Safer prescribing and monitoring of high-risk medicines

SU WOOD

General practice is now responsible for prescribing more high-risk medicines with regular monitoring requirements. This article discusses some of the medicines that require more intensive monitoring, and the systems Primary Care Networks can put in place to ensure safer prescribing of these medicines.

Ps are being asked to take on more prescribing that, in the past, would have been reserved for specialists. Much of this prescribing is for high-risk medicines with regular monitoring requirements. The new GMS contract Quality and Outcomes Framework (QOF) quality indicator for prescribing safety states that “in May 2012, the GMC published its report Investigating the prevalence and causes of prescribing errors in general practice which found that 1 in 20 prescriptions contained an error in terms of medication or monitoring”. The guidance highlights that “better monitoring of potentially toxic medications and the creation of safe systems to support drug monitoring” should be a priority.

This year, there is a focus upon lithium monitoring, NSAID prescribing and use of valproate in the GP contract. Other areas to reduce prescribing risk and improve monitoring are likely to be assessed in future years, and so setting up a robust system for monitoring all high-risk medicines now will not only reduce risks for patients, but will enable practices to be ready for future safer prescribing quality indicators.

What are high-risk medicines and what makes them high risk?
All medicines have the potential for adverse effects, so regular medication review should be routine. However, some medicines are particularly high risk:
• Firstly, because of the effects the drug has on the body, for example methotrexate, which can affect the immune system, or valproate, which can affect the unborn child.
• Secondly, because of how changes in the patient’s condition can affect the way the body processes the drug. For example, if kidney function is reduced, elimination of renally excreted drugs will be slower, increasing blood levels and risk of adverse effects. Use of direct oral anticoagulants (DOACs) requires assessment of kidney function to reduce the risk of
<table>
<thead>
<tr>
<th>Drug</th>
<th>Blood monitoring*</th>
<th>Example regular monitoring**</th>
<th>Other monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine</td>
<td>FBC weekly for the first 4 weeks <em>(BNF)</em> or 8 weeks <em>(SmPC)</em>, then monthly or at least every 3 months; caution in renal or hepatic impairment</td>
<td>FBC, U&amp;Es + LFTs weekly for 8 weeks after each dose increase then monthly x 4, then 3-monthly (assuming stable and no dose increase)</td>
<td>Urine tests (protein and blood) with each blood test</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>FBC before each treatment</td>
<td>FBC + U&amp;Es every 2 weeks before each treatment</td>
<td>Urine tests (protein and blood) with each blood test</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>Monitor kidney function, potassium, magnesium, liver function before initiating treatment then regularly thereafter</td>
<td>FBC, U&amp;Es +LFTs 2-weekly for 8 weeks after each dose increase then monthly x 4 then 3-monthly (assuming stable and no dose increase)</td>
<td>Regular monitoring of blood pressure is required – suggest BP at each blood test Urate and lipids 3-monthly</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Use with caution in hepatic or renal impairment</td>
<td>U&amp;Es annually in those over 70 years or if pre-existing renal impairment or when known hypertension/diabetes</td>
<td>Annual visual acuity test</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>FBC/LFTs before treatment then every 2 weeks for 6 months then every 8 weeks; impaired liver function and moderate to severe renal function are contraindications Monitor blood pressure</td>
<td>FBC, U&amp;Es +LFTs 2-weekly for 6 months after each dose increase then monthly x 4 then 2-monthly (assuming stable and no dose increase)</td>
<td>Blood pressure must be checked before the start of leflunomide treatment with each blood test</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Committee for the Safety of Medicines <em>(CSM)</em> advice: FBC/ kidney function tests *(U&amp;Es)/ LFTs before treatment then repeated weekly until stabilised and then every 2–3 months</td>
<td>FBC, U&amp;Es + LFTs weekly for 8 weeks after each dose increase then monthly x 4 then 3-monthly (assuming stable and no dose increase)</td>
<td></td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>FBC weekly for the first 4 weeks, twice a month for 2 months, then every month in the first year</td>
<td>FBC, U&amp;Es +LFTs weekly for the first 4 weeks, twice a month for 2 months, every month in the first year, then 3-monthly (assuming stable and no dose increase)</td>
<td></td>
</tr>
<tr>
<td>Myocrisin <em>(IM gold)</em></td>
<td>FBC before each IM injection</td>
<td>FBC prior to each injection – review results prior to giving next injection</td>
<td>Urine tests (protein and blood) with each blood test</td>
</tr>
<tr>
<td>Penicillamine</td>
<td>FBC before treatment then every 1 or 2 weeks for the first 2 months then every 4 weeks; caution in renal insufficiency</td>
<td>FBC every 2 weeks for 8 weeks after every dose increase then monthly</td>
<td>Urine tests (protein and blood) with each blood test</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>FBC/LFTs before treatment then monthly for the first 3 months <em>(BNF)</em> FBC/LFTs before treatment then every 2 weeks for the first 3 months, monthly for the next 3 months, then 3-monthly; U&amp;Es monthly for the first 3 months <em>(SmPC)</em></td>
<td>FBC, U&amp;Es +LFTs 2-weekly for 8 weeks after each dose increase then monthly x 4 then 3-monthly (assuming stable and no dose increase)</td>
<td>Urine tests (protein and blood) 3-monthly</td>
</tr>
</tbody>
</table>

