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SAFER USE OF HIGH RISK MEDICINES

Waitemata District Health Board
Best Care for Everyone

ATYPICAL ANTIPSYCHOTICS – BETTER, BUT NOT PERFECT

- MANAGE METABOLIC SYNDROME
- MONITOR FOR ADVERSE EFFECTS AND MANAGE EARLY
- UNDERSTAND THAT THERE ARE SOME POTENTIALLY SERIOUS ADVERSE EFFECTS
- TAKE CARE IF THERE IS A RISK OF DELIRIUM

In general, atypical antipsychotics have replaced the older 'typical' antipsychotics such as haloperidol and chlorpromazine for treating schizophrenia, bipolar disorder, and other severe mental illness, although zuclopenthixol is still popular. Atypical antipsychotics have a lower propensity for causing Parkinson-like disorders,[1] and have more distinct clinical profiles.[2]

Typical antipsychotics are not selective for any of the four dopamine pathways in the brain and so can cause a range of adverse effects, particularly extrapyramidal symptoms.[2]

Atypical antipsychotics are a heterogenous group of medicines which include **amisulpride**, **aripiprazole**, **olanzapine, paliperidone, quetiapine, risperidone,** and **ziprasidone**. **Clozapine** is also an atypical antipsychotic which has a specific adverse reaction profile and higher risks associated with its use (visit www.saferx.co.nz to view the clozapine bulletin for more information).

There is a great variability of individual response with all antipsychotics; they act on a range of receptors, having distinct properties and adverse effect profiles. In general, start at a low dose and carefully titrate upwards to reduce the occurrence of adverse effects[3] which are often dose-related. Treatment should be continued for 4 to 6 weeks before it is considered ineffective; combinations of medicines should be avoided (unless during switching) due to the increased risk of adverse effects.[2]

Some adverse effects require careful monitoring and management, and some can be serious such as diabetes, stroke and cardiac death.[4] Be cautious when prescribing these medicines to older adults, and people with cardiovascular risk factors such as obesity, diabetes or high cholesterol.[3]

MANAGE METABOLIC SYNDROME

Metabolic syndrome includes rapid weight gain, raised plasma glucose and abnormal lipid profiles. Schizophrenia itself is associated with insulin resistance and diabetes; the risk of diabetes is increased further with antipsychotic medicines.[2]

An increase in body weight of several kilos within 4-6 weeks of commencing therapy, along with hyperglycaemia and type 2 diabetes have occurred with people taking atypical antipsychotics. The risk is greatest with clozapine and olanzapine, but cases have also been reported with risperidone and quetiapine. The risk of metabolic syndrome appears to be lower with amisulpride, ziprasidone and aripiprazole.[5,6]

Due to the associated risks of cardiovascular morbidity and mortality, everyone who is prescribed antipsychotics, should be provided with advice about diet and lifestyle interventions, monitored for the emergence of diabetes[7] and have lipid levels checked regularly (see table).

Weight gain

Olanzapine in particular is associated with weight gain. Long-term studies, over 48 weeks have demonstrated a mean weight gain of 5.6kg. Teenagers are more likely to gain weight than other groups. If there is an increase of over 2kg in weight within the first 2 weeks, consider a change of medicine.[3]

Metformin is used (off-label) up to 1.5g per day in divided doses, to prevent and reduce antipsychotic weight gain and to treat glucose intolerance. If a patient taking an atypical antipsychotic is also prescribed metformin, review the indication before deprescribing, even if current HbA1c is normal.

Diabetes

People with schizophrenia have an increased risk of diabetes. Avoid olanzapine in particular if risk factors such as obesity or a family history of diabetes are present. Monitor for symptoms of diabetes during treatment.[3]

Lipids

Use atypical antipsychotic medicines with caution if the lipid profile is abnormal. Everyone taking antipsychotic medicines needs to have lipids monitored during treatment[3] and lipid lowering medication prescribed if indicated.

