Chapter 3: Clinical Review, Therapeutic Drug Monitoring and Adverse Drug Reaction Management

INTRODUCTION

Clinical review, therapeutic drug monitoring (TDM) and adverse drug reaction (ADR) management contribute to the quality use of medicines by ensuring safe and appropriate dosage and administration of medicines, improving response to therapy and minimising medicines-related problems.

Clinical review, TDM and ADR management commence when a patient presents or is admitted to a health service organisation and continue as routine activities throughout the episode of care in conjunction with assessment of current medication management and other clinical pharmacy activities.

OBJECTIVE AND DEFINITION

Objective

Clinical review, TDM and ADR management aim to ensure safe and appropriate treatment with medicines. Review of patient-specific clinical information assists in the understanding of a patient's clinical progress and treatment options. Ongoing clinical review and TDM is essential to re-evaluate and modify therapeutic goals as the patient's condition and response to therapy change.

Definition

Clinical review is the review of patient-specific clinical information including patient parameters to evaluate their response to medication therapies and to detect and manage potential or actual medicines-related problems. It may include interpreting biochemical and other tests, evaluating the patient's signs and symptoms identified from interviews with the patient and review of the health record.

TDM is the interpreting and monitoring of measured drug concentrations in body fluids to optimise medicine efficacy and minimise toxicity. TDM applies the disciplines of pharmacology, pharmacokinetics, pathology and clinical medicine.

ADR management is the prevention, detection, assessment, management, documentation and reporting of ADRs. An ADR is a response to a medicine that is noxious and unintended, and which occurs at doses normally used or tested in humans for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function.[1] An unexpected therapeutic response may be a side effect but not an adverse reaction.

EXTENT AND OPERATION

All patients should have a clinical review, TDM and ADR management as appropriate throughout the episode of care in parallel with assessment of current medication management. See *Chapter 2: Assessment of current medication management*.

Clinical review of patient's medication therapy should be undertaken in conjunction with the assessment of current medication management as a routine activity. Collating this information enables the pharmacist to identify and prioritise patient-specific medicines-related problems, formulate a management plan and develop and monitor treatment goals.

Extensive TDM monitoring for every patient is impractical due to cost and time. Medicines to be monitored should be prioritised according to risk assessment. Local criteria need to be established that identify the patient groups with a high risk of measurable adverse effects or medicine interactions that require extensive monitoring. See *Chapter 8: Prioritising clinical pharmacy services*.

POLICY AND PROCEDURE

Clinical Review

Information about a patient's signs, symptoms and progress may be obtained from:

- their medication history or medication reconciliation documentation
- reviewing their health record
- a discussion with other healthcare team members
- a discussion with and review of the patient
- their clinical data
- their laboratory investigations.

Examples of patient-specific clinical information may include:

- routine observations, e.g. temperature, blood pressure
- weight
- fluid balance
- urine output
- biochemistry results, e.g. electrolytes, creatinine
- haematology results
- microbiology results
- radiological investigations
- bowel charts
- peak flow/spirometry
- nutrition
- pain scores.

Document information that is not readily available on the medication administration record, medication management plan (MMP) or in the patient's health record according to local policy.

Interpret and evaluate the clinical information obtained by referring to the:

- clinical features and pathophysiology of conditions treated
- indication for an investigation, and its sensitivity and specificity
- timeframe of drug-related effects (may include expected adverse effects)
- patient's medication history
- planned outcome(s) of treatment
- patient's pharmacogenomics and genetic markers, especially as they relate to drug handling and monitoring of suitability of certain drugs.

Identify actual and potential medicines-related problems. Prioritise these according to their risk and urgency. Liaise with the prescriber to resolve any issues and document these in the health record, MMP or equivalent, according to local policy. See *Chapter 13: Documenting clinical activities*.

Therapeutic Drug Monitoring

TDM may be used to optimise therapy for medicines where there is a known relationship between measured concentration in body fluids and pharmacological effect. There are a number of specific indications for monitoring the concentrations of medicines in body fluids including:

- suspected toxicity due to a medicine and/or metabolite
- suboptimal response to medicines
- potential drug interactions
- patient is not medically stable
- following initiation or change to the medicines regimen
- previous ADRs or toxicity
- post overdose or poisoning and determination of antidote dose needed
- patient adherence issues.

TDM is indicated for patients being treated with medicines with the following characteristics:

- narrow therapeutic index
- high risk
- significant adverse effects profile
- large degree of patient variability in pharmacodynamics
- associated with clinically significant interactions.

TDM may also be indicated for patients who have an altered clinical status and changes in pharmacodynamics. Particular patient groups include those:

- with renal or hepatic impairment
- undergoing dialysis and haemofiltration
- with uncompensated cardiac dysfunction
- who are pregnant
- at extremes of age, i.e. elderly or paediatric (especially neonates)
- who are obese, undernourished or have diminished muscle mass
- who have burns, cystic fibrosis and polymorphisms.

