ISSN 1391-0736

# The Sri Lanka Prescriber

September-December 2020; Volume 28, No. 3&4

CONTENTS



***The Sri Lanka Prescriber*** *is sponsored by the State Pharmaceuticals Corporation of Sri Lanka as a service to the medical profession.*

# The Sri Lanka Prescriber





Copies of the *Sri Lanka Prescriber* and inquiries from Ms Suranganie Perera, Deputy General Manager, Marketing, and Ms Anusha Gunatilleke, Manager Promotions and Publicity (Telephone 2338102), State Pharmaceuticals Corporation, P. O. Box 1757, 75, Sir Baron Jayathilake Mawatha, Colombo 1.

Price per copy Rs 50.00 (students Rs 25.00). Personal callers may also obtain copies from the Departments of Pharmacology at the Medical Faculties in Colombo, Galle and Sri Jayewardenepura.

**Published by**
Department of Pharmacology
Faculty of Medicine
271, Kynsey Road, Colombo 8, Sri Lanka.
Telephone: + 94 11 2695300 Ext 315
E-mail: phrm_cmb@hotmail.com
*and*
State Pharmaceuticals Corporation
75, Sir Baron Jayathilake Mawatha, Colombo 1.
Telephones + 94 11 2320356-9
Fax: + 94 11 447118
E-mail: prmanager@spc.lk Web site: www.spc.lk

**Printed by**
Ananda Press
82/5, Sir Ratnajothi Saravanamuttu Mawatha,
Colombo 13.
Telephone: + 94 11 2774793
E-mail: anandapress@ymail.com


**Cover picture**

## William Ernest Henley (1849-1903)

An ailing, half-starved journalist in his early twenties was making his slow and pitiful way on crutches to the Old Edinburgh Infirmary. The year was 1873, and the man was William Ernest Henley, the 'Laureate of the Hospital'. Even as a schoolboy in his native Gloucester, where his father kept a bookshop, Henley had to struggle with the disease that all his life was to hold him in its grip – tuberculous arthritis of his feet. Though it did not cause his own death – he died through an accident when leaving a moving railway carriage – tuberculosis probably carried off his little daughter Margaret, the 'Golden Wonder Child', who inspired Wendy in Sir James Barrie's *Peter Pan*. As a youngster Henley lost one leg through his disease, and in early manhood, though he had submitted to every form of treatment that medical knowledge and quackery alike could devise, he was threatened with the amputation of the other foot. This he refused, and, against the advice of his own doctor, persuaded Joseph Lister to have him admitted to the wards of the Edinburgh Infirmary. Two years later, after drastic surgical treatment which spared him amputation, Henley left the Infirmary.

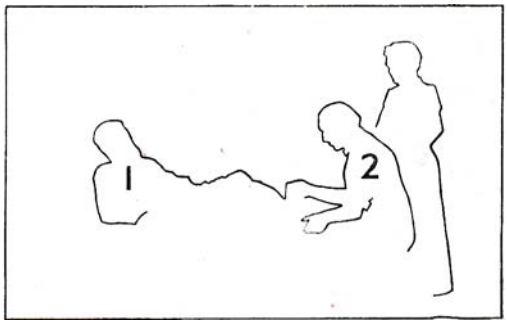
His impressions of those two years he has handed down to us in a series of poems entitled *In Hospital*, published in 1888. In them, he paints with a quick and assured touch, with insight, imagination, and often humour, the conditions, routine, patients, events, and personalities – particularly Lister – of hospital life; more, with simple delicacy he seizes the very atmosphere and elusive emotional fabric of the wards. Only in rare moments is there bitterness; mostly the robust lines testify to the mental vigour and the courage which have made adjustment to ill-health through the conscious acceptance of the facts as he found them. His determination to write was never impaired by the depression of an exhausting disease. Nevertheless, it was with a wild joy that he could write on his discharge from hospital:

'Carry me out
Into the wind and sunshine
Into the beautiful world . . .

These are the streets:
Each is an avenue leading
Whither I will

Free . . .
Dizzy, hysterical, faint,
I sit, and the carriage rolls on
Into the wonderful world.'

