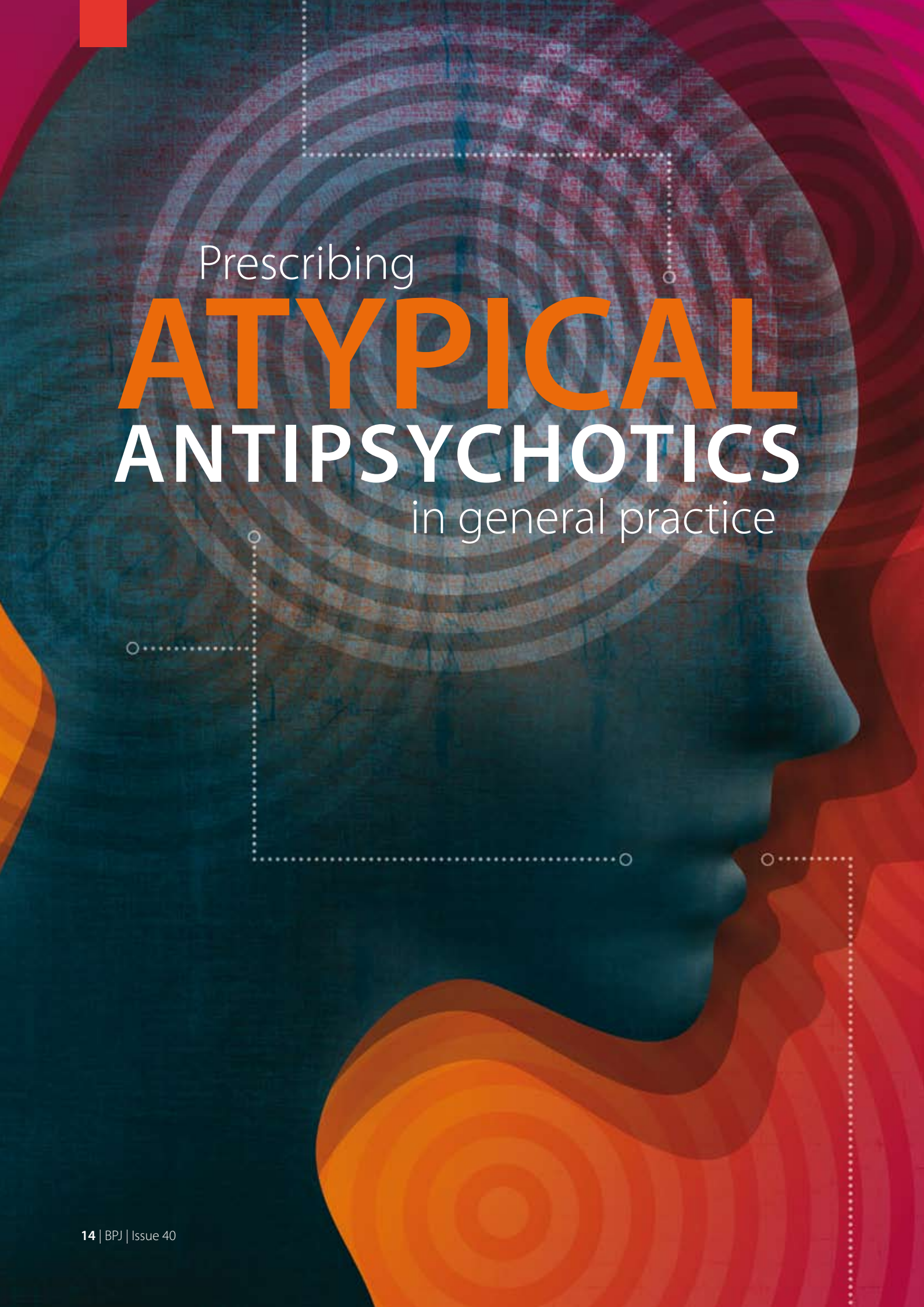


Prescribing ATYPICAL ANTIPSYCHOTICS in general practice

Prescribing of atypical antipsychotics is increasing

Antipsychotic medicines are classified as "typical" or "atypical". Typical antipsychotics, also known as traditional or first-generation antipsychotics, include haloperidol and chlorpromazine. Atypical antipsychotics, also known as second generation antipsychotics, include quetiapine, risperidone and olanzapine. Both types of antipsychotics act in a similar way by blocking receptors in the dopamine pathway, but atypical antipsychotics are less likely to cause the extrapyramidal adverse effects associated with the older typical antipsychotics. However, atypical antipsychotics, along with typical antipsychotics, are associated with serious adverse effects, such as diabetes mellitus, stroke and cardiac death.[1]