Some factors to consider before initiating TDM include:

- patient's clinical status and recent progress (particularly relating to clinical signs of medicine effect or toxicity)
- patient adherence with prescribed medicines regimen
- benefit of TDM and the impact on patient, e.g. multiple blood collections and ability to obtain TDM samples and to analyse them in a timely fashion.

The therapeutic range describes the range of medicine concentrations most commonly associated with optimal effect and minimal toxicity. It serves as a guide to therapy and must always be used in conjunction with an assessment of clinical response. The target concentration and empiric dosing of a medicine may depend on the desired clinical response, e.g. cyclosporin levels relative to the time since transplantation, digoxin levels to manage atrial fibrillation.

To interpret drug concentrations other details need to be known to relate the measured concentration to therapeutic effect. Data to record when taking samples include time of sampling, time of last dose and duration of current medicines regimen. When interpreting results, consider the following:

- drug, dose, formulation and dosing schedule
- method of administration
- indication for treatment
- reason for TDM
- duration of current medicines regimen
- time of last dose
- time of sampling
- prior drug monitoring and other relevant laboratory results
- patient-specific factors, e.g. renal and hepatic function, cardiac status, age, weight
- relevant pharmacokinetic and pharmacodynamic properties of the drug
- potential for drug interactions
- other environmental factors, e.g. smoking
- potential for sampling or measurement error
- local laboratory parameters
- pharmacogenomics and genetic markers especially as they relate to drug handling and monitoring of suitability of certain drugs for particular patients.

Pharmacokinetic calculations and simulated computer profiles can be used as a guide in assessing patient dose. However, consider the assumptions and limitations of such programs when interpreting TDM data.

Inform the prescriber of the results of TDM in a timely manner, including recommended action and future monitoring requirements. Document any recommendations in the patient health record, MMP or equivalent, or electronic health record, where appropriate.

Adverse Drug Reaction Management

ADR management involves the detection, assessment and correlation, management, documentation and prevention of ADRs. The emphasis of ADR management is on preventing ADRs and preventing re-exposure of patients who have already experienced an ADR.

Detecting Adverse Drug Reactions

Identify and monitor patients susceptible to ADRs. Particular patient groups include:

- those who have previously experienced ADRs
- those with multiple disease processes
- those on a large number of medicines
- those with renal or hepatic impairment
- geriatric or paediatric patients
- those treated with medicines known to have a high incidence of adverse effects
- those treated with medicines known to be associated with serious adverse effects
- those treated with drugs with a low therapeutic index
- those taking medicines with the potential for multiple interactions
- those with abnormal investigation results.

Orders for single doses of medicines, such as antihistamines, adrenaline and corticosteroids may indicate that an adverse reaction has occurred.

Encourage nursing and medical staff and patients/carers to report any suspected ADRs.

Suspected Adverse Drug Reactions

When an ADR is suspected, assess the details of the ADR in the context of patient-specific and medication-related factors.

Patient-specific factors include:

- age, gender, race, organ function, height, weight
- diagnosis and other relevant comorbidities prior to reaction
- previous exposure to suspected or related drug(s).

Medication-related factors include:

- non-prescription drugs, complementary and alternative therapies
- recently ceased medicines
- suspected causative drug (name, dose, route of administration, manufacturer, batch, date and time commenced, date and time discontinued [if applicable], indication).

Comprehensive adverse reaction details include:

- description of the reaction
- time of onset and duration of reaction
- complications and sequelae
- treatment and outcome of treatment
- relevant investigation results or autopsy report.

When assessing the likelihood that a suspected ADR was caused by a particular drug, review the relevant literature and where appropriate consult with other health professionals. Causality of a suspected medicine with an adverse reaction may be:[2]

- **Certain** – a clear association is established between administration of the drug and the reaction, the results of investigations confirm that there is a relationship between administration of the drug and the reaction, the reaction recurs on re-exposure to the drug, or the reaction is known to occur with the suspected drug.
- **Probable** – the reaction is known to occur with the suspected drug, and there is a possible association between the reaction and administration of the drug, the reaction resolves or improves on withdrawal of the suspected drug and other medicine therapy remains unchanged, or an uncommon clinical event occurs in the absence of other potentially causative factors.
- **Possible** – an alternative explanation for the reaction exists, more than one drug is suspected, recovery follows withdrawal of more than one medicine or the association between the reaction and administration of the medicine is unclear.
- **Doubtful** – another cause is more likely to have accounted for the clinical event, e.g. underlying disease.

Managing and Reporting Adverse Drug Reactions

The likelihood of the suspected medicine(s) having caused the reaction and the clinical significance of the reaction are considered when assessing whether to continue treatment with the suspected medicine(s). In many cases a reasonable alternative treatment will be available. Recommend treatment options for the ADR and, if appropriate, recommend alternative treatments. Important issues to consider when managing ADRs include the:

- patient's condition
- requirement for therapy (whether treatment can be ceased)
- risks and benefits associated with continuing therapy with a medicine suspected to have caused an adverse reaction, including factors such as causality and the seriousness of the reaction
- relative efficacy and safety of other therapeutic alternatives
- prophylactic use of other medicines to prevent future adverse reactions
- consideration of rechallenge and desensitisation for the medicine.