*Key to Illustration




1. William Ernest Henley 2. Joseph Lister

# Aspirin in primary prevention; whom to prescribe?

## Introduction

Aspirin is one of the most widely used drugs in medicine. Since its invention, aspirin was widely used for anti-inflammatory effects during the first half of the 20th century, but its use declined following the development of paracetamol and ibuprofen which have less adverse effects. However, later with the discovery of antithrombotic (antiplatelet) effects of low dose aspirin, it became clear that aspirin was highly effective in the secondary prevention of cardiovascular disease (CVD) and its use increased significantly, and this benefit is undoubted. Subsequently large scale primary prevention trials provided evidence of small-to-modest CVD benefits with aspirin in high risk patients albeit with mild increased risk of bleeding. These findings led to the recommendation of aspirin for primary prevention. Further to that, observational studies showed a lower incidence of colorectal cancer with long term aspirin use. With such evidence aspirin use for primary prevention of CVD was added to the guidelines in the year 2000 [1]. Later, with growing evidence of significantly increased risk of bleeding, guidelines were changed to use aspirin in primary prevention only for patients with high CVD risk. According to the latest evidence, the benefits of aspirin in primary prevention is not consistent with an unfavorable benefit risk assessment and the AHA/ACC guideline on primary prevention of CVD 2019 recommends against using it [2]. The present article aims to summarise the latest evidence and the current recommendations for the use of aspirin in primary prevention.

### Evidence

Aspirin was recommended for primary prevention following 2 large scale landmark studies; Physicians' Health Study in 1989 and Women's Health Study in 2005. Physicians' Health Study assessed the effect of aspirin in primary prevention of CVD in 22,071 participants, for an average follow-up period of 60.2 months and found that it reduces the risk of myocardial infarction by 44%, but the evidence concerning stroke and total cardiovascular deaths remained inconclusive. The study observed a non-significant rise in intracerebral hemorrhage (ICH) and gastric ulcer.

Women's Health Study, evaluated aspirin in primary prevention of CVD among 39,876 apparently healthy female health professionals aged 45 years and older for an average follow-up period of 10.1 years and concluded that it lowered the risk of stroke by 17% without affecting the risk of myocardial infarction or death from cardiovascular causes, but with a 1.4 times increased risk of gastrointestinal bleeding requiring blood transfusion.

The evidence on aspirin primary prevention was not consistent and several studies done later-on identified mixed findings. Therefore, the effect of aspirin in primary prevention of CVD was studied in three large randomized trials in different populations and were published in 2018 .

A Study of Cardiovascular Events in Diabetes trial (ASCEND trial), studied aspirin primary prevention in 15,480 patients with diabetes with no evidence of CVD, followed up for a mean of 7.4 years and found that aspirin reduced serious vascular events by 12%, but with 29% increase in major bleeding episodes. This study did not detect any difference in the incidence of GI adverse effects, any cancer or in all-cause mortality.

Aspirin to Reduce Risk of Initial Vascular Events trial (ARRIVE trial), followed up 12,546 high-risk participants without diabetes for a mean of 5 years and found no difference in major vascular events (4.3% vs 4.5%) or CVD deaths (2.55 vs. 2.57%) but found that the risk of bleeding was doubled. The overall incidence of serious adverse events was similar in both treatment groups.

Aspirin in Reducing Events in the Elderly trial (ASPREE) followed up 19,114 ≥70 year old individuals without previous CVD from Australia and USA for a mean of 4.7 years and found that there was no benefit towards reducing death, dementia, or persistent physical disability. In fact this study showed an increased risk of higher all-cause mortality (HR, 1.14), major bleeding and high cancer mortality.

Since the evidence is conflicting several recent meta-analyses were done and they found that aspirin primary prevention is associated with reduced risk of myocardial infarction and colorectal cancer (with long term use more than 10 years) but at a high risk of major extracranial bleeding and with no effect on stroke or total mortality [3] (Table 1).

**Table 1. Meta-analysis of aspirin primary prevention trials**

| Outcome | Number of participants (number of studies) | Relative effect (95% Confidence Interval) | Conclusion |
|---|---|---|---|
| Total mortality | 161,660 (13 RCTs) | Relative Risk 0.97 (0.93 to 1.02) | No effect |
| Myocardial infarction (non-fatal events) | 142,566 (12 RCTs) | Relative Risk 0.83 (0.76 to 0.90) | Reduced risk |
| Stroke (non-fatal events) | 127,433 (12 RCTs) | Relative Risk 0.95 (0.85 to 1.06) | No effect |
| Major extra cranial bleed | 155,911 (11 RCTs) | Relative Risk 1.46 (1.32 to 1.62) | Increased risk |
| Colorectal cancer (incidence) | 14,033 (4 RCTs) | Hazard Ratio 0.76 (0.60 to 0.96) | Reduced risk (effects after 10 yrs) |

RCT – Randomized Controlled Trial

*Adapted from: Vandvik PO, Lincoff AM, Gore JM, et al. Primary and Secondary Prevention of Cardiovascular Disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141: e637S.

