CONSULTATION DRAFT

Enclosure No:	X/XXXXX/XXXX
Agenda item No:	XX – Medicines Identified as Low Value for Prescribing in NHS Wales (2026 review)
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1.0 Action for consultees

Consultees are asked to consider and comment on the enclosed draft document, *Medicines Identified as Low Value for Prescribing in NHS Wales (2026 review)* and the associated Equality and Health Impact Assessment (EqHIA) form.

2.0 Purpose

The purpose of this document is to provide an update to the set of recommendations from the three current Low Value for Prescribing papers, supporting the effective use of resources within NHS Wales.

A task and finish group, with representation from all health boards, reviewed the existing recommendations. The remit of the group was to decide whether each 'medicine/medicine group' should be retired, retained or refined. In summary, the task and finish group made the following suggestions for the current low value medicines:

- Medicines to be continued (safety domain) – co-proxamol, chloral hydrate, minocycline, paracetamol/tramadol combination products.
- Medicines to be continued (efficiency domain) – doxazosin modified release, oxycodone/naloxone combination products, perindopril arginine, rubefacients, probiotics, ascorbic acid, alimemazine, blood glucose testing strips.
- Medicines to be continued (efficiency domain) and to be supported with a separate comprehensive evidence review – liothyronine, armour thyroid, lidocaine plasters, omega-3 fatty acids.
- Medicines to be discontinued from the active recommendations – tadalafil, aliskiren, ketovite, selenium and silk garments.

Consultees are asked to provide any comments on the recommendations that have been continued or discontinued.

Where recommendations have been continued, this paper provides a draft of the updated recommendations. The background information to these has been reviewed and where relevant updated. For some medicines, the task and finish group felt that a more in-depth literature review needed to be conducted. These have been included as appendices within the paper and consultees are asked to consider the information provided.

Consultees may also wish to provide suggestions for medicines to be considered for inclusion within future updates to the Low Value for Prescribing work.

2.1 Process

- March 2026: Draft document considered by AWPAG
- *April 2026: Draft document out for consultation*
- *June 2026: Consultation comments and responses considered by AWPAG*

- *September 2026: Document presented to AWMSG for endorsement*

2.2 Consultees

Consultees include, but are not limited to:

- Directors of Pharmacy
- Medical Directors
- Assistant Medical Directors
- Health Board Chief Executives
- Directors of Nursing
- Local Medical Committees
- Directors of Public Health
- General Practitioners Committee Wales
- Royal College of General Practitioners
- BMA Cymru
- Llais Cymru
- Community Pharmacy Wales
- Public Health Wales
- Welsh Government
- NHS Wales JCC
- NICE - The National Institute for Health and Care Excellence
- AWMSG members and deputies
- AWPAG members and deputies

Contents

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 routinely 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 routine 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 exceptions 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 routine 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.

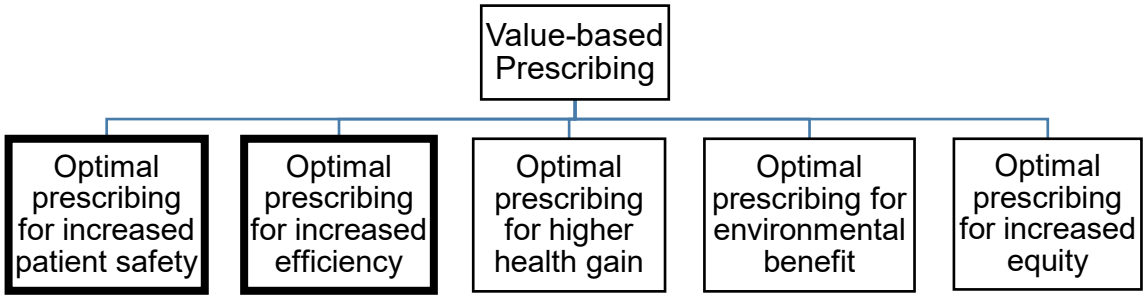
The low value for prescribing series has produced three guidance papers. The first low value for prescribing paper was endorsed by AWMSG in October 2017, with a second paper following in December 2018[6,7]. The third paper was endorsed by AWMSG in February 2020[8]. The immediacy of the final endorsement 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:

- Medicines to be continued (safety domain) – co-proxamol, chloral hydrate, minocycline, paracetamol/tramadol combination products.
- Medicines to be continued (efficiency domain) – doxazosin modified release, oxycodone/naloxone combination products, perindopril arginine, rubefacients, probiotics, ascorbic acid, alimemazine, blood glucose testing strips.
- Medicines to be continued (efficiency domain) and to be supported with a separate comprehensive evidence review – liothyronine including desiccated thyroid extracts (e.g. Armour Thyroid), lidocaine 5% plasters, omega-3 fatty acid compounds.
- Medicines to be discontinued from the active recommendations – tadalafil, aliskiren, ketovite, selenium and silk garments.

