Concerns about quetiapine

SUMMARY
Quetiapine is subsidised by the Pharmaceutical Benefits Scheme to treat schizophrenia and bipolar disorder. An extended-release formulation is also approved for use, but not subsidised, for treatment-resistant depression and generalised anxiety disorder.

There is increasing off-label prescribing of quetiapine for indications such as insomnia that have little evidence to support them. This prescribing is often for at-risk patients, such as people with personality or social vulnerabilities and those at risk of metabolic complications or cardiovascular events.

More evidence is required to support prescribing decisions regarding these off-label indications. In the meantime prescribers should be supported with alternatives to prescribing for these conditions, such as psychological therapies that have a better evidence base and safety record.

Introduction
Quetiapine is a short-acting antipsychotic that is available in immediate and extended-release formulations. It is registered by the Therapeutic Goods Administration (TGA) and subsidised by the Pharmaceutical Benefits Scheme (PBS) for the treatment of schizophrenia and bipolar I disorder. The extended-release preparation is also registered for treatment-resistant depression and generalised anxiety disorder, but these indications are not subsidised by the PBS. In 2014, quetiapine was the 10th most expensive drug on the PBS.

There is a high level of evidence to support the approved indications of quetiapine, but it is being increasingly used off label. Often, clinicians are faced with difficult decisions about prescribing antipsychotics for off-label indications when dealing with distressed patients and inadequate resources for psychological treatments and other support. However, there is growing concern from within the medical community and regulatory bodies regarding the potential harm from prescribing antipsychotics off-label, particularly immediate-release quetiapine.

These concerns have been expressed in media reports of large increases in quetiapine prescribing to Australian soldiers returning from recent deployments, with a significant proportion of these personnel not accessing psychological therapies for post-traumatic stress disorder. Internationally, there have been a number of high-profile court cases in the media concerning deaths related to quetiapine involving drug interactions or overdose.

Off-label prescribing
Between 2000 and 2011 in Australia, there was around a twofold increase in the dispensing of antipsychotic drugs, with the greatest increase seen for quetiapine. Quetiapine’s use increased from 0.01 to 2.3 defined daily doses/1000 population/day. These changes cannot be accounted for by patients being switched from older to newer drugs or changes in the diagnosis of long-term mental illness over the last decade. Much of this escalating use may relate to prescribing antipsychotic drugs for indications that are not included in the approved product information. This off-label prescribing is commonplace in psychiatry and is sometimes justifiable as some off-label indications are supported by national consensus guidelines and medicines information services. For instance, in addition to its TGA-approved indications, quetiapine may have a role in anorexia nervosa. Regulatory decisions often lag behind the generation of evidence from clinical trials.

A brief history of quetiapine
Quetiapine was first registered in 1997 and by 2010 it was the fifth biggest selling pharmaceutical in the USA, with annual sales of US$6.8 billion. However, in 2010 the manufacturer of quetiapine agreed to pay US$520 million following government allegations of promoting off-label prescribing. This included promoting the drug to non-psychiatrists for indications such as anger management, dementia and sleeplessness. There were also allegations of remunerating doctors for articles that had been ‘ghostwritten’ by other people to promote off-label uses.

A patent extension was granted for the extended-release formulation in 2010 until 2017 for very similar indications to the immediate-release formulation which came off patent in 2012. There are now around 17 generic forms of quetiapine available in Australia.
Quetiapine

Who is prescribing quetiapine for what?

Concerns about the off-label use of antipsychotics prompted an evaluation by the Drug Utilisation Subcommittee of the Pharmaceutical Benefits Advisory Committee in 2013. Off-label use was most evident for the 25 mg strength of quetiapine. The usual therapeutic dose range for the approved indications is 400–800 mg/day. The 25 mg dose has no uses that are evidence based other than for dose titration in older patients. However, the report found that 23.3% of all patients taking quetiapine were taking the 25 mg strength alone. Most (66%) initial prescriptions for quetiapine were written by GPs, suggesting that the indications were not schizophrenia or bipolar disorder. The Drug Utilisation Subcommittee recommended liaison with TGA and drug companies to reduce the number of 25 mg tablets in a pack and to reduce the number of repeats from five to zero. Improved advice and support for prescribers was also suggested, leading to an NPS MedicineWise publication on the role of low-dose quetiapine.