## Discussion

Benefits of aspirin in primary prevention of CVD is less clear even though it's benefit in secondary prevention is well established. Aspirin prevents myocardial infarction, and ischemic stroke, but increases hemorrhagic strokes and major bleeding when used in the primary prevention of cardiovascular disease.

Aspirin use in primary prevention is different to secondary prevention and needs careful consideration due to several reasons. In primary prevention, aspirin is given to apparently healthy people, and it will be used for prolonged periods. Further, the validity of recommendations of previous large-scale primary prevention trials to current preventive practice remain uncertain as those trials were done at a time when CVD risk factors were less well controlled compared to now; i.e. smoking was more common, blood pressure control was suboptimal, and aggressive lipid lowering was rare during that period. Furthermore, definition and diagnosis of acute coronary syndromes have become more objective with invention of cardiac biomarkers in current era and this may also have had an effect on the differences observed in the primary endpoints of older and newer aspirin primary prevention trials. Therefore, in primary prevention, where the risk is determined largely by age and the presence or absence of risk factors, the benefit of aspirin according to latest evidence is exceptionally small compared to its risks. Hence, the recommendation that treating physicians should consider probable benefits and harms of aspirin in each individual patient before making a decision [4] (Box 1). We need to think how we can explain the different outcomes observed of aspirin primary prevention trials done before twenties and now.

**Box 1. Factors to be considered when prescribing aspirin for primary prevention**

- Assessment of the individual's risk for each outcome
  - Degree of cardiovascular risk
  - Risk of colorectal malignancy
  - Risk of bleeding
  - Risk of total mortality
- Assessing the value the patient places on immediate increase in risk of bleeding versus delayed potential benefit on cardiovascular disease and cancer
- Assessment of the relative value, the individual places on preventing specific outcomes
- Patient's attitude to inconvenience of long-term daily therapy

Experts argue against the conclusions of the recent aspirin primary prevention trails. One argument against the ASPREE trial is that weight-adjusted dosing of aspirin might be superior to the one-dose-fits-all strategy [5]. However, the ASPREE trial group had stratified participants according to body-mass index (BMI), and had not found any association of BMI categories and the lack of effect of aspirin on disability-free survival. Currently this hypothesis is being validated in a systematic review and we should get an answer once it is published.

Another view against the conclusions of the ASPREE trial is that, deaths from cardiovascular causes and deaths from non-cardiovascular causes were competing risks in this

trial and the hazard ratio for death from cardiovascular causes was non-significantly less with aspirin (0.82; 95% CI, 0.62 to 1.08). However, this means that deaths from non-cardiovascular causes would have been higher among participants who received aspirin than among those who received placebo. However, this argument is not valid as the ultimate goal of primary prevention is to increase disability-free survival or postponement of death from any cause, not just from CVDs.

Another argument against the ASPREE trial results is that the benefits of use of low-dose aspirin in healthy elderly was observed only for less than five years which may not be adequate as most previous studies which described benefits of aspirin primary prevention detected benefits with long term follow-up after 10 years or more.

## Conclusion

Based on the ASPREE, ARRIVE, and ASCEND trials, the ACC/AHA guidelines concluded that the risk of adverse effects of aspirin outweighed its potential benefits, and therefore recommends that most adults without a history of cardiovascular disease should not be prescribed low-dose aspirin daily for primary prevention of CVD on a routine basis; especially the adults over 70 years and those with an increased risk of bleeding. It is recommended that the decision to use aspirin for primary prevention of cardiovascular diseases, should be made based on shared decision making, taking into consideration the probable benefit and harm of aspirin in relation to each individual.

### The way forward

Compared to low dose aspirin in primary prevention trials, statins have been shown to reduce the risk of major vascular events by 25% with an enviable safety profile, minus the bleeding complications of aspirin. Thus, beyond a healthy diet, exercise, and cessation of smoking, the best strategy for primary prevention of cardiovascular diseases would simply be to prescribe a statin, instead of aspirin. However, there are mixed opinion on this also.

### References


1. U.S. Preventive Services Task Force. Aspirin for the primary prevention of cardiovascular events: recommendation and rationale. *Ann Intern Med* 2002: **136**(2); 157-60.
2. Raber I, McCarthy CP, Vaduganathan M, et al. The rise and fall of aspirin in the primary prevention of cardiovascular disease. *Lancet* 2019: **393**(10186); 2155-67.
3. Mahmoud AN, Mohamed MG, Elgendy AY, Elgendy IY, Bavry AA. Efficacy and safety of aspirin for primary prevention of cardiovascular events: a meta-analysis and trial sequential analysis of randomized controlled trials. *Eur Heart J* 2019: **40**(7); 607-17.
4. Capodanno D and Angiolillo DJ. Aspirin for Primary Cardiovascular Risk Prevention and Beyond in Diabetes Mellitus. *Circulation* 2016: **134**(20); 1579-94.
5. Rothwell PM, Cook NR, Gaziano JM, et al. Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials. *Lancet* 2018: **392**(10145); 387-99.



