forms of hypothyroidism, as per search strategy). Defined reporting outcomes included the following hypothyroidism symptoms: mood, clinical status, quality of life (QoL), cognitive function, depression, anxiety, anger, psychological distress and physical symptoms (pain and fatigue). A narrative synthesis and summary table of the outcomes reported by the included studies indicated no evidence in favour of either combination therapy or levothyroxine monotherapy with respect to alleviating persistent symptoms of hypothyroidism[37].

Nassar et al. (2024) reported 16 RCTs investigating combination therapy (liothyronine and levothyroxine) or desiccated thyroid extract (DTE, 2 RCTs, discussed in Desiccated thyroid extracts section) compared with levothyroxine monotherapy for hypothyroidism (primary forms, as per search strategy). Defined reporting outcomes included measurements of thyroid profile, lipid profile, heart rate, sex hormone-binding globulin (SHBG) and QoL metrics; availability of these outcomes across included RCTs was not uniform. While thyrotropin (TSH) levels were not found to be altered by altered by combination therapy; across 4 reporting studies, total T4 levels were significantly lower and, across 6 reporting studies, total T3 levels were significantly higher. Combination therapy, compared with monotherapy, was not found to significantly alter heart rate, SHBG level or lipid profile across reported studies. No significant effect of combination therapy on QoL measures was reported nor on mental health measurements except for GHQ-28 scores where an improvement with combination therapy was reported[38].

Millan-Alanis et al. (2021) reported 18 RCTs, 11 of which were used in meta-analysis, investigating the benefits and harms of combination therapy (liothyronine and levothyroxine) compared with levothyroxine monotherapy for hypothyroidism (primary or central forms, as per search strategy). Defined reporting outcomes included clinical status, QoL, psychological distress, depressive symptoms and fatigue as well as an evaluation of patient preferences for either treatment. No differences between treatments were observed for any of the defined reporting outcomes above. Subgroup analysis was available for treatment duration, liothyronine dose and dosing frequency per day whereby combination therapy was provided a statistically significant effect on depressive symptoms and psychological distress where liothyronine dose was higher than 10 micrograms. More patients preferred combination therapy when compared with monotherapy or having no preference[39].

Akirov et al. (2020) reported 7 RCTs investigating patient preference for combination therapy for hypothyroidism (of any cause) not in the hospital setting. A pooled prevalence rate for preference of combination therapy over monotherapy was not significantly different from chance. Sensitivity analyses of combination therapy preferences indicated where improvement in mood and symptoms were reported, there was a higher rate of combination therapy preference[40].

Based on the evidence available comparing combination therapy and monotherapy for hypothyroidism, levels of AEs are similar between treatments, as are measures of effectiveness (in relation to changes in symptoms or biomarkers). There are some exceptions to the latter as one review[38] noted combination therapy was found to be associated with improved emotional distress (lower GHQ-28 scores), however this reflected 2 RCTs. Another review reported a link between improvement in depressive symptoms and psychological distress when liothyronine dose was higher than 10 micrograms, reflecting 4 RCTs[39]. Patient preference for combination therapy was

notable, with one study linking this preference to reported improvements in mood and symptoms[40].

7.1.2 Desiccated thyroid extract

A follow-up search for evidence for desiccated thyroid extract (DTE) was performed which used MEDLINE and was restricted from 1 January 2017 until 1 December 2025. Results from this search were sifted and screened by an AWTTC author. Of the 52 publications identified (no duplications), 12 were relevant by title and 11 relevant by abstract; 3 of these were captured by 1 systematic review (which specifically focused on DTE, described below), 4 were surveys that are part of the Treatment of Hypothyroidism in Europe by Specialists: an International Survey (THESIS) project, 1 was a survey of patient experiences and 1 was a narrative review. This evidence summary includes 2 systematic reviews, which both include the same 2 RCTs from the same research group[41,42], described below.

Nassar et al. (2024) (introduced in the previous section) reported 16 RCTs investigating combination therapy (14 RCTs) or DTE (2 RCTs, both used Armour Thyroid tablets) compared with levothyroxine monotherapy for hypothyroidism. In both double-blinded crossover RCTs, DTE was found to increase TSH and serum/plasma T3 levels and decrease plasma T4 levels when compared with levothyroxine monotherapy. While some of the reported changes in cardiovascular measures differed between RCTs (e.g. high-density lipoprotein levels and heart rate), no significant differences were found for QoL measures or symptom scores[38].

