From this pharmacy CPD module on methotrexate non-adherence you will learn:

• How methotrexate should be prescribed, including concurrent use of folic acid, in rheumatoid arthritis
• The common side effects, including blood dyscrasias, of this DMARD
• How you can help patients who may be non-adherent to their prescribed methotrexate
• About the common misconceptions that surround the use of this drug

This article has been initiated and funded by Roche Products Limited and Chugai Pharma UK. Andrew Pothecary has received a honorarium for authoring this article.
Methotrexate was first launched as a treatment for certain cancers in 1947, then introduced for the treatment of rheumatoid arthritis (RA) in the 1980s(1). It is currently licensed for the treatment of rheumatoid arthritis, psoriasis, and cancers. However, it is widely used off-licence for other autoimmune and inflammatory conditions, such as Crohn’s disease(2), psoriatic arthritis(3) and systemic lupus erythematosus(4).

The mechanism of action of methotrexate is unclear. It irreversibly inhibits dihydrofolate reductase, blocking DNA synthesis in dividing cells. This accounts for most of its action when used in the treatment of cancers. It probably also acts in other ways when used to treat RA – for example, by interrupting cell signalling in the immune system(5) or by inhibiting certain cellular pathways(6).

When used to treat RA, methotrexate is always taken as a single once-weekly dose, on the same day each week. Patients will usually start on a low dose of methotrexate (7.5mg weekly) and the dose will gradually be increased according to tolerance and effect – to a maximum dose of 25mg per week(7).

Folic acid and methotrexate
The British Society for Rheumatology (BSR) strongly recommends that folic acid is prescribed to all patients taking methotrexate, at a minimum dose of at least 5mg per week to reduce the risk of side effects(5, 8). You should be aware that this is an unlicensed use for folic acid(2). You should check with the patient or carer which brand of injection they usually have(11).

How should methotrexate be prescribed?
Methotrexate is available as an oral liquid, 2.5mg and 10mg tablets, and subcutaneous injections in both pens and pre-filled syringes(9).

1. Patients on low-dose oral methotrexate (that is, weekly dosing for non-cancer conditions) should only be prescribed and dispensed one strength of tablets.
2. Before starting methotrexate, the patient should be counselled on treatment, including dosing schedules and monitoring, and provided with a patient-held monitoring booklet – this should be checked each time methotrexate is dispensed.
3. Prescriptions and dispensed item labels should not state “as directed”, but must specify the dose (in terms of the number of tablets) to be taken each week.

Additionally, it is advisable for subcutaneous methotrexate to be prescribed by brand name, to ensure patients always receive the injection device they are familiar with. If you are faced with a prescription for generic methotrexate injections, you should check with the patient or carer which brand of injection they usually have(9).

Side effects
Common side effects of methotrexate include nausea, vomiting, or diarrhoea. These are usually mild, only lasting between 24 and 48 hours after dosing. With continuation of treatment, patients find side effects often improve. If the side effects are severe or persistent, patients could have their folic acid dose increased or could be switched to injections(2, 3).

Overview

Risk of serious side effects
Methotrexate can make patients more susceptible to infection and, although rare, can also cause liver damage or pneumonitis (lung inflammation). Patients should have annual influenza vaccinations – as they are in an “at-risk” group they should receive this through the NHS – and be vaccinated against pneumococcal pneumonia(10).

If patients on methotrexate for their rheumatoid arthritis seek advice about gastrointestinal symptoms, you should refer them to their rheumatology team. Patients should be able to access specialist advice, usually via a telephone helpline(11).

Other side effects can include mouth ulcers, hair loss (usually minor) and skin rashes. Mouth ulcers may be treated with over-the-counter (OTC) products, but if patients are suffering from multiple or persistent ulcers, or are concerned about any other side effects, they should be referred to their specialist team.

Methotrexate and blood tests
Blood monitoring is required while patients are on methotrexate, as blood disorders may occur. The BSR recommends patients have fortnightly blood tests until they are on a stable dose of methotrexate for six weeks – followed by monthly blood tests for three months, then once every three months thereafter.

However, some patients may require more frequent blood tests if they have other conditions that might increase their risk of methotrexate toxicity, such as chronic kidney disease(7).

These blood tests will usually include:
- a full blood count (to monitor the production of red and white blood cells and platelets)
- liver and kidney function tests(15)
- a test for inflammatory markers (usually C reactive protein) to monitor disease activity and response to treatment(19)

Drinking alcohol with methotrexate can increase the risk of liver damage, so patients should only drink in small amounts to avoid binging – no more than 14 units per week, taken over several days, though some rheumatologists may recommend stricter limits(15).