**Dr. KCD Mettananda,** MBBS, MD, FRCP, PhD, *Senior Lecturer and Consultant Physician, Department of Pharmacology, Faculty of Medicine, University of Kelaniya, Sri Lanka.*
E-mail: chamilametta@hotmail.com


## Self-assessment questions on aspirin

**1. Which of the following is true /false regarding aspirin primary prevention in a 50-year-old otherwise healthy man? Aspirin,**

a. Reduce risk of stroke
b. Reduce risk of myocardial infarctions
c. Reduce risk of colorectal cancer
d. Reduce risk of extra-cranial bleeding
e. Reduce risk of total mortality

**2. Regarding aspirin,**

a. It is recommended for cardiovascular protection in people without diabetes
b. It is recommended for all patients with type-2 diabetes
c. It is recommended for cardiovascular protection in the elderly
d. Colorectal cancer prevention requires long term use
e. It increases the risk of major extracranial bleeding, with no impact on incidence of ischaemic stroke or total mortality

*(Answers on page 13)*

# 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.



**Keywords:** chronic renal insufficiency, creatinine, drug dosage calculations, glomerular filtration rate

*(Aust Prescr 2019; **42**: 163-7)*


## 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.

*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)

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.

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

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

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

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

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

Adjusted ideal body weight (kg):
= IBW + 0.4 × (weight - IBW)

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

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).

***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 quanti-fying 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.

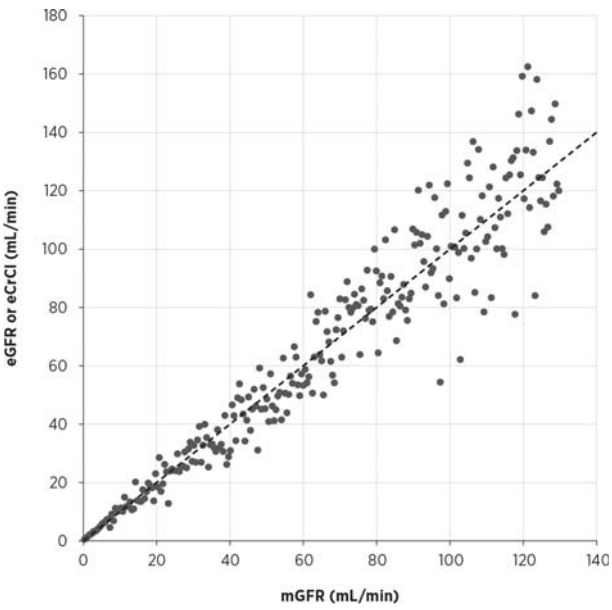
In obese patients (BMI above 30 kg/$m^2$), automated eGFR can underestimate GFR, and eCrCl based on actual body weight will overestimate GFR.[10,14,15] In these patients, eCrCl based on adjusted ideal body weight (Box 1) or de-indexed eGFR are more reliable estimates of GFR[14,15] (see Box 2 for an example). 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]

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]

*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

## *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

**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 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.

## *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 | Overestimates GFR, use de-indexed |

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

## 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.

*Acknowledgement: Darren Roberts acknowledges support of the Clinician 'Buy-Out' Program, St Vincent's Centre for Applied Medical Research.*