Riis et al. (2024) prepared a systematic review on available evidence investigating potential risks and benefits of DTE for the treatment of hypothyroidism up until 6 January 2024. Evidence for the use of DTE was limited, with the same 2 RCTs described previously captured as well as 9 non-randomised studies of intervention (NRSIs) and 3 case reports. Defined reporting outcomes included QoL (primary outcome), symptoms, treatment preference, AEs, thyroid hormone levels, thyroid autoantibodies, cardiovascular measures and gene polymorphisms. When reported (excluding 3 case studies), 6 of the studies used Armour Thyroid tablets, 1 used Thyranon thyroid tablets and 1 used either ERFA thyroid or Armour Thyroid tablets. In addition to this, doses and treatment regimens also differed across included studies. The authors found opposing results as reported for the RCTs (e.g. no significant differences for quality of life measures and symptom scores) when compared with the NRSIs which reported improvements in persistent symptoms[43].

7.1.3 Guidelines

Both NICE NG145 (2023), and the British Medical Journal Best Practice Primary Hypothyroidism guidance (2025) which references NG145, advise not routinely offering liothyronine (either alone or in combination with levothyroxine) for primary hypothyroidism[13,44]. The most recent PrescQIPP Liothyronine bulletin (314) from 2023 similarly recommends not initiating new patients on liothyronine, that it should be started on the advice of an NHS consultant endocrinologist and only if no alternative treatment is available or appropriate. After starting treatment, if no evidence of ongoing clinical benefit is apparent after 3 to 6 months, treatment should be discontinued and switched to levothyroxine monotherapy. Liothyronine should not be used as monotherapy unless the patient has a confirmed allergy or intolerance to levothyroxine or its excipients[11].

A Joint British Thyroid Association (BTA) and Society for Endocrinology (SfE) Consensus Statement (2023) outlines the conditions for which initiating liothyronine (as combination therapy) treatment of primary hypothyroidism may be appropriate, with emphasis on clinicians not feeling obliged to start or continue treatment if they judge it to not be in the patient's best interest[14]. The statement was developed during face-to-face meetings, by virtual consultation with lead reviewers and a systematic search of the literature. The statement was revised following consultation with BTA and SfE executives and with other organisations. The first recommendation states that most patients should be treated with levothyroxine alone, however the recommendations which follow outline a number of different investigations and/or levothyroxine adjustments to carry out before considering a trial of liothyronine. In the UK, liothyronine is available as licensed 5, 10, and 20 microgram preparations. The lack of clinical benefit evidenced in numerous clinical trials is acknowledged alongside the benefit experienced by some receiving liothyronine treatment. The remaining recommendations detail an approach for initiating combination therapy, ideally with the support of an endocrinologist, and when to deprescribe. Of note, the guidance advises patients to use the 5 or 10 microgram preparation for doses lower than 20 micrograms. The statement is clear that liothyronine should not be used as monotherapy unless the patient has a confirmed allergy or intolerance to levothyroxine or its excipients[14]. The NHS England document, Liothyronine – advice for prescribers, incorporates both the BTA and SfE Consensus Statement as well as NG145 with respect to treatment of hypothyroidism with liothyronine[15].

The Specialist Pharmacy Service (SPS) updated the guidance, Avoid prescribing desiccated (natural) thyroid extract (2026), which recommends levothyroxine for an underactive thyroid[12]. When requested, DTE should not be initiated in primary care, the guidance states that it should be reserved for initiation by an NHS endocrinologist on a case-by-case review, which is also supported by the joint BTA/SfE consensus statement summarised above[14]. The guidance advises considering referring people already using DTE to an NHS endocrinologist for review in addition to information about switching from and concerns with DTE.

7.1.4 Economic evaluations

Results from the economic evaluations search were sifted and screened by an AWTTC author. After de-duplication, 134 economic evaluations were identified, 1 of which had conducted a cost utility and value of information analysis, described below. When sifting the same economic evaluation search, 3 publications focused on prescribing trends were identified and 1 piece of correspondence, while a google search identified a second piece of correspondence. These results were described in a subsequent section (Prescribing trends).

Hughes et al. (2021) undertook a health technology reassessment (NHS primary care setting), performing cost utility and value of information analyses, on the cost-effectiveness of liothyronine as combination therapy compared with levothyroxine monotherapy for people with hypothyroidism whose symptoms have not responded to monotherapy. In developing an economic model, health utilities were obtained from a survey of people with hypothyroidism (n = 54), the likelihood of the addition of liothyronine in returning patients to age-matched population heath was based on a survey of endocrinologists (n = 5) and GPs (n = 3) who also provided estimates of healthcare resource use by patients. The perspective of the NHS was adopted with a 10-year time horizon and the analysis was reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards statement.

