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EDITORIAL

The Prescribing Skills Assessment: a step towards safer prescribing

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Prescribing is a complex task that can involve multiple members of a healthcare team. It encompasses the gathering of information, clinical decision making, communication, review and legal requirements.

Medication errors cause serious harm to patients including death, at an estimated annual global cost of US$42 billion.[1] These errors occur across communities[1,2,3] and hospitals.[1-6] In Australia, in 2016–17, 33% of adverse events during inpatient care were due to 'adverse effects of drugs, medicaments and biological substances'.[4]

In 2017, the World Health Organization (WHO) launched 'Medication Without Harm' as its third Global Patient Safety Challenge.[1] It aims to reduce the rate of 'severe, avoidable medication-related harm' by 50% over five years. Australia is a partner in this initiative.

Medication errors are complex and involve multiple stakeholders.[1,2,5-7] Prescribing errors involve underlying factors such as the knowledge and skills of the prescriber, in addition to supervision, patient factors, and prescribing system failures.[5-7]

Despite regulatory support for medication safety, many current Australian medical graduates are not adequately prepared to prescribe safely. The Australian Medical Council stipulates that – 'on entry to professional practice' medical graduates should be able to 'prescribe medications safely, effectively and economically using objective evidence'.[8] Medication safety is also a requirement of the National Safety and Quality Health Service Standards.[9] However, work presented at the 2016 National Intern Readiness Forum[10] and in both the 2017 and 2018 Australian Medical Council / Medical Board of Australia surveys,[11,12] reported that supervisors and interns have concerns that many are not sufficiently prepared to prescribe upon graduation.

Strategies to enhance the performance of new graduates are likely to have a significant impact on medication safety, given that junior doctors write the majority of prescriptions in hospitals. They have a current error rate of 7–10%.[3,5] However, medical programs face significant challenges to ensure that graduates are prepared for prescribing. The teaching and assessment of clinical pharmacology and therapeutics has declined in many institutions. There are limited opportunities for hands-on experience, due to legal restrictions on student prescribing, compounded recently by difficulties in accessing electronic prescribing systems. The NPS MedicineWise National Prescribing Curriculum provides excellent online teaching modules, but it is not an assessment tool. It is well known that assessment is a powerful driver for student learning.

In response to similar challenges, an online platform called the Prescribing Safety Assessment was developed by the British Pharmacological Society and the Medical Schools Council Assessment in the UK.[3,7] This teaches and assesses multiple domains relevant to pharmacological therapy,[3,7] raising the profile of clinical pharmacology and therapeutics in the curriculum. It provides students with a breadth of clinical scenarios in which to legally practise multiple facets of prescribing and medication reviews, with timely feedback. Before full registration as independent prescribers, UK medical graduates are required to demonstrate a basic level of knowledge and skills by passing the Prescribing Safety Assessment.

Since 2016, increasing numbers of medical schools in Australia have implemented an international version of the Prescribing Safety Assessment called the Prescribing Skills Assessment.[13] This has also involved a collaboration with New Zealand medical schools. A cross-institutional, multidisciplinary group of nearly 50 doctors and pharmacists has regionalised this tool for the Australasian context. The Prescribing Skills Assessment is endorsed as a feasible and appropriate measure of prescribing competency for medical graduates by the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists. It has the potential to be part of a range of approaches to the assessment of clinical pharmacology, therapeutics and prescribing, as outlined in the recent Assessment of Prescribing in Health (ASPRINH) Project,[14] particularly taking into account its ability to accommodate large cohort sizes across multiple locations and institutions.

In scenarios from community and hospital-based contexts, candidates sitting the online Prescribing Skills Assessment (practice tests and the main two-hour assessment) are required to consider the results of clinical assessments and investigations to write prescriptions, and to identify inappropriate treatment choices, adverse drug reactions and interactions. They must decide on the most important

information to communicate to patients to maximise medication safety, in addition to considering how best to monitor the effect of treatment and if any adjustments to therapy are required. It provides experiential learning with feedback in key areas as outlined in WHO's Medication Without Harm strategy.[1] These are 'polypharmacy' and 'high-risk situations', particularly in the young, older people and those with comorbidities involving kidneys and liver.[1] The tool also gives experience in common areas of deficiency, such as dose selection,[1,2,5,6] error-prone drugs,[2,3,5,6,7] generic drug names,[2,5] use of safe abbreviations[2,3] and prescribing under time constraints for multiple patients.[5,6]

The Australian Medicines Handbook has supported the Prescribing Skills Assessment by providing access for students doing the assessments. This linkage encourages the use of a formulary as an integral component of medication safety and counters the misconception that looking things up suggests a lack of competence,[5] rather than a strategy to reduce errors.

During 2018, there were 31 summative assessments in nine Australian medical schools involving 2225 students. This equates to automated marking of 133,500 medicines safety-related assessment items, including 17,800 prescriptions. Every student had personal access to a similar number of items with automated feedback (in addition to marking) for their own personal study. This is a step towards addressing graduates' calls for more 'hands-on prescribing' in medical school.[5]

In 2019, 12 of the 22 medical schools across Australia and New Zealand are preparing to implement the Prescribing Skills Assessment. An additional two schools have joined this group, to create and standard-set exam items. The aspiration is to contribute to the global reduction in medication errors, through enhanced experiential training and documentation that graduates have achieved an acceptable standard. The current preparedness and performance of the candidates is under analysis, and the effect on medication errors and patient safety is a target for future research.

An educational intervention such as the Prescribing Skills Assessment needs to be accompanied by a suite of other undergraduate and postgraduate initiatives to improve prescribing safety. Examples include additional assessment tools,[14] the ongoing use of standardised medication charts,[2] e-prescribing (with decision support),[2,7] training in medication reconciliation,[2] interprofessional teamwork,[2,7] patient-centred shared decision making,[7] self-care and reflective practice. Training in patient advocacy including 'speaking up',[15] and task prioritisation have important roles.

Finally, the rise of prescribing by non-medical healthcare professionals[14] raises new challenges for co-ordination of patient-centred prescribing. These and other challenges offer future opportunities to adapt the Prescribing Skills Assessment to other disciplines,[3] with linked interprofessional educational innovations.

The authors are part of a collaboration, working in conjunction with the British Pharmacological Society and the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) to implement the Prescribing Skills Assessment in Australasia.

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Letters to the Editor

Adolescent self-harm: over-the-counter medicines fly under the radar

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We read with interest the recent article on adolescent self-harm by Joel King and co-authors.[1] It is important that clinicians, patients and families are aware of the lack of evidence for prescription medicines in this area, and the potential benefits of psychological therapies.

The need for new strategies to address adolescent self-harm is increasingly urgent. Child and adolescent self-harm is rapidly increasing in Australia.[2-4] We found a 98% increase in self-poisonings in people aged 5–19 years in 2006–2016, with a cohort effect showing that those born after 1997 are particularly at risk. The peak age of self-poisoning is getting younger. There is also a large increase in dispensing of psychotropic drugs to this cohort, particularly antidepressants,[2] despite the lack of evidence for benefits.

The article mentioned harm minimisation by prescribing limited quantities of drugs. However, the problems presented by over-the-counter medicines were not addressed. Paracetamol and ibuprofen are the top two drugs taken in overdose by young Australians[2] and are widely available. Many countries do not allow non-pharmacy sales of these medicines,[5] and in Denmark paracetamol can only be purchased by people aged over 18 years.[6] The UK has restricted pack sizes of paracetamol to decrease harms from self-poisoning.[7] Australia has room to move in this legislative space. The recent decisions by the Therapeutic Goods Administration to up-schedule modified-release paracetamol to Schedule 3 (Pharmacist Only) and paracetamol–codeine to Schedule 4 (Prescription Only) indicate the considerable scope for harm minimisation using strategic rescheduling.

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Nicholas Buckley has received National Health and Medical Research Council grant funding to support clinical toxicology (including suicide) research.

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Sonja Cabarkapa, Joel King and Fiona Leow, the authors of the article, comment:

The letter makes some valuable comments, especially regarding the urgency of this issue which is indeed cause for concern. The focus of our article was to address the commonly raised questions around treatment of self-harm in a GP setting. The letter offers pertinent considerations in prevention by addressing the restrictions on the sale of over-the-counter medicines and the legislative changes made by other countries. Similar strategies should be considered by the Australian Government.

Recent evidence suggests that self-harm displayed on social media poses a risk to vulnerable users through exposure leading to contagion.[1] This combined with unlimited multimedia access and cyber-bullying are additional social factors that need addressing. While not all self-harm behaviour is followed by suicide, patients who self-harm remain at significant and persistent risk of suicide.[2]

Self-harm remains a multifaceted issue requiring prompt attention from a societal viewpoint and prospective studies in this area remain limited. Further research can identify strategies to help reduce rates of self-harm which should be a major priority for national suicide prevention programs.

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ARTICLE

Stopping and switching antipsychotic drugs

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SUMMARY

In general, specialist advice should be sought when stopping or switching antipsychotics.

While antipsychotics are often needed long term, there are circumstances when clinicians, patients and families should reconsider the benefits versus the harms of continuing treatment.

Withdrawal syndromes, relapse and rebound can occur if antipsychotics are discontinued, especially if they are stopped abruptly. Generally, they should be reduced and stopped slowly, ideally over weeks to months.

Relapse of psychosis and exacerbation occur in most patients with psychotic disorders, occasionally with drastic consequences. Sometimes this occurs many months after stopping antipsychotics.

Switching from one antipsychotic to another is frequently indicated due to an inadequate treatment response or unacceptable adverse effects. It should be carried out cautiously and under close observation.

Introduction

Stopping antipsychotic drug therapy is feasible and appropriate in a number of clinical circumstances. For patients who require long-term treatment, switching to another antipsychotic may be needed if their response to treatment has been inadequate, or unacceptable adverse effects have occurred.

For patients with serious psychiatric illness, stopping or switching antipsychotics requires referral to a specialist if possible. However, for patients on small off-label doses of antipsychotics for behavioural disturbance in dementia or for sleep problems, it may be reasonable for the GP to taper the dose and stop treatment with careful monitoring.