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. 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 routinely 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.

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 routine 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 specific patient exemptions identified.

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

Recommendation rationale	Value-based Prescribing domain	NHS Wales primary care expenditure 2024–2025
Lidocaine 5% plasters	**Efficiency**	**£1,658,385**

Rationale:
Lidocaine 5% plasters are licensed in adults for post-herpetic neuralgia (PHN) only. A search of the evidence was carried out in November 2025; 6 systematic reviews and 5 economic evaluations were identified and are described in more detail in their respective appendices (Appendix 7.1.1 and Appendix 7.1.3).

The AWMSG-endorsed All Wales Pharmacological Management of Pain Guidance, specifies lidocaine 5% plasters should only be considered in PHN where oral therapy has resulted in no response or side effects are limiting use[11]. AWMSG's All Wales Analgesic Stewardship Guidance states that lidocaine 5% plaster use in primary care should be restricted to its licensed indication; that long term use should be assessed for continued need, with the view to either discontinue treatment or have a longer period between applications; that off-label use should only be initiated by pain specialists in secondary care, in line with MHRA guidance; and, that lidocaine 5% plaster prescriptions for unlicensed indications should be reviewed to discontinue or switch to a licensed alternative wherever possible[12]. Any need for continued prescribing in these circumstances should be made as a shared decision and should be subject to regular review. Further information on the use of off-label medicines is available in the AWMSG-endorsed Understanding Unlicensed Medicines and accompanying patient information leaflets[13].

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 the prescribing of lidocaine 5% plasters in primary care should be restricted to the licensed indication of post-herpetic neuralgia (PHN) in patients for whom alternative treatments have proved ineffective or where alternative treatments are contra-indicated.

- Patients on long-term therapy with lidocaine 5% plasters should be assessed for continued need, with the view to discontinuing treatment or having a longer plaster free period between applications.
- Off-label use should only be initiated by pain specialists in secondary care and should be in line with MHRA guidance on the use of off-label and unlicensed medicines.

- Patients being prescribed lidocaine 5% plasters for an unlicensed indication should be reviewed with the intention of discontinuing treatment or switching to a licensed alternative wherever possible.
- Stop if no clear benefit within 28 days.

Patient exemptions:
No patient exemptions identified.

Table 2 (continued). Medicines identified as low value for prescribing within NHS Wales and not recommended for routine 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[14].

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[15].

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 7.2.1, Appendix 7.2.3 and Appendix 7.2.4). 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 7.2.2).

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[16]. 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[17].

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

Recommendation[18]:
Within NHS Wales it is recommended that liothyronine is not routinely prescribed for treating primary hypothyroidism in patients who are not under the care of an endocrinologist. After initiation and a period of oversight by the endocrinologist, it may be appropriate for ongoing prescribing of liothyronine to be continued in primary care. The following table summarises recommendations on the use of liothyronine in specific patient populations.

Indication and treatment regimen	Action for General Practitioners and NHS Consultants
Hypothyroidism Patients currently receiving liothyronine monotherapy, or liothyronine and levothyroxine combination therapy	Patients currently prescribed liothyronine, or levothyroxine and liothyronine combination therapy, for hypothyroidism should be reviewed to consider switching to levothyroxine monotherapy where clinically appropriate. In some cases, a retrospective review of the basis for 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 self-funding should not be offered NHS prescribing unless they meet the criteria in this guidance. The consultant 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.
Hypothyroidism Levothyroxine and liothyronine combination therapy for new patients	In rare situations where patients 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
Oncology – Thyroid disease	Prescribing liothyronine in thyroid cancer, where it is used as an adjuvant to radioactive iodine treatment, 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.

Indication and treatment regimen	Action for General Practitioners and NHS Consultants
Resistant depression Liothyronine monotherapy, or liothyronine and levothyroxine combination therapy	All patients currently receiving liothyronine for a psychiatric indication should be reviewed by a consultant NHS psychiatrist, who should consider switching to an alternative treatment where clinically appropriate, or levothyroxine monotherapy where hypothyroidism is diagnosed. Patients continuing to receive liothyronine should be overseen by a consultant NHS psychiatrist.
Use of unlicensed thyroid extracts (e.g. Armour thyroid, ERFA Thyroid), plus compound thyroid hormones, iodine containing preparations, dietary supplementation	The prescribing of unlicensed liothyronine and thyroid extract products is not supported.

Patient exemptions:
This recommendation does not apply to the use of liothyronine post thyroidectomy in thyroid cancer patients. Prescribing in thyroid and parathyroid cancer should only be addressed by specialists in secondary/tertiary care.

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

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 7.3.1 and Appendix 7.3.3).

