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British Association of Dermatologists' guidelines for the safe and effective prescribing of methotrexate for skin disease 2016

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R.B.W. has acted as a Senior U.K. Investigator on a placebo-controlled clinical trial of subcutaneous methotrexate (MEDAC; specific); and has received honoraria/consultancy fees from AbbVie, Amgen, Celgene, Novartis, Boehringer, Lilly, LEO Pharma, Pfizer, Janssen-Cilag and Xenoport (nonspecific). C.H.S has been involved in clinical trials involving systemic therapy for psoriasis, sponsored by the Medical Research Council, Novartis UK, Pfizer UK, Regeneron Pharmaceuticals and Janssen-Cilag (nonspecific). B.K. has been involved in clinical trials sponsored by AbbVie, Janssen, Merck Sharpe Dolme and Pfizer (nonspecific); has received honoraria/consultancy fees from AbbVie, Janssen, Merck Sharpe Dolme, Novartis and Pfizer (nonspecific); and is a Member of Scientific Advisory Board for AbbVie, Celgene, Novartis and Pfizer. P.D.Y. has received honoraria from LEO Pharma, Pfizer and AbbVie (nonspecific).

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This is a new set of guidelines prepared for the British Association of Dermatologists (BAD) Clinical Standards Unit, which includes the Therapy & Guidelines Subcommittee (T&G). Members of the Clinical Standards Unit that have been involved are P.M. McHenry (Chairman T&G), K. Gibbon, D.A. Buckley, I. Nasr, V.J. Swale, C.E. Duarte Williamson, T. Leslie, E. Mallon, S. Wakelin, S. Ungureanu, P. Hunasehally, M. Cork, J. Donnelly (British National Formulary), C. Saunders (British Dermatological Nursing Group), A.G. Brain (BAD Scientific Administrator), L.S. Exton (BAD Information Scientist), M.F. Mohd Mustapa (BAD Clinical Standards Manager).

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1.0 Purpose and scope

The overall objective of the guideline is to provide up-to-date, evidence-based recommendations for the safe and effective use of methotrexate (MTX) in children and adults and its extensive on- and off-label applications for inflammatory dermatoses only. The document aims to (i) offer an appraisal of all relevant literature up to October 2015, focusing on any key developments; (ii) address important, practical clinical questions relating to the primary guideline objective; (iii) provide guideline recommendations that, where appropriate, take into account health economic implications; and (iv) discuss potential developments and future directions.

The guideline is presented as a detailed review with highlighted recommendations for practical use in the clinic (see section 18.0), in addition to an updated patient information leaflet [available on the British Association of Dermatologists' (BAD) website, http://www.bad.org.uk/for-the-public/patient-information-leaflets].

2.0 Stakeholder involvement and peer review

The guideline development group (GDG) consisted of consultant dermatologists. The draft document was made available to the BAD membership, the British Dermatological Nursing Group, the Primary Care Dermatological Society, the British Society for Paediatric and Adolescent Rheumatology, the British Society of Rheumatology, the British Society of Gastroenterology, the Royal College of Obstetrics and Gynaecology, the Psoriasis and Psoriatic Arthritis Alliance and the Psoriasis Association for comments, which were actively considered by the GDG. Following further review, the finalized version was peer reviewed by the Clinical Standards Unit of the BAD (made up of the Therapy & Guidelines Subcommittee) prior to publication.

3.0 Methodology

This set of guidelines has been developed using the British Association of Dermatologists' recommended methodology,[1] and with reference to the Appraisal of Guidelines Research and Evaluation (AGREE II) instrument (www.agreetrust.org).[2] Recommendations were developed for implementation in the National Health Service using a process of considered judgement based on the evidence. PubMed, MEDLINE and Embase databases and the Cochrane Library were searched for meta-analyses, randomized and nonrandomized controlled clinical trials, case series, case reports and open studies involving MTX to October 2015; search terms and strategies are detailed in the Supporting Information. Additional relevant references were also isolated from citations in reviewed literature, as well as specific targeted searches for drug interactions, combination therapy, pretreatment tests and latent tuberculosis reactivation. All identified English-language titles were screened and those relevant for first-round inclusion were selected for further scrutiny. The abstracts for the shortlisted references were then reviewed by all members of the working group and the full papers of relevant material obtained; disagreements in the final selections were resolved by discussion with the entire development group. Case reports and case series were only considered if there was no higher-quality evidence available. The structure of the guidelines was then discussed, with headings and subheadings decided; different co-authors were allocated separate subsections. Each co-author then performed a detailed appraisal of the selected literature with discussions within the GDG to resolve any issues, and all subsections were subsequently collated, circulated within the GDG and edited to produce the final guidelines.

4.0 Limitations of the guideline

This document has been prepared on behalf of the BAD and is based on the best data available when the document was prepared. It is recognized that under certain conditions it may be necessary to deviate from the guidelines and that the results of future studies may require some of the recommendations herein to be changed. Failure to adhere to these guidelines should not necessarily be considered negligent, nor should adherence to these recommendations constitute a defence against a claim of negligence. Limiting the review to English-language references was a pragmatic decision, but the authors recognize this may exclude some important information published in other languages.

5.0 Plans for guideline revision

The proposed revision date for this set of recommendations is scheduled for 2021; where necessary, important interim changes will be updated on the BAD website.

6.0 Introduction

MTX is an immunosuppressant drug that occupies a key place in the management of many autoimmune and inflammatory skin diseases. Although MTX has been widely prescribed in dermatology since the 1960s, there has never been dermatology-specific guidance on the use of this important drug. Furthermore, although considered an old drug, recent high-quality randomized controlled trials (RCTs) of MTX use in psoriasis, in particular, and an improved understanding of drug action, pharmacokinetics, pharmacogenetics and toxicology, make such guidelines timely.

6.1 Methotrexate metabolism and possible mechanism of action

The exact mechanism of action of MTX in inflammatory dermatosis continues to be the subject of much debate.[3] However, recent advances in both rheumatology and dermatology have improved this understanding with postulated anti-inflammatory effects mediated via adenosine pathways. Additionally, inhibition of nucleic acid synthesis in activated T cells and keratinocytes accounts for some of the immunomodulatory effects of MTX. MTX is best considered as a prodrug as it may be converted to polyglutamyl derivatives by the enzyme folylpolyglutamate synthetase, which are then preferentially retained within cells.[3] This is a dynamic process with removal of glutamate residues under the control of γ-glutamyl hydrolase. Up to seven glutamate residues may be added to MTX with increasing anti-inflammatory and immune-modulating activity of the drug with higher-order MTX polyglutamates (Fig. 1).

After a single oral dose, the maximum serum concentration is reached within 1–2 h.[4] When given orally, bioavailability is 70%, but may range from 25% to 70%.[4] Bioavailability is improved by parenteral dosing. Only a small fraction of MTX is metabolized, and the main route of elimination is through the kidney. Additionally, inhibition of nucleic acid synthesis in activated T cells/keratinocytes and Janus kinase/signal transducers and activators of transcription signalling pathways likely account for some of the immunomodulatory effects of MTX.[5]

7.0 Indications

7.1 Licensed indications: adults

7.1.1 Chronic plaque psoriasis (strength of recommendation A; level of evidence 1++; see Appendix 1)

Until recently, data on the efficacy of MTX were limited to two RCTs in small numbers of patients comparing MTX and ciclosporin. These studies showed that the 75% reduction in the baseline Psoriasis Area and Severity Index (PASI 75) for MTX was > 60% in both trials. In one of the studies there

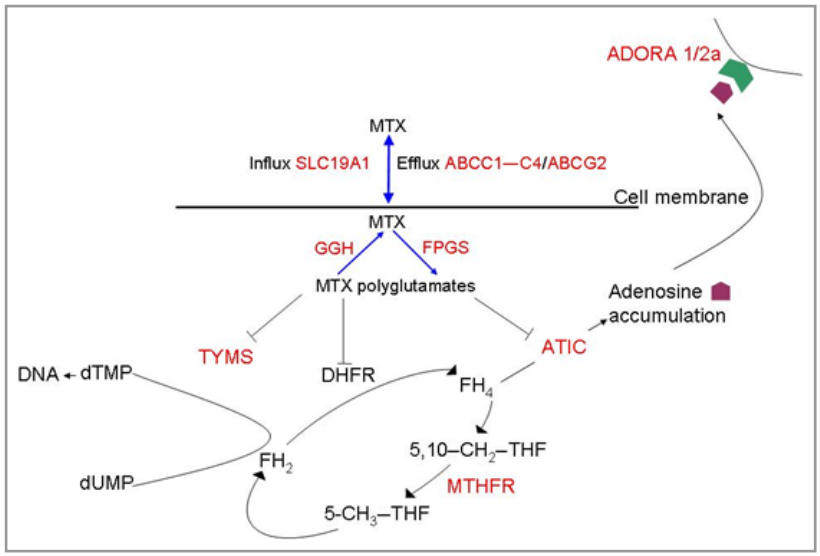

Fig 1. A postulated mechanism of action of methotrexate (MTX) in inflammatory dermatosis.[3] MTX is transported into the cell via the solute carrier family 19, member 1 (SLC19A1). It can be transported actively out of the cell by the adenosine triphosphate (ATP)-binding cassette transporters, including ATP-binding cassette, subfamily C (CFTR/MRP), members 1–4 (ABCC1–4), and ATP-binding cassette, subfamily G, member 2 (ABCG2). Within the cell it undergoes polyglutamation (activation) under the enzymatic control of folylpolyglutamate (FPGS). This is a dynamic process where glutamate residues can be removed by γ-glutamyl hydrolase (GGH). In the polyglutamated form MTX inhibits aminoimidazole-4-carboxamide ribonucleotide transformylase (ATIC), which is likely to account for some of its anti-inflammatory effects via an intracellular rise in adenosine acting on a number of adenosine receptors (ADORA), including ADORA A1 and 2a. Inhibition of the folate pathway may not be as important to its mechanism of action in psoriasis, but MTX also influences the enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR), which catalyses the conversion of 5,10-methylenetetrahydrofolate (5,10-CH_2-THF) to 5-methyltetrahydofolate (5-CH_3-THF), a co-substrate for homocysteine remethylation. The polyglutamated form of MTX also inhibits thymidylate synthase (TYMS), which converts deoxyuridylate (dUMP) to deoxythymidylate (dTMP) in the *de novo* pyrimidine biosynthetic pathway.