The mean utility value for those surveyed was 0.53, ranking them in the bottom decile of 100 chronic diseases. The economic analysis suggests that combination therapy may represent a cost-effective treatment option for people who remain symptomatic with monotherapy alone despite free levothyroxine and TSH concentrations within reference ranges. The ICER fell below the NICE cost-effectiveness threshold (£20,000 per QALY) at £11881 per QALY gained however the probability of combination therapy being cost-effective at this threshold was 0.557 which reflects the uncertainty that continued use would result in a positive net health benefit. With respect to the value of information analysis, the Expected Value of Sample Information (EVSI) was calculated and based on a population EVSI of £3.64 million per year, the value of a clinical trial would be expected to exceed its cost within 1 year. The authors acknowledge a number of caveats to the analyses, e.g. the model is a simple representation of what is a complex clinical management problem, however the analyses required assumptions to be made[45].

A health technology reassessment (UK setting) suggests liothyronine as combination therapy for people with hypothyroidism whose symptoms have not responded to monotherapy could be a cost-effective treatment option, with the ICER falling below the NICE cost-effectiveness threshold at £11881 per QALY gained, however there is uncertainty that continued use would result in a positive net health benefit[45].

7.1.5 Prescribing trends

Heald et al. (2024) investigated the effect of prescribing policies (e.g. the BTA and SfE Consensus statement) and the 2020 Competitions and Marketing Authority (CMA) ruling, on prescribing data for levothyroxine, natural desiccated thyroid (NDT) and liothyronine from 2016 to 2022 in England. The authors found that while the total amount of prescriptions for liothyronine had fallen within that timeframe (to 0.2% of all hypothyroidism medications), their cost accounted for 14% of all hypothyroidism medication costs. This was considered due to the cost of the 5 and 10 microgram preparations remaining much more expensive than the cost of 20 microgram preparations while, in practice, the BTA and SfE Consensus statement recommends a lower dose of 5-10 micrograms twice each day. The number of GP practices issuing liothyronine prescriptions also fell over that time[46].

This same research group (Stedman et al. 2021) had previously investigated the effect of earlier prescribing policies and liothyronine price inflation, following its de-branding in 2007, on liothyronine and levothyroxine prescribing data in both England and Wales. Advanz acquired Tertroxin (liothyronine tablets developed in 1950s) in 1992 (already long off-patent). In 2007, Advanz decided to de-brand product and to supply instead as generic drug[47]. At that time, guidelines (e.g. BTA, 2016) advised combination therapy only when patients had not benefited from levothyroxine monotherapy and when considered appropriate by an endocrinologist. Despite the high cost of liothyronine, its categorisation as a ‘low priority for funding’ medicine within Wales and in England (e.g. should not be routinely prescribed in primary care), and ambiguous national guidelines, liothyronine was still widely prescribed across Wales and England at that time[48].

Stedman et al. (2021) have also used a variety of NHS GP practice datasets and regression modelling to evaluate geographical variation in levothyroxine and liothyronine prescribing across GP practices in England and what factors may be associated with that variation. The authors found that the 135 clinical commissioning groups (CCGs) within which a GP practice was located was the greatest factor in the

approach to both levothyroxine and liothyronine prescribing. Factors associated with increased levothyroxine prescribing were the proportion of people registered with diabetes and chronic obstructive pulmonary disease at a GP practice and rates of antidepressant prescribing, while the proportion of people with obesity and of people with significant socioeconomic deprivation were associated with reduced prescribing. Factors associated with increased liothyronine prescribing were antidepressant use and the percentage of people with type 2 diabetes achieving HbA1c control of 58 mmol/mol or less, whereas obesity, diabetes and smoking were associated with reduced prescribing[49].

An earlier piece of correspondence that reported on an analysis of NHS England open prescribing data from August 2013 to July 2018 had identified that, while the median number of monthly liothyronine prescriptions per 195 CCGs had fallen over that time, the most substantial changes in prescribing coincided with the biggest increase in liothyronine cost. When analysing this prescribing data alongside deprivation data, liothyronine prescriptions were found to have become significantly lower over that timeframe in areas that were more deprived compared with areas that were least deprived[50].

Despite national measures to reduce its prescribing, which have been effective, the overall cost of liothyronine has increased and discrepancies in its prescribing exist (e.g. in England). All of the above studies reported in this section were prepared by the same research group based in Wales.