Antipsychotics in Australia

There are many drugs with antipsychotic efficacy available, including both oral and depot formulations. They differ in their adverse effects and effectiveness (Table 1). Historically, antipsychotics have been divided into typical (or conventional) and atypical (or novel) types. However, this simple dichotomisation cannot account for the heterogeneity in a range of characteristics with antipsychotic drugs old or new. This includes their likelihood of causing extrapyramidal effects, hyperprolactinaemia, weight gain and metabolic syndrome, sedation versus activation, and cardiac effects (Table 1).

Some antipsychotics are more effective for psychosis than others – clozapine has been recognised as the most effective antipsychotic drug, followed by a mid-efficacy group of amisulpride, olanzapine, risperidone and paliperidone, then the remaining novel and old antipsychotics such as haloperidol and chlorpromazine.[1] Some drugs, such as olanzapine, quetiapine, risperidone, asenapine and ziprasidone, were also found to be effective in mania, mixed states and maintenance treatment of bipolar mood disorder.[2]

Off-label use

Psychiatrists also use some antipsychotics such as olanzapine, quetiapine and risperidone for off-label indications. An example would be adjunctive initial treatment of severe major depression when rapid relief of agitation, insomnia and suicidality is needed while waiting for antidepressants to take effect. As a consequence, GPs are seeing a broad spectrum of patients (not merely those with schizophrenia) who have been started on antipsychotics, often in combination with other psychotropic drugs. It has been common practice to continue these antipsychotics long term, especially when treatment of an acute episode has been reasonably successful. However, long-term antipsychotic use can have serious consequences including tardive dyskinesia, weight gain, metabolic syndrome, diabetes and cardiovascular complications.[3]

Withdrawing antipsychotics

When stopping an antipsychotic, individual circumstances must be carefully considered including illness severity and history, risk of relapse and its consequences, treatment response and prognostic factors, and the patient's social situation (Box 1). If possible, antipsychotics should be stopped very slowly under close medical observation. Abrupt discontinuation can result in rebound psychosis which can be more severe than before treatment

Table 1 **Antipsychotic drugs available in Australia**

Antipsychotic drug *	Formulation	Drug half-life	Notes on adverse effects
Amisulpride	Tablets	12 hours	Low sedation risk, can be activating, dose-dependent EPS, hyperprolactinaemia, low risk of metabolic syndrome, high risk QTc prolongation (very dangerous in overdose)
Aripiprazole	Tablets	75 hours (95 hours for dehydroaripiprazole)	Initially activating, initial akathisia risk, low sedation, low risk of metabolic syndrome, very low risk of increasing prolactin
	Long-acting injection	46 days for 400 mg every 4 weeks	
Asenapine	Wafers	24 hours	Mildly sedative, dose-dependent EPS, low–moderate risk of metabolic syndrome
Brexpiprazole	Tablets	91 hours	Initially activating with possible akathisia, low sedation, low risk of metabolic syndrome
Chlorpromazine	Tablets, oral liquid, injection	15–30 hours, multiple metabolites	Sedative and tranquillising, anticholinergic, moderate risk of EPS, postural hypotension, photosensitivity, moderate risk of metabolic syndrome, hyperprolactinaemia
Clozapine	Tablets, oral liquid	12 hours (4–66 hours)	Sedative, anticholinergic, postural hypotension, paralytic ileus, agranulocytosis, convulsions, high risk of metabolic syndrome, cardiac effects, nocturnal hypersalivation, urinary incontinence
Flupentixol	Long-acting injection	3 weeks – 3 months	Moderate–high risk of EPS, moderate risk of metabolic syndrome, hyperprolactinaemia
Haloperidol	Tablets, oral liquid, injection	21 hours	High risk of EPS, hyperprolactinaemia, low risk of metabolic syndrome
Haloperidol decanoate	Long-acting injection	3 weeks	
Olanzapine	Tablets, wafers, injection	33 hours	Moderately sedative and tranquillising, high risk of weight gain and metabolic syndrome, moderately anticholinergic, low risk of hyperprolactinaemia
Olanzapine pamoate monohydrate	Long-acting injection	30 days	
Lurasidone	Tablets	18 hours	Mildly sedative, low risk of metabolic syndrome, low–moderate risk of dose-dependent EPS, low–moderate risk of hyperprolactinaemia, low risk of QTc prolongation, nausea
Paliperidone	Tablets, injection	23 hours	Low risk of sedation, low risk of dose-dependent EPS, high risk of hyperprolactinaemia
Paliperidone decanoate	1-monthly long-acting injection	25–49 days	
	3-monthly long-acting injection	84–95 days with deltoid injection, 118–139 days with gluteal injection	
Periciazine	Tablets	12 hours	Moderately sedative and tranquillising, moderate risk of dose-dependent EPS
Quetiapine	Conventional tablets	7 hours, first active metabolite norquetiapine 12 hours	Sedative and tranquillising, low risk of EPS, low risk of hyperprolactinaemia, moderate–high risk of weight gain and metabolic syndrome, anticholinergic
	Modified-release tablets		Drug effects longer lasting so used once daily
Risperidone	Tablets, oral liquid, injection	3-17 hours, 9-hydroxy-risperidone 24 hours	Mild–moderate sedation, risk of initial postural hypotension, low risk of dose-dependent EPS, high risk of hyperprolactinaemia
	Long-acting injectable microspheres	Approximately 11 days (steady state occurs after 4 x 2-weekly injections)	

Continued over page

Table 1 **Antipsychotic drugs available in Australia (continued)**

Antipsychotic drug *	Formulation	Drug half-life	Notes on adverse effects
Ziprasidone	Capsules, injection	6–10 hours	Mild–moderate sedation, initial risk of activation and akathisia, low risk of dose-dependent EPS, low risk of metabolic syndrome, high risk of QTc prolongation, low risk of hyperprolactinaemia
Zuclopenthixol	Tablets	20 hours	Mild–moderate sedation, moderate–high risk of EPS
Zuclopenthixol acetate	Intermediate-acting injection	Approximately 2 days	
Zuclopenthixol decanoate	Long-acting injection	19 days	

* Droperidol and ziprasidone mesylate injection are omitted as they are only used acutely.
EPS extrapyramidal symptoms (dystonia, akathisia, pseudo-parkinsonism, tardive dyskinesia)

Box 1 **When to consider stopping antipsychotics**

Psychiatrist review may not be required

- Antipsychotic (e.g. low-dose quetiapine) has been used for anxiety or sleep disturbance, and ongoing treatment is not needed or desired.
- Antipsychotic has been used for disturbed behaviour in dementia but may no longer be needed because of behavioural or environmental interventions.
- Antipsychotic has been trialled for off-label indications and has proven ineffective.

Psychiatrist review required

- Full recovery after first episode of psychosis and patient has been well for 12 months.
- Recurrent psychosis when:
  - patient has fully recovered and been well for 12–24 months
  - illness severity and other risk factors allow
  - patient and family wish to re-evaluate the benefits and harms of ongoing treatment.
- Bipolar mood disorder when antipsychotic is no longer necessary, especially when lithium monotherapy is appropriate.
- Full recovery after drug-induced psychosis and evaluation suggests treatment may no longer be needed (e.g. illicit drug use has stopped).
- Psychotic depression that has responded to treatment and psychosis is no longer evident.
- Patient has responded to early treatment with sedating antipsychotic (e.g. quetiapine and olanzapine) for severe agitated depression and adjuvant antipsychotic therapy is no longer necessary.

was started. This is not uncommon when stopping clozapine as a result of complications such as agranulocytosis or myocarditis.[4] Depending on the pharmacological action of the antipsychotic, several withdrawal syndromes can occur (Table 2).

Some antipsychotics (particularly depot injections) have long half-lives and are unlikely to be associated with significant withdrawal symptoms (Table 1).

After a first episode of psychosis in schizophrenia and related disorders, stopping antipsychotics is considered when the patient has made a full recovery and been well for at least 12 months.[5] Up to 40% of patients who have experienced a single episode of psychosis may remain well after stopping their antipsychotics or at least require only low doses.[6]

If there have been a number of episodes of psychosis, or recovery is incomplete, ongoing antipsychotic treatment is usually recommended as the chance of exacerbation or relapse is high if the drug is stopped. In patients who have experienced more than one episode but have fully recovered and been well for at least 12 months with antipsychotics, gradual dose reduction accompanied by close observation can be considered. Illness severity, treatment complications (e.g. obesity), previous pattern of relapse, risk to self and others, and the psychosocial consequences of relapse should be carefully considered in the harm–benefit assessment. Repeated episodes of psychosis worsen longer term prognosis. As the risk of relapse after a second episode is high, most clinicians would recommend long-term treatment.[6]

Patients who have experienced psychotic depression and have responded to a combination of antidepressants and antipsychotics with or without electroconvulsive therapy, can often be continued on antidepressant drugs alone. There are no clear guidelines for when antipsychotics can be withdrawn in these patients. However, after the patient has been recovered for some time, it is often possible to gradually reduce the dose while continuing to monitor the patient's mental state (especially if serious risk factors like suicidality were present initially).

Patients who have been started on sedating antipsychotics for severe agitated depression, anxiety or insomnia can often be taken off them, especially if there has been significant clinical improvement.

Antipsychotics for behavioural disturbance associated with dementia and other brain diseases should be reviewed and deprescribing should be considered due to the serious adverse effects and lack of evidence for long-term use.[7]

Switching antipsychotics

There are a number of clinical situations in which switching from one antipsychotic to another is considered. Review by a psychiatrist is indicated before switching, particularly in complex clinical situations or when urgent switching is necessary (Box 2). When choosing a drug to switch to, it helps to know which antipsychotics have a lower risk of the common adverse effects associated with long-term therapy. Table 3 lists antipsychotics that have lower risks of adverse effects such as extrapyramidal and anticholinergic symptoms, weight gain, postural hypotension and hyperprolactinaemia.[1,8]

Switching is not necessarily a panacea. Illness exacerbation may occur during the switch, and new adverse effects may emerge. When switching is being undertaken due to an inadequate response, it is important to ensure the dose of the first antipsychotic has been optimised, the patient has been treated for an adequate amount of time, and that they are adhering to treatment.[9]

The choice of the new drug will be partly determined by the reasons for the switch, but probable efficacy, adverse effects, dosing regimen and patient or carer preferences also need to be taken into account. Broad characteristics of antipsychotics are given in Table 1, but more details may be necessary and expert advice could be valuable in making drug choices.