was no significant difference between the treatment success of MTX vs. ciclosporin.[6,7]

However, in the era of the biologics, high-quality prospective data from two RCTs and an open-label randomized trial with large MTX-treated cohorts (n = 110, n = 163 and n = 215, respectively) being compared with patients treated with biologics have become available.[8–10] These data have shown that MTX achieves a PASI 75 in around 37–40% of patients. The first study comparing adalimumab with MTX for treatment of moderate-to-severe psoriasis found that after 16 weeks of treatment MTX had achieved a PASI 75 in 35·5% of patients.[8] In this trial the placebo response was high (18·9%); this fact, allied to the seemingly low PASI 75 for MTX, raised some doubt about whether this truly reflected the efficacy of MTX. Further larger studies, including a 24-week, blinded RCT of MTX vs. briakinumab and a 16-week, open-label RCT comparing MTX with infliximab, appear to have confirmed the efficacy of MTX at around the 40% PASI 75 level. Longer-term efficacy data for MTX are sparse with the only high-quality data coming from the briakinumab vs. MTX study, which set a further primary efficacy end point at week 52. Only 23·9% of patients achieved a PASI 75 at week 52; nonetheless, MTX can be considered as an ongoing, long-term option for treating psoriasis so long as there are no safety concerns (see Sections 11.0 and 14.0). The discrepancy between the efficacy of MTX based on early head-to-head studies with ciclosporin, and more recent comparisons with biologics, is most likely due to an inaccurate effect–size estimate in the earlier studies owing to small sample size. Additional possible factors include the split dosing schedules chosen and lack of clarity on folic acid supplementation in the study by Heydendael *et al.*[7]

Despite the discrepancy in the true efficacy level of MTX, recent guidance published on the care of patients with psoriasis by the National Institute for Health and Care Excellence (NICE) has reaffirmed MTX's status as the first-line systemic agent for people with any type of psoriasis when it can be considered under the following scenarios:[11,12] psoriasis that cannot be controlled with topical therapy and has a significant impact on physical, psychological or social well-being, and one or more of the following apply: (i) psoriasis is extensive (e.g. > 10% of body surface area affected or a PASI score > 10); (ii) psoriasis is localized and associated with significant functional impairment and/or high levels of distress (e.g. severe nail disease or involvement at high-impact sites); (iii) phototherapy has been ineffective, cannot be used or has resulted in rapid relapse (rapid relapse is defined as > 50% of baseline disease severity within 3 months).

It is crucial to consider the presence of psoriatic arthritis in patients with psoriasis, as MTX can be an important agent for most patterns of psoriatic arthritis, although notably not for spondyloarthropathy.[13] If psoriatic arthritis is suspected in

patients with psoriasis, early involvement of a rheumatologist is recommended, so that effective and rapid therapeutic decisions can be made, in keeping with NICE guidance.[12]

7.2 Unlicensed indications: adults

In the UK, MTX use for cutaneous disorders is only licensed to treat psoriasis. However, low-dose MTX is commonly used to treat many other dermatological conditions. The evidence for its efficacy in other cutaneous disorders is outlined in the following subsections.

7.2.1 Inflammatory skin disease

Atopic eczema (strength of recommendation D; level of evidence 3) There has been one single-blinded RCT comparing MTX with azathioprine in adult atopic eczema. In this study, 20 of 42 patients received MTX, with an average improvement of 42%, as measured by severity scoring with SCOring Atopic Dermatitis (SCORAD). Patients were started on a dose of 10 mg weekly. This was titrated up by 2·5–5·0 mg, to a maximum of 22·5 mg weekly, if 25% improvement in SCORAD had not been achieved since the last visit (weeks 2, 4, 8, 12 and 24). MTX was shown to be at least equivalent to azathioprine at week 12, using an average MTX dose of 20 mg weekly. Both groups had a similar number of adverse events. No severe or serious adverse events were noted.[14] This study was limited by its small size, and may have been underpowered to detect a clinically significant difference between the two groups.

In an open-label study of 60 patients with a very diverse range of eczematous disorders, a 68% mean reduction in Eczema Area and Severity Index score was reported in those given MTX in doses of up to 7·5 mg weekly ($n = 30$) compared with a 21% reduction in those given just folic acid 5 mg daily ($n = 30$).[15] In this study, 40% of patients had atopic eczema, 31% had contact dermatitis, 12% had pompholyx, 8% had seborrhoeic dermatitis, 5% had lichen simplex chronicus and 3% had discoid eczema. The study lacks detail about how the patients were randomized, and was further limited by a lack of dose escalation, and the short duration of eczema flare-up in some patients. An open-label, noncontrolled prospective study of 12 patients showed an average of 54% improvement in six-area, six-sign atopic dermatitis (SASSAD) score at 12 weeks with a median dose of 15 mg weekly.[16] MTX was found to be well tolerated in this group with no serious adverse events. There have been two retrospective case series of nine and 20 patients, respectively.[17,18] Both studies reported patients responding within 3–8 weeks. In the former, 66% of patients achieved complete remission within 3 months with a maximum dose of 20 mg weekly. In the latter, 65% of patients achieved > 70% improvement in the physician global assessment (PGA) with a median dose of 25 mg weekly.

Cutaneous sarcoidosis (strength of recommendation C; level of evidence 2+) There have been no RCTs for MTX in cutaneous sarcoidosis, and just one showing that MTX has steroid-sparing effects in acute pulmonary sarcoidosis.[19] However, there was a high dropout rate in this study, and when analysed on an intention-to-treat basis, the effect was similar to placebo. One open-label prospective study showed total clearance of cutaneous sarcoidosis in 12 out of 16 treated cases,[20] with the majority clearing within the first 4 months of treatment. In this study, 15 of the 16 patients also had sarcoidosis at other sites.

7.2.2 Autoimmune disorders

Systemic sclerosis (scleroderma) (strength of recommendation D; level of evidence 3) Two RCTs have assessed the efficacy of MTX in systemic sclerosis in adults. The first examined the efficacy of intramuscular MTX vs. placebo in 29 patients with systemic sclerosis affecting organs other than just the skin.[21] The study was limited by a small sample size, and showed that there was improvement in skin score and lung function over 24 weeks, but these changes were not statistically significant. A larger, placebo-controlled RCT of 71 patients with early diffuse cutaneous systemic sclerosis based its primary outcome on skin scores and PGA, and again showed more improvement with MTX, although it was not statistically significant.[22] This study was a well-conducted, multicentre trial, but, in most cases, doses were not escalated above 15 mg per week. There have been two open prospective studies of MTX in limited cutaneous systemic sclerosis. The first evaluated the effects of MTX and pulsed methylprednisolone in 15 patients using objective skin scores, patient visual analogue scores, ultrasonography and histopathology: 14 patients were judged to have improved.[23] The second studied patients taking MTX only, and found six of nine patients had an improved objective skin score, and seven of eight patients had less skin tightness at the end of a 24-week treatment period.[24]

Bullous disorders (strength of recommendation D; level of evidence 3) There have been no RCTs of MTX in pemphigoid or pemphigus.

There have been three small open-label prospective studies of MTX in pemphigoid in combination with potent topical corticosteroids until clinical remission was achieved (average 2–3 weeks).[25–27] In these studies, a total of 45 patients were treated with MTX using low doses (5–15 mg weekly), with all 11 patients in one of these studies responding well within the first month.[25] In total, 34 of the 45 patients were in remission at the end of the studies (up to 24 months). There have been three retrospective cohort studies of MTX in bullous pemphigoid; these studies used low doses of MTX: 5–10 mg weekly.[28–30] One of these studies comprised 70 patients and found 76% of patients remained in remission on MTX alone, although the median follow-up was limited to 8·5 months.[30] The largest study comprised 138 patients, 98 of whom received MTX (37 of these in combination with oral prednisolone), using a median dose of just 5 mg weekly. At 24 months, 43% of patients treated with MTX monotherapy were in remission (35% in the MTX and prednisolone combined group), with a median time of 11 months to achieve

this.[28] These data suggest that MTX can be effective at controlling bullous pemphigoid, either in combination with corticosteroids or as a monotherapy. RCTs are warranted to show whether MTX alters the natural progression of the disease compared with corticosteroids alone.

A large, retrospective, single-centre cohort study of 185 patients with pemphigus vulgaris, including 53 who received MTX, suggested clinical improvement in 79% of patients when MTX was used at doses between 10 and 50 mg weekly in combination with oral corticosteroids.[31] However, no objective measurements of improvement were recorded, and the doses of MTX administered were higher than those routinely used for skin disorders. There have been three small retrospective cohort studies using MTX as an adjuvant to corticosteroids for pemphigus vulgaris. These showed that 66–76% of patients could be weaned off prednisolone successfully or have doses reduced within 6–18 months using MTX doses of 10–25 mg weekly. All three studies were small (maximum of 30 patients) but show consistent results.[32–34] A placebo-controlled RCT of adjuvant MTX is now warranted.

