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Balancing benefits and harms of antipsychotic therapy

An Australian survey found that about 80% of people with a psychotic illness* taking risperidone or olanzapine reported one or more troublesome side effects and worsened quality of life.¹ Another study found that more than half of those tested had significant risk factors for cardiovascular disease or diabetes.² In this *NPS News* we discuss ways to achieve the most favourable balance of clinical benefits and adverse effects for people with a psychotic illness or behavioural symptoms of dementia.

* Schizophrenia, bipolar disorder/mania, schizoaffective disorder, depressive psychosis or other psychosis.

Consider differences in adverse effect profiles when choosing between antipsychotics

Data from recent trials reveal in detail the relative benefits and harms associated with specific antipsychotics. Adverse effect profiles vary as much from drug to drug as they do between the groups of 'conventional' and 'atypical' antipsychotics. Nevertheless, lack of tolerability and efficacy are commonplace with all antipsychotics; patients often experience sedation and extrapyramidal symptoms.³⁻⁵

Metabolic disturbance is now one of the most important concerns with long-term antipsychotic use. All of the newer antipsychotics cause greater weight gain than haloperidol, with the exception of aripiprazole and ziprasidone.⁶ The US National Institute of Mental Health CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) schizophrenia study indicated that olanzapine had the greatest propensity to increase weight, waist circumference and fasting triglycerides, after an average of 9 months of treatment.^{†4,7} Data from other trials suggest that clozapine causes a similar degree of weight gain to olanzapine.⁸

Despite differences, no single antipsychotic is a clear winner in terms of overall clinical effectiveness for schizophrenia. The 2009 UK National Institute for Health and Clinical Excellence (NICE) guidance for schizophrenia was based on a systematic analysis of clinical data including relapse and discontinuation rates, as well as rates of adverse effects. The authors concluded that the evidence does not allow for any general recommendation for one antipsychotic over another, except for clozapine for people whose illness does not respond adequately to other antipsychotics.⁹

These findings underline the need to assess the risk of adverse effects and to monitor for both therapeutic benefit and harm. Treatment choices should consider individual risk of extrapyramidal and metabolic adverse effects, and previous experience of antipsychotics.⁹ Recommendations for monitoring and evidence relating to antipsychotic switching in psychotic disorders are discussed on page 2.

† The CATIE phase 1 trial compared olanzapine, perphenazine, quetiapine, risperidone and ziprasidone.

Case review — Andrea

Andrea is a 35-year-old woman with schizophrenia (first episode 11 years ago). She is a smoker (30 cigarettes/day), has a BMI of 30, BP 125/80, no recorded fasting blood glucose or lipids, and no other current diagnoses. Her medication consists of olanzapine 30 mg once daily. Her symptoms have been well controlled since her last change of medicine 12 months ago but she complains of excessive daytime drowsiness. She is also worried about her weight, which has increased by 15 kg in the last year. Andrea lives on her own but has occasional contact with her brother.

What are the options for managing Andrea's adverse effects?

- Dose reduction, considering previous response to treatment.
- Offer lifestyle interventions for weight loss and consider referral (see below).
- Consider switching antipsychotic in consultation with a psychiatrist.

What else should be done for Andrea's physical health?

- Test fasting blood glucose and lipids, and if abnormal review drug choice.
- Offer help with smoking cessation: use 5A approach, nicotine patches. Refer for allied health or support groups.
- Monitor other adverse effects according to the checklist in Table 1.