### References

1. Australian Bureau of Statistics. National health survey: first results, 2017-18. ABS Catalogue No. 4364.0.55.001. https://www.abs.gov.au/AUSSTATS/abs@.nsf/ DetailsPage/4364.0.55.0012017-18 [cited 2019 Sep 1]
2. Australian Bureau of Statistics. Australian health survey: biomedical results for chronic diseases, 2011-12. ABS Catalogue No. 4364.0.55.005. https://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/4364.0.55.0052011-12 [cited 2019 Sep 1]
3. Ko S, Venkatesan S, Nand K, Levidiotis V, Nelson C, Janus E. International statistical classification of diseases and related health problems coding underestimates the incidence and prevalence of acute kidney injury and chronic kidney disease in general medical patients. Intern Med J 2018;48:310-5. https://doi.org/10.1111/imj.13729
4. Roberts DM, Sevastos J, Carland JE, Stocker SL, Lea Henry TN. Clinical pharmacokinetics in kidney disease: application to rational design of dosing regimens. Clin J Am Soc Nephrol 2018;13:1254-63. https://doi.org/10.2215/CJN.05150418
5. Lea-Henry TN, Carland JE, Stocker SL, Sevastos J, Roberts DM. Clinical pharmacokinetics in kidney disease: fundamental principles. Clin J Am Soc Nephrol 2018; 13:1085-95. https://doi.org/10.2215/CJN.00340118
6. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41. https://doi.org/10.1159/000180580
7. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al.; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604-12. https://doi.org/10.7326/0003-4819-150-9-200905050-00006
8. Ludlow M, Jesudason S, Johnson DW. Automatic reporting of estimated glomerular filtration rate in Australia turns 13: re-examining the impact. Med J Aust 2018;209:244-5. https://doi.org/10.5694/mja18.00544
9. Johnson DW, Jones GR, Mathew TH, Ludlow MJ, Doogue MP, Jose MD, et al.; Australasian Creatinine Consensus Working Group. Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: new developments and revised recommendations. Med J Aust 2012;197:224-5. https://doi.org/10.5694/mja11.11329
10. Michels WM, Grootendorst DC, Verduijn M, Elliott EG, Dekker FW, Krediet RT. Performance of the Cockcroft-Gault, MDRD, and new CKD-EPI formulas in relation to GFR, age, and body size. Clin J Am Soc Nephrol 2010;5:1003-9. https://doi.org/10.2215/CJN.06870909
11. Delanaye P, Guerber F, Scheen A, Ellam T, Bouquegneau A, Guergour D, et al. Discrepancies between the Cockcroft-Gault and Chronic Kidney Disease Epidemiology (CKD-EPI) equations: implications for refining drug dosage adjustment strategies. Clin Pharmacokinet 2017;56:193-205. https://doi.org/10.1007/s40262-016-0434-z
12. Dowling TC, Wang ES, Ferrucci L, Sorkin JD. Glomerular filtration rate equations overestimate creatinine clearance in older individuals enrolled in the Baltimore Longitudinal Study on Aging: impact on renal drug dosing. Pharmacotherapy 2013;33:912-21. https://doi.org/10.1002/ phar.1282
13. Björk J, Grubb A, Gudnason V, Indridason OS, Levey AS, Palsson R, et al. Comparison of glomerular filtration rate estimating equations derived from creatinine and cystatin C: validation in the Age, Gene/Environment Susceptibility-Reykjavik elderly cohort. Nephrol Dial Transplant 2018;33:1380-8. https://doi.org/10.1093/ndt/gfx272
14. Chew-Harris JS, Chin PK, Florkowski CM, George P, Endre Z. Removal of body surface area normalisation improves raw-measured glomerular filtration rate estimation by the Chronic Kidney Disease Epidemiology Collaboration equation and drug dosing in the obese. Intern Med J 2015;45:766-73. https://doi.org/10.1111/imj.12791
15. Bouquegneau A, Vidal-Petiot E, Moranne O, Mariat C, Boffa JJ, Vrtovsnik F, et al. Creatinine-based equations for the adjustment of drug dosage in an obese population. Br J Clin Pharmacol 2016;81:349-61. https://doi.org/10.1111/bcp.12817
16. Matzke GR, Aronoff GR, Atkinson AJ Jr, Bennett WM, Decker BS, Eckardt KU, et al. Drug dosing consideration in patients with acute and chronic kidney disease – a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2011;80:1122-37. https://doi.org/10.1038/ ki.2011.322

**Maurizio Stefani,** *Advanced trainee*[1,2], **Richard F Singer,** *Staff specialist*[3], **Darren M Roberts,** *Staff specialist*[1,3,4], *Conjoint associate professor*[2]

[1]*Department of Clinical Pharmacology and Toxicology, St Vincent's Hospital, Sydney*

[2]*St Vincent's Clinical School, University of New South Wales, Sydney*

[3]*Department of Renal Medicine, Canberra Hospital and Community Services, Canberra*

[4]*Department of Renal Medicine and Transplantation, St Vincent's Hospital, Sydney*

This article is reproduced from the *Australian Prescriber* 2019;**42**:163-7 by prior arrangement, courtesy of *Australian Prescriber*.

# Lithium therapy and its interactions


## Summary

Lithium is one of the most effective mood stabilisers for people with a mood disorder. However, many of these patients are also taking other medicines that could potentially interact with lithium.

To minimise the risk of relapse, it is usually necessary to maintain the lithium serum concentration between 0.6 mmol/L and 0.8 mmol/L.

Lithium clearance is easily influenced by drugs that alter renal function such as ACE inhibitors, angiotensin receptor antagonists, diuretics, and non-steroidal anti-inflammatory drugs.