Lupus erythematosus (strength of recommendation B; level of evidence 2++)
A double-blinded, placebo-controlled RCT of 41 patients has shown that MTX can be used successfully as a steroid-sparing agent in controlling systemic lupus erythematosus (SLE) and allow reduction in corticosteroid dose. This study showed a significant reduction in SLE disease activity index scores for MTX compared with placebo (17% vs. 84%, respectively) after 6 months in the 20 patients receiving MTX 15–20 mg weekly.[35] There have been two single-centre retrospective studies of MTX reported for treating cutaneous lupus, including patients with subacute cutaneous lupus, discoid lupus, chilblain lupus and lupus profundus. In the largest, a cohort of 43 patients was treated with MTX 7·5–25·0 mg weekly. Ninety-eight per cent of patients showed a significant decline in disease activity, as measured by the cutaneous lupus activation index, by 8 weeks.[36] A small case series of 12 patients with cutaneous lupus showed at least partial remission in 10 patients with clearance of > 75% of lesions using doses of 10–25 mg weekly.[37]

7.2.3 Lymphoproliferative disorders (strength of recommendation C; level of evidence 2+)

Both the European Organisation for Research and Treatment of Cancer and the joint BAD and UK Cutaneous Lymphoma Group guidelines recommend low-dose MTX to control primary cutaneous T-cell lymphoma (CTCL) at stage IIB and above.[38,39] There are no RCTs to support its use, but a retrospective study of 69 patients with mycosis fungoides showed that 33% of patients achieved at least partial remission.[40] In a study of erythrodermic CTCL, 59% of 29 patients achieved at least partial remission.[41,42] A further retrospective study of patients with CTCL that was previously treatment refractory showed at least a partial response in 66% of patients when treated with a combination of MTX and bexarotene.[43]

7.2.4 Other indications

MTX has been used for treating lymphomatoid papulosis, pityriasis lichenoides and palmoplantar pompholyx,[44–51] but evidence for its efficacy is limited to case reports. Other possible indications supported by case reports include oral lichen planus, dermatomyositis, cutaneous vasculitis (including cutaneous polyarteritis nodosa, Behçet disease and erythema elevatum diutinum), pyoderma gangrenosum, necrobiosis lipoidica, granuloma annulare, alopecia areata, chronic idiopathic urticaria, Hailey-Hailey disease and Langerhans cell histiocytosis.[52–67]

Licensed and unlicensed indications for use in adults are listed in Table 1.

7.3 Children

7.3.1 Indications

MTX is used in children for the same conditions as in adults but is not licensed for any dermatological condition. There

Table 1 Licensed and unlicensed indications for methotrexate in adults

	Strength of recommendation
Licensed indications	
Psoriasis	A
Unlicensed indications	
Lupus erythematosus – systemic and cutaneous (DLE, SCLE, chilblain lupus, lupus profundus)[a]	B
Cutaneous sarcoidosis[a]	C
Lymphoproliferative disorders (including CTCL, mycoses fungoides, lymphomatoid papulosis, pityriasis lichenoides)	C
Alopecia areata	D
Atopic eczema	D
Bullous pemphigoid[a]	D
Chronic spontaneous/idiopathic urticaria	D
Cutaneous small vessel vasculitis (including cutaneous polyarteritis nodosa, Behçet disease and erythema elevatum diutinum)	D
Dermatomyositis	D
Granuloma annulare	D
Hailey-Hailey disease	D
Langerhans cell histiocytosis	D
Necrobiosis lipoidica	D
Oral lichen planus	D
Pemphigus[a]	D
Pyoderma gangrenosum	D
Systemic sclerosis (including limited systemic sclerosis)/localized scleroderma (morphoea)[a]	D

DLE, discoid lupus erythematosus; SCLE, subacute cutaneous lupus erythematosus; CTCL, cutaneous T-cell lymphoma.
[a]Methotrexate generally used as a steroid-sparing agent rather than monotherapy.

have been few RCTs specifically in the paediatric population supporting its efficacy in dermatological conditions.

In *atopic eczema*, a small open-label RCT of 40 children, aged 8–14 years with severe atopic dermatitis, found an equivalent reduction in SCORAD compared with treatment with ciclosporin at a dose of 2·5 mg kg^{-1} daily over a 12-week period, using a fixed dose of MTX of 7·5 mg weekly.[68] However, both ciclosporin and MTX were used at low doses, and there was a general lack of detail in the paper about how results were analysed. There have been three retrospective cohort studies with a total of 86 children treated with MTX for eczema, although one study included a further 16 children with psoriasis or nonspecified inflammatory skin disease.[69–71] The children were aged between 2 and 18 years and were treated with MTX doses of up to 15 mg weekly, with the greatest effect noted within the first 12 weeks. MTX was reported as being effective in 75–83% of children, but this was often subjective and details of how efficacy was assessed are lacking. Nausea was the most common side-effect and was reported in 14–16% of children in two of the studies but was not mentioned in the largest study of 46 children.

An RCT of 70 children showed significant improvement with MTX compared with placebo in *localized scleroderma* (morphoea) over a 12-month period using doses of 0·5 mg kg^{-1} weekly (this was combined with oral prednisolone for the first 3 months in all children).[72] This study, which used an objective assessment of disease (thermography), demonstrated response to treatment in two-thirds of patients, as defined by absence of new lesions, a reduction in the percentage of thermal change by at least 10% compared with baseline, and a reduction or decreased extension of the target lesion.

Surprisingly, there have not been any RCTs in children with psoriasis on MTX; however, it is used frequently in clinical practice. Retrospective case series of children (from as young as 2 years of age) support its use.[73,74] MTX has also been used effectively for other conditions such as pityriasis lichenoides et varioliformis acuta and dermatomyositis.[50,71,73,75]

7.3.2 Dosing

MTX is generally well tolerated in the paediatric population.[76,77] Dosing studies in children are limited, but standard clinical practice is to prescribe around 0·2–0·4 mg kg^{-1} weekly,[73,74,78] although doses of up to 0·7 mg kg^{-1} are used occasionally. Treatment is given for the shortest possible duration, using the lowest dose necessary to achieve good control, and should not exceed 25 mg per week. Reduction in the frequency of folic acid supplementation to once a week should also be considered, especially if issues with taking oral tablets are anticipated.

7.3.3 Monitoring

The side-effect profile is similar to adults, and monitoring is generally the same (see Section 10.3), with the exception of serum aminoterminal peptide of procollagen III (PIIINP) (patients with psoriasis only), where values are high in growing children. Pretreatment testing for HIV should be done at the clinician's discretion. There is no evidence in the dermatology/rheumatology literature to support the use of liver biopsies in children with normal liver function tests (LFTs), and this is not mentioned in the British Society for Paediatric and Adolescent Rheumatology guidelines.[79] Obesity may be a relative contraindication to MTX, as obese children appear to have an increased risk of LFT abnormalities.[80]

8.0 Contraindications

8.1 Relative contraindications (strength of recommendation C; level of evidence 2+)

Relative contraindications to MTX treatment are (i) mild-to-moderate renal impairment; (ii) mild-to-moderate liver dysfunction; (iii) history of hepatitis B and C; (iv) gastritis; (v) excessive alcohol intake; (vi) patient unreliability; (vii) recent live vaccinations; and (viii) male partners of women wishing to conceive.

8.2 Absolute contraindications (strength of recommendation C; level of evidence 2+)

Absolute contraindications to MTX treatment are (i) marrow dysfunction or failure; (ii) being on dialysis; (iii) severe renal dysfunction; (iv) severe hepatic dysfunction/cirrhosis; (v) women attempting to conceive, and pregnancy and breastfeeding; (vi) immunodeficiency states (in some cases relative, see Section 9.7); (vii) active tuberculosis or hepatitis virus infections; (viii) pulmonary fibrosis or significantly reduced lung function; (ix) active peptic ulceration; (x) concurrent trimethoprim therapy (see Section 11.7); and (xi) hypersensitivity to MTX.

9.0 Pretreatment counselling and screening

Patients should be counselled about the benefits and risks of taking MTX, screened for possible contraindications prior to starting treatment, and a full drug history should be taken (see Section 14.0). They should be advised particularly regarding alcohol intake (see Section 9.2), the need to avoid pregnancy (see Section 9.3), the need for regular blood tests, the increased risk of infection and possible drug interactions. It is important that the once-weekly dose schedule is explained clearly and understood by the patient.

9.1 Information for patients

Patients should be counselled about the weekly dosing schedule and it should be recommended that only 2·5-mg tablets are used, in order to avoid accidental and potentially life-threatening toxicity. All patients should be given written information about MTX prior to starting treatment, and it is helpful to provide a patient-held record book, an example of which

has been produced by the National Patient Safety Agency (http://www.nrls.npsa.nhs.uk/resources/?entryid45=59800). Patients should be aware that MTX is an immunosuppressant and that they may need to stop treatment (usually temporarily) if they develop an intercurrent infection that fails to settle after a few days or respond to conventional treatment (see Section 12.5).