Antipsychotics are indicated for the treatment of schizophrenia and related disorders and in some circumstances to treat the behavioural and psychological symptoms associated with dementia (risperidone only). International experience shows that antipsychotics are being increasingly used for off-label conditions (e.g. anxiety, insomnia).[2, 3]

The use of atypical antipsychotics has been increasing in New Zealand (Figure 1) and it is likely that off-label use is a factor in this increase. Special Authority prescribing restrictions have recently been removed from olanzapine (Page 22). Risperidone (excluding depot injection and dissolving tablets) and quetiapine have been available without restriction since 2009 and 2008 respectively.

Key concepts

- Use of atypical antipsychotics, such as quetiapine and olanzapine, is increasing and in many cases, they are being prescribed "off-label" – this is a worrying trend due to their potential to cause harm
- Atypical antipsychotics should only be used for specific indications and used with caution, especially in elderly people and young adults
- Atypical antipsychotics are indicated for the treatment of schizophrenia and related disorders and in some circumstances to treat the behavioural and psychological symptoms associated with dementia (risperidone only)
- Antipsychotics are not a first-line treatment for anxiety and are not recommended for post-traumatic stress disorder or insomnia

Traditionally, General Practitioners have been responsible for writing repeat prescriptions for patients, once an atypical antipsychotic has been initiated by a psychiatrist after confirmation of a diagnosis such as schizophrenia.

If a General Practitioner wishes to initiate treatment, then it is best to only prescribe for the recognised indications and to discuss the treatment plan with a psychiatrist (or other relevant clinician) before prescribing. Be particularly cautious when prescribing these medicines for elderly people, younger people and those at increased cardiovascular risk, especially as a result of obesity, diabetes or high cholesterol.

Adverse effects of atypical antipsychotics

Most adverse effects are common to all antipsychotics, both typical and atypical, but occur to varying degrees for individual medicines (Table 1).

Common, dose related adverse effects include:[4]

- Sedation – especially with clozapine, olanzapine and quetiapine
- Anticholinergic effects such as dry mouth, constipation and blurred vision – especially with clozapine and olanzapine
- Dizziness and postural hypotension – especially with clozapine, risperidone and quetiapine

