**High-risk medications: a guide for pharmacy professionals**

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After reading this article, you should be able to:

* Understand which medications are considered high-risk and why, including their potential for causing significant harm if used incorrectly.
* Implement safety measures to reduce the risk associated with high-risk medications.
* Recognise how pharmacists contribute to safer use of high-risk medications.

Medications are the mainstay of treatment for a range of conditions, yet it is widely recognised that medication errors are one of the leading causes of patient harm, with 1 in 20 patients exposed to preventable harm (1). It could be argued that all medication is high-risk, given the correct conditions; research has identified that particularly within acute hospitals, it is the cumulative effect of moderate-harm medication incidents, rather than single catastrophic errors, that usually result in preventable deaths (2).

However, the potential for significant harm or death from medication errors is greatly increased when certain ‘high-risk’ medications are involved (3,4). High-risk medications have the potential to cause significant patient harm even when used as intended, posing challenges for pharmacists and other healthcare professionals (2,5).

Researchers have struggled to establish the prevalence of prescribing errors of high-risk medications. One systematic review reported error rates ranging from 0.24 to 89.6 per 100 medication orders (6). The Institute for Safe Medication Practices (ISMP) has said that, although incident rates for high-risk medicines are not necessarily higher than with other medicines, the consequences are more likely to be significant when incidents do occur (7). This article explores the factors that classify a medication as ‘high-risk’ and some of the key considerations surrounding these medications, providing insights into their use, monitoring, and prevention of potential complications.

**What makes a medication high risk?**

The World Health Organization (WHO) cites high-risk medications as one of the key factors associated with significant patient harm, alongside:

* Healthcare professionals (poor prescribing practices, human factors);
* Complex patients (renal/liver impairment, allergies, extreme body weight) and vulnerable patients (children, older people, people with learning disabilities);
* Work environment (high-risk settings: perioperative, neonatal, emergency care) and transitions between care settings (2,4).

Medications can be deemed high-risk for various reasons, and specific medications may differ in risk between different healthcare sectors and countries (8). Because of the high costs and increased mortality associated with high-risk medications, medication safety organisations have attempted to establish definitions and lists to raise awareness for healthcare professionals (6). For example, the ISMP published a ‘List of High-Alert Medications in Acute Care Settings’, containing 13 specific medications (including insulin U-500 and oral methotrexate), and 21 medication classes (including antithrombotic agents, insulin and opioids)(7)***.*** Some of the medications listed, such as chemotherapy, parenteral therapies and anaesthetic agents, are specific to highly specialised areas and therefore fall outside the scope of this article. However, several of the medications are widely recognised as high risk and transcend all healthcare sectors and will be covered in detail.

A medication can be considered high-risk when its use carries a higher probability of causing severe harm or adverse effects to a patient (8). Potential contributing factors are often overlapping; therefore, most high-risk medications may fall into more than one category:

* Narrow therapeutic range;
* Serious adverse effects;
* Monitoring requirements;
* Interactions;
* Withdrawal effects;
* Time critical;
* Complex or unusual dosing.

**Medications with narrow therapeutic range**

One class of medications highlighted as high-risk by the WHO includes drugs with a narrow therapeutic range, where the drug concentration needed to produce a therapeutic effect is close to that which produces adverse effects (8,9). These medications often require therapeutic drug monitoring to guide prescribing decisions around dosing; patient harm arises when the process for therapeutic drug monitoring is not followed correctly, leading to toxicity or sub-optimal dosing (9). In addition, these drugs are more likely to be susceptible to drug interactions or physiological changes, leading to severe adverse effects. Two common medications in this class are digoxin and lithium. Other drugs that require therapeutic drug monitoring include theophylline, phenytoin, carbamazepine, warfarin, ciclosporin, tacrolimus, gentamicin, and vancomycin (18).

***Medication example: Digoxin***

Patients who are therapeutically stable on digoxin don’t require routine monitoring of digoxin levels (10). However, a meta-analysis in 2015 found that patients taking digoxin for heart failure or atrial fibrillation had a 21% increase in mortality compared with patients not prescribed digoxin, with researchers highlighting the need for close monitoring due to the risk of toxicity (11). It is imperative that practitioners are aware of the signs of digoxin toxicity and circumstances in which toxicity is more likely to occur, for example, in overdose, drug interactions, renal impairment, hypothyroidism, and electrolyte disturbances (12). Where digoxin toxicity is suspected, serum digoxin concentration should be monitored appropriately, as digoxin toxicity can occur even when the plasma digoxin concentration is within the therapeutic range; levels should always be interpreted with caution and in conjunction with the patient’s clinical presentation (12).