Depending on the pharmacology of the antipsychotic, switching may result in withdrawal syndromes, particularly anticholinergic withdrawal with drugs such as quetiapine, clozapine, chlopromazine and olanzapine. Changing from one antipsychotic to another (when, for example, seeking a drug with a lower risk of weight gain) can result in loss of efficacy and withdrawal symptoms. It is essential for patients and carers to be informed about the possible consequences of switching, and an action plan for how to deal with any difficulties should be formulated.

Clozapine

When a patient is being switched from clozapine to another antipsychotic, rebound psychosis and other serious withdrawal effects may occur irrespective of which drug is substituted. Clozapine discontinuation should be done under the guidance of a psychiatrist. The dose should be gradually tapered, not stopped suddenly.[10] However, sometimes this may be unavoidable if, for example, agranulocytosis has occurred.

Switching strategies

In contrast to switching antidepressants, a drug-free period between stopping the first antipsychotic and starting the second is not recommended due to the risk of relapse. Table 4 lists the different methods of changing from one antipsychotic or formulation to another. Whether switching from an oral to a depot antipsychotic, depot to depot, or depot to oral, specific instructions need to be followed (Table 4).

Direct switch

While it is possible to stop the first drug and start the second drug the next day, this may result in withdrawal symptoms and possible drug interactions. When the first antipsychotic is aripiprazole or brexpiprazole, a direct switch can be made as both these drugs have very long half-lives and no anticholinergic effects.

Table 2 **Withdrawal syndromes associated with antipsychotic drugs**

Type of withdrawal syndrome	Causative antipsychotics	Clinical manifestations
Cholinergic syndrome	Chlopromazine, clozapine, olanzapine, quetiapine	Nausea, vomiting, headache, restlessness, anxiety, insomnia, fatigue, malaise, myalgia, diaphoresis, rhinitis, paraesthesia, loose bowels
Dopaminergic syndrome	All antipsychotics in Table 1	Withdrawal dyskinesia, akathisia, dystonia, tardive dyskinesia
Rebound psychosis	Clozapine	Psychosis above pre-treatment levels, illusions, hallucinations, catatonia

Box 2 **When to consider switching from one antipsychotic to another**

Psychiatrist review required if possible

- Inadequate clinical response for acute symptoms despite dose optimisation and adequate duration of treatment trial.
- Poor control of chronic symptoms and persistence of functional disabilities during maintenance therapy.
- Relapse despite adequate prophylactic or maintenance treatment of a psychotic illness.
- Persistence of certain symptoms of psychotic illness (e.g. negative symptoms and cognitive dysfunction) despite adequate doses of one antipsychotic, which may respond better to an alternative drug.
- Unacceptable adverse effects at low therapeutic doses before a clinical response in susceptible individuals (e.g. extrapyramidal effects in Asian patients). Consider switching to an antipsychotic with a lower risk for the adverse effect.
- Emergence of unacceptable adverse effects during treatment with one antipsychotic (e.g. increased appetite and problematic weight gain), which may improve with an antipsychotic that has a lower risk.
- Need to change the antipsychotic drug due to a physical complication (e.g. ziprasidone is contraindicated in cardiovascular illness, antipsychotics that cause significant hyperprolactinaemia are contraindicated in breast cancer).
- Request from patient or carer to change drugs due to unacceptable adverse effects (e.g. sexual dysfunction with an antipsychotic that has caused hyperprolactinaemia).
- Poor treatment adherence – consider changing from an oral antipsychotic to a long-acting depot injectable form.

Table 3 **Switching antipsychotics based on risk of adverse effects**

Adverse effect	Recommended order of replacement drug (listed from lower to higher risk of adverse effect)
Extrapyramidal effects	Clozapine Quetiapine Olanzapine (low-dose) Aripiprazole Brexpiprazole Ziprasidone
Anticholinergic effects	Risperidone Paliperidone Ziprasidone Asenapine Lurasidone Haloperidol Aripiprazole Brexpiprazole
Weight gain	Haloperidol Ziprasidone Lurasidone Aripiprazole Amisulpride Asenapine
Postural hypotension	Haloperidol (oral and decanoate) Periciazine Flupentixol Amisulpride Aripiprazole
Hyperprolactinaemia	Aripiprazole Asenapine Quetiapine Clozapine Ziprasidone Olanzapine (low-dose)
QTc prolongation	Lurasidone Aripiprazole Paliperidone Haloperidol
Sedation	Amisulpride Paliperidone Aripiprazole Brexpiprazole
Sexual dysfunction	Aripiprazole Brexpiprazole Quetiapine (conflicting evidence)

Source: references 1 and 8

Cross titration

Evidence indicates there may be little difference in the risk of relapse with immediate and gradual antipsychotic stopping or switching.[11] Most psychiatrists use the cross-titration strategy. This involves a reduction of the first antipsychotic while introducing the second drug.

Continuation with slower titration and discontinuation

A slower approach to titration is to continue the first antipsychotic for a period at its usual dose while gradually increasing the therapeutic dose of the second antipsychotic. The first antipsychotic can then be gradually reduced and stopped. The risk of relapse is minimised with this approach, but there may well be additive adverse effects during the process.

Interactive switching tool

An interactive tool provides specific switching guidelines for different antipsychotics, including from one oral antipsychotic to another and from one depot antipsychotic to another.

Conclusion

There are a variety of clinical circumstances in which stopping an antipsychotic should be considered and undertaken if appropriate. When it is necessary to switch from one antipsychotic to another during the course of treating psychoses, clinicians need to have some understanding of the pharmacokinetics and dynamics of antipsychotic drugs in order to plan and carefully monitor a switching regimen. This usually involves a period of both drugs being used simultaneously.

Stopping and switching antipsychotics can result in serious consequences, particularly a relapse of psychosis which may entail serious risks and worsen long-term prognosis. Withdrawal syndromes related to cholinergic and dopaminergic effects may occur depending on the characteristics of the antipsychotics involved. <

Conflict of interest: none declared

Antipsychotic switching tool

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Go online to use this interactive tool.

Table 4 **Techniques for changing from one antipsychotic or formulation to another (psychiatrist review required)**

Change	Comment
Direct switch: First antipsychotic is stopped and next antipsychotic is started on the following day	Simplest strategy but expertise is required and may be best carried out in an inpatient setting. Risk of discontinuation symptoms from first antipsychotic may be substantial. There may be a significant risk of drug interactions depending on individual drug characteristics. Should be avoided if possible when switching from clozapine.
Cross titration: First antipsychotic is gradually reduced while second antipsychotic is gradually increased to therapeutic dose	Most common strategy used in clinical practice. Provides some balance between minimising risk of relapse and minimising risk of adverse effects during overlap. Expertise required due to differing pharmacokinetics and possibility of drug interactions.
Continuation with slower titration and subsequent discontinuation: First antipsychotic is continued at usual dose, second antipsychotic is gradually titrated up to near therapeutic dose, then first antipsychotic is gradually reduced and stopped, while dose of second antipsychotic is increased to its therapeutic dose	Most conservative strategy suitable for patients with a high risk of relapse. However, there will be significant overlap of the two antipsychotics with a likelihood of adverse effects during switch. There is also the risk that the planned discontinuation of the first antipsychotic never takes place or therapeutic dose of second antipsychotic is not reached.
Formulations	
Oral to depot	Specific instructions need to be followed for each particular depot. Continuation of oral antipsychotic may be required for some time after injecting depot depending on the characteristics of depot drug.
Depot to depot	Need to follow instructions with new depot for changing from previous depot drug. This is most commonly undertaken as a direct switch but, because of the long half-lives, it is in effect a cross titration.
Depot to oral	Because of the long half-lives, depot formulations can be stopped immediately. For all oral antipsychotics except clozapine, the oral drug should be started on the date that the depot antipsychotic was due. Clozapine requires a very slow titration at the start of therapy. As the effective dose of clozapine varies so much between patients, it is common to continue the depot antipsychotic until clozapine has reached therapeutic plasma concentrations or has shown significant clinical effect.

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ARTICLE

Amiodarone in the aged

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SUMMARY

Amiodarone is a highly effective antiarrhythmic drug, but can have serious adverse effects, particularly in older patients. If possible it should not be used purely for controlling the heart rate.

If a prescription for amiodarone is contemplated, particularly for an older patient, consult a cardiologist. Avoid amiodarone in patients with significant conduction system disease, significant liver or pulmonary disease, or hyperthyroidism.

Regular monitoring of the patient, clinically and biochemically, is required to identify complications at an early, treatable stage. Maintain a high level of suspicion if a patient taking amiodarone is experiencing adverse reactions and presents with new symptoms.

Consider potential drug interactions when other drugs are prescribed with amiodarone. The effects and toxicities of amiodarone may persist weeks after it is stopped.

Introduction

Amiodarone is widely considered to be the most effective antiarrhythmic drug available.[1] It is commonly used to treat atrial fibrillation and ventricular arrhythmias. Amiodarone, and its active metabolite desethylamiodarone, have multiple effects on cardiac depolarisation and repolarisation. Although it primarily blocks potassium channels, amiodarone potentiates its effect through all four of the classic Vaughan Williams mechanisms of antiarrhythmic action.

Despite its efficacy, amiodarone is a challenging drug to use in clinical practice due to its prolonged half-life, multiple adverse effects and drug interactions. These adverse effects are particularly problematic for older people who are more susceptible to drug toxicities and who have higher rates of polypharmacy. There is also a lack of information regarding the safety of amiodarone in older people.[2] A cardiologist's opinion is recommended before prescribing.