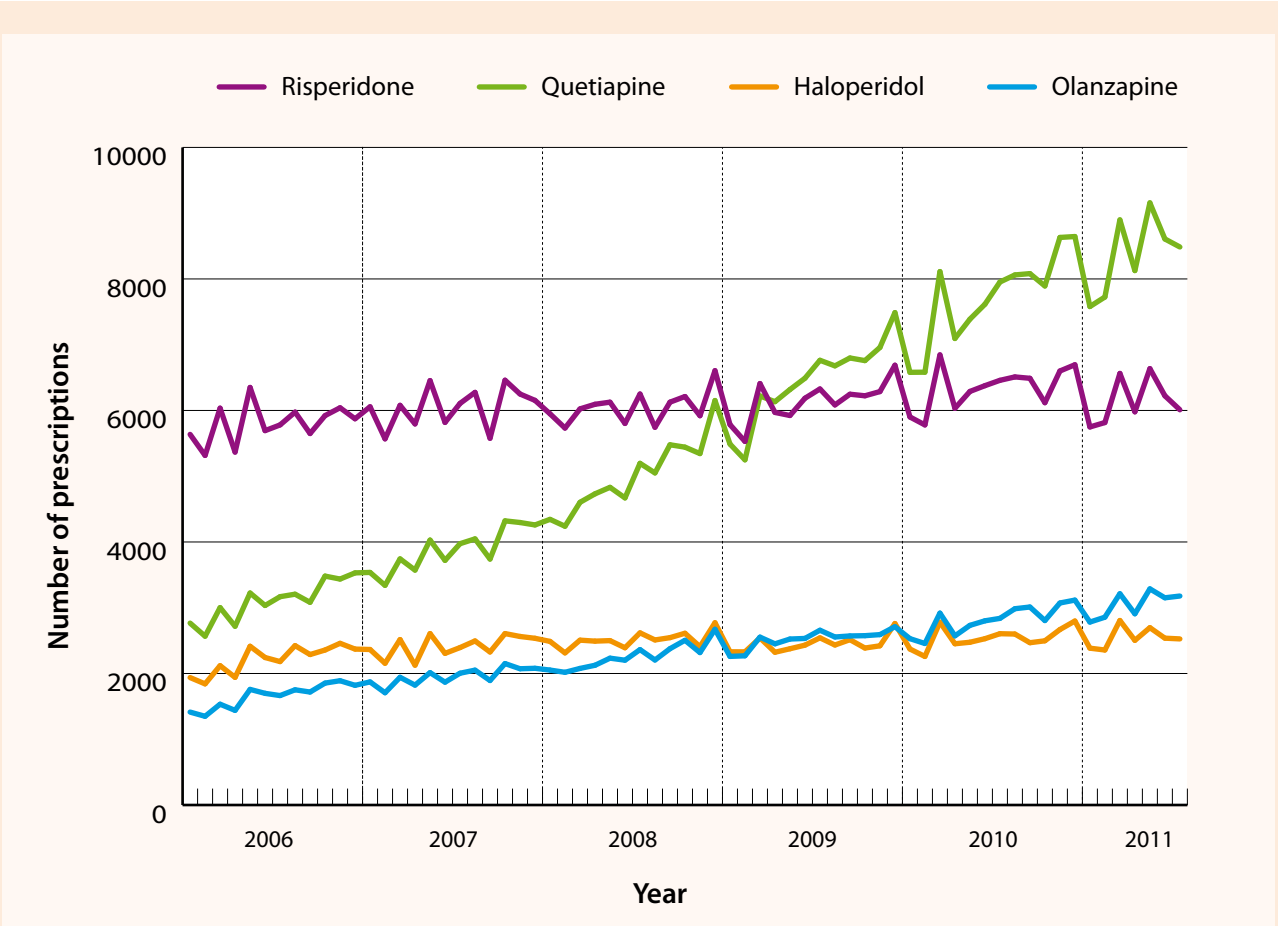


Figure 1: Use of selected typical and atypical antipsychotics by General Practitioners in New Zealand, 2006–2011 (dispensing data from the Pharmaceutical Warehouse database).

As experience has grown, significant adverse effects associated with atypical antipsychotics have emerged, such as the development of diabetes, dyslipidaemia, weight gain, metabolic syndrome, increased risk of stroke (particularly among elderly people), elevated risk of sudden cardiac death, seizures and tardive dyskinesia.[5] These adverse effects are also associated with typical antipsychotics.

Metabolic adverse effects

Metabolic adverse effects associated with antipsychotics are of particular concern because of the increase in cardiovascular morbidity and mortality.[4] Olanzapine and clozapine are particularly associated with substantial weight gain, dyslipidaemia and hyperglycaemia.[4] People taking these medicines often report that they always feel hungry. Weight gain can be substantial – a gain of 2 kg in two weeks should prompt a medicine review. All patients prescribed antipsychotics should be given appropriate advice on diet and lifestyle interventions and monitored carefully for diabetes.[7]

See: "Monitoring for metabolic disorders in patients taking antipsychotic drugs", BPJ 3 (Feb, 2007)

Extrapyramidal effects

Atypical antipsychotics are generally considered to cause fewer extrapyramidal adverse effects than typical antipsychotics. A meta-analysis showed clozapine, olanzapine and risperidone to be significantly less commonly associated with extrapyramidal symptoms than low potency typical antipsychotics (i.e. chlorpromazine 600 mg daily or equivalent).[8] The majority of studies have found no differences within the atypical group in terms of extrapyramidal effects.[5]