*SmPC recommendations5* unless otherwise stated; **NB. follow any local shared care guidelines FBC = full blood count; ALT = alanine aminotransferase; SGPT = serum glutamic-pyruvic transaminase; LFTs = liver function tests; U&Es = urea and electrolytes

Table 1. The SmPC licence monitoring requirements for the disease modifying anti-rheumatic drugs (DMARDs) often included in shared care monitoring

prescriber.co.uk
bleeding that would be increased if blood levels were raised, as detailed in the BNF\textsuperscript{4} and Summary of Product Characteristics (SmPCs) for each drug.\textsuperscript{5}

Both these areas of risk can be mitigated by regular monitoring and assessing the results against the recommendations for prescribing.

It is important that any change in monitored parameters should trigger a consideration of the medicines prescribed. For example, when doing routine diabetes monitoring, if kidney function is shown to be reduced, all medicines should be assessed. If any are renally eliminated and have recommendations for altered prescribing in reduced kidney function, the creatinine clearance should be calculated and any adjustments made to reduce the risk from increased blood levels (as highlighted in the recent MHRA Drug Safety Alert on prescribing medicines in renal impairment,\textsuperscript{6} and discussed in more detail in the recent Prescriber article on drug management in patients with reduced kidney function\textsuperscript{7}).

**Which medicines need more intensive monitoring?**

The NHS Specialist Pharmacy Service (SPS), which supports medicines optimisation across the NHS, has a regularly updated document of suggestions for therapeutic drug monitoring in adults in primary care.\textsuperscript{5} There are likely to be local guidelines for monitoring, particularly for shared care medicines initiated by specialist services and then handed over to the general practice to prescribe and monitor. The following updates my 2014 Prescriber article ‘A protocol for drugs that require regular monitoring’.\textsuperscript{9}

**DMARDs**

Disease modifying anti-rheumatic drugs (DMARDs), such as methotrexate and azathioprine, have a long list of potentially dangerous side-effects and can only be safely prescribed if carefully monitored. The SPS still lists the National Patient Safety Agency (NPSA) document ‘Towards safer use of methotrexate’\textsuperscript{12} to highlight the risks and how to mitigate them. From July 2004 to 2006, the NPSA received 165 reports of patient safety incidents involving oral methotrexate; many of these would have been avoidable if correct monitoring had been carried out.

The British Society for Rheumatology, British Health Professionals in Rheumatology Standards and the British Association of Dermatologists guideline for DMARD therapy (2008) states that, whatever DMARD is considered appropriate for a patient, it is paramount that the patient is carefully monitored so that there is no delay in the detection of any untoward effect of the drug.\textsuperscript{10} Table 1 shows the SmPC licence monitoring requirements for DMARDs and an example regular monitoring schedule; most areas will have shared-care guidelines for monitoring with local rheumatology, renal, dermatology and/or gastroenterology departments.

**Other medicines with specified blood monitoring requirements**

Many other medicines have regular monitoring requirements specified in their SmPC and in the BNF. Table 2 details the recommended monitoring for lithium, amiodarone and mesalazine. Lithium monitoring is currently highlighted as a QOF quality indicator for prescribing safety.