Amiodarone can have adverse effects in multiple organ systems including the lungs, heart, liver, thyroid, gut, skin, nerves and eyes.[3] Its use is also implicated in a range of drug–drug interactions with commonly prescribed cardiovascular drugs.[4]

Indications

Amiodarone is one the most frequently prescribed antiarrhythmic drugs for atrial fibrillation.[5] It is used by 8–11% of patients.[6]

Atrial fibrillation is the commonest arrhythmia in older adults, with an estimated prevalence of 9% in people over the age of 80 years. The primary goals in management are to prevent disabling symptoms through rhythm or rate control and to reduce the risk of stroke with anticoagulation.[7]

Several major trials have compared rate and rhythm control in patients with atrial fibrillation. They found no significant difference in all-cause mortality, cardiovascular death and composite end points including death, stroke, major bleeding, cardiac arrest and congestive cardiac failure.[7] In fact, the AFFIRM study of over 4000 patients showed a trend towards increased mortality with rhythm control, particularly in older patients.[8] The differences were partly explained by non-cardiac deaths with antiarrhythmic therapy that was thought to be more toxic in those with serious medical conditions. There were no differences between the two groups in terms of cardiovascular mortality, deaths due to arrhythmia, vascular events or rates of ischaemic stroke.[9] The majority of the patients treated with rhythm control in AFFIRM were managed with amiodarone. Other, smaller studies have shown similar increases in non-cardiac mortality in patients taking amiodarone.[9,10]

Based on the trial results, rate control is preferred to rhythm control for patients with atrial fibrillation. Either beta blockers or non-dihydropyridine calcium channel blockers can be used.

The 2018 Australian Clinical Guidelines for the Diagnosis and Management of Atrial Fibrillation[11] state, 'Amiodarone should be considered a last-line option for chronic pharmacological rate control, given its toxicity profile.' Amiodarone may be considered for maintenance of sinus rhythm as a second-line drug,

or a first-line drug in the setting of left ventricular dysfunction, left ventricular hypertrophy or coronary artery disease. While no comment is made specifically about older patients in the guidelines, beta blockers should still be considered first-line drugs in this population.[11] For patients on long-term treatment, the indication for continuing amiodarone should be reviewed.

Intravenous amiodarone is indicated to terminate acute ventricular tachycardia in haemodynamically stable patients. It can also be used in the acute management of patients who become haemodynamically stable after maximal energy shock. Amiodarone can suppress events in patients with ischaemic heart disease and non-ischaemic cardiomyopathy who have recurrent ventricular arrhythmias.[12]

Pharmacokinetics and dosing

Amiodarone has incomplete and erratic absorption following oral administration. It is markedly lipophilic, resulting in a large volume of distribution (average approximately 66L/kg) and subsequently a long half-life.[4] Estimates of half-life vary, however a terminal half-life of up to 142 days has been reported as tissue stores deplete.[1] The principal active metabolite, desethylamiodarone, is reported to have a half-life of 60–90 days in chronic oral dosing.[13] Most of the drug is excreted via the liver and gastrointestinal tract by biliary excretion.

The plasma half-life and drug concentrations of amiodarone are further increased in older people due to an increased volume of distribution resulting from proportional increases in body fat. While the plasma concentration of amiodarone can be estimated, this is of limited value as the measurement is inaccurate and does not correlate well with efficacy or adverse effects.[1]

The typical maintenance dose of amiodarone is 200 mg per day. In older patients, decreasing the dose to 100 mg per day is advised, particularly if the indication is atrial fibrillation rather than a life-threatening arrhythmia.[4] The lowest effective loading and maintenance dose should be used in older patients and dose increases should be undertaken with caution. Unlike in ventricular arrhythmias, loading doses are often unnecessary for treating atrial fibrillation.

Given the long half-life, it may take weeks before dose increases yield clinically apparent effects, suggesting the need for cautious and slow up-titration. Similarly, clinicians should be aware that the effects and toxicities of amiodarone can still be present weeks to months after stopping the drug.

Drug interactions

Amiodarone inhibits cytochrome P450 (CYP) enzymes 3A and 2C and the drug transporter P-glycoprotein.[9] This leads to impaired metabolism and, potentially, increased sensitivity of patients to several drugs including warfarin, digoxin, non-steroidal anti-inflammatory drugs, statins and benzodiazepines.[14]

If amiodarone is added to warfarin, the warfarin dose must be reduced and INR should be closely monitored.[6] Interactions between amiodarone and the direct thrombin inhibitor dabigatran have been associated with a 50–200% increase in the area under the curve, resulting in a potentially increased risk of bleeding.[15] Similarly, non-randomised studies have reported a potential increase in the risk of bleeding with concurrent use of amiodarone and rivaroxaban,[16] although this interaction has not been described with apixaban and amiodarone.[17]

Amiodarone can also lead to bradyarrhythmias with an increased risk of complete heart block when used in combination with beta blockers or calcium channel blockers. Amiodarone commonly causes QT prolongation on the ECG and should be used with caution when combined with other drugs that also prolong the QT interval. However, induction of polymorphic ventricular tachycardia is uncommon.[1]

Grapefruit juice inhibits CYP3A4 leading to significantly reduced conversion of amiodarone to its active metabolite desethylamiodarone. Grapefruit juice should therefore be avoided with amiodarone therapy.[18]

Organ-specific complications

Older people are at an increased risk of the organ-specific complications of amiodarone. This is because of changes to pharmacokinetics as well as higher rates of medical comorbidities, physiological deterioration in renal and hepatic function, and higher rates of cognitive, motor and sensory impairment.[14] Older people may also present with non-specific complaints secondary to amiodarone including fatigue, nausea and anorexia. A high index of suspicion should be maintained if an older patient presents with new symptoms. Regular monitoring is recommended (see Table). The long half-life of amiodarone means that complications may emerge after the drug is ceased.

In a review of 1020 cases of reported amiodarone-induced toxicity, the most commonly reported adverse reactions were thyroid disorders, followed by skin reactions such as photosensitivity. Pulmonary toxicity was the third most common adverse event, but is considered the most serious as it is associated with increased mortality.[19]

Table **Monitoring for organ-specific complications of amiodarone**

Baseline assessments: Liver function, thyroid function, ECG, lung function, chest X-ray, review other drugs.

Organ	Complications	Symptoms	Suggested monitoring	Recommendation
Lungs	Acute inflammation, chronic fibrosis	Cough, increased breathlessness	Yearly chest X-ray Prompt assessment of new respiratory symptoms possibly with chest X-ray and pulmonary function tests	Stop amiodarone, start steroids Refer to respiratory physician
Heart	Bradycardia, heart block, QT prolongation	Dizziness, syncope, collapse, fatigue	Yearly ECG	Reduce dose
Liver	Hepatitis	Often asymptomatic Nausea, gastrointestinal disturbance	6–monthly liver function tests	Discontinue if transaminases >3 x normal Avoid in severe liver disease
Thyroid	Hypothyroidism 20% Hyperthyroidism 3%	Often asymptomatic Fatigue, palpitations, weight change	6–monthly thyroid function tests	Start thyroxine for hypothyroidism Discontinue in hyperthyroidism and consider antithyroid drugs, prednisone, or surgical thyroidectomy and refer to an endocrinologist
Skin	Photosensitivity		Physical examination at baseline, then as needed based on signs or symptoms	Stress importance of sunscreen and skin protection
Eyes	Corneal deposits 100% Optic neuritis <1%		Examination at baseline if there is an underlying abnormality, examinations thereafter as needed	Avoid or stop in presence of optic neuritis

Thyroid

Amiodarone may lead to both hypo- and hyperthyroidism. Patients who already have thyroid abnormalities, such as nodular goitre or Hashimoto's disease, are likely to have a higher risk of complications.

Amiodarone-induced hypothyroidism is more common in iodine-sufficient countries and typically occurs within the first two years of therapy. It is treated with thyroxine to normalise the concentrations of thyroid-stimulating hormone.

Amiodarone-induced thyrotoxicosis can occur suddenly and at any time during treatment. The management includes stopping amiodarone, and considering antithyroid therapy, prednisone or surgical thyroidectomy.[20,21]

Thyroid dysfunction may be asymptomatic, particularly in older patients,[22] and therefore the diagnosis should be based on biochemical tests. Clinical and laboratory assessments are needed at the start of treatment. Thyroid function should be monitored every six months. Clinical symptoms or changes in cardiac function should also prompt evaluation of thyroid function.

Skin

Photosensitivity is common following treatment with amiodarone. All patients should be cautioned to use sunscreen and cover exposed skin. Blue skin discolouration can occur, but typically resolves several months after stopping amiodarone.

Lungs

Pulmonary toxicity occurs in approximately 2–5% of patients taking amiodarone and is the adverse effect most associated with increased mortality.[23] The death rate ranges from 9% in patients who develop a chronic pneumonia to 50% in those with acute respiratory distress syndrome.[24]

Pulmonary toxicity is more common in older patients and in patients with underlying lung pathology.[1,19] It increases threefold for every 10 years of age in patients over 60 years old compared with those under 60 years.[24] Toxicity can occur at any time during the course of treatment. Those at the greatest risk are patients who have taken a daily dose of 400 mg or more for more than two months, or a lower dose, commonly 200 mg daily, for more than two years.[25]

Common presentations include acute or subacute cough and progressive dyspnoea.[20] Routine screening is of limited value as symptoms can develop rapidly. Patients who present with new respiratory symptoms should be promptly investigated.[26]

Pulmonary function tests typically show restriction as well as a decreased diffusing capacity of the lungs for carbon monoxide (DLCO). High resolution CT of the chest generally reveals diffuse ground glass and reticular abnormalities.

The treatment of pulmonary toxicity involves stopping amiodarone and often giving corticosteroids. Prolonged courses may be needed because of the long half-life of amiodarone.

Heart

Sinus node dysfunction and conduction disease are common in older patients so a careful assessment is needed before starting amiodarone.[27,28] Bradycardia and heart block occur in 1–3% of patients treated with amiodarone. Its use is therefore relatively contraindicated in patients with second- or third-degree heart block who do not have a pacemaker.

Gut

The gastrointestinal effects of amiodarone include nausea, anorexia and constipation. They can occur in up to 30% of patients and are more common in older people. The effects tend to improve with dose reduction.[3]

Liver

Hepatic toxicity occurs commonly in patients receiving long-term amiodarone. Liver enzymes should be checked every six months.[3] If concentrations reach three times the upper limit of normal, amiodarone should be discontinued, unless the patient has a life-threatening arrhythmia.