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ATYPICAL ANTIPSYCHOTICS

MONITOR FOR ADVERSE EFFECTS AND MANAGE EARLY

Cardiovascular effects

Current users of typical or atypical antipsychotics have an increased risk of sudden cardiac death compared with non-users, and former-users of these medicines. The risk increases significantly with higher doses[4] and with combinations of antipsychotic medicines.[2]

Atypical antipsychotic medicines can prolong the QT interval and lead to ventricular tachyarrhythmias. Prolongation of QT interval has been observed especially with **ziprasidone** and to a lesser extent with **risperidone**8 and **aripiprazole**.[2] Tachycardia has been observed with **risperidone, olanzapine, quetiapine** and less so with **ziprasidone**.[8] An increased risk of stroke has been associated with all antipsychotic medicines.

If there is evidence of pre-existing cardiovascular disease or if there are cardiovascular risk-factors, *an ECG may be required prior to initiating treatment with antipsychotic medicines*.[2] *Everyone* with schizophrenia should have a physical health check-up each year, including a cardiovascular disease risk assessment.[2]

Note: Clozapine has a known association with myocarditis and cardiomyopathy, and there have been case reports with other atypical antipsychotics.[9] Symptoms of myocarditis are similar to congestive heart failure and include fever, chest pain, fatigue, shortness of breath.[10]

Postural hypotension and hypertension

Postural hypotension can occur with medicines that cause a significant alpha adrenergic blockade, this includes **risperidone, olanzapine and quetiapine.** Inform older adults and their caregivers about the increased risk of postural hypotension and falls with these medicines. There have also been cases of severe hypertension leading to collapse with **risperidone.**[11]

Movement disorders

'Typical' antipsychotics should never be prescribed to people with Parkinson's disease; atypicals should be used very cautiously due to the potential exacerbation of symptoms.[2] Higher doses of **risperidone** (>6mg/day) and **amisulpride** (>300mg/day) are associated with Parkinson-like adverse effects, such as tremor, muscular rigidity, acute dystonia. These symptoms usually occur gradually and are more common with older adults.[2] **Risperidone, amisulpride, aripiprazole** and **olanzapine** may cause akathisia (including agitation and restlessness).[12]

Although new-onset tardive dyskinesia is less likely to occur with atypical, compared with typical antipsychotics, it has been estimated to occur in 1-2% of people, and in up to 3% of people taking **risperidone.** This is of particular concern because it may not be evident initially, may worsen on treatment withdrawal,[3] and can be irreversible.[2]

Sexual dysfunction

Hyperprolactinaemia has been observed with **risperidone, palperidone** and **amisulpride** with associated sexual dysfunction, gynaecomastia and osteoporosis in at-risk populations. Sexual dysfunction is one of the main causes of non-adherence to antipsychotic medicines. Risperidone, in particular is associated with this; dose reduction or switching medicines may be necessary.[4] The antipsychotic medicines with the lowest risk of sexual dysfunction appear to be **aripiprazole, ziprasidone** and **quetiapine.** There have been case reports of priapism with **risperidone** and **olanzapine.**[13,14]

Note: Sensitive questioning may be needed to uncover sexual side effects because people may be reluctant to volunteer this information. Discuss the possibility of sexual dysfunction prior to and during treatment to provide reassurance and support adherence.[15] Treatment non-adherence is a major risk factor for relapse.[16]

Other side effects

Anticholinergic effects such as constipation and blurred vision can occur particularly with **clozapine** and **olanzapine**. Sedation has been associated with **clozapine**, **olanzapine** and **quietiapine**.[3]

Mood or behaviour changes (eg, anxiety, irritability, in extreme cases suicidal thoughts and self-harm) can occur with people taking these medicines; advise them and their caregivers to report any concerns.[17]

Concomitant use of other centrally acting medicines has the potential to increase adverse effects such as somnolence, drowsiness and sedation. People who are obese or have a history of sleep apnoea may be more sensitive to these effects.[18]