**DOACs**

DOACs (apixaban, dabigatran, edoxaban, rivaroxaban) are examples of medicines that have dosing requirements that mean monitoring is required, but there are no defined monitoring schedules in the SmPCs. As kidney function can change over time, or with disease, regular monitoring is needed. SPS states that there should be national guidance to help prescribers monitor kidney function for DOAC dosing.\textsuperscript{11} Table 3 shows an example schedule of monitoring for DOACs to ensure regular checks.\textsuperscript{12}

**NSAIDs**

One of the current QOF quality indicators for prescribing safety is to “reduce the rate of potentially hazardous prescribing, with a focus upon the safer use of NSAIDs in patients at significant risk of complications such as gastro-intestinal bleeding”.\textsuperscript{1} NSAIDs are also well known to adversely affect kidney function and caution is advised: reducing use and regular monitoring would reduce risk.

**Medicines that can affect the unborn child**

Teratogenic medicines can affect development of the unborn child, so monitoring where there is risk of pregnancy is important. There has recently been particular attention on the prescribing of valproate for women of childbearing potential, and the latest MHRA Drug Safety Alert states that valproate medicines must not be used in women of childbearing potential unless the Pregnancy Prevention Programme is in place.\textsuperscript{3} Other medicines that are contraindicated during pregnancy, for example statins and ACE inhibitors,\textsuperscript{2} are likely

---

**Table 2. Examples of other drugs that require regular blood monitoring according to the Summaries of Product Characteristics (SmPCs)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Blood monitoring requirements detailed in the SmPC/BNF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>TFTs/LFTs before treatment and then every 6 months</td>
</tr>
<tr>
<td>Lithium</td>
<td>Lithium levels every 3 months when stable; renal function (U&amp;Es)/TFTs 6-monthly</td>
</tr>
<tr>
<td>Mesalazine</td>
<td>Patients on mesalazine should have renal function monitored (with serum creatinine levels measured) prior to start of treatment. Renal function should then be monitored periodically during treatment, for example every 3 months for the first year, then 6-monthly for the next 4 years and annually thereafter, based on individual patient history.</td>
</tr>
</tbody>
</table>

U&Es = urea and electrolytes, TFTs = thyroid function tests, LFTs = liver function tests.
Table 3. An example schedule of renal function testing for direct oral anticoagulants (DOACs) based on level of kidney function (taken from Cambridge and Peterborough CCG guideline12)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Blood tests</th>
<th>Creatinine clearance</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>FBC/LFTs</td>
<td>&gt;60ml/min</td>
<td>Every 12 months</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>U&amp;Es</td>
<td>30–60ml/min, patient &gt;75 years or fragile</td>
<td>every 6 months</td>
</tr>
<tr>
<td>Edoxaban</td>
<td></td>
<td>&lt;30ml/min (except dabigatran – contraindicated)</td>
<td>every 3 months</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FBC = full blood count; U&Es = urea and electrolytes; LFTs = liver function tests. More frequent U&Es/LFTs advised where intercurrent illness may impact on renal or hepatic function.

What does a safe system for monitoring, review and prescribing look like?

Every time a prescriber signs a prescription for a DMARD or other drug needing regular monitoring, they need to be certain that the required blood tests and other monitoring have been done within the appropriate time scale and that the results are within the normal range. Having a robust protocol for regular monitoring of high-risk medicines can:

- Allow prescribers to be confident that the required monitoring has been undertaken, ie that:
  - all patients on drugs that require regular monitoring are identified
  - correct tests have been carried out
  - tests have been done at the required frequency
  - procedures continue to function optimally through regular auditing
- Reduce risks for patients
- Reduce risk of litigation for practitioners where lack of monitoring causes harm
- Provide a good example of safe practice for Care Quality Commission (CQC) inspection.

The key factors needed for a safe monitoring system are as follows:

- The system must have the ability to carry out monthly searches to ensure all patients requiring monitoring are correctly identified, and monitoring is carried out at the correct frequencies.
- A lead member of the clinical team needs to be identified to develop and regularly review the practice policy. This person would oversee the ongoing procedure, check test results, ensure monitoring is set up for the correct tests at the correct frequency and deal with any problems (for example non-attenders).
- A lead member of the clinical team needs to be identified to run the monitoring scheme, ensuring patients are identified and attend for their monitoring.
- Regular audit must be part of the scheme to ensure that the procedure is identifying all patients prescribed drugs needing regular monitoring, and that all patients have the correct tests at the recommended frequencies. This needs to include regular checks to ensure that hospital monitoring is being carried out in situations where primary care is prescribing with secondary care doing the regular blood tests.
- It is important to specify who in the team is responsible for, and will carry out, each of these different roles. They can be carried out by any of the team the individual surgery deems appropriate. For example, a practice pharmacist could set up and oversee the procedure, the practice nurses/phlebotomists take the tests, and a member of the admin team run the monthly searches and oversee attendance.