Other adverse effects

Neurological toxicity associated with amiodarone can include ataxia, paraesthesia and tremor. In a frail older patient these effects could increase the risk of falls. These neurological effects are often dose-related and improve when the dose is reduced.

Corneal microdeposits are visible on slit lamp examination in nearly all patients treated with amiodarone for three months. These deposits rarely affect vision or necessitate discontinuation of amiodarone.[21] Optic neuropathy and optic neuritis have been described in a small number of patients, however a causal relationship has not been well established.

Conclusion

In older adults, the use of toxic drugs for non-life-threatening indications should always be avoided. Amiodarone is a highly effective antiarrhythmic, however its unpredictable pharmacodynamics and broad adverse-effect profile make it a challenging drug to use safely in clinical practice. Its use should be reviewed in older patients with multiple comorbidities. Safer alternative drugs should be used preferentially in older patients with atrial fibrillation or minor ventricular arrhythmias, such as ventricular ectopy and non-sustained ventricular tachycardia.

When ongoing treatment with amiodarone is required for older patients, care should be taken to use the lowest effective dose. Patients often require dose reductions as they age, in consultation with the patient's cardiologist.

Regular monitoring of liver and thyroid function and pulmonary symptoms is required to identify complications at an early stage. Amiodarone toxicity often presents atypically and insidiously, particularly in older patients. New symptoms in a patient taking amiodarone should always be considered as potential adverse effects. ≺

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

1. Amiodarone is the preferred drug for rate control in atrial fibrillation.
2. The development of corneal microdeposits is an indication to stop amiodarone.

Answers on page 175

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ARTICLE

How to adjust drug doses in chronic kidney disease

SUMMARY

Drugs excreted by the kidney require dose reduction in chronic kidney disease. This adjustment depends on the severity of the disease and what proportion of the drug is eliminated by the kidneys.

The estimated glomerular filtration rate can generally be used to guide dose adjustment in patients with stable kidney function. However, the formula can be misleading in some patient subsets and other approaches are required.

At extremes of body mass, the estimated glomerular filtration rate can under- or overestimate kidney function. It may need to be adjusted for body surface area, particularly for drugs with a narrow therapeutic range or requiring a minimum concentration to be effective. Close monitoring of drug effect and toxicity is also needed and can be supported by therapeutic drug monitoring.

For short courses of drugs with a wide therapeutic index, dose adjustment may not be needed.

Alternative methods for quantifying kidney function include the Cockcroft-Gault formula (estimates creatinine clearance) or direct measures of glomerular filtration rate using exogenous isotope compounds. These are not commonly required.

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Introduction

Chronic kidney disease is defined by a glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 or evidence of glomerular-tubular injury, for example haematuria or proteinuria. The diagnosis is becoming more common with 1.0% of Australians being diagnosed in 2017–18. In those over 75 years old, the prevalence was 4.6%.[1] However, biochemical results indicate the actual prevalence may be closer to 10% in adults,[2] and more than 30% in a hospital population.[3]

Many drugs are eliminated by the kidney to some extent. If the dosage is not appropriately decreased in a patient with chronic kidney disease, drug concentrations can increase, risking adverse drug reactions. On the other hand, unnecessary decreases in dosage may result in undertreatment, or changing to an alternate drug with a narrower therapeutic index, lower efficacy or both. Examples include changing a patient with chronic kidney disease from metformin to a sulfonylurea (lower effectiveness and reduced long-term benefit), or rivaroxaban to warfarin (narrower therapeutic index and requiring more blood tests).

The requirement for dose adjustments in adults with chronic kidney disease should be anticipated at the point of prescribing. It is important for prescribers to understand that there are different methods of calculating the dose adjustments in these patients.

The influence of kidney disease on drug prescribing

The need for and extent of dose adjustment depends on the severity of chronic kidney disease, the proportion of the drug eliminated by the kidney, the risk of adverse effects from the drug, the duration of treatment and if the drug has active or toxic metabolites that rely on the kidney for elimination.[4] Drug toxicity due to an inappropriately high dosage is seen after multiple doses due to drug accumulation, rather than after the first dose.[5] The dose adjustment in patients with kidney disease involves increasing the dosing interval or reducing the dose.

Quantifying kidney function

GFR is the key clinical measure of kidney function. In general, for drugs that are excreted by the kidney, a decrease in GFR is associated with a decrease in drug clearance and the dosage needs to be reduced.

The GFR can be quantitated in multiple ways and each has advantages and disadvantages. The measured GFR (mGFR) is the gold standard but it is resource intensive and expensive, so the estimated GFR (eGFR) is used to classify and monitor the severity of chronic kidney disease (Table 1).

Serum creatinine-based formulae

GFR can be assessed using serum creatinine-based formulae – Cockcroft-Gault[6] and CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration)[7]. Since

creatinine is an end product of muscle breakdown, each formula allows for the serum creatinine concentration to be adjusted for body mass based on patient characteristics.

The Cockcroft-Gault formula estimates creatinine clearance (eCrCl) and incorporates age, sex and body weight (Box 1).[6] Because eCrCl was validated against measured CrCl based on 24-hour urine collection, it overestimates the actual GFR given that creatinine is both filtered and secreted in the nephron tubules. The usual units for eCrCl are mL/minute and multiple online calculators are available. However, by 2010 most laboratories in Australia were using a newer creatinine assay standardised to isotope dilution mass spectrometry (IDMS) which resulted in a 10–20% decrease in creatinine concentrations. This, in turn, will increase the eCrCl compared to what would have been calculated pre-2010.

The CKD-EPI formula estimates GFR because it was validated against GFR measured using exogenous filtration markers.[7] It incorporates age and sex into a relatively complicated formula. These demographics are known at the time of blood collection so the eGFR is automatically calculated and reported by the laboratory. The units for the automated eGFR are mL/min/1.73 m^2 and it is now an accepted method for the classification and monitoring of chronic kidney disease (Table 1).[8,9]

The initial report describing the CKD-EPI formula did not observe an effect of age or body mass index (BMI) on the accuracy of its prediction.[7] However, it should be noted that the initial report was based on a population who were mostly younger than 66 years old with a mean body surface area of 1.90–1.93 m^2 and a BMI of 27–28 kg/m^2 (mean height 170 cm, mean weight 79–82 kg). The automated eGFR may not therefore apply to patients with different demographics. Since the body surface area for most patients is higher than 1.73 m^2, the actual GFR in such a patient will be higher than that reported by the laboratory. The eGFR can be de-indexed (converted to actual mL/min) by multiplying the automated eGFR by the patient's body surface area (m^2) and then dividing by 1.73 (see Box 1).

Table 1 **Relationship between glomerular filtration rate and stage of chronic kidney disease***

Kidney function stage	eGFR (mL/min/1.73 m^2)
1	≥90
2	60–89
3a	45–59
3b	30–44
4	15–29
5	<15 or on dialysis

eGFR estimated glomerular filtration rate

* The stage of chronic kidney disease is not only based on eGFR, but also on an assessment of kidney damage (eg. proteinuria, haematuria)

Box 1 **Formulae used in estimating glomerular filtration rates**

Cockcroft-Gault creatinine clearance (mL/min):
= (140 – age) x weight ÷ serum creatinine x 0.814 (x 0.85 if female)

De-indexed eGFR (mL/min):
= eGFR (mL/min/1.73 m^2) x patient's body surface area ÷ 1.73

Body surface area (m^2):
= 0.007184 x weight$^{0.425}$ x height$^{0.725}$

Ideal body weight (kg):
= (height – 152.4) x 0.9 + 45.5 (+ 4.5 if male)

Adjusted ideal body weight (kg):
= IBW + 0.4 x (weight – IBW)

Serum creatinine (micromol/L), weight (kg), height (cm), age (years)
eGFR estimated glomerular filtration rate
IBW ideal body weight

Measured GFR

The mGFR is determined after giving an exogenous filtration marker, such as ^{51}Cr-EDTA, ^{125}I-iothalamate, DTPA or MAG3. It is the most reliable method of quantifying GFR because these markers are filtered and not substantially secreted into or reabsorbed from the nephron. The mGFR can be indexed by adjusting for a standard body surface area of 1.73 m^2.

The mGFR methods require parenteral administration of the exogenous marker and multiple blood and sometimes urine samples over time. The incremental gain from the mGFR above eGFR is uncertain in most cases, but they are used in specialist practice before a unilateral nephrectomy when considering the split GFR in each kidney.

Serum cystatin C-based formulae

Cystatin C is another endogenous solute that can be used to estimate GFR. However, the test is not universally offered by pathology laboratories in Australia at present.

Cystatin C is less influenced by muscle mass, so it may be advantageous in patients at extremes of body weight or those with cirrhosis. An alternative CKD-EPI formula has been developed to incorporate cystatin C.

How accurate are eGFR and eCrCl?

There is debate about which formula – Cockcroft-Gault or CKD-EPI – is preferred for drug dosing because neither is a perfect representation of the true value of the GFR.

First, the criteria generally applied in developing these formulae are that the estimated value should be within 30% of the gold standard value (e.g. mGFR). For an eGFR or eCrCl in any patient at any time, the true GFR or CrCl could be nearly half or double that of the estimated value (so the absolute variability increases at higher GFRs, see Fig.). This significant uncertainty probably reduces the impact of the IDMS-standardisation of creatinine assays on the calculated eCrCl.

Second, the eCrCl and automated eGFR do not give exactly the same results and eCrCl generally overestimates mGFR.[10] For patients with a body surface area that is substantially different from 1.73 m^2, the eGFR can be de-indexed to give units of mL/minute (Box 1). This value is used to inform drug dosing. For example, for the average patient enrolled in the study that developed the CKD-EPI formula,[7] the mean actual GFR (mL/min) is approximately 10% higher than the automated eGFR, and more than 30% higher for those who are taller or heavier.