7.2 Omega-3 fatty acid compounds

The All Wales Therapeutics & Toxicology Centre (AWTTC) undertook a scoping search on 13 October 2025 and the most recent literature search was completed on 7 January 2026 to find evidence for the use of omega-3 fatty acid compounds (omega-3 FAs) to treat any indication (licensed or unlicensed) in adults and children. MEDLINE, Embase and the Cochrane Library were searched from 1 January 2018 until 7 January 2026 as well as key resources such as PrescQIPP and TRIP. The search strategies were based on a published Cochrane review's search strategy and were restricted to English language publications[51]. One search was restricted to secondary studies (e.g. systematic reviews), where reduction in symptoms, prevention/reduction in risk of symptoms and, separately, adverse events (AE) were the outcomes of interest. A separate search was restricted to economic evaluations and used an economic search filter provided by Canada's Drug Agency (described under 'Economic evaluations'). The full search strategy is available on request. Given the long-standing interest in omega-3 FAs' potential use for many different therapeutic indications, the clinical search results were extensive and included nearly 200 Cochrane reviews. For this reason, and as Cochrane reviews are recognised worldwide as the highest standard in evidence-based healthcare, we have focussed on reporting the results from Cochrane reviews within the clinical evidence summary. Results from the literature search were sifted and screened by an AWTTC author. After de-duplication, 190 Cochrane reviews were identified, 15 were relevant by title, 10 of these were relevant by abstract and full text. This evidence summary includes 10 Cochrane reviews, 1 of which was referenced within the 2022 update of this guidance (included here for completeness), and 1 PrescQIPP bulletin, all of which are described below.

7.2.1 Clinical

All 10 Cochrane reviews included searches of MEDLINE, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL), 9 used ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), 5 used EBSCO's CINAHL database while the remaining resources were used within 1-2 studies such as Web of Science, PsychINFO, *meta*Register of Controlled Trials (*m*RCT), BIOSIS Citation Index and others. Two of the publications utilised specialised registers published within CENTRAL, the Cystic Fibrosis Trials Register and the Pregnancy and Childbirth's Trials Register. These registers are maintained by Information Specialists and contain trials identified from the databases above. All 10 Cochrane reviews were intervention reviews, which assessed the effectiveness/safety of the same treatment (e.g. omega-3 FAs), however the population (and outcome measures) of each of the reviews differed, illustrating the wide variety in potential therapeutic uses of omega-3 FAs. All 10 Cochrane reviews employed the GRADE approach to rate the certainty in the evidence (also known as the quality of evidence), which reflects the confidence that the truth lies on one side of a specified threshold or within a specific range (Table 8)[52]. GRADE classifies the potential limitations of the body of evidence into five categories (e.g. study design limitations, inconsistency, imprecision, indirectness and publication bias).

Table 8. GRADE Working Group grades of evidence

GRADE Working Group grades of evidence	
High certainty	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Middleton et al. (2018), updating an earlier published review, reported 70 RCTs investigating the effects of omega-3 FAs, as supplements or as dietary additions, during pregnancy compared with no omega 3 fatty acid compounds on four groups of outcomes: birth/infant (7), maternal (7), child/adult (7) and health service (4)[53]. When receiving omega-3 FAs, the quality of evidence (Table 1) was high for three birth/infant outcomes:

- preterm birth < 37 weeks (26 RCTs) – reduced risk
- early preterm birth < 34 weeks (9 RCTs) – reduced risk
- low birth weight (15 RCTs) – reduced risk.

When receiving omega-3 FAs, the quality of evidence (Table 1) was moderate for three birth/infant outcomes, two maternal outcomes and one health services outcome:

- perinatal death (10 RCTs) – possible reduced risk
- small-for-gestational age/intrauterine growth restriction (8 RCTs) – little or no difference
- large-for-gestational age (6 RCTs) – possible small increased risk

- prolonged gestation > 42 weeks (6 RCTs) – possible increased risk
- gestational length (41 RCTs) – possible increased risk
- infant admission to neonatal care (9 RCTs) – possible reduced risk.

The evidence for remaining outcomes was of low quality (14) or very low quality (2)[53]. The use of omega-3 FAs during pregnancy for these outcomes is unlicensed.

Tam et al. (2018) reported 5 RCTs investigating the effects of omega-3 FA supplementation for maintenance of long-term vascular access (e.g. arteriovenous fistulas [AVFs] and grafts [AVGs]) in end-stage kidney disease (ESKD) patients undergoing high quality haemodialysis compared with placebo[54]. For AVFs, when receiving omega-3 FAs, the certainty of evidence (Table 1) was moderate for:

- loss of patency (1 RCT) – probably little or no difference
- death (1 RCT) – probably little or no difference.

When reported, the evidence for remaining outcomes, for both AVFs and AVGs, was of low quality (2) or very low quality (5)[54]. The use of omega-3 FAs in ESKD patients undergoing high quality haemodialysis for these outcomes is unlicensed.