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 cardiovascular (CV) events in adults, outlining the circumstances for which it is appropriate to prescribe[19]. It is excluded from the 'Omega-3 FA' basket of medicines. 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 – do not offer omega-3 FAs to prevent CV disease.
- NG185 – do not offer or advise people to use either omega-3 FA capsules or omega-3 FA supplemented foods to prevent another myocardial infarction.
- CG71 – people with familial hypercholesterolaemia should not routinely be recommended to take omega-3 FAs.
- NG49 – do not offer omega-3 FAs to adults with non-alcoholic fatty liver disease (NAFLD) because there is not
- enough evidence to recommend their use.
- NG220 – do not offer omega-3 or omega-6 FAs to treat multiple sclerosis (MS) because there is no evidence they affect relapse frequency or progression.
- CG170 – do not use omega-3 FAs to manage sleep problems in autistic children and young people.
- ESUOM19 – an evidence summary for use of omega-3 FAs in people with schizophrenia found the available evidence to be limited and available results to be inconsistent.

The PrescQIPP bulletin (343)[20] from 2024 on omega-3 FA compounds and other fish oils aligns with NICE guidance and makes a number of recommendations:

- do not initiate new patients on omega-3 FA compounds and other fish oils in primary care, except for icosapent ethyl in line with NICE TA805
- deprescribe omega-3 FAs for existing patients, except for icosapent ethyl in line with NICE TA805
- refer patients back to specialists for review, when omega-3 FAs have been when prescribed for specialist indications, or when recommended by specialist lipid clinic
- if appropriate, patients should be prescribed icosapent ethyl in line with NICE 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 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[20].

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 omega-3 fatty acid compounds are not routinely prescribed.

- Advise health boards that omega-3 FAs should not be prescribed in primary care due to limited evidence of clinical/cost effectiveness.
- Omega-3 FAs for existing patients should be deprescribed.

Patient exemptions:
Patients using omega-3 fatty acid compounds who have severe 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 routine 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 routinely prescribed. **Patient exemptions:** No specific patient exemptions identified. However, in exceptional circumstances, if there is a need for the oxycodone and naloxone combination product to be prescribed, this should be in a cooperation arrangement with a multi-disciplinary team and/or healthcare professional.		

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

Recommendation rationale	Value-based Prescribing domain	NHS Wales primary care expenditure 2024–2025
Rubefacients (excluding NSAIDs and capsaicin)	**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[21]. 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 routinely prescribed. **Patient exemptions:** No routine exceptions have been identified.		

Table 2 (continued). Medicines identified as low value for prescribing within NHS Wales and not recommended for routine 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[22]. 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[23]. 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 7.5). 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[24]. 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 routinely prescribed. • Advise health boards that probiotics should not be prescribed in primary care due to limited evidence of clinical effectiveness. **Patient exemptions:** No exceptions have been identified.		

Table 2 (continued). Medicines identified as low value for prescribing within NHS Wales and not recommended for routine 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[25]. 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 2020 which would challenge the existing recommendation. **Recommendation:** Within NHS Wales it is recommended that ascorbic acid is not routinely prescribed. • Advise health boards that prescribers in primary care should not initiate ascorbic acid tablets for any new patient. **Patient exemptions:** 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 routine 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[26]. The paracetamol and tramadol combination product is also more expensive than purchasing the individual components as separate products[27].

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*"[28]. 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[29]. Due to the extra cost of a combination product, paracetamol and tramadol combination product should not be routinely 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 7.7). 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 routinely prescribed.

- Patients currently prescribed paracetamol and tramadol combination product should be reviewed and switched to an alternative product where appropriate.

Patient exemptions:
No specific patient exemptions identified.

277 **Table 2 (continued). Medicines identified as low value for prescribing within NHS Wales and not recommended for routine**
278 **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[30]. Chloral hydrate is classified within the BNF as being less suitable for prescribing in insomnia[28]. It has a narrow therapeutic index, no reversal agent, can result in re-sedation and has been associated with patient fatalities[31].

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[32].

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

- Advise health boards that prescribers should not initiate chloral hydrate in primary care for any new patient.
- Advise health boards that if, in exceptional circumstances, there is a clinical need for chloral hydrate to be prescribed, this should be undertaken in a cooperation arrangement with a multidisciplinary team and/or other healthcare professional.

Patient exemptions:
Must be initiated by a specialist, or in conjunction with a specialist, and is only indicated for short-term treatment.

Table 2 (continued). Medicines identified as low value for prescribing within NHS Wales and not recommended for routine 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[33].

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[28]. 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[34].

A search of the evidence was carried out in February 2026; the results of which are described in more detail in the appendix (Appendix 7.8). 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 routinely prescribed.

- Advise health boards that prescribers in primary care should not initiate minocycline for any new patient with acne.
- Advise health boards to support prescribers in deprescribing minocycline in all patients with acne and, where appropriate, ensure the availability of relevant services to facilitate this change.