Common signs of digoxin toxicity (12,13):

* Nausea, vomiting, and diarrhoea;
* Visual disturbances (e.g. blurred vision, colour changes: green/yellow discolouration);
* Arrythmias;
* Confusion.

For more information on this topic see the article ‘[Digoxin monitoring and toxicity management’](https://pharmaceutical-journal.com/article/ld/digoxin-monitoring-and-toxicity-management)

***Medication example: Lithium***

Lithium has long been recognised as a high-risk medication, with a patient-safety alert on safer lithium therapy issued by the National Patient Safety Agency (NPSA) in 2009 due to high numbers of incident reports linked to toxicity and monitoring (14). There are various considerations when prescribing lithium to mitigate risk, including (15,16):

* Extensive baseline monitoring;
* Brand prescribing: non-bioequivalence of lithium carbonate and lithium citrate;
* Patients issued with lithium information booklet (provides written information and tracks monitoring);
* Serum lithium concentrations: monitored at specified regular intervals or if acutely unwell, showing signs of toxicity, or altered sodium or fluid status.

Lithium levels should be interpreted in the context of the patient’s clinical presentation, as toxicity can occur at normal lithium levels; the target lithium level varies depending on the indication, therefore specialist advice should be sought if toxicity is suspected (17).

Common signs of lithium toxicity (15,16):

* Lethargy, slurred speech, light-headedness, confusion;
* Coarse tremor, lack of coordination;
* Nausea, vomiting, and diarrhoea.

For more information on this topic see the article ‘[Lithium monitoring and toxicity management’](https://pharmaceutical-journal.com/article/ld/lithium-monitoring-and-toxicity-management)

**Medications with serious adverse effects**

A medication may be classed as high-risk when it has the known potential for a serious adverse drug reaction. This could be despite correct use, or due to use outside of the marketing authorisation (e.g. medication errors, overdose, or misuse) (19). Drug reactions can be augmented (type A) reactions: where the adverse effect is an exaggeration of the drug’s usual action, for example, bleeding with an anticoagulant, or hypoglycaemia with insulin. Or it can be a bizarre (type B) reaction: where the reaction is not expected based on the drug’s mode of action, for example, anaphylaxis with penicillin (19).

In situations where severe adverse effects can be predicted, proactive steps can be taken to reduce the risk. Life-threatening respiratory depression caused by opioids usually occurs in acute pain management in patients who have not developed opioid tolerance, or in persistent pain where there are large dose increases or changes in route or formulation (20). Resources such as ‘Opioids Aware’ by the Faculty of Pain Medicine raise awareness and provide guidance for healthcare professionals on how to start, titrate, switch and deprescribe opioids safely (20). In the case of direct oral anticoagulants, steps can be taken to reduce the risk of bleeding by ensuring that the patient is prescribed an appropriate dose, considering the patient’s age, weight and creatinine clearance (21).

Where adverse drug reactions are unpredictable, monitoring can be employed to detect adverse drug reactions in a timely manner. Azathioprine is a disease-modifying antirheumatic drug (DMARD) with the known and potentially fatal complication of myelosuppression (22). Current guidelines require baseline thiopurine methyltransferase (TMPT) levels to be checked so that azathioprine can be avoided in patients with absent TPMT levels (who would be at increased risk of developing severe myelosuppression) (23). However, normal TPMT activity doesn’t exclude the risk of myelosuppression, so full blood count (FBC), alongside other parameters such as liver function tests (LFTs) and renal function, must be checked at frequent intervals (24). Comparable guidelines exist for other DMARDs with similar risks of serious adverse effects, such methotrexate, mercaptopurine, sulfasalazine, and leflunomide.

Patients should be made aware of any potential serious adverse effects and how to identify them early: for example, tendonitis with fluoroquinolone antibiotics (25). Fluoroquinolones, such as ciprofloxacin, carry a specific MHRA warning that details the patient information that should be provided to every patient (26).