Downie et al. (2019) reported 34 RCTs investigating the effects of omega-3 FA supplementation on dry eye signs and symptoms[55]. When receiving omega-3 FAs, compared with either placebo or no treatment, the certainty of evidence (Table 1) was moderate for improvement in Schirmer scores test at one month (7 RCTs), the evidence for the remaining five outcomes was low. When receiving omega-3 FAs in combination with conventional therapy, compared with conventional therapy, the certainty of evidence (Table 1), when reported, was low. When receiving omega-3 FAs, compared with omega-6 FAs, the certainty of evidence (Table 1) was moderate for reduction in dry eye symptoms (using OSDI scoring) at one month (4 RCTs), the evidence for the remaining five outcomes was low. The authors also presented findings for the comparison between combined omega-3 FA and omega-6 FA supplementation which we have excluded from this summary[55]. The use of omega-3 FAs for dry eye of any kind is unlicensed.

Watson et al. (2020) reported 5 RCTs investigating the effects of omega-3 FA supplementation on cystic fibrosis symptoms in children and adults, compared with placebo[56]w. For all six outcomes, the quality of evidence was very low. This was due to very low participant numbers, low event rates, limited reporting and poor study design. The authors found no consistency in relation to timepoints or outcome measurements used across studies. The available evidence was not adequate to support any change in clinical practice[56]. The use of omega-3 FAs for cystic fibrosis is unlicensed.

Abdelhamid et al. (2020) reported 86 RCTs investigating the effects of omega-3 FAs, as supplements or as dietary additions from either plant (short-chain) or animal (long-chain) sources, on several cardiovascular (CV) outcomes compared with usual or lower intake of omega-3 FAs[51]. When receiving a higher intake of long-chain omega-3 FAs, the certainty of evidence (Table 1) was high for two outcomes:

- all cause mortality (45 RCTs) – little or no difference to risk
- CV events, number of participants experiencing any CV event (43 RCTs) – little or no difference to risk.

The certainty of evidence (Table 1) was moderate for two outcomes:

- CV mortality (29 RCTs) – probably makes little or no difference to risk
- Stroke (31 RCTs) – probably makes little or no difference to risk.

The evidence for remaining outcomes was of either low certainty (3) or very low certainty (2). The number needed to treat for an additional beneficial outcome (NNTB) for coronary heart disease mortality and coronary heart disease events (both low certainty evidence) was 334 (95% CI 200 to infinity) and 167 (95% CI 100 to 500) respectively. When receiving a higher intake of short-chain omega-3 FAs (e.g. alpha-linolenic acid [ALA]), the certainty of evidence (Table 1) was moderate for four outcomes:

- all cause mortality (5 RCTs) – probably little or no difference to risk
- CV events, number of participants experiencing any CV event (4 RCTs) – probably little or no difference to risk
- coronary heart disease mortality (3 RCTs) – probably little or no difference to risk
- arrhythmias (2 RCTs) – probably slightly reduces risk, number needed to treat for an additional beneficial outcome (NNTB) was 91 (95% confidence interval [CI] 56 to 1000)

The evidence for remaining outcomes was of either low certainty (2) or very low certainty (2). The NNTB for CV events (low certainty evidence) was 500 (95% CI 125 to -334). When receiving a higher intake of either long-chain or short-chain omega-3 FAs, the certainty of evidence (Table 1) was high for six outcomes:

- measures of adiposity by weight (14 RCTs) – little or no difference
- measures of adiposity by BMI (15 RCTs) – little or no difference
- serum total cholesterol (30 RCTs) – little or no difference
- serum triglyceride (27 RCTs) – serum triglyceride reduced by about 15% (0.24 mmol/L)
- serum high-density lipoprotein (30 RCTs) – little or no difference
- serum low-density lipoprotein (25 RCTs) – little or no difference.

The certainty of evidence (Table 1) was moderate for three outcomes:

- serum triglyceride (6 RCTs) – probably makes little or no difference
- serum high-density lipoprotein (6 RCTs) – probably makes little or no difference
- serum low-density lipoprotein (7 RCTs) - probably makes little or no difference.

The evidence for remaining outcomes was of either low certainty (1) or very low certainty (2). Based on NNTB, the authors conclude that increasing long-chain omega-3 FAs slightly reduces serum triglycerides while increasing ALA slightly reduces the risk of arrhythmias[51]. Omega-3 FAs are licensed for hypertriglyceridaemia as a supplement to diet when dietary measures alone are insufficient to produce an adequate response however it is unlicensed for the remaining outcomes.

Appleton et al. (2021), updating an earlier published review, reported 28 RCTs investigating the effects of omega-3 FA supplementation on major depressive disorder (MDD) in adults, compared with placebo[57]. For all six outcomes, the certainty of evidence was either low (2) or very low (4). The authors conclude that the

effects of omega-3 FA supplementation compared to antidepressants are very imprecise and uncertain, and that more complete evidence is required for both potential positive and negative effects of omega-3 FAs for MDD[57]. The use of omega-3 FAs for MDD in adults is unlicensed.

