National Prescribing Service Limited

Results

Case study 47: Antipsychotic drugs for schizophrenia

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ABN 61 082 034 393 | Level 7/418A Elizabeth Street Surry Hills NSW 2010 | PO Box 1147 Strawberry Hills 2012
Phone: 02 8217 8700 | Fax: 02 9211 7578 | email: info@nps.org.au | web: www.nps.org.au

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Case study 47
Antipsychotic drugs for schizophrenia

Scenario

Zac (25 years old) was diagnosed with paranoid schizophrenia several years ago. He has experienced three episodes of psychoses in the past three years, and was commenced on olanzapine 5 mg daily after the first episode.

His last episode occurred eight months ago, during which Zac was preoccupied with thoughts that he was being spied on. He lost his job at the local supermarket, and relationships with family members broke down as he feared that they would betray him to the spies. Following this episode, his olanzapine dose was increased from 10 mg to 15 mg daily.

Zac has not experienced any delusions since then, and now has a good understanding of his condition. He is currently maintained on 15 mg olanzapine daily to prevent another relapse. He maintains regular contact with his GP and the relationship with his family has improved. He has started working at the local fruit and vegetable shop.

Zac presents today and states that he wants to stop his olanzapine because he has been symptom free, he is also very concerned and feeling a bit down about his weight gain (20 kg increase since commencing olanzapine, current body mass index 29 kg/m^2). He also states that his mother insisted he tells you about her recent diagnosis of type 2 diabetes. Zac's last fasting blood glucose concentration, measured 3 months ago, was 6.3 mmol/L (this was normal before he started olanzapine). He has no other medical conditions or allergies.

1. a) Given Zac's concern, what would you recommend regarding his olanzapine? (please choose one response only)

- ☐ Continue olanzapine ▸ ☐ Same dose ☐ Higher dose ☐ Lower dose
- ☐ Change olanzapine to another antipsychotic drug
- ☐ Stop olanzapine
- ☐ Other (please specify)

b) Please give reason(s) for your recommendation.

2. Regardless of your decision in Question 1, if Zac were to continue taking olanzapine, what steps would you recommend to address the:

a) weight gain?

b) blood glucose concentration?

3. a) Regardless of your decision in Question 1, if Zac were to change from olanzapine to another antipsychotic drug, what would you choose?

Drug	Dose	Frequency	Route

b) What are the potential advantages of switching to the alternative antipsychotic drug you chose in part (a) compared to continuing with olanzapine as described in the case?

c) What are the potential disadvantages of switching to the alternative antipsychotic drug you chose in part (a) compared to continuing with olanzapine as described in the case?

Summary of results

At the time of publication, 1003 responses had been received. This report summarises responses from 200 general practitioners.

Case synopsis

Zac, a 25-year-old patient diagnosed with paranoid schizophrenia, has experienced three episodes of psychoses in the past three years. He is currently treated with olanzapine 15 mg daily and has not experienced any delusions in the past eight months. He now has a good understanding of his condition, family relationships have improved and he has started working again.

Zac wants to stop his olanzapine because he has been symptom free and is very concerned about his significant weight gain. There is also family history of type 2 diabetes.

Continuing or switching olanzapine

- Given Zac's concern about weight gain, respondents recommended switching from olanzapine to another antipsychotic drug (35.5%) or decreasing the dose of olanzapine (35.5%); however, 27.5% would continue olanzapine at the current dose (15 mg).
- Respondents who would switch from olanzapine to another medication were concerned about the adverse effects of olanzapine (significant weight gain and potential to develop diabetes), especially as there is family history of diabetes and Zac wants to cease olanzapine. Other antipsychotic drugs were thought to have less effect on weight and blood glucose concentrations.
- Respondents who would continue olanzapine at a lower dose were also concerned about the adverse effects of olanzapine but acknowledged that given the good response to olanzapine, lowering the dose may be appropriate.
- Respondents who would continue olanzapine at the current dose emphasised that the schizophrenia was well controlled on 15 mg olanzapine and suggested other ways of managing the adverse effects.

Managing adverse effects of olanzapine

- To manage Zac's weight gain, respondents recommended for Zac be referred to a dietitian (61%) and/or exercise physiologist (10%), to increase exercise (57%) or have a regular exercise program (23.5%), modify his diet (48.5%) and consider a weight-management program (5.5%).
- To manage Zac's elevated blood glucose concentration, respondents would conduct an oral glucose tolerance test (40.5%), monitor blood glucose regularly (37%), manage other risk factors (e.g. lipids, blood pressure) (20.5%) and refer Zac to a dietitian (19%). They would also encourage Zac to modify his diet (33%), increase exercise (26.5%) and lose weight (14%).