It is therefore prudent for prescribers to monitor and adjust the lithium dose to avoid adverse effects or loss of efficacy



**Keywords:** bipolar disorder, lithium, mood disorders

*(Aust Prescr 2020; **43**: 91-3)*


## Introduction

Driven by new research reinforcing the unique benefits of lithium, there has been a worldwide resurgence in the prescription of lithium. In clinical practice it is used predominantly to stabilise mood.[1] It remains one of the most effective options for bipolar disorder,[2] along with the newer atypical antipsychotics.[3] Lithium also serves as an effective adjunctive option for recurrent or resistant major depressive disorder and has anti-suicidal properties which are invaluable in the management of mood disorders.

Lithium is simple to administer and is usually well tolerated. Routine management of patients receiving lithium monotherapy is relatively straightforward.[4] However, complications can arise when other drugs are added that could potentially interact with lithium.

Regular monitoring of lithium plasma concentrations and other safety parameters is essential. Results should be communicated to the patient and everyone involved in their care. Aids are available to assist prescribers with lithium management, including an Australian tool called the 'Lithiumeter'.[4]

### Indications for lithium

Patients with classic, episodic and remitting bipolar disorder with a family history and no psychiatric comorbidity are most likely to respond to lithium. Typically, lithium is effective in about a third of patients – with response rates up to two-thirds in those whose relatives have achieved good responses.[5] It is likely that people who commence lithium early in the course of their illness may have greater likelihood of response. In major depressive disorder, lithium is used to augment antidepressant drugs.

### Lithium monitoring

Lithium has a very narrow therapeutic window for maintenance therapy. Too little lithium risks undertreatment of the mood disorder and increases the risk of relapse. Too much lithium increases the risk of both acute and chronic toxicity. Lithium concentrations should always be measured 12 hours after the last dose.

For the maintenance phase of treatment, recent guidelines recommend that patients maintain a serum concentration of 0.6-0.8 mmol/L to maximise therapeutic benefit.[6] For acute treatment in mania, serum concentrations should be increased to 0.6-1.0 mmol/L as tolerated. In depression, concentrations can be in the range of 0.4-0.8 mmol/L. In practice, target concentrations and monitoring practices are often inconsistent. Not all pathology laboratories use the same reference ranges, therefore noting whether the lithium concentration is consistent with the patient's presentation and the guidelines is essential.

As a part of optimising lithium dosing, clinicians may notice that a specific concentration achieves the most therapeutic benefit during euthymic periods and during manic and depressive episodes. Taking note of this is essential and helps to ensure stability of these patient-specific concentrations over time, particularly during each illness phase.

Maintenance of the therapeutic concentration (and adherence) is the strongest predictor of long-term stability. However, in some patients, stabilising their mood is not always possible with lithium alone. A trial with other mood stabilisers, such as adjunctive sodium valproate or an atypical antipsychotic, is often necessary.

A recommended monitoring schedule for lithium in a patient not taking other drugs is outlined in the Box.[4] Drug interactions are more likely to affect patients as they get

older because of declining renal function and the accumulation of medical comorbidities. Close monitoring and dose adjustments are therefore often needed as patients get older.

In patients taking concomitant drugs, extra care should be taken because of the risk of drug interactions. Lithium concentrations should be closely monitored around the time of medication changes – at least just before and when the drugs have reached steady states. Lithium's half-life is about 24 hours, so a steady state is usually achieved after 5-7 days. A complete list of lithium drug interactions can be found at MIMS Online or Drugs.com.

Regular monitoring is required until a therapeutic concentration of lithium is reached and maintained, and any time that the patient presents with symptoms of lithium toxicity.[7] Conditions leading to haemodynamic and volume changes such as dehydration, febrile illness, gastrointestinal loss, drug interactions, perioperative management and surgery can affect lithium serum concentrations and levels should be rechecked in these circumstances.

Prescribers should contact the treating psychiatrist or consult a medicines information pharmacist if they are unsure how to manage a patient. Having up-to-date serum lithium concentrations at hand will assist.

**Adverse effects of lithium**

Regular long-term monitoring of lithium concentrations is essential to avoid both acute and chronic toxicity. Physical examinations and laboratory investigations should be performed at baseline and regular intervals after that (see Box).

Common acute adverse effects include tremor, polydipsia, polyuria, dysgeusia, nausea and diarrhoea (see Table). Prescribers can reassure patients that these adverse effects are usually transient after starting treatment. They are often dependent on the serum concentration of lithium and frequently subside within days or weeks. Nephrogenic diabetes insipidus (polyuria and polydipsia) is a common adverse effect of lithium.