When the automated eGFR is an unreliable estimate of eCrCl or mGFR

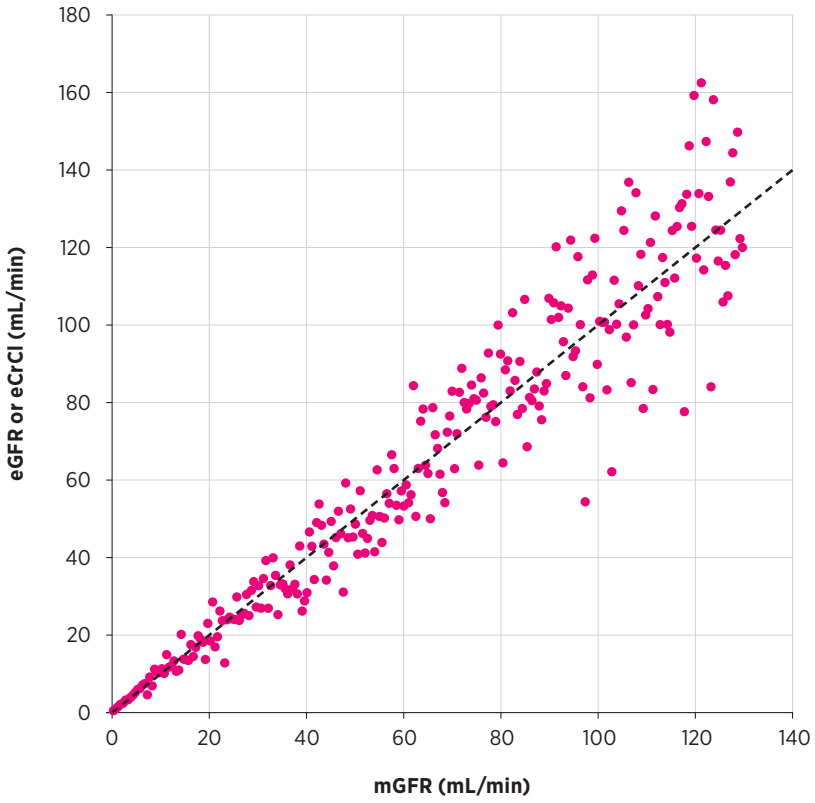
Some dosing recommendations are based on eCrCl so it is useful to understand how eGFR relates to eCrCl and the gold standard measurement mGFR.

The eGFR and eCrCl formulae were validated in people older than 18–20 years, and advancing age is associated with imprecision. For example, a study in patients over 60 years of age found that eCrCl and de-indexed eGFR were within 10% of each other in only 45% of cases and in most of these cases the eCrCl was lower than eGFR.[11] The eCrCl was more likely to be lower in patients with a lower body weight (e.g. less than 60 kg) and increased age (e.g. older than 80 years).[11] Unfortunately, mGFR was not measured in this study to assess the accuracy of the two serum creatinine-based formulae.

A study in 269 people aged 70 years and older noted that the absolute bias by eCrCl was less than that of de-indexed CKD-EPI (bias -3.2 ± 14.2 mL/min vs +7.1 ± 15.1 mL/min) compared to measured CrCl.[12] However, another larger study (n=805) with a similar population except for a slightly higher average BMI found that the mean bias of de-indexed CKD-EPI was +2.7 mL/minute compared to mGFR,[13] supporting the use of CKD-EPI.

In obese patients (BMI above 30 kg/m^2), automated eGFR can underestimate GFR, and eCrCl based on actual body weight will overestimate GFR.[10,14,15] In these patients, eCrCl based on adjusted ideal body weight (Box 1) or de-indexed eGFR are more reliable estimates of GFR[14,15] (see Box 2 for an example). The opposite is true with eGFR for those who are underweight (BMI less than 18.5 kg/m^2) with correction for body surface area resulting in a lower GFR estimate.[10]

Fig. **Correlation of eGFR and eCrCl with mGFR***



* The correlation of eGFR is imprecise, for example eGFR 30 mL/min may reflect an mGFR of 20–40 mL/min. The error on the prediction of mGFR from eGFR, and vice versa, increases at higher GFRs. Data based on simulation.

eCrCl estimated creatinine clearance

eGFR estimated glomerular filtration rate

mGFR measured glomerular filtration rate

The accuracy of these formulae may also vary depending on the GFR. For example, automated eGFR may be more accurate than indexed eCrCl at lower GFRs (e.g. less than 30 mL/min) and younger ages (e.g. under 40 years old).[10]

The impact of these patient characteristics on estimates of GFR are summarised in Table 2.

There are many other reasons why drug clearance (renal and non-renal) does not adequately correlate with creatinine-based measures of kidney function.[5]

Dose adjustment based on kidney function

Despite these complexities and limitations, international and local expert groups support the use of automated eGFR to guide drug dosing.[16] Overall, this appears reasonable given that potential benefits from a particular method (even if it was

Box 2 Different methods to assess glomerular filtration rate yield different results

A 42-year-old man is 1.75 m tall, weighs 132 kg (body mass index 43 kg/m^2 and body surface area of 2.5 m^2) and has a serum creatinine concentration of 300 micromol/L.

Glomerular filtration rate indexed to body surface area 1.73 m^2 for chronic kidney disease staging:

- automated eGFR 21 mL/min/1.73 m^2
- indexed measured GFR (DTPA) 19 mL/min/1.73 m^2
- indexed measured 24-hour creatinine clearance 36 mL/min/1.73 m^2.

Each of these methods place this man somewhere between Stage 3 and late Stage 4 chronic kidney disease.

Actual glomerular filtration rate for drug dosing:

- de-indexed eGFR 30 mL/min
- measured GFR (DTPA) 27 mL/min
- measured 24-hour creatinine clearance 52 mL/min
- eCrCl (actual body weight) 53 mL/min
- eCrCl (ideal body weight) 28 mL/min
- eCrCl (adjusted ideal body weight) 38 mL/min.

Therefore, if a drug's dosage is reduced when a patient's GFR is <30 mL/min, the dose for the patient is usually higher if the de-indexed eGFR is used to guide dosing. The preferred formula to guide dosing is not certain at this time, but eCrCl based on actual body weight and measured 24-hour CrCl are likely to overestimate the actual GFR.

DTPA diethylenetriaminepentacetate (isotope to measure GFR)
eCrCl estimated creatinine clearance (Cockcroft-Gault formula)
eGFR estimated glomerular filtration rate (automated)
GFR glomerular filtration rate

Table 2 Impact of patient characteristics on estimates of GFR

Patient characteristic	eCrCl	eGFR
Reduced GFR	May be less accurate	May be more accurate
Actual BSA >1.73 m^2	Depends on body weight only, height is not incorporated	Actual GFR is >30% higher for taller or heavier individuals
Older age (>70 years)	Acceptable	Acceptable
Younger age (<40 years)	May be less accurate	May be more accurate
Obesity (e.g. BMI >30 kg/m^2) or weight >120 kg	Overestimates GFR, use adjusted ideal body weight	Underestimates GFR, use de-indexed eGFR
BMI <18.5 kg/m^2 or weight <60 kg	Acceptable, use actual body weight	Overestimates GFR, use de-indexed eGFR

eCrCl is estimated creatinine clearance as determined by the Cockcroft-Gault formula. The formula was validated against a 24-hour creatinine clearance and the units are mL/min. Actual body weight is commonly used in the calculations. The eCrCl is usually higher than the actual GFR.

eGFR is the estimated glomerular filtration rate as determined by the CKD-EPI formula. The formula was validated against a measured glomerular filtration rate and the units are mL/min/1.73 m^2 body surface area.

BSA body surface area
BMI body mass index
GFR glomerular filtration rate

used to establish the therapeutic dose) are likely to be reduced in most cases due to inherent errors associated with any of these methods.

Drug information resources do not apply a consistent approach to the dosing of drugs in the context of kidney disease. For example, metformin and rivaroxaban dosing is based on creatinine clearance (presumably Cockcroft-Gault eCrCl), eplerenone on eGFR, and tranexamic acid on eGFR or serum creatinine depending on the resource. For lithium or sotalol, guidance for dose reduction is generally vague and a conservative approach is recommended for initial dosing and up-titration.

Small deviations in eGFR are not likely to be clinically meaningful and should not lead to an immediate dose adjustment (or cessation) but instead prompt ongoing monitoring of kidney function.

A more careful approach may be warranted for drugs with a narrow therapeutic index. This is particularly the case if the patient's eGFR is close to a threshold prompting dose adjustment, the patient has a body surface area that differs significantly from 1.73 m^2, and the drug requires a minimum concentration to be effective (e.g. antimicrobials). In such cases, the eGFR should be corrected (de-indexed) for the body surface area, and drug efficacy and toxicity should be monitored. Therapeutic drug monitoring is also useful for some medicines such as digoxin, lithium and potentially oral anticoagulants.

Conclusion

Automated eGFR is an adequate measure of kidney function for drug dosing in most cases, but there are notable exceptions requiring further consideration. Dose adjustment in chronic kidney disease always requires decision making on a case-by-case basis. Alternative laboratory methods for guiding drug dosing are being researched, such as tests based on cystatin C, and may have a useful role in the future. <

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NEW DRUGS

New drugs

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Binimetinib plus encorafenib

Approved indication: metastatic melanoma

Binimetinib
Mektovi (Pierre Fabre)
15 mg film-coated tablets

Encorafenib
Braftovi (Pierre Fabre)
50 mg and 75 mg capsules

Many cases of melanoma involve the BRAF mutation. This results in the production of an abnormal protein kinase which promotes tumour cell growth. Drugs, such as vemurafenib and dabrafenib, that can inhibit this BRAF kinase may therefore improve survival in patients with melanoma. Another step in the pathway leading to tumour cell growth involves the MEK enzymes. These are the targets of drugs such as cobimetinib and trametinib. For patients with BRAF mutations, current treatment involves a combination of a BRAF inhibitor and a MEK inhibitor.[1] Encorafenib (BRAF inhibitor) and binimetinib (MEK inhibitor) are an example of such a combination for the treatment of unresectable or metastatic melanoma.