**Medications with monitoring requirements**

Medications with the potential to cause severe adverse effects usually overlap with those that require specific or regular monitoring. Some high-risk medications, such as DMARDs, are managed under shared-care protocols, to enable safe prescribing to continue in primary care once treatment has been initiated by a hospital specialist. Shared-care protocols are essential to support effective prescribing and monitoring and improve patient safety (27). However, they are only effective if everyone involved understands and carries out their responsibilities.

Most high-risk medications have specific monitoring requirements. The Specialist Pharmacy Service (SPS) has produced a quick-reference summary of monitoring requirements for a range of medicines to support healthcare professionals (30).

***Medication example: Clozapine***

Clozapine is an atypical antipsychotic with particularly strict monitoring requirements. It is effective in the treatment of schizophrenia, but its use is restricted because of the risk of serious blood dyscrasias (28). Clozapine manufacturers in the UK have their own mandatory monitoring systems to ensure patient safety, requiring blood tests at specific time intervals before providing further supply (28). However, patient harm can still occur when clinical decisions are being made by healthcare professionals who are unfamiliar with the risks associated with clozapine; failure to understand and comply with the monitoring requirements for clozapine can lead to clozapine-related toxicity and adverse effects, or unintentional missed doses or discontinuation (29). An important role for pharmacists is understanding the need to establish the following information for patients prescribed clozapine (28,29):

* Brand (and monitoring system);
* Current dose;
* Adherence (missed doses for more than 48 hours require re-titration);
* Date of last FBC and required frequency;
* Signs of toxicity (e.g. constipation, sore throat);
* Impact of interacting medications on clozapine levels;
* Impact of lifestyle changes (smoking, caffeine intake) on clozapine levels.

**Medications susceptible to interactions**

Medications with a narrow therapeutic range are highly susceptible to drug interactions, leading to potential patient harm. Common examples include digoxin, theophylline, warfarin, and carbamazepine, all of which have many drug interactions listed in the British National Formulary (31). These include potential toxicity with enzyme inhibitors (e.g. clarithromycin) and potential sub-therapeutic effects with enzyme inducers (e.g. St. John’s Wort, phenytoin) (31). An awareness of drug interactions is required to avoid potentially life-threatening consequences of drug interactions with commonly prescribed medicines – for example, there is a risk of myelosuppression when trimethoprim is co-prescribed with methotrexate (32).

Medications may not necessarily be classed as high-risk themselves but can become high-risk when used in combination. The risk of life-threatening torsades de pointes is increased when multiple QT-prolonging drugs are given together (33). The risk of respiratory depression is increased when multiple central-nervous-system depressants (opioids, alcohol, gabapentin/pregabalin) are used in combination.

The impact of smoking or smoking cessation on drug levels is clinically relevant with certain high-risk medications; toxins released in tobacco smoke are responsible for the induction of certain cytochrome P450 enzymes (34). Specific examples include clozapine, olanzapine and theophylline; therapeutic drug monitoring is recommended if a patient stops smoking. (34,35).

**Mediations with potential to cause dependency or withdrawal symptoms**

Medications with the potential to cause dependence or withdrawal symptoms may be considered high-risk because of the need for safe prescribing and withdrawal management (36). In some cases, sudden withdrawal can lead to life-threatening situations, such as the risk of adrenal crisis and death when steroids are omitted in patients with adrenal sufficiency. This is a risk for patients with primary adrenal insufficiency, such as Addison’s disease, but also includes patients on oral, inhaled or topical steroids for other conditions. Patients on long-term steroids may also be at risk of adrenal crisis at times of physiological stress, for example acute illness, trauma or surgery, and so increased steroid doses may be required (37). A National Patient Safety Alert in 2020 promoted the patient-held Steroid Emergency Card to enable ‘at risk’ patients to be identified and managed appropriately (38).

Medications used in Parkinson’s disease can cause severe harm if withdrawn suddenly, potentially leading to the development of acute akinesia or neuroleptic malignant-like syndrome (reduced consciousness, fever, marked rigidity and raised creatinine kinase) (39). Due to the nature of Parkinson’s disease, there are several precipitating factors that could lead to sudden drug withdrawal, such as loss of swallow, gastrointestinal problems, onset of confusion or hallucinations, loss of adherence, or a need to switch therapy (40). As Parkinson’s disease and its medication regimens are complex, it is recommended that the patient’s specialist team are involved in any changes, to reduce the risk of patient harm (41).