Chronic adverse effects include subjective cognitive effects, thyroid and parathyroid dysfunction, and renal dysfunction (see Table). Some patients may report more mild neurocognitive effects such as 'brain fog', 'emotional greying', 'slowing', 'shakiness', anomia, and 'reduced creativity'. The higher the lithium concentration, the greater the risk of toxic presentations. In the long term, or with higher blood concentrations or repeated acute fluctuations, lithium leads to end-stage renal failure in 1% of patients (over 15 years treatment).[8] However, it should be noted that most patients do not experience renal adverse effects.

**Common drug-drug interactions with lithium**

The most common and noteworthy drug-drug interactions with lithium are pharmacokinetic in nature. The lithium ion is extensively absorbed in the gastrointestinal tract. The main determinant of serum concentrations is renal excretion, therefore the main drug interactions occur when co-administered drugs alter renal function, specifically modifying glomerular filtration and tubular reabsorption. The most commonly prescribed drugs that have the potential to interact with lithium are ACE inhibitors, angiotensin II receptor antagonists (sartans), diuretics, and non-steroidal anti-inflammatory drugs (NSAIDs). Combinations of these are frequently used, so prescribers should be aware of their additive effects for a patient taking lithium.

## *Box* Monitoring schedule for lithium therapy

Baseline assessments and follow-up of patients should be performed:

- during the early maintenance phase (e.g. baseline, 7 days, 14 days and 28 days) then at 3, 6 and 12 months, then annually

and

- when there are any changes in presentation
- following abnormal findings
- when altering the treatment regimen

Regularly check the following:

- serum lithium concentrations and mood and stability over time
- renal function
  - electrolytes, urea, creatinine
  - estimated glomerular filtration rate
- thyroid and parathyroid function
  - hyroid stimulating hormone
  - calcium
- blood and cardiometabolic tests
  - full blood count, glucose, lipids, liver function tests
  - ECG
  - weight, BMI, umbilical girth
  - diet and eating behaviour
  - exercise and hydration
  - other comorbidities
- adverse effects
- cognition
- global functioning
- treatment adherence

Based on reference 4

*Table* **Major adverse effects of lithium therapy**

| Toxicity | Adverse effect | Action |
|---|---|---|
| Acute | Any acute adverse effect or presentation | Measure lithium concentration |
| | Headache, fatigue | Consider stopping lithium |
| | Thirst, taste | Review medication |
| | Arrythmias | Hospitalisation |
| | Nausea, vomiting, diarrhoea, polyuria | Review hydration and consider haemodialysis |
| | Tremor | Monitoring and review medication |
| Chronic | Cognitive effects, ataxia, agitation, confusion, sluggishness | Monitor changes, optimise lithium concentrations, neurological referral |
| | Thyroid or parathyroid dysfunction | Monitor changes, optimise lithium concentrations, endocrinology referral |
| | Renal dysfunction | Monitor changes, optimise lithium concentrations, nephrology referral |

***ACE inhibitors and angiotensin II receptor antagonists***

Several case reports and hospital admission studies have shown that ACE inhibitors and angiotensin II receptor antagonists can increase lithium serum concentrations and increase the chance of toxicity. Closer monitoring of lithium concentrations is needed when people start either of these drugs and the lithium dose will probably need to be reduced until a stable therapeutic concentration has been achieved. Closer monitoring is also required when these drugs are stopped.

***Diuretics***

When any diuretic is used, lithium concentrations must be carefully monitored. Thiazide and thiazide-like diuretics increase sodium reabsorption which decreases the clearance of lithium and significantly elevates lithium concentrations in serum. This is enough to fall out of the therapeutic range in many cases. As a rule of thumb, many prescribers halve the lithium dose then up- or down-titrate the dose with monitoring. Other prescribers avoid thiazide diuretics altogether.

Amiloride is recommended as a diuretic because it blocks entry of lithium through the epithelial sodium channel in the collecting duct. This reduces lithium accumulation and may improve kidney function in patients on long-term treatment.[9]

Other diuretics such as the osmotic methylxanthine (e.g. theophylline) and loop (e.g. furosemide (frusemide)) and potassium-sparing (e.g. spironolactone) diuretics may also alter lithium concentrations.

***Non-steroidal anti-inflammatory drugs***

Patients on lithium therapy should be advised to avoid NSAIDs. Regular use is more problematic than episodic use. NSAIDs differentially alter lithium concentrations by multiple mechanisms, and one of these is to reduce prostaglandin E2 by inhibiting cyclo-oxygenase. This reduces vasodilation of the afferent arteriole which decreases blood flow to the glomerulus. This decreases glomerular filtration and consequently lithium excretion. If NSAIDs are indicated, they should be used under medical guidance with closer monitoring of lithium concentrations. Lower lithium doses may be required.

