Te Awakairangi Health NETWORK

Update **March 2016**

Monitoring Atypical Antipsychotics and Mood Stabilisers – what and why

Background

The association between atypical antipsychotics (AAPs) and metabolic adverse effects is well established and over time, can lead to metabolic syndrome, poor cardiovascular outcome and Type 2 diabetes. Although it is difficult to separate the contributions of illness, lifestyle and medication factors to these risks, there is now a greater recognition of the need to monitor patients treated with antipsychotic medications for metabolic disturbances.

Atypical Antipsychotics

Each drug has its own risk profile, but all AAPs have been shown to cause some metabolic adverse effects to varying degrees (see Table 1). A dose-effect relationship, if present, is estimated to be small and metabolic effects can occur at low dosages.

Weight gain is also a well-established side effect of antipsychotic therapy, so the rationale for, and goals of monitoring metabolic parameters during the course of antipsychotic treatment are well-defined.

Goals of metabolic monitoring include:

- Identification of individuals at high risk of metabolic disorder (metabolic syndrome, pre-diabetes, severe obesity) for prevention and health promotion initiatives
- Early identification of treatable metabolic conditions (diabetes, dyslipidaemia, and hypertension)
- Tracking and linking of metabolic disturbances in relation to antipsychotic treatment

Key Messages

- All atypical antipsychotics carry a risk of metabolic disturbance; clozapine and olanzapine have the highest risk, followed by quetiapine and risperidone
- Early recognition and management of metabolic and other complications will have the greatest impact on health status of people with mental illness
- Baseline BMI, waist circumference, HbA1c, lipids, LFTs and blood pressure should be recorded then assessed and managed routinely throughout AAP treatment
- Wellbeing interventions eg regular physical activity, nutrition promotion and smoking cessation initiatives reduce cardiovascular and metabolic risk
- Appropriate pre-treatment evaluation, baseline investigations and longitudinal monitoring should also be done for mood stabiliser therapy

Table 1: Comparison of effects of atypical antipsychotics

Generic name (funded brand(s))	Weight Gain	Dyslipidaemia	Hyperglycaemia	Anticholinergic
Clozapine (Clozaril, Clopine)	+++	+++	+++	+++
Olanzapine (Zypine)	+++	+++	+++	+++
Quetiapine (Quetapel)	++	++	++	++
Risperidone (Risperon, Risperidone Actavis, Risperdal)	++	++	++	0
Amisulpride (Solian)	+/0	+	+	0
Ziprasidone (Zusdone, Zeldox)	+/0	+	+	+
Aripiprazole (Abilify)	+/0	+	0	0

The information contained within this bulletin is to be used in conjunction with the diagnostic & clinical skills of the clinical practitioner. While the writer has taken all possible care in compiling the information contained herein, the general practitioner is responsible for the use of the information. This bulletin has been compiled by the Clinical Pharmacy Team at Te Awakairangi Health Network. For further information please contact the clinical pharmacists on ph 04 566 5320.

Weight gain

Weight gain is recognised as one of the main causes of non-compliance and discontinuation of treatment. No antipsychotic should be considered body weight-neutral because all have the potential for significant weight gain (>7% in body weight), which has been reported in up to 50% of patients receiving long-term treatment for schizophrenia. The greatest amount of weight gain occurs within the first weeks of treatment and can be substantial – a gain of 2 kg in two weeks should prompt a medication review.

Dyslipidaemia

Hypertriglyceridemia is the lipid abnormality most consistently reported with patients on AAPs. Recent studies have shown that clozapine, olanzapine and, to a lesser extent, quetiapine are associated with elevations in triglyceride and total cholesterol levels.

An increase in serum lipids is associated with an increase in body weight; therefore, agents associated with the lowest increase in body weight would also be expected to have a lesser risk of inducing serum lipid changes.