Other medications that have potentially serious withdrawal symptoms include opioids, benzodiazepines, antidepressants and antipsychotics. These groups of medicines should be withdrawn gradually, taking a shared-decision-making approach with the patient (36,42).

**Time-critical medicines**

Medicines are classed as time-critical if they need to be given at a certain time to ensure they are safe or work effectively; these include medicines where delayed administration can cause immediate harm, for example, Parkinson’s medications. Medicines deemed to be time-critical according to the Care Quality Commission include those that:

* Should be given at a time related to food intake;
* Contain paracetamol;
* Are prescribed for Parkinson’s disease;
* Should be taken at a certain time to maximise effectiveness (43).

***Medication example: Insulin***

Insulin is a medication for which timing relative to food intake is critical, particularly with rapid-acting, short-acting and mixed insulins, where onset of action needs to be considered. Rapid-acting insulin analogues (e.g. Novorapid) should be given immediately before food, whereas soluble insulin (e.g. Actrapid) should be given 30 minutes before food (44). Mistiming of insulin in relation to food can result in potentially serious hypoglycaemia or hyperglycaemia: ‘right time’ is one of the ‘6 steps to insulin safety’ (45).

***Medication example: Parkinson’s disease medications***

Sudden withdrawal of Parkinson’s medications can lead to life-threatening withdrawal symptoms. However, even a short delay can result in increased risk of falls, swallowing difficulties (leading to increased risk of aspiration), anxiety, tremors, rigidity and pain (46). ‘On time’ is therefore defined as being within 30 minutes of the patient’s prescribed administration time (46). This is a particular issue during hospital admissions, where medications might be prescribed outside of the usual drug round times, or ward pressures can prevent timely prescribing and/or administration (47).

**Medications with complex dosing**

A final consideration is medication with complex or unusual dosing schedules, which are more susceptible to errors due to unfamiliarity of dosing for both patients and healthcare professionals. An example of this is once-weekly methotrexate, which has been linked with serious and fatal overdoses due to inadvertent once-daily administrations; these incidents led to a number of key prescribing and dispensing recommendations in a 2006 patient safety alert (48). Another example of safety directives being issued to address known risks is insulin (49). The frequency and dose are variable depending on the insulin type and a number of patient-specific factors. Other examples include drugs that have loading doses, such as amiodarone, or apixaban for treatment of venous thromboembolism.

**Strategies to reduce risk**

Although it is tempting to focus safety improvement initiatives solely on specific medications or groups of medicines considered to be high-risk, the most effective safety improvements are those directed at underlying causes (2). Research in primary care concluded that most effective safety improvements could be made through using existing information technology and improving team communication and continuity of care, which are contributory factors in many cases of patient harm (50).

It is also important that we address other contributors to patient harm, for example by applying the principles of human factors and optimising the interaction between people, systems, and environments (51). Integrating medication-related improvements into broader healthcare challenges is more likely to be effective. However, a core safety principle is to focus efforts on areas where the risk of severe harm or death is most likely to occur, which often include high-risk medications (2).

**Conclusion**

The safe management of high-risk medicines is a critical responsibility for pharmacists. By staying informed, adhering to evidence-based guidelines, and maintaining clear communication with patients and healthcare teams, pharmacists play a vital role in minimising harm and improving outcomes for patients. Vigilance, ongoing education, and a proactive approach are essential to ensuring the safe use of high-risk medicines. Thankfully, many high-quality resources are available to support pharmacy professionals in this task.

**Useful resources**

* [SPS drug monitoring guide](https://www.sps.nhs.uk/home/tools/drug-monitoring/)
* [“The Six Steps to Insulin Safety”, a free e-learning module from the PCDS - DiabetesontheNet](https://diabetesonthenet.com/diabetes-news/six-steps-to-insulin-safety-e-learning-module/)
* [Time critical medication and Get It On Time campaign resources | Parkinson's UK](https://www.parkinsons.org.uk/professionals/resources/time-critical-medication-and-get-it-time-campaign-resources#:~:text=Patients%20with%20Parkinson%E2%80%99s%20are%20at%20risk%20of%20significant,prescribed%20time.%20Even%20short%20delays%20can%20worsen%20symptoms.)
* [MHRA drug safety updates](https://www.gov.uk/drug-safety-update)

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