UNDERSTAND THAT THERE ARE SOME POTENTIALLY SERIOUS ADVERSE EFFECTS

Neuroleptic Malignant Syndrome (NMS)

NMS is a rare but potentially fatal adverse effect of all antipsychotic medicines. This is more common in young men taking higher doses and is often associated with hot weather and exercise. Symptoms include muscular rigidity, pyrexia, confusion, urinary incontinence, disorientation, tachycardia and sweating. If these symptoms occur, urgent assessment at the Emergency Department is required, the medicine stopped and supportive treatment provided.[12]

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ATYPICAL ANTIPSYCHOTICS

This syndrome can last for up to 5-7 days after discontinuation.[2]

Please remember that like the older antipsychotics, atypicals are linked to rare cases of raised hepatic enzymes and blood dyscrasias.[19] Arrange blood counts if unexplained infection or fever develops.[2]

TAKE CARE WITH BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA (BPSD)

In some cases antipsychotics are used to manage BPSD if non-pharmacological treatment is ineffective. **Risperdone** is the only atypical antipsychotic currently indicated for BPSD.[3] Antipsychotics will not be effective for wandering, social withdrawal, shouting, pacing, touching or cognitive defects.

There is an increased risk of mortality and an increased risk of stroke in people with dementia who are prescribed antipsychotic medicines. Older people are also more susceptible to postural hypotension, hyperthermia in hot weather and hypothermia in cold weather. It is advisable when initiating treatment to use half the adult dose, or less depending on comorbidity and other medicines, and to review efficacy and the emergence of adverse effects regularly.[2]

OFF-LABEL PRESCRIBING

Atypical antipsychotics are frequently prescribed for anxiety, and have also been used for sedation and post traumatic stress disorder. These indications are 'off-label' so the prescriber needs to discuss the decision to prescribe with the patient (and their family), **obtain consent and document** this in the patient's notes. Be aware that there is still limited documented evidence to support off-label use.[3]

Anxiety

The usual treatment of anxiety is initial psychological therapy and, if necessary SSRIs may be used. The efficacy of SSRIs should be assessed after 12 weeks before other medicines are considered.[3]

Post traumatic stress disorder (PTSD)

Psychological therapies, social support, and if necessary antidepressants (usually SSRIs) are recommended first-line. There is a lack of evidence to support antipsychotics for this condition.[3]

Insomnia

Sleep hygiene techniques should be explored prior to the use of any pharmacological treatments (see SafeRx® bulletin 'Hypnotics'). If necessary, zopiclone and short-acting benzodiazepines may be used, rather than antipsychotics or SSRIs.[3]

MONITORING RECOMMENDATIONS[2]

Parameter	Frequency	Comments
Full Blood Count	Initially then annually	
Urea and Electrolytes	Initially then annually	
Liver Function Test	Initially then annually	Not required for amisulpride
Lipid profile	Initially, at 3 months and annually	Clozapine or olanzapine, monitor every 3 months for the first year, then annually
Weight	Initially, regularly during first 3 months, then annually	Clozapine or olanzapine, monitor every 3 months for the first year, then annually
Fasting Blood Glucose	Initially, at 4-6 months, then annually	Clozapine or olanzapine, also test after one month
ECG	Initially if risk factors	Refer to individual datasheets
Blood Pressure	Initially and during dose titration	
Prolactin	Initially, at 6 months, then annually if clinical concerns	For higher risk medicines (amisulpride, risperidone) or if clinical concerns
CVD Risk Assessment	Annually	For everyone with schizophrenia