Patient exemptions:
No routine exceptions have been identified

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

Recommendation rationale	Value-based Prescribing domain	NHS Wales primary care expenditure 2024–2025
Doxazosin modified release tablets	**Efficiency**	**£95,708**

Rationale:
Doxazosin is licensed for the treatment of hypertension and benign prostatic hyperplasia (BPH). It has a long half-life of 22 hours making it suitable for once daily dosing. Immediate release and modified-release forms of doxazosin are available. Both are administered once daily and so a modified-release version of doxazosin offers no advantage in terms of patient adherence[35].

A search of the evidence was carried out in February 2026; the results of which are described in more detail in the appendix (Appendix 7.9). At the time of publication, no significant relevant evidence has been published since 2020 which would challenge the existing recommendation.

The Specialist Pharmacy Service (SPS) offers guidance on switching strategies for doxazosin modified-release tablets to standard release as both versions are similarly effective, well tolerated and have no apparent difference in adverse effect profile[35].

Recommendation:
Within NHS Wales it is recommended that doxazosin modified-release tablets are not routinely prescribed.

- Patients currently prescribed doxazosin modified-release tablets should be reviewed and switched to an immediate release preparation.
- For patients prescribed doxazosin tablets for the treatment of hypertension, review may be an opportunity to take into account NICE NG136 (last updated February 2026) recommendations, which place alpha-blockers at step 4 (for consideration in resistant hypertension and a blood potassium level of more than 4.5 mmol/l)[36].

Patient exemptions:
No specific patient exemptions identified.

Table 2 (continued). Medicines identified as low value for prescribing within NHS Wales and not recommended for routine 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[37,38]. 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 routinely prescribed. • Patients currently prescribed perindopril arginine should be reviewed and switched to an alternative product where appropriate. **Patient exemptions:** No specific patient exemptions identified.		

Table 2 (continued). Medicines identified as low value for prescribing within NHS Wales and not recommended for routine 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[28]. 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 routinely prescribed. • Advise health boards that prescribers in primary care should not initiate alimemazine for any new patient. • Advise health boards to support prescribers in deprescribing alimemazine in all patients and, where appropriate, ensure the availability of alternative treatment options. **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 routine 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 (costing greater than £10 for 50 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[40].

Recommendation:
Within NHS Wales it is recommended that blood glucose monitoring strips costing greater than £10 per 50 strips are not routinely prescribed.

- Advise health boards that prescribers in primary care should not initiate blood glucose testing strips that cost greater than £10 per 5 strips for any new patient with type 2 diabetes.
- Advise health boards to support prescribers in deprescribing blood glucose testing strips that cost greater than £10 for 50 strips for patients with type 2 diabetes and, where appropriate, ensure the availability of relevant services to facilitate this change.

Patient exemptions:
Patients with type 2 diabetes who have been trained in carbohydrate counting and utilise an appropriate carbohydrate counting meter.

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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	Doxazosin modified release
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
	Lidocaine plasters
	Omega-3 fatty acids

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
Doxazosin tablets MR	£95,708
Lidocaine 5% plasters	£1,658,385
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
Doxazosin tablets MR	16,500	36,463	9,108	13,773	7,245	4,191	8,428
Lidocaine 5% plasters	426,183	315,990	179,587	258,386	249,099	57,823	171,317
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
Doxazosin tablets MR	26.19	51.01	16.83	29.22	18.05	29.54	20.98
Lidocaine 5% plasters	676.48	442.10	331.87	548.15	620.70	407.52	426.40
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
Doxazosin tablets MR	£614
Lidocaine 5% plasters	£344,632
Liothyronine oral preparations	£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. **Lidocaine 5% plasters**
   - NICE CG173: Neuropathic pain in adults: pharmacological management in non-specialist settings
   - NICE CG173: 4-year surveillance: neuropathic pain – pharmacological management
   - PrescQIPP bulletin 350: Lidocaine plasters
   - Off-label or unlicensed use of medicines: prescribers' responsibilities
   - AWMSG: Understanding unlicensed medicines

3. **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

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

5. **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

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

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

8. **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

9. **Doxazosin modified release tablets**
   - NICE NG136: Hypertension in adults: diagnosis and management

- Specialised Pharmacy Service (SPS): Switching doxazosin XL tablets to doxazosin standard tablets