Both drugs should be swallowed whole with water. Grapefruit juice should be avoided as it interacts with encorafenib. At the recommended doses steady state is reached within 15 days. Both drugs are mainly cleared by metabolism. As the metabolism of encorafenib involves cytochrome P450 (CYP) 2C19, 2D6 and 3A4, there are many potential drug interactions. Strong inhibitors of CYP3A4 such as clarithromycin and itraconazole should be avoided. Liver disease will increase the concentrations of both drugs. A reduced dose of encorafenib is advised in mild hepatic impairment (Child Pugh A) and the combination should not be used at all with greater impairment.

The terminal half-life is about nine hours for binimetinib and six hours for encorafenib. Little active drug is excreted in the urine. No dose reductions are required in patients with mild or moderate renal impairment, but there are no data about the combination in severe impairment (<30 mL/min/1.73 m^2).

The main study of encorafenib and binimetinib was an open-label phase III trial involving patients with a BRAF mutation and locally advanced, unresectable or metastatic melanoma. One group of 192 patients was assigned to take encorafenib 450 mg once daily with binimetinib 45 mg twice daily. Another group of 194 was randomised to take encorafenib 300 mg daily and a third group of 191 was assigned to take vemurafenib 960 mg twice daily. After a median follow-up of 16.6 months, the median progression-free survival was 14.9 months with the combination. This was longer than with encorafenib alone (9.6 months) and vemurafenib (7.3 months).[2]

After two years, the overall survival with the combination was 57.6% compared to 49.1% with encorafenib and 43.2% with vemurafenib. At a median follow-up of 36.8 months, the median overall survival was 33.6 months with the combination, 23.5 months with encorafenib and 16.9 months with vemurafenib.[3]

The safety data for the trial included 570 patients. Adverse events led to 15% of the patients in the encorafenib groups and 17% of the vemurafenib group stopping treatment. Most patients required reduced doses because of adverse effects. Common adverse events that were more frequent with encorafenib plus binimetinib than with encorafenib alone included nausea, vomiting, diarrhoea, muscle spasms, hypertension, altered liver function and increased creatine kinase. Although they were common, skin reactions such as rashes were less frequent with the combination than encorafenib alone.[3] Serious adverse events related to the combination include haemorrhage, left ventricular dysfunction and ocular toxicities such as retinopathy. There is a risk of new cancers such as squamous cell carcinoma.

As animal studies show fetal toxicity, the combination should not be used in pregnancy. Women should use effective contraception during treatment and for at least one month afterwards.

Although there was a significant difference in overall survival for encorafenib plus binimetinib over vemurafenib, there was no statistical advantage over encorafenib alone.[3] This is despite the combination including a higher dose (450 mg) of encorafenib. The protocol of the trial has been revised so that the dose of encorafenib will be 300 mg, either alone or in the combination. This will make it easier to assess whether giving binimetinib with encorafenib adds significantly to the efficacy of encorafenib.

Other combinations of BRAF and MEK inhibitors are available and currently it is not possible to say which is the best. When the quality-of-life data for encorafenib and binimetinib are released they may assist with this choice. There are few data to show

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

that this combination would be effective in patients whose cancer has progressed during treatment with a different BRAF inhibitor. This combination is only approved for patients with a confirmed BRAF mutation.

T manufacturer provided the product information

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, and the European Medicines Agency.

NEW DRUGS

Aust Prescr 2019;42:170–1
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Lumacaftor/ivacaftor

Approved indication: cystic fibrosis

Orkambi (Vertex)
film-coated tablets containing 100 mg/125 mg or 200 mg/125 mg
sachets of granules containing 100 mg/125 mg or 150 mg/188 mg

Cystic fibrosis is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. These mutations affect the functioning of the CFTR protein which is a chloride channel that helps regulate the transport of water and chloride. Affected individuals have impaired chloride transport leading to thickened mucus which interferes with normal lung function.

Lumacaftor/ivacaftor is a new fixed-dose combination product for patients with cystic fibrosis from two years of age. It is specifically indicated for those who are homozygous for the F508del mutation, which accounts for about 45% of affected patients. This is a severe form of the disease as they have little or no CFTR protein on their cells. Lumacaftor is a newly approved chemical entity whereas ivacaftor is already available as monotherapy and in combination with tezacaftor.

The lumacaftor/ivacaftor combination works by improving CFTR activity in the lungs. Like tezacaftor, lumacaftor helps with cellular processing of the CFTR protein so more is present on the cell surface. Ivacaftor improves the function of CFTR and increases chloride transport.

The approval of the lumacaftor/ivacaftor combination is primarily based on two phase III trials (TRAFFIC and TRANSPORT)[1] of 1108 patients (aged ≥12 years) with the homozygous F508del mutation. At baseline, patients had a mean forced expiratory volume in one second that was 61% of the predicted normal value ($ppFEV_1$). Patients were randomised to ivacaftor (250 mg every 12 hours) plus lumacaftor (400 mg every 12 hours or 600 mg once daily), or placebo. After 24 weeks of treatment, both doses of lumacaftor/ivacaftor had produced statistically significant improvements in $ppFEV_1$ over placebo (2.6–4%) (see Table). Also, pulmonary exacerbations were less with combination treatment, including episodes that led to hospitalisation or the need for intravenous antibiotics.[1]

In a 96-week extension study of the TRAFFIC and TRANSPORT trials (PROGRESS trial), the mean absolute change in $ppFEV_1$ remained above baseline in patients continuing the lumacaftor 400 mg plus ivacaftor 250 mg dose. However, the difference from baseline was no longer statistically significant, presumably because lung function was deteriorating with age.[2] The annualised rate of pulmonary exacerbations in these patients remained lower than the placebo rate in the TRAFFIC and TRANSPORT trials (0.65 vs 1.14).

Lumacaftor/ivacaftor has also been assessed in children aged 6–11 years in a placebo-controlled phase III trial (204 patients).[3] After 24 weeks of treatment, those randomised to the combination had statistically significant changes in $ppFEV_1$ over those randomised to placebo (2.4%) (see Table).

Table **Efficacy of lumacaftor/ivacaftor in cystic fibrosis (homozygous F508del mutation)**

Drug regimen (patients)	Improvement in $ppFEV_1$ after 24 weeks of treatment*	Pulmonary exacerbations†
TRAFFIC trial (549 patients aged ≥12 years)[1]		
Lumacaftor 600 mg/day plus ivacaftor 250 mg vs placebo	4%	79 vs 112
Lumacaftor 400 mg every 12 hours plus ivacaftor 250 mg vs placebo	2.6%	73 vs 112
TRANSPORT trial (559 patients aged ≥12 years)[1]		
Lumacaftor 600 mg/day plus ivacaftor 250 mg vs placebo	2.6%	94 vs 139
Lumacaftor 400 mg every 12 hours plus ivacaftor 250 mg vs placebo	3%	79 vs 139
Paediatric trial (204 patients aged 6–11 years)[3]		
Lumacaftor 200 mg every 12 hours plus ivacaftor 250 mg vs placebo	2.4%	Not available

* mean difference versus placebo in absolute change from baseline in percentage of predicted forced expiratory volume in one second ($ppFEV_1$) from baseline
† number of pulmonary exacerbations recorded in 24 weeks

During the TRAFFIC and TRANSPORT studies, more patients in the treatment groups than in the placebo group discontinued because of an adverse event (4.2% vs 1.6%). Reasons for discontinuing included elevated creatine kinase (4 patients), haemoptysis (3), bronchospasm (2), dyspnoea (2), pulmonary exacerbation (2) and rash (2).[1] Adverse events that were more common with treatment than placebo included dyspnoea (14% vs 7.8%), diarrhoea (11% vs 8.4%) and nausea (10.2% vs 7.6%).

A similar safety profile was observed with longer term treatment,[2] and in children aged 6–11 years.[3,4] In an open-label trial of 60 children aged 2–5 years, the combination was generally well tolerated. Adverse events included cough (63%), vomiting (28%), fever (28%), diarrhoea (10%), constipation (12%), and elevated alanine aminotransferase (13%) and aspartate aminotransferase (10%).[5]

Chest tightness and abnormal breathing were more common at the beginning of treatment, particularly in patients with poorer lung function at baseline ($ppFEV_1$ <40%). These patients should be started on a lower dose (one tablet/12 hours for the first two weeks) and need additional monitoring.

Lumacaftor has the potential to cause many drug interactions. It is a strong inducer of cytochrome P450 (CYP) 3A and may decrease serum concentrations (and efficacy) of many drugs that are metabolised by this enzyme (e.g. corticosteroids, azole antifungals, clarithromycin, erythromycin, oral contraceptives). Lumacaftor also inhibits and induces P-glycoprotein, CYP2C8 and CYP2C9, and induces CYP2B6 and CYP2C19. The product information should be checked before prescribing lumacaftor/ivacaftor as co-administration of some drugs is not recommended and others may require dose adjustment.

The recommended lumacaftor/ivacaftor dose is two 200 mg/125 mg tablets every 12 hours for patients older than 12 years and two 100 mg/125 mg tablets every 12 hours for children aged 6–11 years. For those aged 2–5 years, the recommended dose is one 100 mg/125 mg sachet every 12 hours for children weighing less than 14 kg and one 150 mg/188 mg sachet every 12 hours for those weighing 14 kg and over. Granules should be taken in a teaspoon of soft food or liquid and tablets should be swallowed whole. This medicine should be taken with fatty foods.

Maximum serum concentrations of lumacaftor and ivacaftor are reached approximately four hours after administration. The half-life is around 26 hours and most of the dose is excreted in the faeces. Dose reductions are recommended in hepatic impairment and are outlined in the product information.

This fixed-dose combination for cystic fibrosis (homozygous F508del mutation) is associated with a slower rate of decline in pulmonary function in patients aged six years and over. Efficacy data in children aged 2–5 years old are limited. It is not clear how the efficacy of lumacaftor/ivacaftor will compare to the other recently approved combination for this indication – tezacaftor/ivacaftor – which is approved for those 12 years and older. However, prescribers should be aware the lumacaftor/ivacaftor combination is a strong inducer of the CYP3A enzyme so has more drug interactions.