Antipsychotic switching in schizophrenia

Adverse effects and lack of efficacy are common barriers to continuing antipsychotic treatment, as demonstrated by discontinuation rates in randomised controlled trials. Careful switching, in consultation with a psychiatrist, is clearly preferable to risking relapse because of non-adherence.¹⁰ Before switching, guidelines recommend investigating adherence, and taking practical measures in response to any problems.¹⁰

There is some evidence that switching from olanzapine to aripiprazole, perphenazine, quetiapine, risperidone or ziprasidone can mitigate weight gain or metabolic disturbance.^{11,12} However, this benefit came at the cost of higher rates of withdrawal from the trials for the participants who switched.^{11,12} There is also limited evidence from one small trial that switching to quetiapine can improve problematic extrapyramidal symptoms.¹³ Otherwise, there is surprisingly little high-quality evidence for the benefits of switching. In fact, a recent re-analysis of CATIE results suggested that those who were receiving olanzapine, quetiapine or risperidone before the trial and were assigned to a different drug in the study were no better off in terms of schizophrenia symptoms or quality of life than those who continued with their previous treatment.¹²

Lifestyle interventions for people with psychosis

Almost everyone with a psychotic illness can benefit from support to achieve daily exercise, good diet and cessation of smoking.^{10,14,15} These lifestyle interventions may improve physical health and mitigate the negative effects of antipsychotics on weight and metabolism. Studies also indicate that exercise can have a positive effect on the mental health and wellbeing of people with schizophrenia.¹⁵

GP referral to an allied health professional (such as a psychologist, dietitian or exercise physiologist) is one option for supporting positive lifestyle changes (see *NPS News 51* at www.nps.org.au/news_51). Health professionals can also provide motivational interviewing to encourage behaviour change. Resources from the Lifescrpts program (www.health.gov.au/lifescrpts) such as self-assessment forms and action plans may be useful.

Initiatives specifically for people with mental illness include:

- *Mind + Body initiative* — promoting physical health and wellness with a range of resources available for individuals and non-government mental health organisations. Call the SANE Helpline 1800 18 7263, email helpline@sane.org or visit the website www.sane.org.
- *activate: mind & body* — a collaboration between Queensland Health and General Practice Queensland that aims to improve the physical and oral health of people with severe mental illness. The website www.activatemindandbody.com.au has information for people with mental illness, carers, GPs and other mental health service providers.

Review checklist for people receiving long-term antipsychotics

People with mental illnesses such as schizophrenia often have poor physical health. Contributing factors include lifestyle, alcohol and illicit drug use and the adverse effects of antipsychotics.¹⁶ General practice has a key role in caring for the physical health of people who are taking antipsychotics long term. Regular monitoring of risk factors for serious adverse effects, including cardiovascular disease, diabetes and extrapyramidal symptoms (see Table 1) — in collaboration with other mental health professionals — is one aspect. GP follow-up can also improve rates of participation in preventive health screening programs e.g. mammography and Pap smears.

Table 1: Suggested monitoring and review frequency for people taking antipsychotics long term.*^{10,17–19}

Suggested monitoring	Review frequency
Weight and waist circumference	Every visit
Blood pressure	Every 6 months (olanzapine) / Annually (other antipsychotics)
Fasting serum lipids	Every 6 months (olanzapine) / Annually (other antipsychotics)
Fasting blood glucose	Every 6 months (olanzapine) / Annually (other antipsychotics)
Electrocardiogram	Annually
Ask about extrapyramidal symptoms and examine for rigidity, tremor and abnormal involuntary movements (i.e. tardive dyskinesia)	Every 6 months
Ask about menstrual and sexual problems, gynaecomastia and galactorrhoea. Test prolactin levels if symptoms suggest hyperprolactinaemia	Annually
Ask about any other adverse events e.g. sedation, anticholinergic effects	Every visit
Ask about smoking status	Every visit
Ask about alcohol and illicit drug consumption	Every visit

* Additional monitoring is recommended when treatment is started, or for people with risk factors for adverse events (e.g. hepatic impairment). Patients receiving clozapine have specific, mandatory monitoring requirements that are not described in this publication.