10. Alimemazine

- NICE CKS: Urticaria

11. 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 Lidocaine 5% plasters

The All Wales Therapeutics & Toxicology Centre (AWTTC) undertook a scoping search on 13 October 2025 and a literature search on 11-13 November 2025 to find evidence for the use of lidocaine plasters to treat pain both according to its license, for the symptomatic relief of neuropathic pain associated with previous herpes zoster infection in adults, and any non-licensed indications. MEDLINE, Embase and the Cochrane Library were searched from 1 January 2017 until 11 November 2025 as well as key resources such as PrescQIPP and TRIP. As there is a lot of variation in the terms used to reflect 'lidocaine plasters' within the literature (e.g. lidocaine plaster or patch, lidocaine medicated plaster or patch, lidocaine 5% plaster or patch etc.), and as the focus of the search was lidocaine plasters and not a single or set number of indications, the search strategy was designed to capture publications interested in this treatment irrespective of indication. 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 (e.g. pain measurements) 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, 57 clinical studies were identified, 30 (systematic reviews with or without meta-analyses) were relevant by title, 14 of these were relevant by abstract and 6 of these were relevant by full text. This evidence summary includes 6 systematic reviews, one of which includes updated recommendations on the treatment of neuropathic pain by the Special Interest Group on Neuropathic Pain (NeuPSIG) of the International Association for the Study of Pain (IASP), and 4 additional pieces of guidance, described below.

7.1.1 Clinical

All 6 systematic reviews included searches of Pubmed/MEDLINE, 6 used Embase, 4 used Cochrane databases, 3 used ClinicalTrials.gov, 2 used Web of Science, Google Scholar, the Database of Abstracts of Reviews of Effects (DARE) and the International Clinical Trials Registry Platform (ICTRP) while the remaining resources were used within single studies, CINAHL, PsychInfo, KRS Evidence, the EU Clinical Trials Register and three Chinese resources (China Biology Medicine database, China National Knowledge Infrastructure (CNKI) database and Wanfang database). All 6 systematic reviews restricted their searches to randomised controlled trials (RCTs) and while 2 sought broader interventions (e.g. any treatment for neuropathic pain or any pharmacological and neuromodulation intervention etc.), 3 specified lidocaine patch and 1 specified topical lidocaine. The defined populations varied (e.g. acute localised pain, postsurgical pain, perioperative pain, posttraumatic pain, peripheral neuropathic [PNP] of various origins and neuropathic pain according to the

IASP definition) which resulted in the indications of the included studies also being varied. Although inclusion/exclusion criteria were varied, all 6 systematic reviews had a defined primary outcome as change in pain measurement(s).

The Special Interest Group on Neuropathic Pain (NeuPSIG) of the International Association for the Study of Pain (IASP) sought to update its recommendations for the treatment of neuropathic pain by undertaking an evidence search, systematic review and meta-analysis of the evidence, and a series of expert consensus meetings and anonymous online voting based on the results[41]. GRADE was used to assess the certainty of effect estimates and to develop recommendations based on certainty of evidence, as well as effect size, cost and harms. The group comprised experts in basic science, clinical trials, clinical management, evidence synthesis and people with lived pain experience. Of the 313 RCTs that met inclusion criteria, 284 investigated any pharmacological and 29 investigated any neuromodulation intervention for the IASP definition of neuropathic pain; 4 of these studies investigated lidocaine plasters (n = 487)[42-45]. Defined primary reporting outcome was the proportion of responders, 50% or 30% reduction in baseline pain intensity or moderate pain relief. Meta-analyses were performed for interventions separately and, for lidocaine plasters, forest plots were prepared for the primary outcome risk difference (n = 3) and for the risk difference based upon the number of withdrawals (n = 4). These values were used to calculate a combined number needed to treat (NNT), 14.5 (7.8 to 108.2), and number needed to harm (NNH), 178.0 (23.9 to ∞), for lidocaine plasters. NeuPSIG made a weak recommendation suggesting lidocaine plasters as second line treatment for people living with PNP in a localised area, and potentially as first line treatment for vulnerable patients (e.g. older adults, people with multiple diseases or polypharmacy). The supporting evidence for this recommendation was of very low certainty (GRADE) however the recommendations also considered lidocaine plasters' wide availability, very good safety profile and a patient preference for them (although they are also considered to be high cost)[41].

Felemban et al. (2024) reported 10 RCTs (n = 523) focused on the use of lidocaine plasters for acute localised pain resulting from musculoskeletal and neuropathic entities, as the authors were interested in their use within A&E. Defined outcome was change in pain score (any validated scale) from baseline to endpoint determined by individual RCTs (and IASP criteria if the term acute was not specified). The time points for final pain assessment ranged between 1 hour and 28 days. The evidence available for primary outcome analysis, considered to be of low quality (GRADE), indicated that lidocaine patches were more effective in controlling musculoskeletal and neuropathic pain than placebo patches. The risk of adverse events was similar between lidocaine and placebo patches and, with more evidence available, it was considered to be of moderate quality (GRADE)[46].