Side effects
- jaundice (yellowing of the skin or eyes)(2)
- shortness of breath
- unexplained bruising or bleeding
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Methotrexate can cause birth defects, so female patients must take reliable contraceptive precautions during treatment and for three months after their last dose. Men do not need to stop taking methotrexate before trying for a baby, although this has been advised in the past(15).

The following case study offers an example of a non-adherent methotrexate patient who is being treated for RA.

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A missed dose

Emily, 34, is one of your regular patients. She was diagnosed with RA about 18 months ago, and has come in for her annual medicines use review (MUR). According to her PMR, she is taking the following medication:

- methotrexate 20mg weekly
- folic acid 5mg weekly, the day following methotrexate
- hydroxychloroquine 200mg once daily
- sulfasalazine 1g twice daily
- levothyroxine 150 micrograms daily
- naproxen 500mg twice daily, when required
- omeprazole 20mg once daily, when required (on days when taking naproxen)
- desogestrel 75 micrograms once daily.

During the MUR, Emily mentions that she doesn’t always take her methotrexate as directed. “I don’t always take my methotrexate – I forget to take it about once a month,” she says. “I also lower my dose to 15mg when I do take it, but I haven’t discussed this with my doctor or anyone from the rheumatology team. You see, I think my rheumatoid arthritis is well controlled and I didn’t want to take such a high dose. By taking the lower dose, I was able to keep the nausea at bay.”

Emily also explains that she needs to take naproxen every day or else she starts to experience more joint pain and swelling. After asking some more questions and using the methotrexate adherence questionnaire (see p9), you find out that Emily intentionally misses doses of methotrexate depending on what activities she has planned – such as a holiday or visiting family for a weekend – as it sometimes causes her to suffer from nausea.

**What is rheumatoid arthritis?**

RA is an inflammatory disease. It usually affects the small joints of the hands and feet, although any joint lined with synovium (a specialised tissue) can be affected. These joints will swell up and become painful. If untreated, joints will become damaged, resulting in joint deformity, loss of function, and disability. It is a systemic disease and can affect the whole body, including the heart, lungs, and eyes. Generalised symptoms such as malaise (feeling unwell) can be common. RA can develop at any age and affects between two to three times more women than men.

**How is RA treated?**

Current guidelines recommend treating patients early with the aim of getting the disease into remission as quickly as possible, to prevent damage to the patient’s joints. Patients will often initially be prescribed corticosteroids (usually oral prednisolone or intramuscular methylprednisolone) or non-steroidal anti-inflammatory drugs (NSAIDs) to provide quick relief from their symptoms. One or more disease-modifying antirheumatic drugs (DMARDs) are usually prescribed at the same time, but these are slower-acting and can take several months to start working.

Methotrexate is considered the gold standard treatment for RA and is the usual first-choice DMARD. If methotrexate is ineffective, other DMARDs may be added to the treatment regimen, and it is not unusual for patients to be on triple therapy with methotrexate, sulfasalazine and hydroxychloroquine.

If a patient’s condition is still symptomatic despite treatment with DMARDs, their rheumatologist may consider them for treatment with targeted therapies, such as biologics. Biologics are significantly more expensive than DMARDs, and there are several National Institute for health and Care Excellence, Scottish Medicines Consortium and All Wales Medicines Strategy Group guidelines regulating their use in the NHS.

**How is RA disease activity measured?**

RA disease activity can be measured and tracked using the disease activity score (DAS28). This is a composite score calculated using:

- the patient’s C-reactive protein level (CRP is a substance produced by the liver that increases in the presence of inflammation in the body)
- the number of joints out of 28 that are tender and/or swollen
- the patient’s assessment of their general health over the past week, on a scale of 0 to 100 (where 100 is the worst score).
The resulting score gives an indication of disease activity; 5.1 or above is considered to be severe, whereas 2.6 or below indicates that the patient is in remission.

Patients can self-assess and track their DAS28 using the Know Your DAS app (available on the Android and Apple app stores) or a paper record available from the National Rheumatoid Arthritis Society (NRAS). Many patients find it useful to see how their score relates to how much their RA is affecting their daily activities.

**What should you recommend to Emily?**

You should advise Emily to contact the rheumatology team responsible for her care. Most rheumatology departments operate a telephone helpline service that enables patients to seek advice if they are having problems with their condition or medication. Information on this service is usually given to patients at their outpatient appointments, but can often be found on local hospital websites.