Table 1: Relative frequency of common adverse effects of antipsychotics (Psychotropic Expert Group, 2008).[6]

	Extrapyramidal	Sedation	Weight gain	Hyperglycaemia	Anticholinergic	Orthostatic hypotension
Atypical antipsychotics						
Risperidone	🟠🟠	🟠🟠 initially	🟠🟠	🟠🟠	🟢	🟠🟠 initially
Quetiapine	🟡*	🔴🔴🔴	🟠🟠	🔴🔴🔴	🟠🟠	🟠🟠
Olanzapine	🟡	🔴🔴🔴	🔴🔴🔴	🔴🔴🔴	🔴🔴🔴	🟡
Clozapine	🟡	🔴🔴🔴	🔴🔴🔴	🔴🔴🔴	🔴🔴🔴	🟠🟠
Amisulpride	🟠🟠*	🟡	🟡	🟡	🟢	🟡
Aripiprazole	🟡	🟡	🟡	🟢	🟢	🟡
Ziprasidone	🟡	🟠🟠	🟡	🟡	🟡	🟠🟠
Typical antipsychotics						
Haloperidol	🔴🔴🔴	🟡	🟠🟠	🟠🟠	🟡	🟡
Chlorpromazine	🟠🟠	🔴🔴🔴	🔴🔴🔴	🔴🔴🔴	🔴🔴🔴	🔴🔴🔴

Approximate frequency of adverse effects: 🟢 (<2%) = negligible or absent; 🟡 (>2%) = infrequent; 🟠🟠 (>10%) = moderately frequent; 🔴🔴🔴 (>30%) = frequent. * rarely a problem at usual therapeutic doses

Monitoring requirements for clozapine

Patients using clozapine require close monitoring as it can cause neutropenia, which may progress to a potentially fatal agranulocytosis.

Blood tests (white cell count and absolute neutrophil count) are required:[12]

- Ten days before commencing treatment
- Each week of the first 18 weeks of treatment
- Every four weeks during treatment
- Four weeks after discontinuation
- After discontinuation due to abnormal blood tests, until levels return to normal

Patients who present with evidence of infection, e.g. sore throat, fever or flu-like symptoms require an urgent complete blood count. Patients should also be advised to report any such symptoms.

Other adverse effects

Constipation is commonly associated with clozapine use and can be severe and even life-threatening. Co-prescription of a laxative for patients taking clozapine is recommended.

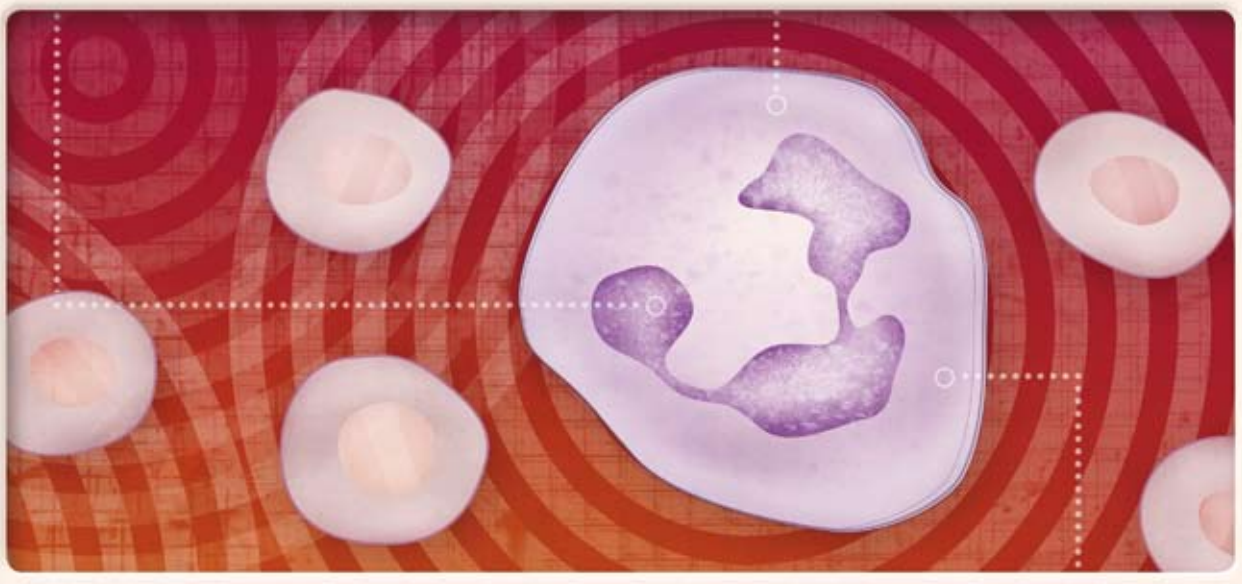
Additional adverse effects of clozapine are similar to other antipsychotics, but antimuscarinic effects (e.g. dry mouth, blurred vision, urinary retention), sedation and weight gain are often more pronounced.