Mao et al. (2024) reported 7 RCTs (n = 585) investigating the use of topical lidocaine, compared with placebo or no topical lidocaine, for post-surgical neuropathic pain. Except for one, all of the included RCTs investigated lidocaine plasters. Defined reporting outcomes included pain intensity (as measured by scales or rescue medication use), adverse events, and health-related quality of life. The evidence available for pain relief comprised 1 RCT investigating lidocaine cream and 4 RCTs investigating lidocaine plasters and was of moderate certainty (GRADE). Based on this evidence, the likelihood of pain relief from topical lidocaine treatment was increased with a relative risk (RR) of 1.98 (95% CI: 1.04 to 3.76; P = 0.04). For change in pain scores, with 1 RCT investigating lidocaine cream and 5 RCTs

investigating lidocaine plasters (low certainty of evidence), standardised mean difference (SMD) pooled estimate was -0.70 (95% CI: -1.46 to 0.06; P = 0.07) for treatment with topical lidocaine. High certainty evidence, with 1 RCT investigating lidocaine cream and 5 RCTs investigating lidocaine plasters, showed that topical lidocaine did not increase the adverse event risk with pooled RR of 1.04 (95% CI: 0.93 to 1.16; P = 0.51)[47].

Shi et al. (2023) reported 12 RCTs (n = 617) investigating the use of lidocaine plasters on post-operative wound pain management. Defined primary reporting outcome was cumulative intravenous morphine equivalent use within 24 hours postoperatively, calculated as weighted mean difference (WMD) in mg. The evidence available for this outcome, 8 RCTs (n = 402), was of moderate certainty (GRADE). Based on this evidence, WMD was -4.61 mg (95% CI: -8.09 to -1.14; p=0.009), meaning people receiving lidocaine plasters required less morphine within 24 hours of surgery than people receiving placebo (6 patches, 1 routine postoperative analgesia, 1 intravenous saline infusion), however this did not exceed the threshold for clinical significance[48].

Moisset et al. (2020) reported 131 RCTs investigating any treatment for chronic neuropathic pain (lasting at least 3 months) available for use in France; 3 of these studies investigated lidocaine plasters (n = 250) and had been captured by the NeuPSIG review (above)[42,44,45]. Similarly to the NeuPSIG review, the defined primary reporting outcome was pain intensity, measured as the NNT for a 50% decrease in pain intensity (or a 30% decrease in pain intensity or at least moderate pain relief); efficacy was assessed based on effect size, absolute difference between treatment and placebo or NNT. Meta-analysis was not performed, instead, GRADE was used to assess evidence quality and recommendations were formed in line with AGREE II guidelines[49]. The authors made a weak recommendation suggesting the use of lidocaine plasters first line for PNP in which the pain is confined to a limited area, due moderate quality evidence (GRADE) and an excellent safety profile[50].

Buksnys et al. (2020) prepared a network meta-analysis investigating the efficacy and safety of lidocaine plasters with pregabalin (300 mg or 600 mg daily) for chronic PNP using 43 RCTs (comparators included no treatment or placebo in addition to pregabalin). The defined reporting outcomes were any measure of pain or any measure of quality of life, as used in the RCT, and, for safety, any adverse event (AE), any serious AE, discontinuation due to AE or specific AE. The defined population of PNP was broad and included diabetic peripheral neuropathy, postsurgical or posttraumatic pain and PNP of various origins. The network meta-analysis showed that there was no clear difference between lidocaine plasters and pregabalin (300mg or 600mg daily) for almost all outcomes except change in EQ-5D (in favour of lidocaine plasters) and the safety measures any AE and dizziness (600 mg) and discontinuation due to AE (300 mg and 600 mg). The authors recommend lidocaine plasters for any PNP as a safe alternative to pregabalin[51].

Authors defined taking evidence from RCTs, however there was a lot of variation across included RCT criteria (e.g. with respect to indications, pain definition, study protocol, lidocaine patch use, outcomes, pain scales, follow-up time/timepoints, sample size, reporting etc.) and again in RCT selection by authors. Based on the evidence available, lidocaine plasters were generally found to have a better safety profile than comparators and to be more effective at treating pain than placebo patches. The heterogeneity of the evidence base resulted in weak recommendations

(GRADE) for the use of lidocaine plasters as the evidence needed was not of high certainty.

7.1.2 Guidelines

The All Wales Medicine Strategy Group's (AWMSG) All Wales Analgesic Stewardship Guidance (last updated July 2023) advises reviewing all lidocaine plaster prescriptions[12]. The guidance states that lidocaine plaster use in primary care should be restricted to its licensed indication; that long-term use should be assessed for continued need, with the view to either discontinue treatment or have a longer period between applications; that off-label use should only be initiated by pain specialists in secondary care in line with MHRA guidance and that lidocaine 5% plaster prescriptions for unlicensed indications should be reviewed to discontinue or switch to a licensed alternative wherever possible. The guidance references NeuPSIG's first publication that provided treatment recommendations for neuropathic pain[52] and was adapted from the 'Quality Prescribing in Chronic Pain: A Guide for Improvement 2018-2021' document produced by the Scottish Government and NHS Scotland (2018) which is itself now being updated (consultation deadline 31 October 2025). AWMSG's All Wales Pharmacological Management of Pain Guidance, developed to support prescribers in making the best choices in relation to medicines for pain, specifies how lidocaine plasters should be prescribed (Figure 1)[11].