Alvarez Campano et al. (2022), updating an earlier published review, reported 9 RCTs investigating the effects of omega-3 FAs on functional outcomes and dependence in people with stroke or transient ischaemic attack (TIA), compared with placebo or open control (no placebo)[58]. Results were assessed separately for short (up to three months) and longer (more than three months) follow-up studies. For all seven outcomes, when short follow-up, the certainty of evidence was either low (3) or very low (4). When longer follow-up, the certainty of evidence was either low (4) or very low (1) when reported. The authors conclude that there is insufficient high certainty evidence to either support or refute the use of omega-3 FAs after stroke[58]. The use of omega-3 FAs for stroke recovery is unlicensed.

Campisi et al. (2024) reported 5 RCTs investigating the effects of omega-3 FA supplementation on clinician diagnosed depression or self-reported depression symptoms in children and adolescents, compared with either placebo, wait list controls, no treatment/supplementation or standard care[59]. The certainty of evidence available was either low or very low, that omega-3 FAs may have little to no difference on attrition, AEs, depression remission or self-reported depression symptoms. The authors highlighted that omega-3 FAs may reduce self-reported depression symptoms as 0.34 standardised mean difference (SMD) was between an SMD of 0.2 (small effect) and 0.5 (moderate effect). This was based on very low certainty evidence[59]. The use of omega-3 FAs for depression symptoms in children and adolescents is unlicensed.

Mohammady et al. (2024), updating an earlier published review, reported 15 RCTs investigating the effects of omega-3 FA supplementation for intermittent claudication, compared with placebo or active control[60]. The certainty of evidence available was either low (1 outcome) or very low (6 outcomes), and the authors were either unable to draw conclusions for the primary outcomes (quality of life, pain-free walking distance and maximal walking distance) due to the poor body of evidence[60]. The use of omega-3 FAs for intermittent claudication is unlicensed.

Britten-Jones et al. (2025) reported 2 RCTs investigating the effects of long-chain omega-3 FA supplementation for diffuse distal symmetrical polyneuropathy (DSPN), a peripheral nerve impairment in diabetes mellitus, compared with placebo or no treatment[61]. When reported, the certainty of evidence was either low (3 outcomes) or very low (for AE and serious AE). The authors did not make any conclusions about the effects of omega-3 FA supplementation for this indication due to the lack of high certainty evidence[61]. The use of omega-3 FAs for DSPN is unlicensed.

7.2.2 Guidelines

NICE TA805 (2022) recommends icosapent ethyl (an ethyl ester of eicosapentaenoic acid [EPA], a long-chain omega-3 FA) as an option for reducing the risk of CV events in adults, outlining the circumstances for which it is appropriate to prescribe[17]. There are no NICE guidelines which recommend prescribing any other omega-3 FAs, for any indication, while there a number which state that omega-3 FAs should not be offered for specific indications: NG238, NG185, CG71, NG49, NG220 and CG170, as well as an evidence summary (ESUOM19).

The omega-3 FA compounds and other fish oils PrescQIPP bulletin (343)[16] from 2024 aligns with NICE guidance and makes a number of recommendations:

- not initiate new patients on omega-3 FA compounds and other fish oils in primary care, except for icosapent ethyl in line with TA805
- deprescribe omega-3 FAs for existing patients, except for icosapent ethyl in line with TA805
- refer patients back to specialists for review, when omega-3 FAs have been when prescribed for specialist indications [62-64], or when recommended by specialist lipid clinic
- if appropriate, patients should be prescribed icosapent ethyl in line with TA805.

Detailed recommendations for patients prescribed warfarin who stop taking omega-3 FAs (e.g. these patients are advised to inform their anticoagulant clinic of the change) are also outlined, in addition to highlighting a dose-dependent increased risk of atrial fibrillation in patients with established CVD or CV risk factors when taking omega-3 FAs (compared to placebo). If atrial fibrillation develops, omega-3 FA supplementation should be permanently discontinued.

7.2.3 Economic evaluations

Results from the economic evaluations search were sifted and screened by an AWTTC author. After de-duplication, 685 economic evaluations were identified, 20 were relevant by title and 2 were relevant by abstract and full text described below (Table 9). Neither of the indications investigated within these publications is licensed within the UK and use of omega-3 FAs for these indications within the UK constitutes off-label use.