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REFERENCES

1. Margolese H, Chouinard G, Kolivakis T et al. Tardive dyskinesia in the era of typical and atypical antipsychotics. Part 2: incidence and management strategies in patients with schizophrenia. Canadian Journal of Psychiatry 2005;50(11):703-14.
2. New Zealand Formulary, Antipsychotic Drugs www.nzf.org.nz/nzf_2098.html (Accessed 16-04-18)
3. Monasterio E, McKean A. Prescribing atypical antipsychotics in general practice. Best Practice Journal 2011; 40:14-23 www.bpac.org.nz/BPJ/2011/november/docs/bpj_40_antipsychotics_pages_14-23.pdf (Accessed 16-04-18)
4. Ray W, Chung C, Murray K et al. Atypical antipsychotic drugs and the risk of sudden cardiac death. New England Journal of Medicine 2009;360(3):225-35 www.nejm.org/doi/full/10.1056/NEJMoa0806994#t=article (Accessed 16-04-18)
5. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects. A comprehensive literature review. CNS Drugs 2005;19(Suppl 1):1-93.
6. Henderson D. Atypical antipsychotic-induced diabetes mellitus: how strong is the evidence. CNS Drugs 2002;16(2):77-89.
7. Kessing L, Thomsen A, Mogensen U, Andersen P. Treatment with antipsychotics and the risk of diabetes in clinical practice. The British Journal of Psychiatry 2010;197:266-71 http://bjp.rcpsych.org/content/197/4/266.full.pdf+html (Accessed 16-04-18)
8. Buckley N, Sanders P. Cardiovascular adverse effects of antipsychotic drugs. Drug Safety 2000;23(3):215-28.
9. Coffey S, Williams M. Quetiapine-associated cardiomyopathy. The New Zealand Medical Journal. 2011;124(1336) www.nzma.org.nz/journal/read-the-journal/all-issues/2010-2019/2011/vol-124-no-1337/cc-coffey (Accessed 16-04-18)
10. Khasawneh FT, Shankar GS. Minimizing cardiovascular adverse effects of atypical antipsychotic drugs in patients with schizophrenia. Cardiology Research and Practice. 2014; 273060. www.hindawi.com/journals/crp/2014/273060/ (Accessed 16-04-18)
11. Coulter D. Atypical antipsychotics may cause hypertension. Medsafe Prescriber Update 2003;24(1):4. www.medsafe.govt.nz/profs/puarticles/aahyp.htm (Accessed 16-04-18)
12. Blanchet P. Antipsychotic drug-induced movement disorders. Canadian Journal of Neurological Science 2003;30(Suppl1):101-7
13. Harrison G, Dilley JW, Loeb L, Nelson K. Priapism and quetiapine: a case report. Psychopharmacology Bulletin 2006;39(1):117-9.
14. Westheide J, Cvetanovska G, Albrecht C et al. Prolactin, subjective well-being and sexual dysfunction: an open label observational study comparing quetiapine with risperidone. Journal of Sexual Medicine 2008;5(12):2816-26.
15. Medsafe Publication. Sexual dysfunction associated with antidepressants and antipsychotics. Prescriber Update 2015;36(1):5-7 www.medsafe.govt.nz/profs/PUArticles/March2015SexualDysfunctionAntidepressantsAndAntipsychotics.htm (Accessed 16-04-18)
16. Romans S, McKean A. Bipolar disorder: Identifying and supporting patients in primary care. Best Practice Journal 2014;62:6-17 www.bpac.org.nz/BPJ/2014/July/bipolar.aspx (Accessed 16-04-18)
17. Medsafe Publication. Quetiapine – not without side effects. Prescriber Update 2016. 37(4):61 www.medsafe.govt.nz/profs/PUArticles/December%202016/Quetiapine.htm (Accessed 16-04-18)
18. Medsafe Publication. Atypical antipsychotics interacting with CNS depressants. Prescriber Update 2014;35(1):15 www.medsafe.govt.nz/profs/PUArticles/March2014AtypicalAntipsychoticsInteractCNSDepressants.htm (Accessed 16-04-18)
19. Stanniland C, Taylor D. Tolerability of Atypical Antipsychotics. Drug Safety 2000;22(3):195-214.

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