Figure 2. All Wales Pharmacological Management of Pain Guidance lidocaine plaster prescribing points

Lidocaine 5% plaster	**1 to 2 patches to be applied for 12 out of 24 hours.** Consider when no response to oral therapy or when side effects of oral therapy limit use, for: • **post-herpetic neuralgia only.** **Stop if no clear benefit within 28 days.** Patches can be cut to size for smaller areas of pain to allow multiple use per patch. Lidocaine plasters have been identified as low value for prescribing in NHS Wales.

There is no NICE product on chronic and neuropathic pain that recommends treatment with lidocaine plasters. For example, NICE guidance (NG193) published in 2021 on chronic pain in over 16s, makes no reference to lidocaine plasters for treating neuropathic pain[53].

Healthcare Improvement Scotland's Scottish Palliative Care Guidelines (republished 2019 with further updates ongoing) outlines lidocaine plaster preparations, indications, dosage, administration and practice points as it would be used within palliative care. The guideline notes there being limited evidence for their use and that use should be discontinued if no benefit is found within 2 days[54].

The most recent PrescQIPP Lidocaine mediated plasters bulletin (350) from 2024 was prepared to support the implementation of NHS England guidance on items which should not be routinely prescribed in primary care[55]. It focuses on their use in primary care, for indications such as post-herpetic neuralgia (PHN), and does not cover their use in secondary care (e.g. for post-operative pain or palliative care). The

bulletin recommends restricting prescribing of lidocaine medicated plasters in accordance with national guidance (e.g. AWMSG guidelines), addressing patients' expectations of chronic pain treatments at an early stage and, where treatment with lidocaine medicated plasters is considered appropriate, the bulletin outlines practice points for their use. The bulletin ends by highlighting the limited evidence supporting the use of lidocaine medicated plasters; that they are a relatively costly treatment option; that NICE recommend several other treatments for neuropathic pain that should be used instead; and that, if lidocaine medicated plasters are ineffective or inappropriately prescribed, significant savings are available by reviewing treatment and discontinuing their use[55].

7.1.3 Economic evaluations

Results from the economic evaluations search were sifted and screened by an AWTTC author. After de-duplication, 95 economic evaluations were identified, 22 were relevant by title, 4 of these were relevant by abstract and full text, 3 of which were conference abstracts; all 4 publications reported the outcomes of Markov models built to investigate cost-effectiveness of lidocaine plasters within the health systems of 3 different countries, Brazil, China and Columbia. Characteristics and results from these publications have been extracted (Table 8). All 4 publications found lidocaine plasters to be cost-effective to its comparator (pregabalin or gabapentin). All 4 publications investigated PHN and 3 of these also investigated the unlicensed indication diabetic polyneuropathy (DPN). For a more local context, information from an overview of Markov models investigating the cost-effectiveness of lidocaine plasters in Europe, published prior to the publication of the Low value for prescribing Paper 1, has also been included (Google search)[56].

Liedgens et al. (2013) presented results from nine health economic studies undertaken in eight European countries that compared lidocaine plasters with gabapentin and/or pregabalin in PHN[56]. The included studies were based on a core Markov model (originally designed for the NHS) with data derived from clinical trials, local Delphi panels and official national price and tariff lists. The main outcome was cost per QALY gained and all studies focused on an elderly population with PHN who had insufficient pain relief with standard analgesics and who could not tolerate or had contraindications to tricyclic antidepressants. The original study, taken from the perspective of the NHS and published in 2007, found that six months of lidocaine plaster treatment cost £549 per patient (£936 in 2025 according to Bank of England's inflation calculator), compared with £718 for gabapentin (£1,224.25 in 2025), meaning lidocaine plaster treatment generated 0.05 more QALYs. This meant that lidocaine plasters dominated gabapentin with £2,163 per QALY gained. Probabilistic sensitivity analysis showed that there was a 99.99% chance that lidocaine plasters cost less than £20,000 per QALY relative to gabapentin. The overall results showed that lidocaine plasters are a cost-effective treatment for PHN. Sensitivity analyses demonstrated that the findings were robust and that the outcome was not sensitive to the underlying assumptions of the model. The results show that lidocaine plasters' better safety profile can translate into cost savings[56].

The most recent publications investigating the cost-effectiveness of lidocaine plasters in a UK setting are over a decade old however, based on the included studies, lidocaine plasters have consistently been found to be a cost-effective treatment for PHN (licensed) and DPN (unlicensed) when compared with pregabalin/gabapentin.