Audit continues to be an important tool to identify higher risk patients when setting up a new monitoring protocol, to ensure the system is working as it should, and for quality improvement assessment.

The Prescriber article ‘A protocol for drugs that require regular monitoring’9 is a useful guide to setting up a practice monitoring scheme, and provides an example protocol for planned blood test monitoring. This protocol was developed in practices in Shipley, West Yorkshire from 2007 and has been successfully running since then, with a quarterly full audit cycle presented and discussed at the practice clinical team meeting. The system was commended at CQC inspection, and it has enabled the practices to easily reach monitoring targets.

Prescriber.co.uk
What are the current systems for monitoring high-risk medicines?

GP practice patient record systems do have warning systems for SmPC recommendations, but they only show the guidance when the prescriber newly initiates a drug, and not when reviewing medicines. Some add-on systems, or individual practices, have set up alerts for monitoring; not only do these add to the ‘pop-up’ burden, but they require attention, and possibly action, at the time of prescribing, and may necessitate further appointments for blood tests and follow-up. A robust practice monitoring protocol means prescribers can rely on the system to have ensured regular monitoring and results within normal parameters at the time of prescribing.

Sometimes the hospital continues to monitor shared care drugs, with primary care prescribing the medication. The prescriber at the GP practice needs to know that monitoring has been done regularly and that the levels are as required for safe prescribing before issuing prescriptions. Communication between secondary and primary care is not always timely, and requires any changes to be picked up by practice staff and actioned as required, with the potential for some actions to be missed. The practice monitoring procedure needs to include a regular check that the patient is getting regular hospital monitoring.

Who is best placed to run the monitoring, reviewing and prescribing systems?

Setting up a practice monitoring system means that much of the workload can be automated, with regular searches and recall systems run by admin, and phlebotomists and practice nurses carrying out the blood testing to protocol. To set up and oversee the procedure, there needs to be a member of the team who has competency around the issues of prescribing and risks of these medicines, such as a clinical pharmacist, GP or practice nurse. They need to be able to check blood test results, confirm monitoring and frequency for new patients, deal with any problems and queries arising, and audit the procedure.

With their expertise and focus on medicines, clinical pharmacists are increasingly playing a central role in managing medicines\(^\text{17}\) that are part of shared-care agreements, such as setting up systems for safe monitoring and prescribing of high-risk medicines as part of the QOF quality indicators.\(^\text{14}\) This year, QOF safer prescribing requirements are for lithium monitoring, NSAID prescribing and the valproate Pregnancy Prevention Programme, but it is likely that there will be further medicines safety requirements in future years. Primary Care Network (PCN) clinical pharmacists are expected to provide leadership on person-centred medicines optimisation, which could include the setting up of a monitoring protocol across a network.

How are the current systems likely to change in the future?

NHS England is aiming to have different PCN professions working on the same agenda.\(^\text{18}\) With the new contract Community Pharmacy Quality Scheme also including the monitoring of high-risk medicines (again initially NSAIDs, valproate and lithium),\(^\text{19}\) it needs to be defined how the GP practice, PCN clinical pharmacist and community pharmacist will co-ordinate this monitoring. Monitoring systems could be set up in GP practices through their PCN clinical pharmacist. Community pharmacists could check systems, patient adherence and adverse effects, as they see patients more regularly than other healthcare professionals through the dispensing of prescriptions; this could be enhanced with better access to test results and notes.

Patient record systems, such as SystmOne and EMIS, have the data to be able to provide more patient-specific decision support, and in the future it is likely that the functionality in these systems will be developed further to help prescribers with monitoring requirements. Provision of patient-specific warnings at medication review would be a very useful development in reducing risk from medicines.

References

4. National Institute for Health and Care...
Excellence. BNF. Available from: https://bnf.nice.org.uk

Declarations of interest
None to declare.

Dr Su Wood is a Pharmacist Research Fellow, Leeds Institute of Health Sciences, Leeds University