The concomitant use of some medicines may increase the risk of adverse effects due to:

- A potential for bone marrow suppression, e.g. trimethoprim, co-trimoxazole, nitrofurantoin, sulphonamides, carbamazepine
- An increase in the plasma concentration of clozapine, e.g. erythromycin, ciprofloxacin

Clozapine is classified as a "hospital pharmacy" medicine which means it is only dispensed from a limited number of authorised pharmacies. ~~It is also currently monitored on the Intensive Medicines Monitoring Programme (IMMP)~~.

See "Clozapine: A reminder about safe and effective use". BPJ 14 (Jun, 2008).



* Removed November 2011

Tardive dyskinesia

Rates of new-onset tardive dyskinesia (orofacial and trunk movements) have been estimated at 3% with risperidone and 1% to 2% for other atypical antipsychotics.[5] In comparison, tardive dyskinesia develops in around 20% of people receiving typical antipsychotics.[9] Tardive dyskinesia is of particular concern as it may not be evident immediately, is often resistant to treatment, may be persistent and may worsen on treatment withdrawal.

Atypical antipsychotics for the treatment of schizophrenia and related disorders

Patients with schizophrenia should ideally be managed by a multidisciplinary team, including both primary and secondary care.[10] The early detection and prompt treatment of a first episode of schizophrenia is essential as this can improve health outcomes and possibly even the progression of the illness.[10]

Typical and atypical antipsychotics are used in the treatment of schizophrenia. Both types of antipsychotics are associated with adverse effects and there is also great variability in individual patient response. Therefore the same medicine cannot be recommended for every patient. As a general principle, an antipsychotic is started at a low dose and carefully titrated upwards to avoid or reduce the occurrence of adverse effects.[6]

Australasian guidelines recommend an atypical antipsychotic as first-line treatment for schizophrenia due to their lower risk of extrapyramidal adverse effects compared to typical antipsychotics.[10] However, more recently this recommendation has been challenged due to the concern that metabolic adverse effects associated with atypical antipsychotics are more problematic in the longer term.[11]

Clozapine is recommended in cases of treatment resistance, after the patient has trialled at least two other antipsychotics.[10] This medicine is not initiated in primary care, however, primary care clinicians have a role in monitoring for adverse effects (see opposite).

Pharmacological treatments for schizophrenia should always be used in conjunction with comprehensive psychosocial interventions.[10]

Atypical antipsychotics for the treatment of behavioural and psychological symptoms of dementia

Behavioural and psychological symptoms of dementia (BPSD) include; aggressiveness (verbal outburst, physical violence), activity disturbance (agitation, wandering) and psychotic symptoms. Non-pharmacological treatment is recommended first-line, but in some severe cases antipsychotics are used to manage BPSD.