Table 8. Characteristics of economic evaluations investigating the cost-effectiveness of lidocaine plasters

Lead author	Year	Type	Country (currency)	Indication	Comparison	Model	Based on	Findings
Piedade AD[57]	2017	CA	Brazil (Real)	PHN and DPN*	Pregabalin, gabapentin	Markov	Published studies	**ICER(s)** **PHN**: 19,256.33 BRL versus pregabalin and 19,102.47 BRL versus gabapentin **DPN***: 19,244.16 BRL versus pregabalin and 23,208.75 BRL versus gabapentin **QALY(s)** NR
Zeng F[58]	2021	Full text	China (Yuan)	PHN	Pregabalin	Markov	Published RCT	**ICER(s)** Dominant **QALY(s)** 0.34012 QALY gain with pregabalin 0.42543 QALY gain with lidocaine plasters
Acosta A[59]	2017	CA	Colombia (US dollars)	PHN and DPN*	Pregabalin, gabapentin	Markov	NR	**ICER(s)** **PHN**: 4,880 USD versus pregabalin **DPN***: 4,988 USD versus pregabalin **QALY(s)** NR
Vargas J[60]	2020	CA	Colombia (US dollars)	PHN and DPN*	Pregabalin	Markov	Published RCT	**ICER(s)** **DPN***: 3,673 USD versus pregabalin **QALY(s)** **PHN**: 0.798 QALY gain with pregabalin **PHN**: 0.895 QALY gain with lidocaine plasters **DPN:** 0.831 QALY gain with pregabalin **DPN**: 0.898 QALY gain with lidocaine plasters

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
*unlicensed indication

7.2 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.

7.2.1 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[61].

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[62].

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[63].

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[64].

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[65].

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[63] 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[64]. Patient preference for combination therapy was notable, with one study linking this preference to reported improvements in mood and symptoms[65].

7.2.2 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[66,67], 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[63].

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[68].

7.2.3 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[16,69]. 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[14].

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[17]. 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[17]. 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[18].

The Specialist Pharmacy Service (SPS) updated the guidance, Avoid prescribing desiccated (natural) thyroid extract (2026), which recommends levothyroxine for an underactive thyroid[15]. 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[17]. 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.

7.2.4 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[70].

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[70].

7.2.5 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[71].

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[72]. 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[73].

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[74].

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[75].

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.

7.3 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[76]. 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.

7.3.1 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 9)[77]. 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 9. 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)[78]. 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)[78]. 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[79]. 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)[79]. 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[80]. 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[80]. 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[81]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[81]. 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[76]. 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[76]. 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[82]. 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[82]. 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)[83]. 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[83]. 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[84]. 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[84]. 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[85]. 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[85]. 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[86]. 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[86]. The use of omega-3 FAs for DSPN is unlicensed.

7.3.2 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[19]. 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)[20] 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 [87-89], 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.

7.3.3 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 10). 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.

1601 **Table 10. 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[90]	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[91]	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

1602

7.4 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[92-94]. 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[93,94].

7.5 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)[95].
- 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[96]).
- 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)[97].
- 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)[98].

A number of relevant NICE Clinical Knowledge Summaries (CKS) were also identified and are summarised here, as well as a recent PrescQIPP bulletin (2020)[24] and British Society of Gastroenterology (BSG) guidelines on the management of irritable bowel syndrome (IBS)[99].

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[99]. 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[24]. 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[24].

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[99]. 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[99].

7.6 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[100,101].
- 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[102].
- 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[103].
- 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[104,105].
- 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[106].
- 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)[107].

7.7 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[87,89,108]. 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.

7.8 Minocycline for acne

A search of the evidence was carried out in February 2026. One narrative review focused on minocycline's licensed indication[109], while an additional narrative review

and five systematic reviews investigated off-licensed minocycline use, without any significant findings relating to minocycline's clinical effectiveness[110-115]. Two further systematic reviews and a review of case reports explored the safety profile of minocycline, with no significant findings reported[88,116,117].

7.9 Doxazosin modified release tablets

A search of the evidence was carried out in February 2026. Two systematic reviews focused on doxazosin licensed indications; when comparing between alpha-blockers for BPH, one found doxazosin (8 mg) to have the highest probability of improving quality-of-life while the second, for arterial hypertension management, found it to be associated with a higher risk of cardiovascular disease, particularly heart failure, when compared with chlortalidone (licensed for the treatment of arterial hypertension)[118,119]. Three systematic reviews investigated off-license doxazosin use, without any significant findings relating to doxazosin's clinical effectiveness[120-122]. NICE CKS for both hypertension (updated January 2026) and for lower urinary tract symptoms (LUTS) in men (updated June 2025) states not to use modified-release doxazosin tablets in people with gastrointestinal or oesophageal obstruction, or any degree of stricture[123,124].