TT manufacturer provided additional useful information

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

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NEW DRUGS

Aust Prescr 2019;42:172–3
https://doi.org/10.18773/austprescr.2019.059
First published 13 September 2019

Plitidepsin

Approved indication: multiple myeloma

Aplidin (Specialised Therapeutics) vials containing 2 mg powder for reconstitution

Plitidepsin is a cytotoxic peptide originally found in the sea squirt *Aplidium albicans*. It interacts with a protein (eEF1A2) which is overexpressed in some cancers. This interaction leads to apoptosis. Synthetically produced plitidepsin has been found to have antiproliferative effects on cancer cells. Phase II trials have investigated its activity in tumours such as lung cancer, melanoma and multiple myeloma.

The drug has to be reconstituted and diluted. It is then infused over three hours. In the blood, 80% of plitidepsin is inside blood cells. The metabolism of plitidepsin includes cytochrome P450 3A4. It should therefore not be administered with inhibitors of this enzyme, such as clarithromycin, itraconazole and grapefruit juice. Plitidepsin should also not be administered with enzyme inducers such as carbamazepine, rifampicin or St John's wort. It is not recommended for patients with impaired liver function. Most of the drug is excreted in bile with a half-life of six days.

One of the phase II trials involved 51 patients with refractory or relapsed multiple myeloma. These patients were given an infusion of plitidepsin every two weeks. If the response was suboptimal, dexamethasone could be added. The median number of treatment cycles each patient received was four. In the 47 patients who were evaluable, six had a response to plitidepsin. Four of the 18 patients who added dexamethasone had a response. Progression-free survival was 2.3 months with plitidepsin alone and 3.8 months if dexamethasone was added.[1]

A subsequent open-label phase III trial in multiple myeloma randomised 171 patients to receive plitidepsin with dexamethasone and 84 to receive dexamethasone alone. These patients had previously been treated with at least three, but no more than six, therapies including bortezomib and lenalidomide or thalidomide. Plitidepsin was given on days 1 and 15 of the treatment cycle and dexamethasone was given on days 1, 8, 15 and 22. Patients in the dexamethasone group could cross over to the combined treatment group if there was disease progression after a minimum of eight weeks therapy.[2]

An analysis by an independent review committee found that progression-free survival was a median of 2.6 months with combined therapy and 1.7 months with dexamethasone alone. This difference was statistically significant, but there was no significant difference in overall survival (11.6 months vs 8.9 months).[2]

In patients with multiple myeloma that has not responded to several treatments, adverse events are common. Compared to those who were given dexamethasone alone, adverse events that were more frequent in patients taking plitidepsin included nausea, vomiting, diarrhoea, myalgia, peripheral oedema and fatigue. Liver enzymes are often increased and this can be an indication to interrupt treatment. Other indications for reducing treatment include anaemia, neutropenia, thrombocytopenia and increased creatine kinase. There is a risk of severe hypersensitivity reactions. To prevent infusion reactions, patients must be given intravenous ondansetron, ranitidine and an antihistamine.
The cardiac effects of plitidepsin are uncertain. Atrial fibrillation was more frequent than with dexamethasone alone and unstable atrial fibrillation is a reason for not using plitidepsin.

Patients with multiple myeloma that is refractory or has relapsed after multiple regimens do not have a good prognosis. While giving them plitidepsin and dexamethasone is more likely to induce a response than dexamethasone alone,[2] the consequences are less clear. The increase in progression-free survival is only about one month. Some of the uncertainty arises because in the phase III trial 44% (37/84) of the patients taking dexamethasone crossed over to the combined treatment group. A different analysis of the data allowing for the effect of these crossovers calculated a significant difference in overall survival. The median was then 11.6 months with plitidepsin and dexamethasone compared with 6.4 months for dexamethasone alone. This advantage has to be weighed against the greater toxicity of combination therapy. The trial also excluded sicker patients (Eastern Co-operative Oncology Group status >2).[3]

While the Therapeutic Goods Administration has decided that the balance favours plitidepsin, the European Medicines Agency refused to authorise the marketing of plitidepsin.

T manufacturer provided the product information

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NEW DRUGS

Aust Prescr 2019;42:174–5
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First published 13 September 2019

Tezacaftor/ivacaftor

Approved indication: cystic fibrosis

Symdeko (Vertex)
composite pack of film-coated tablets containing tezacaftor 100 mg/ivacaftor 150 mg and ivacaftor 150 mg

Cystic fibrosis is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. These mutations affect the functioning of the CFTR protein which is a chloride channel that helps regulate the transport of water and chloride. Affected individuals have impaired chloride transport leading to thickened mucus which interferes with normal lung function.

Tezacaftor/ivacaftor is a new combination product for cystic fibrosis. It is approved for patients who are 12 years and over and is specifically indicated for those who are homozygous for the F508del mutation. This mutation accounts for about 45% of affected patients. It is a severe form of the disease as they have little or no CFTR protein on their cells. Tezacaftor/ivacaftor is also indicated for people who are heterozygous for the F508del mutation and have another CFTR mutation that is responsive to this treatment. These patients have less severe disease as they have residual CFTR function.

Ivacaftor has already been approved in Australia for cystic fibrosis – and is available as monotherapy and in combination with lumacaftor. Tezacaftor, the other drug in this combination, is a newly approved drug for this indication.

This combination drug works by improving CFTR activity in the lungs. Tezacaftor, like lumacaftor, helps with cellular processing of the CFTR protein so more is present on the cell surface, and ivacaftor improves the function of CFTR which increases chloride transport.

The fixed-dose combination tablet should be taken in the morning and the ivacaftor tablet should be taken in the evening (12 hours apart), both with fat-rich foods. Maximum concentrations of both drugs are reached 4–6 hours after administration and most of the dose is excreted in the faeces. Dose adjustment is required in moderate–severe hepatic impairment.

The efficacy of tezacaftor/ivacaftor has been assessed in two placebo-controlled phase III trials – EVOLVE[1] and EXPAND.[2] EVOLVE was a parallel group study that enrolled patients who were homozygous for the F508del mutation. EXPAND was a crossover study that enrolled patients who were heterozygous for the F508del mutation and had another mutation associated with residual CFTR function. The primary end point in the trials was absolute change from baseline in the percentage of the predicted forced expiratory volume in one second ($ppFEV_1$). This was measured after 24 weeks in the EVOLVE trial and at four and eight weeks in the EXPAND trial.

Patients had a mean $ppFEV_1$ of 59–62% at baseline. Treatment with tezacaftor/ivacaftor significantly improved $ppFEV_1$ compared to placebo in patients with homozygous and heterozygous genotypes (absolute increase of 4% and 6.8%). It was also better than ivacaftor monotherapy in those with a heterozygous genotype (see Table).[1,2] Patients with the homozygous genotype had significantly fewer pulmonary exacerbations with tezacaftor/ivacaftor than with placebo (estimated annualised rate 0.64 vs 0.99).[1]

In a safety cohort, discontinuations because of an adverse event were similar between the study drugs and the placebo (1.6% vs 2%). Adverse events that were higher with tezacaftor/ivacaftor than with placebo included headache (13.7% vs 11.3%), nasopharyngitis (11.5% vs 9.7%), nausea (7.7% vs 6.7%), sinus congestion (3.4% vs 2.2%) and dizziness (3% vs 2%).

Tezacaftor and ivacaftor are mainly metabolised by cytochrome P450 (CYP) 3A4. Drugs that strongly

Table **Efficacy of tezacaftor/ivacaftor in cystic fibrosis**[1,2]

Drug regimen	Improvement in $ppFEV_1$*
EVOLVE trial (504 patients with homozygous F508del mutation)	
Tezacaftor/ivacaftor vs placebo	4% at 24 weeks
EXPAND trial (244 patients with heterozygous F508del mutation)	
Tezacaftor/ivacaftor vs placebo	6.8% (average of measurements at weeks 4 and 8)
Tezacaftor/ivacaftor vs ivacaftor	2.1% (average of measurements at weeks 4 and 8)
Ivacaftor vs placebo	4.7% (average of measurements at weeks 4 and 8)

* absolute change from baseline in percentage of predicted forced expiratory volume in one second ($ppFEV_1$) from baseline

induce this enzyme (e.g. rifampicin, carbamazepine, phenytoin and St John's wort) may reduce the efficacy of this product and their concomitant use is not recommended. Conversely, moderate and strong CYP3A4 inhibitors (e.g. fluconazole, erythromycin, ketoconazole, clarithromycin) increase concentrations of tezacaftor and ivacaftor, so daily dosing of morning and evening tablets may need to be reduced. Grapefruit and Seville oranges should also be avoided. As ivacaftor may inhibit CYP2C9, co-administered warfarin concentrations could be affected. Similarly, tezacaftor/ivacaftor may affect concomitant glimepiride and glipizide concentrations so caution is urged.

Tezacaftor/ivacaftor improves lung function in patients with cystic fibrosis (aged 12 years or over) who are homozygous for the F508del mutation, and in those who are heterozygous for F508del and have another responsive CFTR mutation. Tezacaftor/ivacaftor seems to be more effective than ivacaftor monotherapy in the heterozygous population. It is not clear how tezacaftor/ivacaftor will compare to lumacaftor/ivacaftor, a similar combination product made by the same company. However, tezacaftor/ivacaftor does appear to have fewer drug interactions.

T T manufacturer provided additional useful information

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A:

ANSWERS TO SELF-TEST QUESTIONS

1 False 2 False

Correction

Blood pressure: at what level is treatment worthwhile? [Correction]

Aust Prescr 2019;42:175
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The article on blood pressure treatment (Aust Prescr 2019;42:127-30) has been corrected. View corrected article.

A conflict-of-interest declaration, received after the original article was published, was received for Vlado Perkovic. It reads:

Vlado Perkovic has served on steering committees, advisory boards, or given scientific presentations supported by Abbvie, Astellas, Astra Zeneca, Bayer, Baxter, MBS, Boehringer Ingelheim, Dimerix, Durect, Eli Lilly, Gilead, GSK, Janssen, Merck, Metavant, Mitsubishi Tanabe, Mundipharma, Novartis, Novo Nordisk, Pfizer, Pharmalink, Relypsa, Retrophin, Sanofi, Servier, Vifor and Tricida.

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