9.2 Alcohol

There is no evidence to suggest a 'safe' level of alcohol intake while on MTX, but it is recommended that all patients limit their alcohol intake to well below the national guidelines while taking MTX.[81] A pragmatic discussion with the patient around occasional consumption of modest volumes of alcohol, especially if they have no other hepatic risk factors, as opposed to no alcohol at all, seems reasonable. Diabetes and obesity may also increase the risk of hepatic impairment,[82,83] and the benefits and risks should be assessed for individual patients prior to treatment, along with regular blood monitoring (see Section 10.3).

9.3 Conception

MTX is a teratogen and causes a specific embryopathy. Therefore, where relevant, women should be counselled about pregnancy and breastfeeding, and should not conceive while taking MTX or for at least 3 months after last taking it.[84] It is recommended that sexually active female patients use two methods of contraception throughout this period, and should have a pregnancy test prior to starting therapy. MTX is excreted into breast milk and so should not be used when breastfeeding. In the event of pregnancy, immediate referral for an obstetric opinion is required.

Controversy exists around the safety of men fathering a pregnancy while taking MTX, and the general advice, based on data linked to high-dose MTX use, is to wait for at least 3 months after the last dose of MTX.[85,86] Low-dose MTX may induce oligospermia,[87] and evidence from animal studies suggests that MTX induces damage to spermatogenesis,[88] but this has not been examined in humans. However, prospective observational studies comprising between 42 and 139 men taking low-dose MTX have not found an increased risk of spontaneous abortion or fetal malformations.[89–91] Therefore, there is no evidence to support interruption of pregnancy following impregnation by a man taking low-dose MTX. However, it is prudent to advise men to delay planning their family for at least 3 months following their last dose of MTX.[89]

Any pregnancy related to paternal or maternal exposure should be reported to the U.K. teratology information service (www.uktis.org) so that further evidence can be collated.

9.4 Pretreatment screening tests

Patients should be aware of the need for, and be able to comply with, regular blood test monitoring throughout the treatment period, and should have a full blood count (FBC), renal and LFTs, including serum [PIIINP (patients with psoriasis only)] hepatitis B and C, and HIV serology (see Section 9.6). Elevation of PIIINP to $> 8{\cdot}0$ mg mL^{-1} should prompt further hepatic investigations. Patients with pretreatment PIIINP levels $> 4{\cdot}2$ mg mL^{-1} but < 8 mg mL^{-1} can be commenced on MTX, but elevation of PIIINP on more than three occasions in a 12-month period should prompt referral for a hepatology opinion. Where there is any doubt as to the patient's varicella zoster (VZV) status, this should also be checked prior to treatment; patients requiring any live vaccinations should be given these at least 4 weeks prior to commencing MTX (see Section 9.8). If a patient has a disease that affects the lungs (e.g. sarcoid), perform a chest X-ray and physical examination, and discuss with respiratory physicians the need for pulmonary function tests at the start of treatment.[92,93] If a patient has known interstitial lung disease, MTX should only be considered after agreement with the respiratory physicians. In elderly patients it is prudent to check the estimated glomerular filtration rate (eGFR) prior to commencing treatment, and reduce the prescribed dose accordingly (see Table 4).

9.5 Tuberculosis

There is a recognized association between biologics and latent tuberculosis (TB) reactivation.[94] However, the link between MTX and TB reactivation is less clearly defined, and there is currently no guidance from the Department of Health or NICE concerning the safety of MTX in patients with latent TB.[95] Patients should be asked about a personal history of TB and a history of TB exposure. Any suspicion of latent TB should result in screening for latent or active TB infection and treatment if positive, prior to commencing MTX.

9.6 Hepatitis B and C

If a patient has evidence of active hepatitis B infection (hepatitis B surface antigen positive and surface antibody negative, or IgM antibody to hepatitis B core antigen positive in combination with hepatitis surface antigen and antibody negative) they are at risk of their disease flaring if treated with immunosuppressant drugs such as MTX,[96] and therefore this is an absolute contraindication. Past infection with hepatitis B (hepatitis B surface antigen negative, but core antibody positive ± surface antibody positive) is a relative contraindication to treatment, and the patient should be made aware of the low risk (< 1%) of reactivation of the infection while on treatment.[96]

The long-term effects of MTX on chronic hepatitis C are unknown, but as both hepatitis C and MTX can cause hepatic fibrosis there may be a synergistic effect leading to more rapid progression of liver fibrosis. Therefore, the risks and benefits of MTX use in patients with hepatitis C need to be weighed up carefully, and patients require close monitoring for progression of fibrosis. Involvement of a hepatologist in the management of such cases is essential. MTX should be avoided in patients with advanced fibrosis or cirrhosis.

9.7 HIV

A patient's HIV status should be checked prior to starting MTX, as patients who are HIV-positive will have an increased risk of leucopenia and opportunistic infections.[97] Psoriasis in HIV-positive patients will often be more severe and refractory to treatments, and in many cases, controlling their viral load may improve control of their psoriasis.[98–100] Immunosuppressants in HIV-positive patients should be minimized, but some patients with severe psoriasis will require systemic treatment, and MTX has been used without adverse events to treat such patients, although evidence is limited to case reports.[97,101] Therefore, if used in these patients, it should be with caution and should be avoided in patients with known opportunistic infections. All such patients should be managed jointly with the local specialists in HIV infection.

9.8 Varicella zoster virus

Varicella infection can be more serious in immunocompromised individuals and the risk of disseminated or haemorrhagic varicella is increased.[102] If a patient has no reported history of chickenpox, VZV serology should be checked. Where serology is negative, the patient should be considered for the varicella zoster vaccination. The Department of Health recommends that if the vaccine is to be given to those already taking immunosuppressants their treatment should be stopped for 6 months prior to the vaccine being administered.[102] Advice should be sought from the local microbiology team about the need and type of vaccination required. Further details on immunization are covered in Section 12.1.

10.0 Dosage and delivery

10.1 Dosage (strength of recommendation B; level of evidence 2++)

MTX is available in oral, subcutaneous, intramuscular and intravenous preparations, administered *once a week* in all formulations (see Section 9.1). Oral MTX is preferred by most dermatologists and patients, with the starting dose dependent on the renal function, age of the patient and associated comorbidities. Consideration can be given to start with the subcutaneous formulation, which may lessen side-effects and be more effective.[103] The initial dose used in four well-designed RCTs in psoriasis varied between 5 and 15 mg, with increments dependent on the response to treatment.[7–10] If the improvement was < 25% to 50% of baseline PASI in the first 6 weeks, the RCTs increased the dose of MTX by 5 mg every 4–6 weeks until a maximal dose of 25 mg a week was reached. NICE recommends incremental dosing of MTX (e.g. starting with an initial dose of 5–10 mg once a week) and gradually increasing up to an effective dose to a maximum of 25 mg weekly. In those with normal renal function a more aggressive dosing regimen may be considered, such as starting at 15 mg once weekly.[10] In the elderly and those with renal impairment or marrow dysfunction, the initial dose can be reduced to 2·5 mg. Patients should be warned that it takes at least 4–8 weeks for the therapeutic effect to manifest once the dose is altered.[104] After the maximal dose of 25 mg a week is reached, assess response to therapy after 3 months (see Section 7.0 – some indications may take longer to respond) and stop treatment if it is ineffective.[12] Once remission is achieved, the goal would be to reduce the medication to the lowest possible dose that brings about control of the condition and permits adequate tolerability.[12] If the disease being treated remains active at the highest doses, or if side-effects are encountered, it is worthwhile considering a change to the subcutaneous formulation before discontinuing the drug.[83,105] The dose for parenteral use is the same as that used orally, although consideration needs to be given to the differences in bioavailability and a lower dosage may be equally efficacious.[103]

10.1.1 Recommendations

In healthy adults, consider starting MTX at doses between 5 and 15 mg weekly. Those with renal impairment may need lower doses, and could be commenced on 2·5–5·0 mg weekly (see Table 4). Once remission is achieved, use the lowest maintenance dose to control the condition. Consider switching to alternative medication or use subcutaneous MTX if minimal efficacy is achieved within 12–16 weeks of treatment.

10.2 Folic acid (strength of recommendation A; level of evidence 1++)

Practice with respect to folic acid supplementation during MTX therapy varies across the U.K. and there is a lack of clear evidence regarding its optimal dosing schedule. Patients with severe psoriasis may have pre-existing folic acid depletion that could be associated with an increased cardiovascular risk through hyperhomocysteinaemia.[106] Studies have shown that the use of folic acid does not have an effect on MTX efficacy, although most of the evidence is from patients with rheumatoid arthritis treated with MTX.[107] The dose of folic acid from previous RCTs of MTX used to treat psoriasis varies between 5 mg weekly and 5 mg daily.[8,108] Folic acid use decreases the mucosal and gastrointestinal side-effects of MTX,[109] and may have a protective effect against hepatotoxicity.[110] There are no conclusive data to prove that haematological complications are reduced with folic acid supplementation.[111] In a meta-analysis, folinic acid supplementation was not shown to have any advantages over folic acid.[107] Given that folinic acid is more expensive, it is currently recommended to use folic acid. In theory, folic acid may compete for cellular uptake of MTX when given on the same day. The recommendations are the same for the treatment of skin diseases other than psoriasis.

10.2.1 Recommendations

Folic acid supplementation is recommended.