Table 9. Characteristics of economic evaluations investigating the cost-effectiveness of omega-3 fatty acid compounds

Lead author	Year	Type	County (currency)	Indication	Comparison	Model	Based on	Findings	Limitations
Buendia JA[65]	2024	Full text	Colombia (USD)	Prevention of wheezing and asthma in newborn*	Without omega-3 FAs	Markov		The mean incremental benefit of omega 3 FA supplementation versus comparator was 0.074 QALY. The incremental cost utility ratio was estimated at 590.68 USD per QALY gained. These outcomes remained robust when subjected to variations in all underlying assumptions and parameter values.	Relative risk extracted from the literature and do not estimate directly from our population Mild to moderate persistent asthma cannot be extrapolated to patients using oral daily corticosteroids or with severe asthma
Bernasconi AA[66]	2025	Full text	USA (USD)	Secondary prevention of CVD*	Usual care	Markov	Intervention studies and SRs	At WTPs below 25,234 USD, usual care is optimal. At 50,000 USD/QALY WTP threshold, 1,000 mg/day omega 3 FA supplementation was most cost effective (ICER of 25,024 USD). At a 100,000 USD/QALY WTP threshold, 2,500 mg/day omega 3 FA supplementation was most cost effective (ICER of 57,981 USD)	Increased Afib risk modelled but mechanism unknown

CA: conference abstract; DPN: diabetic polyneuropathy; ICER: incremental cost-effectiveness ratio; NR: not reported; PHN: post-herpetic neuralgia; QALY: quality adjusted life year; RCT: randomised controlled trial; SRMA: systematic review and meta-analysis; USD: US Dollars; *unlicensed indication

7.3 Oxycodone and naloxone combination products

A search of the evidence was carried out in January 2026; three systematic reviews were identified that included oxycodone and naloxone combination product as an intervention, two of which investigated opioid-induced constipation in people with cancer and people receiving palliative care, and one investigating pain management of surgical patients. All three reviews reported no difference in the risk of adverse effects[67-69]. One review found treatment with combination product significantly improved Bowel Function Index in people with cancer compared to oxycodone with laxatives while another found this treatment led to no significant difference in bowel function in surgical patients when compared to control groups[68,69].

7.4 Probiotics

A search of the evidence was carried out in January 2026 with a focus on Cochrane systematic reviews; 19 systematic reviews were identified that included probiotics as an intervention, the populations on which these reviews focused were varied and, for 15 of the 19 systematic reviews, it was found that probiotics either make little or no difference to the outcomes investigated or there was not enough high-quality evidence to determine any effect of their use.

For the remaining 4 systematic reviews:

- High-certainty evidence was available for two maternal outcomes when comparing probiotics with placebo for prevention of gestational diabetes; with probiotic use probably leading to a higher risk of developing pre-eclampsia (4 RCTs) while they make little to no difference to the risk of needing a Caesarean section (6 RCTs). Moderate-certainty evidence was available for two outcomes (one maternal, one infant) for this same comparison; with probiotic use probably making little to no difference to weight gain during pregnancy (4 RCTs) or to the risk of giving birth to a big baby (4 RCTs)[70].
- Moderate-certainty evidence was available for two outcomes when comparing probiotics with placebo/no treatment for prevention of acute upper respiratory tract infection (URTI); with probiotics likely reducing the number of participants diagnosed with URTIs (4 RCTs) and reducing the number of participants who needed prescribed antibiotics for acute URTIs (8 RCTs[71]).
- Moderate-certainty evidence was available for two outcomes when comparing probiotics with placebo/no probiotics for prevention of necrotising enterocolitis in very preterm or very low birth weight infants; with probiotics probably reducing mortality slightly (54 RCTs) and probably having little or no effect on the risk of late-onset invasive infection (49 RCTs)[72].
- Moderate-certainty evidence was available for two outcomes when comparing probiotics with placebo/no treatment control for prevention of *C difficile*-associated diarrhoea (CDAD) in adults and children; with probiotics probably resulting in a small reduction in adverse events (37 RCTs) and there probably being no difference in length of hospital stay (7 RCTs)[73].

A number of relevant NICE Clinical Knowledge Summaries (CKS) were also identified and are summarised here, as well as a recent PrescQIPP bulletin (2020)[21] and British Society of Gastroenterology (BSG) guidelines on the management of irritable bowel syndrome (IBS)[74].

Of 16 NICE CKS guidelines, 13 of them either do not recommend probiotics or find there to be limited quality evidence to recommend their use either way. This applies to indications for adult and child gastroenteritis; infantile colic; constipation in adults; mild, moderate and severe eczema; antibiotic associated diarrhoea; diarrhoea

prophylaxis for travellers; bacterial vaginosis (not pregnant); candida female genital (pregnant); candida female genital acute infection and otitis media with effusion. The evidence for this advice is limited and, in line with BSG guidelines, dependent on probiotic dose and strain[74]. Secondly, NICE CKS acknowledges that there is some evidence that probiotics may help reduce pain associated with recurrent aphthous ulcers. Lastly, NICE CKS includes the use of probiotics for functional dyspepsia within specialist management, that they may be used as an additional therapy, that while evidence is inconsistent, their use may reduce adverse effects.