**What actions can be taken?**

Unless patients can identify certain foods or activities that cause them to feel nauseous after taking methotrexate, there is little that can be done in terms of lifestyle changes. The rheumatology team could consider the following options in discussion with Emily:

- changing the timing or frequency of the folic acid dose; for example, Emily could try taking her weekly folic acid dose the day before her methotrexate, or increase the dose to 10mg weekly
- switching to methotrexate injections can often be helpful in patients who experience nausea with oral methotrexate, as many patients experience no nausea with injections; patients can self-administer the weekly injection after being trained by their specialist nurse – exact arrangements for supply of the injections may vary
  - consider an alternative DMARD; although Emily is currently on triple therapy, her methotrexate could be switched to another DMARD (for example leflunomide)
  - consider concomitant treatment with an antiemetic agent, such as ondansetron

**Biologic therapy**

If patients still have active disease despite treatment with DMARDs, their rheumatologist may consider them for treatment with targeted therapies such as biologics. These are only prescribed in secondary care and supplied to patients through hospital pharmacies or via homecare suppliers, such as Healthcare at Home or Lloydspharmacy Clinical Homecare. Emily may be eligible under the National Institute for health and Care Excellence criteria for starting treatment with a biologic.

The National Institute for health and Care Excellence guidelines require patients to have active disease (defined as a DAS28 of ≥ 5.1) and to have not responded to, or failed to tolerate, two conventional DMARDs.

The National Institute for health and Care Excellence recommends the biologic therapies adalimumab, etanercept, certolizumab pegol, golimumab, tocilizumab or sarilumab as monotherapy, along with the non-biologic JAK inhibitors tofacitinib or baricitinib as monotherapy, with the non-biologic JAK inhibitors tofacitinib or baricitinib as monotherapy, with the non-biologic JAK inhibitors tofacitinib or baricitinib as monotherapy.

**Concurrent NSAID use**

There is a misconception among some healthcare professionals that there is a blanket ban on using methotrexate in combination with NSAIDs. Methotrexate is commonly used with NSAIDs, including COX-2 inhibitors, to provide pain relief and anti-inflammatory effects. However, prescribing and dispensing software often generate interaction alerts, which can be confusing for patients and healthcare professionals.

The use of methotrexate in combination with NSAIDs is not contraindicated; however, caution should still be advised and patients requiring NSAIDs should have these prescribed, rather than purchasing them OTC. This ensures their condition is monitored and helps to prevent any potential adverse drug reactions. Patients with reduced kidney function are at a greater risk of these adverse effects and the combination should be carefully considered by the prescriber.

**Chemotherapy**

Other common misconceptions include that methotrexate is primarily used for chemotherapy. Although methotrexate can be used for cancer chemotherapy, the doses are between 10 and 20 times higher than those used in RA, and it is used in cycles rather than continuously.

**“Strong” medicine choice**

Some patients are concerned that methotrexate is an “unusual” or “strong” treatment for RA. This is not the case, as current UK guidelines recommend it as an early treatment for the condition. If used and monitored correctly, it is safe and effective in treating the condition early and preventing further reduction in function.

**Close contact concerns**

Some patients may be concerned that because methotrexate is cytotoxic, they must avoid contact with other people. You can explain to these patients that they do not need to avoid kissing or cuddling infants or children, or avoid intimate and non-intimate kissing. In addition, they do not need to take special care to dispose of urine or faeces. Normal standards of personal hygiene will provide sufficient protection.

Additionally, patients taking methotrexate do not need to avoid pregnant women, and there is negligible risk for pregnant women exposed to their partner’s bodily fluids.

**How can pharmacists improve methotrexate adherence?**

RA patients who have higher medication adherence are more likely to have lower disease activity; however, adherence to treatment is variable. Adherence appears to decrease with increasing disease duration, lower disease activity, and a lack of belief that methotrexate is necessary or effective. Side effects may also play a role, with a large number of patients reporting nausea, diarrhea, fatigue or general malaise while taking methotrexate. The NRAS website...
features a useful video on medication adherence aimed at patients, but pharmacists may also find this useful – it is available from www.nras.org.uk/methotrexate.

As poor adherence to treatment is linked to worse outcomes for patients, it is important that support is provided to patients to help them overcome any problems that could be stopping them from taking their treatment as planned.

Community pharmacists have a part to play here, by identifying patients who may be non-adherent to treatment and providing advice to help them take their medicines as prescribed, or by signposting them to an appropriate source of advice, such as their specialist nurse.