10.3 Monitoring (strength of recommendation C; level of evidence 2+)

Full blood count, liver function tests, and urea and electrolytes (U&Es) need to be repeated every 1–2 weeks for the first month and until a steady dosing regimen is achieved – FBC should be performed before dosing in week 2. A downward trend of FBC and neutrophil count could be a sign of toxicity, even if the absolute levels are normal. Similarly, an upward trend in liver transaminases should also be noted. Once the patient is on a stable dose, the assessment can be performed every 2–3 months. Patients with risk factors such as renal insufficiency or advanced age may need closer monitoring, both at the onset of treatment and after dosage increases.[104] Serial elevation of PIIINP may be an indication of hepatic fibrosis and it is suggested that, where available, the test is repeated four times a year (patients with psoriasis only) (see Table 2 and Section 9.6).

11.0 Toxicity

11.1 Bone marrow suppression

Fortunately, deaths related to the use of MTX are rare but when encountered are most often secondary to myelosuppression. Such case reports are sparse and usually in the context of prescribing and dispensing errors, poor renal function and/or concomitant drug use (see Section 11.7). Patients should be made aware of the need to report features of MTX toxicity such as mouth ulceration, of any changes in prescription such as concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) and that intercurrent illness that induces dehydration would be a reason to omit MTX dosing until recovery.

11.2 Hepatotoxicity

MTX is a recognized hepatotoxin, although the significance of its hepatotoxic potential in patients may have been overestimated in the past. MTX can cause drug-induced hepatitis and long-term use in psoriasis may be associated with hepatic fibrosis. Hepatic fibrosis on liver biopsy is accepted as evidence of hepatic injury, although its overall clinical significance is unclear, as most patients do not progress to cirrhosis and clinically significant hepatic dysfunction.[110]

The quality of the studies assessing long-term hepatotoxicity with the use of MTX for skin disease is poor and almost exclusively in psoriasis where there are multiple known factors that can drive risk of liver fibrosis, particularly the metabolic syndrome and alcohol. Data from published long-term, observational cohort studies are at high risk of bias as a result of these confounding variables, selection bias and retrospective design. A recent systematic review and meta-analysis concluded that MTX therapy in psoriasis is associated with a 22% increased risk of hepatic fibrosis but found no evidence that cumulative dose of MTX, diabetes, obesity or alcohol intake increases this risk.[110] A previous meta-analysis that included a mixed population and different study design concluded that hepatic fibrosis was associated with diabetes, obesity and alcohol intake but not cumulative MTX dose.[83] In practice, when using MTX, clinicians (and patients) need to bear in mind that long-term MTX use is associated with an increased risk of liver fibrosis, and that this risk may be greater in those at risk of, or with, pre-existing liver disease.[103,112]

11.2.1 Monitoring for liver toxicity (strength of recommendation C; level of evidence 2+)

The gold standard for assessing liver fibrosis is liver histology. Liver biopsies are associated with significant morbidity and a risk of mortality, estimated to be one in 1000 in a recent U.K. audit.[113] As only a tiny fraction of the liver can be examined, there is a concern that the findings from a liver biopsy may not be representative of the whole organ; furthermore, the procedure is expensive.[114] The routine use of liver biopsy for monitoring MTX hepatotoxicity is no longer recommended.

Standard LFTs appear inadequate in isolation for monitoring for the development of hepatic fibrosis, although they are

Table 2 Recommended action for abnormal test results (strength of recommendation C; level of evidence 2+)[124,206]

Total WBC count $< 3 \times 10^9$ cells L^{-1}	Withhold/decrease dose of MTX; consider discussing with haematologist
Neutrophils $< 1{\cdot}0 \times 10^9$ cells L^{-1}	Withhold/decrease dose of MTX; consider discussing with haematologist
Platelets $< 100 \times$ cells L^{-1}	Withhold/decrease dose of MTX; consider discussing with haematologist
MCV > 105 fL	Consider withholding/decreasing dose of MTX; check serum B12, folate and thyroid function tests; consider discussing with haematologist
AST and ALT increased by less than two times the normal	Repeat LFTs in 2–4 weeks
AST and ALT greater than 2–3 times the normal	Withhold/decrease dose of MTX; consider other risk factors and consider discussing with gastroenterologist
New or increasing dyspnoea or dry cough	Withhold/decrease dose of MTX; repeat chest X-ray and pulmonary function tests and discuss with respiratory team
Severe sore throat, abnormal bruising	Withhold MTX; check FBC immediately

WBC, white blood cells; MTX, methotrexate; MCV, mean corpuscular volume; AST, aspartate aminotransferase; ALT, alanine transaminase; LFT, liver function test; FBC, full blood count.

useful in detecting acute MTX-induced hepatitis.[115–119] A systematic review estimated that standard LFTs are only 38% sensitive and 83% specific for detecting hepatic fibrosis.[110]

11.2.2 Serum aminoterminal peptide of procollagen III (strength of recommendation C; level of evidence 2+)

The knowledge that standard LFTs are inadequate for detecting MTX-induced fibrosis in patients has led to the development of markers of hepatic fibrosis in order to monitor these patients.

PIIINP is a serum biomarker of fibrosis and has only been assessed in patients with psoriasis treated with MTX where several large case series have been reported.[119–121] It is a sensitive marker of fibrosis but is relatively nonspecific.[121]

In a study of 87 patients with psoriasis monitored by serial liver biopsy up to 6 years, no histological evidence of fibrosis was found in those patients with consistently normal PIIINP values.[119] In a similar study comparing serial PIIINP measurements and liver histology in 70 patients with psoriasis monitored for up to 11 years, normal serial PIIINP measurement was associated with an absence of liver fibrosis; in all four patients in whom fibrosis was detected on liver histology, serial PIIINP values had been abnormal.[118]

PIIINP may be raised as a result of active bone remodelling following orthopaedic surgery, skeletal fractures, erosive psoriatic arthritis or in growing children. However, many patients with arthritis do not have raised values, providing reassurance that active liver fibrosis is not present.[83] It may also be less reliable in smokers.[121]

A meta-analysis has estimated the sensitivity of serial PIIINP measurement for detecting fibrosis at 77% with a specificity of 91·5%.[83] The negative predictive value of normal serial PIIINP measurements is 97%, with a positive predictive value of 50%. This analysis assumes a prevalence of hepatic fibrosis of 10%, which is higher than in most recent studies.[121] A more recent meta-analysis assessed the sensitivity and specificity of a single PIIINP measurement and reported rates of 74–77% and 77–85%, respectively.[122] The serial measurement of PIIINP appears to be a cost-effective method of monitoring for hepatic fibrosis in this population.[123] If abnormal PIIINP levels exist then consideration should be given to a hepatology opinion and/or MTX withdrawal. This decision should be made in the context of the risk/benefit of liver biopsy and the risk/benefit of alternative therapy. It is worth noting that serial PIIINP measurement has been studied only in patients receiving MTX for psoriasis and not in RCTs. All the studies have relatively small numbers, are retrospective (except for that of Boffa *et al.*, which was prospective)[118] and suffer from ascertainment bias. These studies assessed serial PIIINP measurement and its use as a single measurement appears to be unreliable. Its validity in other dermatological conditions that are treated with MTX (e.g. sarcoidosis and atopic dermatitis) is unknown.

Hepatic imaging with standard ultrasonography is unable to detect hepatic fibrosis until cirrhosis has developed and gross anatomical changes in hepatic size and blood flow have developed, although it may be useful in detecting steatosis and for assessing patients with abnormal LFTs.[112,115,121,124] Other imaging modalities, such as magnetic resonance imaging and dynamic hepatic scintigraphy, appear insensitive for assessing occult fibrosis.

Transient elastography is a technique that measures liver 'stiffness' using an ultrasound pulse. It may be technically difficult in patients with obesity and is currently available only in specialized centres. However, it has been shown to be both sensitive and specific for the detection of hepatic fibrosis in patients with hepatitis C, and to a lesser degree in alcoholic liver disease and nonalcoholic steatohepatitis.[125]

There is only one study on its use for screening for hepatic fibrosis in patients with psoriasis on MTX therapy.[126] It has been suggested that its accuracy can be improved by combining its score with a serum biomarker of fibrosis such as Fibrotest©. Fibrotest is a patented algorithm that calculates the risk of hepatic fibrosis based on the patient's age, sex and a number of biochemical parameters, including alanine transaminase, haptoglobin, apolipoprotein A1, γ-glutamyltranspeptidase and total bilirubin.[127] A retrospective study compared an enhanced liver fibrosis biomarker with PIIINP and reported that it was as effective as PIIINP in screening for hepatic fibrosis.[128] The use of these tests has not been validated in large cohorts of patients with psoriasis on MTX therapy.

11.2.3 Recommendations

Recommended baseline assessments include serum PIIINP, standard LFTs and consideration of other risk factors for liver disease (e.g. fatty liver disease, alcohol, etc.). Monitor LFTs and PIIINP at least every 3 months (patients with psoriasis only) and consider onward referral for specialist advice if abnormal (see Table 2), specifically in relation to PIIINP. Refer onward for further specialist assessment (i) if PIIINP is > 8 mg L^{-1} on two occasions; (ii) if three measurements are $> 4{\cdot}2$ mg L^{-1} in a 12-month period; or (iii) if > 10 mg L^{-1} on one occasion. The routine use of liver biopsy for monitoring MTX hepatotoxicity is not recommended.

11.3 Pulmonary (strength of recommendation D; level of evidence 4)

Interstitial lung disease is a rare complication of MTX therapy for rheumatoid arthritis and even rarer in patients with psoriasis.[129] Pulmonary toxicity from MTX therapy is not related to the cumulative dose of MTX and is not associated with bone marrow or hepatotoxicity; fatalities have been reported.[130] The symptoms are nonspecific and include a dry cough and dyspnoea. The incidence has been estimated at 0·03% of patients, but large studies are lacking.