***Other drugs***

Acetazolamide for intraocular pressure, glaucoma and epilepsy has been shown to significantly increase lithium clearance.

## Conclusion

Lithium has an important role in the treatment of mood disorders. Prescribers need to be mindful of its potential drug interactions and the impact they can have on patients. Improved knowledge of and confidence with monitoring will contribute to better patient outcomes.

*Gin Malhi has received grant or research support from the National Health and Medical Research Council, Australian Rotary Health, NSW Health, Ramsay Health, American Foundation for Suicide Prevention, Ramsay Research and Teaching Fund, Elsevier, AstraZeneca and Servier; has been a speaker for AstraZeneca, Janssen-Cilag, Lundbeck, Otsuka and Servier; and has been a consultant for AstraZeneca, Janssen Cilag, Lundbeck, Otsuka and Servier.*

*Michael Berk is supported by a National Health and Medical Research Council Senior Principal Research Fellowship (1059660 and APP1156072).*

### References

1. Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. Lancet 2016;387:1561-72. https://doi.org/10.1016/S0140-6736(15)00241-X
2. Vieta E, Berk M, Schulze TG, Carvalho AF, Suppes T, Calabrese JR, et al. Bipolar disorders. Nat Rev Dis Primers 2018;4:18008. https://doi.org/10.1038/nrdp.2018.8
3. Ng F, Mammen OK, Wilting I, Sachs GS, Ferrier IN, Cassidy F, et al. The International Society for Bipolar Disorders (ISBD) consensus guidelines for the safety monitoring of bipolar disorder treatments. Bipolar Disord 2009;11:559-95. https://doi.org/10.1111/j.1399-5618.2009.00737.x
4. Malhi GS, Gershon S, Outhred T. Lithiumeter: Version 2.0. Bipolar Disord 2016;18:631-41. https://doi.org/10.1111/bdi.12455
5. Grof P, Duffy A, Cavazzoni P, Grof E, Garnham J, MacDougall M, et al. Is response to prophylactic lithium a familial trait? J Clin Psychiatry 2002;63:942-7. https://doi.org/10.4088/JCP.v63n1013
6. Malhi, GS, Bassett D, Boyce P, Bryant R, Fitzgerald PB, Fritz K, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Aust N Z J Psychiatry 2015;49:1087-206. http://doi.org/10.1177/0004867415617657
7. Ott M, Stegmayr B, Salander Renberg E, Werneke U. Lithium intoxication: Incidence, clinical course and renal function - a population-based retrospective cohort study. J Psychopharmacol 2016;30:1008-19. https://doi.org/10.1177/0269881116652577
8. Azab AN, Shnaider A, Osher Y, Wang D, Bersudsky Y, Belmaker RH. Lithium nephrotoxicity. Int J Bipolar Disord 2015;3:13. https://doi.org/10.1186/ s40345-015-0028-y
9. Batlle DC, von Riotte AB, Gaviria M, Grupp M. Amelioration of polyuria by amiloride in patients receiving long-term lithium therapy. N Engl J Med 1985;312:408-14. https://doi.org/10.1056/NEJM198502143120705

**Gin S Malhi**[1,2,3], **Erica Bell**[1,2,3], **Tim Outhred**[1,2,3], **Michael Berk**[4,5,6,7]

[1]*Discipline of Psychiatry, Northern Clinical School, University of Sydney*

[2]*Department of Academic Psychiatry, Northern Sydney Local Health District*

[3]*CADE Clinic, Royal North Shore Hospital, Northern Sydney Local Health District*

[4]*IMPACT – the Institute for Mental and Physical Health and Clinical Translation, School of Medicine, Barwon Health, Deakin University, Geelong, Vic.*

[5]*Department of Psychiatry, University of Melbourne, Royal Melbourne Hospital*

[6]*Florey Institute for Neuroscience and Mental Health, University of Melbourne*

[7]*Orygen, The National Centre of Excellence in Youth Mental Health, Melbourne*

This article is reproduced from the *Australian Prescriber* 2020; **43**: 91-3 by prior arrangement, courtesy of *Australian Prescriber.*

## Answers for self-assessment questions on aspirin

**1. FTTFF**

Aspirin in primary prevention reduces risk of myocardial infarction (RR 0.83) and colorectal cancers (OR 0.76).

**2. FFFTT**

Aspirin primary prevention in non-diabetics (ARRIVE trial), in diabetics without evidence of CVD (ASCEND trial) and in elderly (ASPREE trial) have more or equal risks than benefits. Colorectal cancer protection comes with more than 10-year use of aspirin.