Risperidone is the only atypical antipsychotic officially indicated for BPSD. Antipsychotics provide relatively few clinical benefits for people with dementia and in some cases pose a serious risk of an adverse outcome. A recent review predicts that for every 100 people with dementia given an antipsychotic only 20 will derive some clinical benefit and there will be one extra death and one extra stroke.[13]

Atypical antipsychotics should be used with extreme caution in older people, due to an increased incidence of adverse effects, and only used to treat severe symptoms. The decision to use an antipsychotic should be discussed with the patient, family and caregivers. Initial doses should be reduced to half the adult dose or less, taking into account factors such as the patient's weight, co-morbidities, and concomitant medication. Treatment should also be reviewed regularly.[14]

Antipsychotic treatment is not effective for symptoms such as wandering, social withdrawal, shouting, pacing, touching, cognitive defects and incontinence. Patients with these symptoms may respond to interventions such as improvements to the environment.[15]

See: "Antipsychotics in people with dementia – an update and reminder", BPJ 26 (Mar, 2010) and "Antipsychotics in dementia: best practice guide", BPJ Special Edition (Sep, 2008).

Off-label uses of atypical antipsychotics: insomnia, anxiety and post-traumatic stress disorder

In a recent survey in Canterbury, 96% of psychiatrists reported that they prescribed antipsychotics for off-label uses, with quetiapine being the most commonly used. The three most frequent indications for off-label prescribing of quetiapine were; anxiety (89%), sedation (79%) and post-traumatic stress disorder (57%).[16] Overall, it is estimated that between 43% and 70% of atypical antipsychotics prescribed are used for off-label indications.[16] It is generally accepted that there is limited evidence to support the use of antipsychotics for off-label uses, but this practice is now widespread and there is little guidance as to whether it needs to be reduced, or if patients are genuinely benefitting from the use of these medicines for these indications.

Drug company marketing has played a strong role in the increase in use of antipsychotics in recent years. In the United States, two drug manufacturers settled out of court, after being charged with illegally promoting the off-label use of olanzapine and quetiapine.[17, 18] There are reports that quetiapine is increasingly emerging as a drug of misuse in the United States. This trend has not yet been widely reported in New Zealand,[19] but may appear over time. There are some anecdotal reports that quetiapine is a drug of misuse in New Zealand prisons.

Off-label prescribing is legal in most countries, including New Zealand, therefore atypical antipsychotics can be prescribed for indications such as anxiety. However, the prescriber needs to carefully weigh up the risks and benefits and consider other appropriate medicines (or non-pharmacological options) first. The decision to prescribe should be discussed with the patient and their family and carefully documented in the patient's notes.

Anxiety

A selective serotonin re-uptake inhibitor (SSRI) is the first-line pharmacological treatment for generalised anxiety disorder.[20] Psychological treatments, such as cognitive behavioural therapy, are equally effective.[21] Patients should be treated for at least 12 weeks before assessing the efficacy of treatment with a SSRI. Treatment may need to continue for six to 12 months after symptoms of anxiety have resolved.[20]

Benzodiazepines are sometimes trialled for the treatment of anxiety if SSRIs or psychological therapies have been ineffective.[22] However, there is significant concern with tolerance, dependence and misuse associated with this medicine class. Buspirone is funded with Special Authority restriction, for use as an anxiolytic when other medicines are contraindicated or have failed. Tricyclic antidepressants may also be considered in some cases.

There is some evidence that quetiapine may be effective in the treatment of generalised anxiety disorder.[23, 24] Due to the adverse effects associated with quetiapine, it should only be considered for the short-term treatment of anxiety if all other appropriate pharmacological or psychological treatments had been trialled and were ineffective.

For further information see: "Generalised anxiety disorder in adults", BPJ 25 (Dec, 2009).

Post-traumatic stress disorder (PTSD)

PTSD is a psychiatric disorder which develops after exposure to a traumatic event. Three clusters of symptoms are typically present – re-experiencing, avoidance and hyperarousal. Treatment for PTSD involves a combination of psychological therapies, pharmacological treatment and social support. The first-line pharmacological treatment is an antidepressant, usually a SSRI.

There is a lack of evidence to support the use of quetiapine (or other antipsychotics) for the treatment of PTSD.[22]

Insomnia

Insomnia is usually secondary to an underlying cause such as an illness or poor sleep environment. Investigation and

treatment of the underlying cause will usually resolve symptoms of insomnia.