One tool that may be of use to community pharmacists is the Methotrexate Adherence Questionnaire (see p9). It helps to identify patients who may be non-adherent to treatment, and to provide some indication of the possible reasons for this, such as side effects that may be particularly problematic for the patient. Once these issues have been identified, it should be possible to advise the patient on the management of these problems.

The questionnaire asks patients if they have intentionally missed or forgotten any doses. It also asks if the patient has experienced side effects such as nausea, mouth ulcers, or fatigue. For each side effect experienced, the patient is asked to grade the severity from one (very mild) to 10 (very severe). The questionnaire can be used as part of an MUR consultation, as it links well with the MUR questions about side effects, missed doses, and whether patients think their treatment is working.

Alternatively, it can be given to patients to fill in while they wait for their prescription, or to take away and return, and then used as a starting point for a conversation about the patient’s adherence to methotrexate and the rest of their treatment.

Another option is to give the questionnaire to patients and suggest they complete it before their next rheumatology appointment, as this may help them broach the subject of side effects and non-adherence with their specialist team.

Questionnaire

Methotrexate adherence questions(27)

How long has the patient been taking methotrexate?

How satisfied do they feel with their methotrexate treatment? (0-10, 0 = not at all, 10 = very satisfied)

In the last six months, how many weeks have they:

✓ Been advised by a healthcare professional not to take their normal dose of methotrexate?
✓ Forgotten to take their methotrexate?
✓ Decided not to take their methotrexate?

For each of the following side effects, ask patients if they have had the problem and how severe it was on a scale of 1-10 (1 = very mild, 10 = very severe)

✓ Nausea
✓ Mouth Ulcers
✓ Hair Loss
✓ Fatigue, which the patient associates with taking methotrexate

Has the patient had any other problems taking their methotrexate, and if so what were they, and how severe were they?

Do any of these side effects impact on the patient’s life, and if so, how?
References


Tips for your CPD entry on methotrexate non-adherence

Reflect
• How should methotrexate be prescribed, including concurrent use of folic acid, in rheumatoid arthritis?
• What are the common side effects, including blood dyscrasias, of this disease-modifying anti-rheumatic drug?
• How can I help patients who may be non-adherent to their prescribed methotrexate?
• What common misconceptions surround the use of this drug?

Plan
This CPD module provides information about the use of methotrexate in managing rheumatoid arthritis and the concurrent use of folic acid. It explores some of the reasons patients may not adhere to methotrexate treatment and some of the misconceptions about the drug. It also considers what pharmacists can do to help improve adherence to treatment with methotrexate.

Act
• Read more about the use of methotrexate in guidelines from the British Society for Rheumatology and British Health Professionals in Rheumatology at bit.ly/2HePnat
• Read more about the myths and misconceptions associated with methotrexate at bit.ly/2GLAU2c
• Watch a patient video on medication adherence at bit.ly/2v19UKJ

Evaluate
• Are you now confident in your knowledge of the use of methotrexate in the treatment of rheumatoid arthritis?
• Could you give advice and support to patients and carers about the use of methotrexate in the management of rheumatoid arthritis, including encouraging adherence to therapy?
Take the 5-minute test

To receive your logsheet and certificate by email, complete the test below, add your details, then fold and freepost to C+D. Alternatively visit bit.ly/CDMethotrexateCPD to complete the test and receive your certificate and logsheet

1. When used to treat rheumatoid arthritis, methotrexate is always taken as a single once-weekly dose, taken on the same day each week.
   □ True or □ false?

2. Folic acid should be prescribed to all patients taking methotrexate to reduce the risk of side effects.
   □ True or □ false?

3. Folic acid and methotrexate should be taken on the same day.
   □ True or □ false?

4. Common side effects of methotrexate include nausea, vomiting, or diarrhoea.
   □ True or □ false?

5. If patients on methotrexate for their rheumatoid arthritis seek advice about gastrointestinal symptoms, you can recommend OTC medicines.
   □ True or □ false?

6. Blood monitoring is not required while patients are on methotrexate.
   □ True or □ false?

7. Patients on methotrexate should have annual influenza vaccinations.
   □ True or □ false?

8. Methotrexate can cause birth defects, so female patients must take reliable contraceptive precautions during treatment and for three months after their final dose.
   □ True or □ false?

9. Patients taking methotrexate who require NSAIDs should have these prescribed.
   □ True or □ false?

10. Pharmacists can use the Methotrexate Adherence Questionnaire to identify patients who may not be adhering to their methotrexate treatment.
    □ True or □ false?

First name: 

Last name: 

Email: 

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