Ensure all suspected ADRs are communicated appropriately by:

- documenting in the health record, including electronic prescribing or dispensing system and if appropriate attach relevant alert notices/stickers to medicine administration records and health record. See *Chapter 13: Documenting clinical activities*
- documenting in the MMP or equivalent and the electronic health record
- notifying medical and nursing staff (including the original prescriber)
- supplying a record of the ADR to patients/carers when potential for re-occurrence is deemed significant
- reporting to the Therapeutic Goods Administration ADR reporting system and to the manufacturer in the case of a trial, non-marketed or newly-marketed medicine[3]
- documenting ADRs according to local policy.

Likelihood of future ADRs can be minimised by:

- documenting ADRs to avoid patient re-exposure on all medicine orders, including noting when there are no known ADRs
- documenting ADRs in the MMP and the electronic health record
- monitoring patients at risk of ADRs
- judicious use of medicines that have a high incidence of or are known to cause serious adverse effects
- ensuring patient is given a hospital alert wrist band
- providing education and information, including alert cards, to patients who have experienced serious ADRs.

Table 3.1 lists the competencies and accreditation frameworks that are relevant to this chapter.

References

1. Australian Commission on Safety and Quality in Health Care. National safety and quality health service standards. Sydney: The Commission; 2012.
2. World Health Organization. Safety monitoring of medicinal products: guidelines for setting up and running a pharmacovigilance centre. Uppsala: The Organization; 2000. Available from <www.who-umc.org/graphics/24747.pdf>.
3. Therapeutic Goods Administration. 'Blue card' adverse reaction reporting form. Canberra: Therapeutic Goods Administration; 2012. Available from <www.tga.gov.au/pdf/forms/problem-medicines-forms-bluecard-121029.pdf>.
4. Society of Hospital Pharmacists of Australia. Clinical competency assessment tool (shpaclinCAT version 2). In: SHPA standards of practice for clinical pharmacy services. J Pharm Pract Res 2013; 43 (suppl): S50-S67.
5. Australian Pharmacy Profession Consultative Forum. National competency standards framework for pharmacists in Australia. Deakin: Pharmaceutical Society of Australia; 2010.

Table 3.3 Competencies and accreditation frameworks

Relevant national competencies and accreditation standards and shpaclinCAT competencies
shpaclinCAT[4]
Competency unit 1.2 Assessment of current medication management and clinical review
1.2.12 Review and interpretation of patient-specific data 1.2.13 Therapeutic drug concentration monitoring
Competency unit 1.3 Identification, prioritisation and resolution of medicines-related problems
1.3.2 Identification of medicines-related problems 1.3.3 Prioritisation of medicines-related problems 1.3.4 Resolution of medicines-related problems 1.3.5 Documentation of medicines-related problems
Competency unit 2.1 Problem solving
2.1.2 Access information 2.1.3 Abstract information 2.1.4 Evaluation and application of information 2.1.5 Appraisal of therapeutic options 2.1.6 Formulation of a clear decision
Competency unit 2.4 Communication
2.4.1 Patient and carer 2.4.3 Prescribing staff 2.4.4 Nursing staff 2.4.5 Other health professionals
Competency unit 2.5 Personal effectiveness
2.5.1 Prioritisation 2.5.3 Efficiency 2.5.4 Logic 2.5.5 Assertiveness 2.5.6 Negotiation 2.5.7 Confidence

Competency unit 2.6 Team work 2.6.2 Interdisciplinary team 2.6.4 Promotion of rational medicines use
Competency unit 2.7 Professional qualities 2.7.2 Confidentiality 2.7.4 Responsibility for patient care
National competency standards framework for pharmacists[5]
Standard 1.1 Practise legally 3 Respect and protect consumer's right to privacy and confidentiality 4 Support and assist consumer consent
Standard 1.3 Deliver 'patient-centred' care 1 Maintain primary focus on the consumer 2 Address consumer needs
Standard 1.4 Manage quality and safety 1 Protect and enhance consumer safety 2 Respond to identified risk
Standard 2.1 Communicate effectively 1 Adopt sound principles for communication 2 Adapt communication for cultural and linguistic diversity 3 Manage the communication process 4 Apply communication skills in negotiation
Standard 2.2 Work to resolve problems 1 Analyse the problem/potential problem 2 Act to resolve the problem/potential problem
Standard 4.2 Consider the appropriateness of prescribed medicines 1 Gather relevant information 2 Review the prescribed medicines 3 Promote optimal medicines use
Standard 7.1 Contribute to therapeutic decision-making
2 Assess current medication management 3 Recommend change in medication management 4 Support and assist consumer self-management
Standard 7.2 Provide ongoing medication management 1 Seek consumer support 2 Review clinical progress 3 Initiate monitoring and intervention 4 Manage medication management records
National safety and quality health service standards[1]
Standard 4 Medication safety: documentation of patient information 4.7 Documentation of adverse drug reactions
Standard 4 Medication safety: communicating with patients and carers 4.13 Informing patients about treatment options 4.14 Medication management plan