Type 2 Diabetes

Diabetes is reported as being up to three - four times more prevalent in patients with schizophrenia than in the general population, however the precise mechanism by which antipsychotics alter glucose metabolism is unknown.
Although thought to be multi-factorial, studies are often confounded by concomitant weight gain and dyslipidaemia, which are known diabetic risk factors. In many case reports, hyperglycaemia tended to occur within 6 weeks after starting treatment. Most new-onset cases were reversible on discontinuation, suggesting an independent drug-related mechanism with large differences between individual drugs.

Recommended monitoring schedule#

Parameter	Baseline	1 mth	2 mths	3 mths	6 mths	Annually
Weight, BMI, girth	x	x	x	x		x
Blood pressure	x	x	x	x		x
HbA_{1c} (non-fasting)	x			x		x
Lipids (non-fasting)	x			x		x
LFTs	x					x*
Prolactin	x				x	x
Urea, electrolytes, creatinine	x					x
CVD risk assessment						x
Full blood count@	x					x

additional or more frequent screening may be necessary based on a patient's individual risk
*amisulpride – baseline only required
@clozapine – FBC recommended at baseline then every week for 1st 18 weeks, then at least every 4 weeks

Off-label prescribing

There is little evidence to support many of the off-label uses of atypical antipsychotics, including quetiapine. Indications with particularly poor evidence include anxiety, insomnia, post-traumatic stress disorder, behavioural and psychological symptoms of dementia, and substance abuse. Prescribers must discuss the decision to prescribe with the patient (and their family), obtain consent and document this in the patient's notes.

The information contained within this bulletin is to be used in conjunction with the diagnostic & clinical skills of the clinical practitioner. While the writer has taken all possible care in compiling the information contained herein, the general practitioner is responsible for the use of the information. This bulletin has been compiled by the Clinical Pharmacy Team at Te Awakairangi Health Network. For further information please contact the clinical pharmacists on ph 04 566 5320.

Mood stabilisers

Many drugs used to treat bipolar disorder can be considered to stabilise specific mood phases. Based on current evidence, lithium and perhaps sodium valproate are the only drugs effective for both acute treatment and the prevention of future episodes. Other anticonvulsants and antipsychotics have evidence to show that they stabilise certain mood states or illness trajectories. They may be used in acute treatment of bipolar disorder, but there is less evidence for their role in maintenance treatment to prevent recurrence.

Recommended monitoring schedule

	Lithium	Sodium valproate	Carbamazepine	Lamotrigine
Physical exam	Baseline & annually.	Baseline & annually.	Baseline & annually.	Baseline & annually.
Blood pressure	Annual			
Weight & girth	Baseline then frequently if rapid weight gain	Baseline, then at 3 and 6 months	Baseline then after 6 months	
Plasma levels of drug	Test level approx. 12 hrs after last dose. Weekly for 4 weeks until levels stablise, then 3 monthly. Repeat if patient becomes unwell, has significant changes in sodium or fluid intake, or interacting medicines are added or stopped Range: For maintenance, optimal range 0.6 – 0.8 mmol/L for once daily dose.	Use trough level. Monitor 3-4 days after target dose reached, dose change or introduction/ withdrawal of interacting medicine. A level of at least 300 micromols/L is associated with response. Monitor more frequently if patient has history of liver disease, or becomes unwell. Range: 300- 600 micromols/L	Use trough level. Initially 2 weeks after start of therapy, then 2 weeks after dosage change or introduction/ withdrawal of interacting medicine. At steady state monitor every 6 months. Range: 16-50 micromols/L (? 30-50micromols/L in bipolar disorder)	Value of TDM not established but may be useful during pregnancy. Range: 12 – 55 micromols/L. Very slow dose titration to reduce incidence of skin rash.
Thyroid function	Baseline then every 6 months. More often if risk factors present.			
Electrolytes, serum creatinine, eGFR	Baseline then every 6 months. More often if taking interacting medicines or physical deterioration. Test at same time as lithium level. Corrected calcium at baseline then at least annually		Urea and electrolytes every 6 months	
Full blood count	Baseline then if clinically indicated	Baseline then after 6 months	Baseline, after 6 months then annually	
LFTs		Baseline then after 6 months as a minimum	Baseline, after 6 months then annually	

The information contained within this bulletin is to be used in conjunction with the diagnostic & clinical skills of the clinical practitioner. While the writer has taken all possible care in compiling the information contained herein, the general practitioner is responsible for the use of the information. This bulletin has been compiled by the Clinical Pharmacy Team at Te Awakairangi Health Network. For further information please contact the clinical pharmacists on ph 04 566 5320.