Antipsychotics in dementia

Risk of death

Trial data from people with dementia show increased mortality with risperidone, olanzapine, quetiapine and aripiprazole on the order of 1 excess death per 100 people treated for 10–12 weeks, with most deaths of cardiovascular or infectious causes.^{20,21} Observational studies indicate similar risks for conventional antipsychotics and have found an association with community-acquired pneumonia and stroke.^{22–24} Only a minority of people with behavioural symptoms of dementia improve with antipsychotic treatment.²⁵ It follows that the harms of antipsychotic use are likely to outweigh the benefits, unless treatment is reserved for severe aggression or psychotic symptoms unresponsive to non-pharmacological approaches, and ongoing therapy is tailored based on close monitoring of response and adverse effects.²⁶

Case review — Serge

Serge and his daughter Anna are attending for a renewal of Serge's prescriptions. Serge is a 78-year-old man who was diagnosed with dementia (probable Alzheimer's disease) 4 years ago and has experienced a rapid decline in cognition (last recorded mini-mental state examination [MMSE] score 10). He is an ex-smoker, BMI 18, BP 140/90. He is taking perindopril erbumine 4 mg daily. His only other diagnosis is benign prostatic hyperplasia, for which he takes prazosin 2 mg twice daily. He lives with Anna who is also his primary carer. Seven months ago, Serge had a violent episode after which he was started on risperidone (current dose 1 mg/day). Anna reports that Serge has had no outbursts of verbal or physical aggression in the last 2 months. She notes that since starting on the risperidone he has had difficulty stopping and starting walking, with a tendency to shuffle.

What are the issues in reviewing Serge's medication?

- As Serge's symptoms have been stable for some time, and in view of apparent parkinsonian adverse effects, a trial of dose reduction and ultimately withdrawal of risperidone is indicated, starting with a change to risperidone 0.5 mg/day.

What else should be done for Serge's physical health?

- Test fasting blood glucose.

What else can be done to assist Anna in Serge's dementia care?

- Advise Anna to contact her GP or the Dementia Behaviour Management Advisory Service (DBMAS) on 1800 699 799 if behavioural symptoms re-emerge.
- Ensure that Anna is informed about available support services including respite care.
- Alzheimer's Australia (www.alzheimers.org.au) can provide information about carer support and training in non-pharmacological behavioural management techniques.

Discontinuing antipsychotics may lead to improved survival rates over the next 1–3 years. The dementia antipsychotic withdrawal trial (DART-AD) found that after 24 months, people who were randomised to stop their existing antipsychotic regimen had a 71% survival rate, while those who were randomised to continue antipsychotics had a 46% survival rate (Hazard ratio = 0.58 95% CI 0.35 to 0.95 for 24–54 months of follow-up). There were too few participants to analyse cause of death.^{27,28}

When to review and discontinue

Most people with dementia who stop antipsychotics do not show worsening behaviour, particularly if symptoms are already under control.^{28,29} In light of the serious risks, guidelines recommend reviewing the need for antipsychotic therapy for behavioural symptoms of dementia within 3 months of starting and regularly thereafter.²⁶ There is limited evidence for efficacy beyond 3 months and behavioural symptoms tend to vary over time, with or without the use of antipsychotics.³⁰

Update on non-pharmacological approaches

Non-pharmacological approaches are first line for behavioural symptoms of dementia because of a favourable balance of benefits and harms.¹⁰ Systematic reviews of the evidence have concluded that individually tailored interventions are best.^{31,32} While many trials of non-drug approaches have been of poor quality, a recent review found evidence of efficacy even though it only considered studies that met quality requirements, such as an adequate control group.³² The authors concluded that aromatherapy, personalised music, video or audio tapes of family members, muscle relaxation therapy and changes to bathing routines (such as bed baths) significantly reduced behavioural symptoms.³² There are no reliable comparisons between non-pharmacological approaches and antipsychotics, but benefits of either treatment are modest.

An Australian study has demonstrated that introducing a personalised care approach in residential aged care facilities may benefit all residents with dementia.

The study compared 3 interventions:

- staff training in better understanding and responding to behavioural symptoms
- dementia-care mapping (a systematic method of developing individual resident care plans based on histories, needs and preferences)
- usual care.

About 15–25% of the residents had a substantial reduction in agitation after 8 months of either active intervention, while none improved after usual care. Use of antipsychotic drugs did not change significantly in any of the groups.^{33,34}

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