Pre-existing lung disease, psoriatic arthritis and cigarette smoking appear to be risk factors for interstitial lung disease associated with MTX in patients with psoriasis.[131,132]

11.3.1 Recommendations

Enquiry regarding history of pulmonary disease and respiratory symptoms should be made at initiation of MTX and at subsequent visits. Chest X-ray, further investigations and/or respiratory referral are necessary if (i) symptoms are present; and (ii) the patient is > 40 years of age and a cigarette smoker or has a background disease putting them at risk of respiratory complications (e.g. sarcoid).

11.4 Renal (strength of recommendation D; level of evidence 3)

MTX is excreted predominantly by the kidneys;[133] it is filtered in the renal glomeruli and also undergoes active secretion and reabsorption in the renal tubules.[134] Analysis of multiple trials in the rheumatoid arthritis literature suggests that baseline renal function affects the risk of side-effects from MTX – worsening renal function is associated with increasing toxicity.[135] Myelosuppression is the most important cause of MTX-associated death and this is increased significantly in renal dysfunction.[136] Therefore, evaluation of renal function with eGFR is recommended at baseline (Table 3).[137] It should be noted that eGFR can be unreliable when there are extremes of body mass (body builders, muscle wasting disorders) and the serum creatinine can be raised even in the presence of normal renal function. Extrapolating from guidelines in the rheumatology literature, the recommendation is to avoid MTX in those with a creatinine clearance of < 20 mL min^{-1} and to halve the dose in those with a creatinine clearance of between 20 and 50 mL min^{-1} (Table 4).[138]

Fever and diarrhoea and the use of certain drugs (see Section 11.7) could predispose to a sudden worsening of renal function and patients should be warned to omit MTX doses if they are at risk of acute dehydration. NSAIDs are commonly co-prescribed in those with psoriatic arthritis and could predispose to renal dysfunction (see Section 11.7). If patients develop worsening renal function, the FBC should be monitored closely and dose reductions considered.[103] Patients on dialysis are particularly at risk of fatal pancytopenia. This effect could be due not only to accumulation of MTX, but also to an immunological mechanism. The use of haemodialysis, haemoperfusion and plasmapheresis may be ineffective in MTX intoxication.[139]

Table 3 Glomerular filtration rate (GFR) categories for chronic kidney disease

	GFR (mL min^{-1} 1·73 m^{-2})	Description
G1	> 90	Normal or high
G2	60–89	Mildly decreased
G3a	45–59	Mild to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	< 15	Renal failure

Table 4 Methotrexate (MTX) dosage dependent on glomerular filtration rate (GFR)

GFR (mL min^{-1} 1·73 m^{-2})	Dose
> 90	Normal dose
20–50	Half dose
< 20	Avoid MTX

11.4.1 Recommendations

Reduction in MTX dosage should be considered in those with suboptimal renal function. Avoid MTX in patients on dialysis and with a creatinine clearance < 20 mL min^{-1}.

11.5 Nausea (strength of recommendation B; level of evidence 2++)

Nausea is one of the commonest side-effects of MTX, occurring in up to 25% of patients. It tends to occur within 12–24 h of consumption of the medication and is dose-dependent.[140] It may be mild but can also be severe enough to limit therapy. The usual advice is to take the medication before bedtime or with food; folic acid supplementation of up to 5 mg daily has been shown to reduce nausea,[111,141,142] although this has not been replicated in other studies.[143,144] Ondansetron, given at a dose of 8 mg 2 h before the MTX dose and repeated 12 and 24 h later if required can be an effective way of managing the nausea.[145,146] Granisetron is an alternative 5-HT_3 antagonist that has been helpful in MTX-induced nausea for patients with rheumatoid arthritis.[147] Parenteral delivery of MTX may also reduce nausea and should be considered.[148]

11.6 Carcinogenic risk

MTX is used commonly as a chemotherapeutic agent as it inhibits intracellular folate production and as such is toxic to rapidly growing cancer cells. There is considerable debate as to whether MTX therefore carries any increased risk of developing malignancy in those on long-term, low-dose MTX for chronic inflammatory conditions.

There is contradictory literature on malignancy risk associated with low-dose MTX, with most controversy surrounding a possible link with lymphoma. In a long-term study of 248 patients with psoriasis (median follow-up of 7 years) on low-dose MTX assessed for incident malignancies, 10 patients developed malignant neoplasms, including two lymphomas.[149] The authors concluded that MTX therapy, as used in the treatment of psoriasis, did not seem to contribute to the development of malignant neoplasms as the rates were consistent with those expected in any population. In contrast, in a population-based cohort study conducted in the U.K. in 2003,

patients with psoriasis had a 2·95 times increased relative risk of developing lymphoma compared with those without psoriasis.[150] Stern reported that the incidence of lymphoma in patients receiving psoralen combined with ultraviolet A (PUVA) increased only in those patients treated with high cumulative doses of MTX (≥ 36 months of exposure) when compared with that expected in the general population.[151] The main issue with these studies is the potential for misclassification of CTCL as psoriasis.

Nonetheless, the World Health Organization classification of lymphoid neoplasms includes the phenomenon of a lymphoproliferative disease associated with MTX, known as MTX-LPD, which is defined as a lymphoid proliferation or lymphoma in a patient immunosuppressed with MTX.[152] This was based on the finding of numerous reports of patients, the vast majority suffering from rheumatoid arthritis and many of whom were Epstein–Barr virus-positive and on low-dose MTX, developing lymphoproliferative disorders that reversed on stopping MTX.

Overall, the risk of malignancy associated with low-dose MTX use in patients with psoriasis appears consistent with background population rates, but vigilance for lymphoma is advisable.

11.7 Drug interactions

Drug interactions with MTX usually occur due to altered pharmacokinetic effects, such as displacement of protein binding and reduced renal elimination, but can occur as a result of a combination of different mechanisms (see Table 5) – all patients starting MTX should have a detailed medication history taken and a detailed review of potential interactions undertaken. MTX initially binds to serum albumin and therefore drugs that displace this, such as antibiotics, may increase serum MTX levels. Elimination of MTX is principally renal, and therefore interactions are likely to be more significant in patients with reduced renal function, such as in the elderly. As MTX can be hepatotoxic, caution should be used when prescribing this with other drugs that also cause hepatotoxicity, including alcohol, azathioprine and retinoids.[112,153] Some of the most common interactions are described in the following subsections, but co-prescription with biologics, ciclosporin, ultraviolet B (UVB) and retinoids are dealt with elsewhere.

11.7.1 Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs can reduce renal elimination of MTX, leading to toxicity. Case reports have been published following significant morbidity and mortality following co-prescription of some NSAIDs and MTX, in particular following the use of naproxen, diclofenac, ibuprofen and indometacin.[154–157] However, these patients were often also taking other drugs that may also have interacted with MTX (e.g. trimethoprim and allopurinol), and a study by Stewart and Evans failed to show any increase in toxicity in 15 patients on both low-dose MTX and naproxen.[156] Some NSAIDs, such as celecoxib, do not interact with MTX.[158] Where possible, concomitant use of NSAIDs that interact with MTX should be avoided, but if co-prescription is necessary, blood monitoring should occur at least every 2 months.[159]

Table 5 Known drugs that interact with methotrexate (MTX) to increase toxicity

Mechanism	Examples of drugs that may increase MTX toxicity
Reduced renal elimination	Many NSAIDs
	Salicylates
	Penicillin
	Ciclosporin
	Probenicid
	Proton pump inhibitors (possible reduction)
Hepatotoxicity	Statins
	Alcohol
	Azathioprine
	Tetracyclines
Reduced MTX protein binding	Phenytoin
	Penicillin
	Tetracyclines
	Sulfonamides
	Probenicid
	Salicylates
	Retinoids
Folic acid deficiency	Trimethoprim
	Sulfonamides
	Barbiturates
	Nitrofurantoin

NSAID, nonsteroidal anti-inflammatory drug.

11.7.2 Antibiotics

The evidence for antibiotic interactions comes mostly from concomitant use of trimethoprim and sulfamethoxazole (co-trimoxazole) with low-dose MTX resulting in bone marrow suppression.[154,156,160–162] Case reports also show that trimethoprim with MTX can also cause immunosuppression, although most cases are reported in the elderly who often have a degree of renal impairment.[163,164] Co-trimoxazole, trimethoprim and other antifolate drugs should be avoided in patients taking MTX.

Other antibiotics, including penicillins, tetracyclines and ciprofloxacin, have been shown to increase MTX levels when high-dose MTX is used,[165–168] but this does not appear to be an issue in clinical practice. Patients on long-term antibiotics for conditions such as acne may require monitoring more frequently, but if antibiotics are given for a severe infection or an infection that is not responding to standard treatment, MTX should be stopped until the patient recovers and the antibiotic course is complete.

See Table 6 for recommendations for MTX use in clinical practice.