Mood stabilisers are a relatively safe and well-tested therapy. However, increased use of polypharmacy and co-morbid medical/psychiatric conditions can result in potentially important drug interactions which require identification and management.

Early identification and management of these events, together with recommended monitoring is important in order to maximise these drugs' benefits and limit their risks.

How do mood stabilisers work?

There is no specific psychopharmacological mechanism, so how mood stabilisers work is unknown. The possible mechanisms of action of lithium are complex and include:

- altered cell membrane sodium transport
- inhibition of inositol monophosphatase
- reduced protein kinase C activity
- neurogenic/neurotrophic actions
- alterations in serotonin metabolism
- modulation of intracellular signal transduction.

The anticonvulsant drugs used in bipolar disorders may have mechanisms of action which include voltage-sensitive sodium and calcium channels, gamma-aminobutyric acid enhancement or glutamate blockade. Atypical antipsychotics are believed to exert a mood stabilising effect through their monoaminergic actions in treating bipolar depression. In psychotic mania they may have dopamine D_2 antagonism or partial agonism and serotonin $5HT_{2a}$ antagonism.

References

1. Brett J. Concerns about quetiapine. Australian Prescriber. 2015;38(3):95-97.
2. Capital & Coast DHB. Metabolic monitoring. CapitalDoc ID 1.102027. September 2014.
3. Chabroux S, Haffen E, Penfornis A. Diabetes and second-generation (atypical) antipsychotics. Annales d'endocrinologie. 2009; 0003-4266:202-10.
4. Cohn T, Sernyak M. Metabolic Monitoring for Patients on Antipsychotic Medications. Can J Psychiatry. 2006;51(8):492-501.
5. Deepak TS, Raveesh BN, Parashivamurthy BM et al. Clinical Assessment of Weight Gain with Atypical Antipsychotics - Blonanserin vs Amisulpride. Journal of Clinical and Diagnostic Research JCDR. 2015; 9(6):FC07-10.
6. Kessing L, Thomsen A, Mogensen UB et al. Treatment with antipsychotics and the risk of diabetes in clinical practice. Br J Psychiatry. 2010 Oct;197(4):266-71.
7. Khoo J-P. Mood stabilisers. Aust Prescr 2012;35:164-8
8. Musil R, Obermeier M, Russ P, Hamerle M. Weight gain and antipsychotics: a drug safety review. Expert Opinion on Drug Safety. 2015; 14(1):73-96.
9. Nasrallah HA. Atypical antipsychotic-induced metabolic side effects: insights from receptor-binding profiles. Molecular Psychiatry. 2008; 13:27–35
10. Saxena S. Managing Adverse Effects of Mood Stabilizers. Primary Psychiatry. Available from http://primarypsychiatry.com/managing-adverse-effects-of-mood-stabilizers/. Accessed 6 January 2016.
11. Te Pou o Te Whakaaro Nui. Evidence Summary: The physical health of people with a serious mental illness and/or addiction. June 2014.
12. Zeier K, Connell R, Resch W, Thomas CJ. Recommendations for lab monitoring of atypical antipsychotics. Current Psychiatry 2013; 12(9):51-54.

The information contained within this bulletin is to be used in conjunction with the diagnostic & clinical skills of the clinical practitioner. While the writer has taken all possible care in compiling the information contained herein, the general practitioner is responsible for the use of the information. This bulletin has been compiled by the Clinical Pharmacy Team at Te Awakairangi Health Network. For further information please contact the clinical pharmacists on ph 04 566 5320.