Limited-evidence prescribing practices

There is little evidence to support many of the off-label uses of quetiapine. Indications with particularly poor evidence include anxiety, insomnia, post-traumatic stress disorder, personality disorders, behavioural and psychological symptoms of dementia, and substance misuse. For example, a recent literature review of studies using quetiapine to treat insomnia in the absence of comorbid conditions found only two placebo-controlled clinical trials of 31 patients in total. The review concluded that the absence of efficacy and safety data precludes the use of quetiapine for insomnia. Prescribing for indications that are not supported by evidence has safety, ethical and financial implications.

Little is known about the reasons for off-label prescribing, but a historical perspective of sedative and hypnotic prescribing trends shows a move from barbiturates in the 1920s to the 1950s and then to benzodiazepines from the 1960s, mainly because of safety concerns. More recently there have been increasing concerns about the harms of benzodiazepines, in particular alprazolam which was rescheduled from Schedule 4 to 8 in 2014. When prescribers are confronted with requests for prescriptions to treat anxiety and insomnia they are aware of the hazards of benzodiazepines, but may not have access to, or skills in, psychological therapies. Quetiapine has sedative effects, so it is possible that quetiapine is being prescribed instead of benzodiazepines due to perceptions regarding safety and efficacy.

Harms related to quetiapine

While there is limited evidence for the efficacy of quetiapine in off-label indications, prescribing it exposes the patient to potential harm.

Overdose

According to Australian data, quetiapine is now one of the most commonly taken drugs in overdose, even after adjusting for the number of prescriptions. These data are supported by a Melbourne study that found ambulance attendances related to quetiapine were substantially higher than for risperidone and olanzapine, even when adjusted for prescription rates. These cases were often associated with substance misuse. A study of coronial data found that a third of deaths associated with quetiapine did not include a psychiatric diagnosis, raising concerns that off-label use or misuse contributed to the deaths.

Metabolic effects and sudden death

The newer antipsychotic drugs increase weight to different degrees and this contributes to the differing relative risk of insulin resistance, dyslipidaemia and hyperglycaemia. Even at low doses (<200 mg) quetiapine has been linked to significant weight gain. A retrospective study of quetiapine for insomnia found that the most commonly prescribed dose was 100 mg, and there was an average weight gain of 2.2 kg over the average treatment period of 11 months. Taking quetiapine contributes to a significant risk of metabolic complications, often in patients with a number of other cardiovascular lifestyle risk factors such as smoking. Patients need to be monitored for these adverse effects.

There is an increased risk of sudden cardiac death with antipsychotics, with an aggregate adjusted risk–incidence ratio for newer antipsychotics of 1.59 for low-dose and 2.86 for high-dose therapy. Within this, quetiapine accounted for a risk–incidence ratio of 1.88 (95% confidence interval 1.30–2.71).

Adverse events in older people

A study of residential aged-care facilities in Australia found that 22% of antipsychotic prescribing was off label. Prescribing antipsychotics in this population has also been associated with increased risk of fatal pneumonia, stroke, hip fracture and cognitive deterioration. Orthostatic hypotension could contribute to the risk of falls. In 2005 the Food and Drug Administration (FDA) issued a black box warning in the USA because of an increase in sudden cardiac deaths related to antipsychotic drugs in older patients. Despite this warning quetiapine use continued to rise.
**Drug dependence**

Within a population of patients being treated for addiction, 17% reported the past misuse of antipsychotics along with other drugs. Quetiapine appears to be the most prevalent, with reports of increasing use of both prescribed and diverted quetiapine by intravenous drug users. Quetiapine appears to be the most documented antipsychotic bought and sold illicitly on the street. There are also numerous case reports of abuse and dependence.

**Future directions**

There is a pressing need to identify the reasons for the escalating use of quetiapine. Conditions such as insomnia and anxiety have been identified as common indications that lack robust evidence. Gathering evidence is imperative to support or refute the ongoing use of quetiapine for these indications. In the meantime, it is important to support doctors with alternatives to prescribing – for instance with resources to improve assessment and management of these conditions and manage them with psychological therapies that have a greater evidence base.

**Conclusion**

Quetiapine has proven safety and efficacy when used for its approved indications. However, there are concerning increases in the rates of off-label prescribing for indications with limited evidence. Adverse outcomes are most likely to occur in already vulnerable populations such as older people, those with mental health problems and substance misusers. Prescribers should therefore be cautious when considering a prescription for quetiapine for an off-label indication.

**Conflict of interest:** none declared

**REFERENCES**