Table 6 Recommendations in particular clinical situations

Indication	Strength of recommendation
Psoriasis[a]	A
Lupus erythematosus – systemic and cutaneous (DLE, SCLE, chilblain lupus, lupus profundus)[b]	B
Cutaneous sarcoidosis[b]	C
Lymphoproliferative disorders (including CTCL, mycosis fungoides, lymphomatoid papulosis, pityriasis lichenoides)	C
Alopecia areata	D
Atopic eczema	D
Bullous pemphigoid[b]	D
Chronic spontaneous/idiopathic urticaria	D
Cutaneous small vessel vasculitis (including cutaneous polyarteritis nodosa, Behçet disease and erythema elevatum diutinum)	D
Dermatomyositis	D
Granuloma annulare	D
Hailey-Hailey disease	D
Langerhans cell histiocytosis	D
Necrobiosis lipoidica	D
Oral lichen planus	D
Pemphigus[b]	D
Pyoderma gangrenosum	D
Systemic sclerosis (including limited systemic sclerosis)/localized scleroderma (morphoea)[b]	D

DLE, discoid lupus erythematosus; SCLE, subacute cutaneous lupus erythematosus; CTCL, cutaneous T-cell lymphoma.
[a]Licensed, [b]methotrexate generally used as a steroid-sparing agent rather than monotherapy.

12.0 Special circumstances

12.1 Vaccinations

Live-attenuated vaccines in immunosuppressed individuals can predispose them to infection. Therefore, vaccines such as measles, mumps, rubella, varicella, oral polio, typhoid, bacillus Calmette-Guérin and yellow fever should be avoided in patients taking MTX. Live vaccines should be given at least 4 weeks prior to starting MTX, and antibodies should be checked for varicella status if the history of previous infection is unclear. The Department of Health recommends that where live vaccines need to be given for people who are established on an immunosuppressant that it should be stopped for 6 months before the vaccine is given.[102] Inactivated vaccines are safe to give during treatment, but the level of immunity achieved may be lower than in patients not taking MTX.[169] As MTX induces immunosuppression, patients have a higher risk of infection and therefore should be encouraged to receive the annual influenza vaccination (n.b. this should not be the new live influenza vaccine that is being offered to children) and the 5-yearly pneumococcal vaccine. Further information can be found in the U.K. Department of Health's 'Green Book' ('Immunisation against infectious disease').[102]

12.2 Surgery

There have been several prospective randomized studies published in the rheumatology literature comparing the risk of infection or surgical complications in patients who continue with MTX prior to elective orthopaedic surgery with those who stop MTX. The risk of infection and postoperative complication did not appear to be affected following surgery in 64 and 388 patients, respectively.[170,171] No studies have looked at peri-/postoperative complications in patients receiving low-dose MTX for dermatological indications, or in patients following general surgery. Therefore, it is assumed that when MTX is controlling an individual's skin disease, it can be continued during the perioperative period. However, where patients are due to undergo major surgery and have comorbidities such as diabetes, which may alter infection risk, the use of an immunosuppressive drug such as MTX may theoretically augment infection risk, and the decision to continue must be decided on a case-by-case basis.

12.3 Overdose

Symptoms of possible MTX overdose include mucositis, fever, diarrhoea, erythema, ulceration and, rarely, cutaneous necrolysis, and may take 6–23 days to manifest.[172–176] MTX tablets are dispensed as 2·5 mg and 10 mg; both are small tablets of similar appearance. Inadvertent overdose is therefore possible due to confusion over the tablet strength, and patients should be made aware of this. To avoid such confusion, it is recommended that only the 2·5-mg strength is prescribed; the dose should be written out in full in uppercase letters to remove ambiguity around the placement of the decimal point. Furthermore, the frequency of dosing may cause confusion as MTX is typically taken once weekly rather than daily.

In the event of an overdose, early treatment may be life saving. If 1 mg kg^{-1} of MTX (or greater) has been ingested within an hour, the patient should be given activated charcoal.[177] The patient should be admitted to hospital, have their serum MTX levels measured at least 4 h after ingestion and given calcium folinate (folinic acid) as soon as possible. Folinic acid is given by intravenous infusion, using an initial dose of up to 100 mg m^{-2} if the MTX level is unknown, with subsequent oral/intravenous doses every 6 h (see Toxbase for doses to be given when MTX level is available).[177] This is most effective when initiated within a few hours of taking the last MTX dose, with doubtful efficacy if initiated later than 24 h. It should be continued until MTX levels are $< 0{\cdot}05$ μmol L^{-1} or haematological abnormalities have returned to normal and mucosal ulceration has healed.

All patients should be kept well hydrated to improve renal elimination of MTX, and urine alkalization with sodium bicarbonate should be considered to prevent MTX precipitation within the renal tubules. A human granulocyte colony-

stimulating factor such as filgrastim can be used for toxic bone marrow suppression, given subcutaneously at a dose of 5 μg kg^{-1} daily to accelerate myeloid recovery.[178] There is a high risk of mortality associated with MTX overdose, and patients should be monitored carefully for signs of sepsis and treated accordingly.

12.4 History of cancer

There is little known about the effect of giving MTX to those who have a history of cancer. It is advised that where patients are under active follow-up for cancer, the responsible team should be consulted and the decision to start MTX should be discussed with them prior to commencing treatment.

12.5 Intercurrent infections

Low-dose MTX is associated with an increased risk of infection, in particular pneumonia, skin or soft tissue infections and urinary tract infections. A double-blinded randomized trial in patients with rheumatoid arthritis showed a similar rate of infection of 7% in patients taking either MTX or azathioprine for rheumatoid arthritis, with most infections occurring within the first 18 months.[179] It is recommended that MTX is stopped temporarily during severe infection or when infection is not responding to standard treatment, but can be re-started when the infection has cleared.

Opportunistic infections have also been reported in patients taking MTX; these occur at any time, usually within the first 12 weeks of treatment, and the risk remains throughout the treatment course.[180] Most reports are found in patients with rheumatoid arthritis who were on concurrent medications, but opportunistic infections have been reported rarely in patients treated for psoriasis.[181] MTX should be discontinued in patients who develop opportunistic infections.

13.0 Co-prescription

13.1 Biologics

The combination of any biological therapy with MTX is not licensed; however, this practice is increasingly undertaken, in an attempt to improve efficacy and reduce the risk of immunogenicity related to monoclonal-based biologics for the treatment of psoriasis.

MTX has been demonstrated to be safe with potentially improved efficacy when used in combination with tumour necrosis factor (TNF) antagonists.[182–186] MTX has also been combined with ustekinumab, usually in an effort to maintain or improve efficacy.[187] Zachariae *et al.* randomized 59 patients, who had an inadequate response to MTX treatment, to receive either etanercept with a tapered MTX dosing schedule, or combination therapy throughout the whole study period of 24 weeks.[185] It was shown that significantly more patients in the combination group achieved PASI 75 compared with patients who had a tapered MTX dosing schedule.

The optimal safety monitoring for combination therapy of a biologic and MTX has not been determined. Consensus guidelines have reviewed this topic and recommend that all parameters that are monitored for each drug as monotherapy should be assessed for combination therapy, with the monitoring interval defined by the drug with the most stringent monitoring criteria.[188]

MTX indications in dermatology continue to expand and one such example is the potential role of MTX reducing anti-drug antibody formation against biological therapies, thereby prolonging the efficacy of the biological drug. A reduction in immunogenicity has been shown with concomitant MTX use with anti-TNFs in rheumatoid arthritis, Crohn disease and spondyloarthropathy;[189] the same data are not available in psoriasis populations, but it seems likely that a similar reduction in drug antibody formation may be seen.

13.2 Ciclosporin

MTX has been combined with ciclosporin in several studies, with a total patient population of 124. One study randomized patients with psoriatic arthritis and psoriasis to receive either MTX and placebo or MTX and ciclosporin.[190] This study showed a statistically significant difference between groups on PASI and psoriatic arthritis outcomes in favour of combination therapy. In the remaining uncontrolled studies, a beneficial effect of combining MTX with ciclosporin was reported in four.[191,192] One case series reported that three of four patients experienced worsening of their psoriasis, which occurred following a dose reduction of ciclosporin owing to side-effects. There are additional safety concerns, in particular increased immunosuppressive effects, with combining these two drugs such that co-therapy would not be recommended routinely. The most common scenario for use of both drugs is now when transitioning from one therapy to the next.

The evidence for the use of this combination of drugs for other indications is sparse and no recommendation can be made.

13.3 Ultraviolet B

An RCT has shown that combining MTX with UVB is significantly more effective than just UVB in the treatment of psoriasis, allowing fewer UVB treatments compared with UVB alone.[193] MTX has also been combined with PUVA, but has a higher risk of subsequent skin cancers in these patients.[194] However, it is not known if the risk of skin cancers is enhanced following combination of MTX with UVB.

Clinicians should be aware that high and low doses of MTX can be associated rarely with MTX photoreactivation. In this idiosyncratic phenomenon, an individual takes MTX 2–5 days after erythemogenic doses of UV radiation (as erythema begins to subside) and this induces severe erythema and sometimes blistering in areas that were previously exposed to UV but not in UV-protected areas.[195–198] MTX taken immediately after exposure to suberythemogenic doses of UVB or

PUVA has also been reported to cause a delayed erythematous reaction lasting 24 h, which may be due to immediate inhibition of DNA repair pathways.[199]

13.4 Retinoids

No RCTs have examined the efficacy and safety of combined treatment with retinoids and MTX for any indication. Evidence for their use in combination is only from case reports. Both retinoids and MTX are hepatotoxic, and rarely this may be exacerbated if they are prescribed in combination.[200] However, retinoids are prescribed occasionally in conjunction with MTX to good effect.[201,202] More frequently, they are prescribed together for short periods of time when patients are in transition between these two treatments, as both drugs can take several weeks to be effective. Prescribing them together in the short term can help prevent flares of psoriasis, and settle acute episodes,[202,203] but blood monitoring should be performed more frequently to detect any hepatotoxicity.