The Probiotics bulletin (#262) recommends reviewing all patients prescribed probiotics (e.g. branded probiotics) for any indication and discontinuing, explaining that there is insufficient evidence for their continued use[21]. Patients should be advised of probiotics lack of evidence of clinical benefit if they wish to purchase them over the counter. With respect to safety, as probiotics are unregulated, the guideline points out concerns around their potential to disrupt the gut microbiome, to transfer antibiotic resistance genes or to cause serious adverse effects, particularly in patients who are immunocompromised already[21].

Vasant et al. (2021), to update an earlier BSG guideline on IBS, updated existing systematic reviews and network meta-analyses to assess the efficacy of both unlicensed dietary modifications and licensed treatments for IBS[74]. There is a theory that, as the faecal microbiome of patients with IBS is very different from that of people without IBS, this may both be a reason why IBS develops and an opportunity for treatment with probiotics. An update of an earlier meta-analysis (37 RCTs), to include 8 new RCTs, following subgroup analyses according to probiotic types found significant effects on global IBS symptoms or abdominal pain for combinations of probiotics (RR 0.79; 95% CI 0.70 to 0.89), *Lactobacillus* (RR 0.75; 95% CI 0.60 to 0.94), *Bifidobacterium* (RR 0.80; 95% CI 0.70 to 0.91) and *Escherichia* (RR 0.86; 95% CI 0.79 to 0.93). Based on this information (very low evidence quality according to GRADE), this guideline considers it reasonable to advise patients who wish to try probiotics to do so for up to 12 weeks, discontinuing them if there is no improvement in symptoms[74].

7.5 Ascorbic acid (Vitamin C)

A search of the evidence was carried out in January 2026; 33 systematic reviews were identified that included Vitamin C as an intervention, the populations on which these reviews focused were varied and, for 24 of the 33 systematic reviews, it was found that Vitamin C either makes little or no difference to the outcomes investigated, or there was not enough high quality evidence to determine any effect of their use. Six of these studies investigated the effect of Vitamin C on COVID-19; three its effect on sepsis; and two on complex regional pain syndrome.

For the remaining 9 systematic reviews:

- Two reviews investigated the effect of Vitamin C supplementation on periodontal health[75,76].
- One review (15 RCTs) investigated the effect of Vitamin C supplementation on gingival bleeding tendency, and related plasma levels to retinal haemorrhaging; if baseline Vitamin C plasma levels were < 28 mcmol/L (11-28 mcmol/L is the range that protects against scurvy), supplementation reduced gingival bleeding tendency, whereas supplementation did not confer any benefit or reduce this tendency if baseline levels were higher[77].
- One review (8 RCTs) investigated the effect of Vitamin C supplementation on hypertension; a reduction in both systolic and diastolic blood pressure was found after supplementation with Vitamin C, this change was found for a subgroup ≥ 60 years[78].
- Two reviews investigated outcomes for people with type II diabetes mellitus (T2DM), one focusing on serum lipid profile (15 studies) and a second on hypertension (20 studies); the first found Vitamin C supplementation significantly decreased serum triglyceride and total cholesterol while it made no difference to low-density and high-density lipoprotein levels. The second found Vitamin C supplementation reduced systolic blood pressure with stronger effect on people with hypertension and T2DM[79,80].
- One review (10 RCTs) investigated the effect of Vitamin C supplementation on chronic obstructive pulmonary disease (COPD); a significant improvement in two lung function measures following Vitamin C supplementation, FEV1% and FEV1/FVC[81].
- One review (26 studies) investigated the effect of Vitamin C supplementation for prevention of premature rupture of membranes (PROM); women with PROM were found to have significantly lower levels of Vitamin C (18 studies) and supplementation significantly reduced the risk of preterm or term PROM (8 studies)[82].

7.6 Paracetamol and tramadol combination products

A search of the evidence was carried out in January 2026. Three systematic reviews were identified that included paracetamol and tramadol combination product as an intervention; and investigated its licensed indication[62,64,83]. One investigated back pain and osteoarthritis (3 RCTs); another investigated acute non-specific low back pain and included a random effects network meta-analysis (1 RCT); and a third investigated adult pain management (3 RCTs). The network meta-analysis indicated paracetamol and tramadol combination may be associated with increased adverse events compared with placebo. Overall, no significant relevant evidence has been published since 2018 which would challenge the existing recommendation.

7.7 Minocycline for acne

A search of the evidence was carried out in February 2026. One narrative review focused on minocycline's licensed indication[84], while an additional narrative review

and five systematic reviews investigated off-licensed minocycline use, without any significant findings relating to minocycline's clinical effectiveness[85-90]. Two further systematic reviews and a review of case reports explored the safety profile of minocycline, with no significant findings reported[63,91,92].