The first-line treatment is "sleep hygiene" intervention, e.g. advice to avoid alcohol, nicotine and caffeine, avoid stimuli before bedtime, avoid being in bed when not sleeping and learning relaxation techniques.

If this approach fails to resolve the insomnia, pharmacological treatment may be considered for short-term use. Zopiclone or shorter-acting benzodiazepines (e.g. temazepam) are appropriate choices. Use the lowest effective dose for the shortest possible time (less than four weeks and preferably five to ten days).[25] Antidepressants are not recommended for insomnia in the absence of depression or anxiety.[26]

Quetiapine is not recommended for the treatment of insomnia in the absence of psychiatric disorder, e.g. schizophrenia. Quetiapine has been reported to increase total sleep time and sleep efficiency, however, adverse effects such as leg movements and akathisia (restlessness) limit its effectiveness.[27]

For further information see: "Managing insomnia", BPJ 14 (Jun, 2008).

ACKNOWLEDGEMENT Thank you to **Dr Erik Monasterio**, Senior Clinical Lecturer, Christchurch School of Medicine, University of Otago, Consultant in Forensic Psychiatry, Hillmorton Hospital and **Andrew McKean**, Acting Senior Pharmacist, The Princess Margaret Hospital, Christchurch for expert guidance in developing this article.

Olanzapine generic now available – weight gain and diabetes a concern

From 1 June 2011 two generic versions of olanzapine became available for prescription, without restriction – Olanzine and Dr Reddy's Olanzapine (tablet and dissolving forms). The Zyprexa brand of olanzapine is still available, but is now subject to a significant part-charge. Some patients may need to be counselled through the brand change. Inform patients that the orodispersible tablets taste different and may take longer to dissolve.

Olanzapine is approved for the treatment of schizophrenia and related psychoses and bipolar depression. Concern has been expressed, now that olanzapine can be prescribed without a Special Authority approval, that it will be prescribed for off-label indications in the same manner that has occurred for quetiapine. There are a number of conditions in which olanzapine has been used, or is under investigation for use, including Alzheimer's dementia, anorexia, autism, Asperger's disorder, insomnia, anxiety and agitation. As yet, there is no compelling evidence of its effectiveness for these conditions.

When prescribing olanzapine the clinician should be particularly aware of the metabolic adverse effects including weight gain, raised lipid levels, impaired glucose tolerance and new-onset diabetes.[5] Pancreatitis is also reported as a rare complication of olanzapine use.[28]

Table 2: Serious adverse effects of atypical antipsychotics that may be more troublesome with olanzapine[5, 29, 30, 31]

Adverse effect	Comment
Weight gain	Weight gain in people using olanzapine can be 1 to 3 kg greater than that associated with other atypical antipsychotics such as risperidone. In long-term studies (at least 48 weeks) the mean weight gain was 5.6kg. The proportion of patients with clinically important weight gain could be reasonably high as the number needed to harm has been calculated as 4 for a ≥ 7% gain in body weight. Teenagers (age 13–17 years) are more likely to gain weight and to gain more weight than adults. Potential consequences of weight gain should be considered prior to starting olanzapine. **Monitor** weight, waist circumference and BMI. If weight gain is more than 2 kg during the first two weeks then a change of antipsychotic may be necessary.
Diabetes	There is an increased risk of type 2 diabetes in people with schizophrenia. Olanzapine has been associated with a greater risk of new-onset diabetes compared with the other atypical antipsychotics. Use with caution in people with diabetes or other disorders of glucose regulation. **Monitor** HbA_{1c} for signs of worsening glucose control. Avoid use in people with risk factors for diabetes e.g. obesity or family history. If used, **monitor** fasting glucose levels before and periodically during treatment.
Serum lipids	Olanzapine has been associated with increases in triglycerides, LDL cholesterol and total cholesterol and decreases in HDL cholesterol. Use with caution in patients with pre-existing abnormal lipid profile. **Monitor** lipid levels during treatment.

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