14.0 Checklists for methotrexate prescribing

14.1 Prior to prescribing methotrexate

1 Take a full drug history.
2 Ensure there are no contraindications to MTX use (Sections 8.1 and 8.2, and Table 7).
3 Check results of baseline investigations (Section 9.4): (i) FBC; (ii) U&E/eGFR; (iii) liver blood tests; (iv) hepatitis B and C serology (Section 9.6); (v) HIV serology, especially in high-risk groups (Section 9.7); (vi) VZV serology (if no history of varicella; Section 9.8); (vii) consider a baseline chest X-ray.

Table 7 Summary of contraindications

Contraindications (strength of recommendation C)	
Relative contraindications	Absolute contraindications
Mild-to-moderate renal impairment	Marrow dysfunction or failure
Mild-to-moderate liver dysfunction	Patients on dialysis
History of hepatitis B and C	Severe renal dysfunction
Gastritis	Severe hepatic dysfunction/cirrhosis
Alcohol excess	Women attempting to conceive, pregnancy and breastfeeding
Patient unreliability	Immunodeficiency states (in some cases relative)
Recent live vaccinations	Active tuberculosis or hepatitis virus infections
Male partners of women wishing to conceive	Pulmonary fibrosis or significantly reduced lung function
	Active peptic ulceration
	Concurrent trimethoprim therapy
	Hypersensitivity to methotrexate

4 Give special consideration to the following: (i) children (Section 7.3); (ii) hepatic and renal impairment (Sections 9.6, 11.2 and 11.4); (iii) breastfeeding/pregnancy (Section 9.3); (iv) VZV nonimmune – immunization required (Section 12.1); (v) hepatitis B nonimmune – consider immunization in at-risk groups (Section 9.6); (vi) positive HIV serology (Section 9.7).
5 When possible, formulate a plan for duration and eventual withdrawal of therapy.
6 Complete checklist of what to tell patients – prior to prescribing MTX (see below).
7 Supply with a patient information leaflet (if not done previously) and record provision in case notes.
8 Supply with MTX patient monitoring booklet.
9 Arrange for patient to have pretreatment and flu (annual) and pneumococcal (5-yearly) vaccinations.

14.2 What to tell patients prior to prescribing methotrexate

1 Explain the weekly dosing schedule and the tablet strength the patient is being prescribed, i.e. 2·5 mg (Section 9.1).
2 Explain the onset of therapeutic benefit of MTX may not be apparent for 3–12 weeks.
3 Advise (i) against pregnancy; and (ii) the need for effective contraception (Section 9.3).
4 Emphasize the need for toxicity monitoring with regular blood tests. Patients unable to comply should not be given the drug (Section 10.3).
5 Explain if usage is for a licensed or unlicensed indication. For unlicensed indications give a clear explanation of why it is being prescribed (Section 7.0).
6 Advise patients to seek urgent medical attention if they develop signs or symptoms of MTX toxicity, bone marrow suppression or liver impairment. Specifically, warn patient about: (i) fever/flu-like illness; (ii) mouth ulceration; (iii) tiredness; (iv) unexplained bruising or bleeding of the gums; (v) nausea, vomiting, abdominal pain or dark urine; (vi) breathlessness or cough.
7 Advise on the need for pneumococcal vaccine and a yearly influenza vaccination (Section 12.1).
8 Advise patients about limiting alcohol intake (Section 9.2).
9 Warn about potential drug interactions (also detailed in the patient information leaflet) (Section 11.7).

15.0 Economic and practical considerations

MTX is an inexpensive immunosuppressant drug that has been used in the management of many skin diseases. It is available in the form of tablets or via injection (as sodium salt). The U.K. price quoted in the British National Formulary (November 2015) for 24 × 2·5-mg tablets is £2·40, and £2·92 for 48 tablets; the salt solution, in 2-mL vials, is £6·00 for 2·5 mg mL^{-1} and £2·62 for 25 mg mL^{-1}. Based

Table 8 Dosage and delivery and monitoring recommendations for patients using methotrexate (MTX)

Dosage and delivery and monitoring	Recommendation	Strength of recommendation
Dosage	In healthy adults, consider starting MTX at doses of between 5 and 15 mg weekly Those with renal impairment (see Table 4) may need lower doses, and could be commenced on 2·5–5·0 mg weekly Once remission is achieved, use the lowest maintenance dose to control the condition Consider switching to alternative medication or use subcutaneous MTX if minimal efficacy is achieved within 12–16 weeks of starting treatment	B
Folic acid	Folic acid supplementation is recommended	A
Regular monitoring	The FBC, LFTs and U&E need to be repeated every 7–14 days for the first month. Once the therapy has been stabilized, the assessment can be performed every 2–3 months	C
Monitoring for liver toxicity	Recommended baseline assessments include serum PIIINP, standard LFTs and consideration of other risk factors for liver disease (e.g. fatty liver disease, alcohol, etc.) Monitor LFTs, PIIINP at least every 3 months (patients with psoriasis only) and consider onward referral for specialist advice if abnormal (see 'Regular monitoring' above), specifically in relation to PIIINP Onward referral for further specialist assessment (i) if PIIINP is > 8 mg L^{-1} on two occasions; or (ii) if three measurements are $> 4{\cdot}2$ mg L^{-1} in a 12-month period; or (iii) if > 10 mg L^{-1} on one occasion The routine use of liver biopsy for monitoring MTX hepatotoxicity is *not* recommended	C
Monitoring for pulmonary disease	Enquiry regarding history of pulmonary disease and respiratory symptoms should be made at initiation of MTX and at subsequent visits Chest X-ray, further investigations and/or respiratory referral are necessary if (i) symptoms are present; (ii) patient is over 40 years of age and a cigarette smoker, or has a background disease putting them at risk of respiratory complications (e.g. sarcoid)	D
Monitoring renal function	Reduction in MTX dosage should be considered in those with suboptimal renal function Avoid MTX in patients on dialysis and with a creatinine clearance < 20 mL min^{-1}	D

FBC, full blood count; LFT, liver function test; U&E, urea and electrolytes; PIIINP, peptide of procollagen III.

on these figures and an average dose of 20 mg per week, the annual costs associated with the tablet form would be £25·31–£41·60. All healthcare professionals initiating MTX need to factor in additional costs associated with baseline and regular monitoring investigations, as well as the local arrangements and logistics for such investigations (see Table 8).

16.0 Future directions

MTX has been used in dermatology for > 50 years across numerous indications. Despite this, there remain numerous areas around its safe and effective use that could be optimized further and better understood, including, but not limited to, the following: (i) the mechanism of action of MTX in inflammatory skin disease; (ii) if a better pharmacokinetic understanding of the drug would lead to more directed dosing in inflammatory skin disease; (iii) the true utility of MTX in numerous skin conditions where RCT data are lacking, for example blistering skin conditions and cutaneous sarcoidosis; (iv) the optimal dosing schedule and route of administration of MTX; (v) if genetic/epigenetic factors may influence safety and efficacy of MTX;[204,205] (vi) progress with imaging and biomarkers to allow noninvasive monitoring for hepatic fibrosis.[121]

17.0 Recommended audit points

Clinicians prescribing MTX should use audit to evaluate their care against predefined standards. The following parameters are suggested.

1. In the last 20 consecutive patients starting MTX therapy is there clear documentation of a full drug history?
2. In the last 20 consecutive patients starting MTX therapy is there clear documentation of the provision of written patient information and a monitoring booklet?
3. In the last 20 consecutive patients starting MTX therapy is there clear documentation of the results for *baseline* investigations: (i) FBC; (ii) U&E; (iii) LFTs; (iv) hepatitis B and C serology; (v) HIV serology; (vi) VZV serology, if no history of varicella.
4. In the last 20 consecutive patients starting MTX therapy is there clear documentation of compliance with *monitoring* recommendations: (i) FBC; (ii) U&E; (iii) LFTs; (iv) PIIINP.

The audit recommendation of 20 cases per department is to reduce variation in the results due to a single patient, and allow benchmarking between different units. However, departments unable to achieve this recommendation may choose to audit all cases seen in the preceding 12 months.

18.0 Summary

MTX has been used for many indications in dermatology with variable success. Evidence of high quality exists for advocating its use in treating adults with psoriasis who require a systemic therapy. For all other conditions the evidence is less robust, but, nonetheless, MTX may have an important role in more refractory atopic eczema and discoid lupus, for example. Further well-designed studies are required for most other indications given below and collaborative multicentre experiences or studies are required to understand how efficacious MTX truly is for these rare conditions. Over many decades the safety of MTX has been established, but we are still looking for the optimal assessment for potential liver toxicity and the required dosing schedule of supplementary folic acid.

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Appendix 1

Levels of evidence

Level of evidence[a]	Type of evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1−	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies. High-quality case–control or cohort studies with a very low risk of confounding, bias or chance, and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance, and a moderate probability that the relationship is causal
2−	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Nonanalytical studies (e.g. case reports, case series)
4	Expert opinion, formal consensus

RCT, randomized controlled trial. [a]Studies with a level of evidence '−' should not be used as a basis for making a recommendation.

Strength of recommendation

Class	Evidence
A	At least one meta-analysis, systematic review or RCT rated as 1++, and directly applicable to the target population A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results Evidence drawn from a NICE technology appraisal
B	A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4 Extrapolated evidence from studies rated as 2+ Formal consensus
D (GPP)	A good practice point (GPP) is a recommendation for best practice based on the experience of the guideline development group

RCT, randomized controlled trial; NICE, National Institute for Health and Care Excellence.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Data S1. Literature search strategies.