Alternative antipsychotic drug

- The alternative antipsychotic drugs chosen included risperidone (49.5%), quetiapine (17.5%), ziprasidone (10%), amisulpride (7.5%), haloperidol (4.5%) and aripiprazole (4%).
- The main advantages of switching to the alternative drug included fewer tendencies for weight gain, increased blood glucose concentration and metabolic disturbance.
- The main disadvantages of switching included potential loss of control or relapse of symptoms, the alternative drug being less effective for the patient, and potentially a greater risk of other adverse effects (e.g. extrapyramidal symptoms).

Results in detail

Continuing or switching olanzapine

- Given Zac's concern, Table 1 summarises respondents' recommendation about olanzapine.

Table 1

Decision regarding olanzapine	% of respondents (n = 200)
Change from olanzapine to another antipsychotic drug	35.5
Continue olanzapine at a lower dose	35.5
Continue olanzapine at the current dose (i.e. 15 mg daily)	27.5
Discuss with a psychiatrist before deciding	1.0
Cease olanzapine	0.5

- The main reasons for changing to another drug or continuing olanzapine are summarised in Table 2.

Table 2

Reason for changing to another antipsychotic drug	% of respondents* (n = 71)
Adverse effects from olanzapine (significant weight gain and/or potential to develop diabetes)	66.2
Other drugs available (with less potential for weight gain and/or development of diabetes)	26.8
Potential compliance problems if patient is 'forced' to continue olanzapine	15.5
Family history of diabetes	15.5
Patient needs ongoing treatment but is experiencing adverse effects on olanzapine	9.9
Risk of relapse on a lower dose of olanzapine	8.5
Reason for continuing olanzapine at a lower dose	**% of respondents* (n = 71)**
Good response to olanzapine but patient is experiencing adverse effects	21.9
Lower dose may be sufficient for maintaining control with less effect on weight and blood glucose concentration	21.9
Lower dose may be associated with less weight gain and blood glucose disturbance	16.2
Patient is currently stable, so lower dose can be tried	12.4
Patient needs ongoing treatment with olanzapine to prevent relapse	8.6
Lowering the dose is one way of showing the patient his concerns have been heard	4.8
Reason for continuing olanzapine at the current dose	**% of respondents* (n = 55)**
Schizophrenia is well-controlled	67.3
Try other ways of managing adverse effects first (e.g. lifestyle changes)	27.3
Patient needs ongoing treatment on olanzapine to prevent relapse	18.2
Risk of relapse if a lower dose or another drug is tried	12.7

* Respondents may have more than one response

Managing adverse effects of olanzapine

- If Zac was to continue treatment with olanzapine, respondents would recommend the following strategies to manage his weight gain (Table 3) and elevated blood glucose concentration (Table 4).

Table 3

Strategies to manage weight gain	% of respondents* (n = 200)
Refer to a dietitian†	61.0
Encourage patient to increase exercise	57.0
Encourage patient to modify diet	48.5
Encourage a regular exercise program	23.5
Refer to exercise physiologist†	10.0
Consider a weight-management program	5.5

* Respondents may have more than one response

† Some respondents stated the referral would be done as part of an Enhanced Primary Care Team Care Arrangement.

Table 4

Strategies to manage elevated fasting blood glucose concentration	% of respondents* (n = 200)
Conduct an oral glucose tolerance test†	40.5
Monitor blood glucose concentration regularly (e.g. every 6 months)	37.0
Encourage patient to modify diet‡	33.0
Encourage patient to increase exercise	26.5
Assess, manage and monitor other risk factors (e.g. lipids, blood pressure, smoking status)	20.5
Refer to dietitian	19.0
Encourage weight loss	14.0

* Respondents may have more than one response

† Some respondents stated that this was to be preceded by a repeat fasting blood glucose concentration, or a trial of exercise and diet

‡ Specific examples included low-glycaemic-index diet, low-fat diet, low-carbohydrate diet, low-sugar diet or a combination of these

Alternative antipsychotic drug

- If a decision was made to switch Zac from olanzapine to an alternative antipsychotic drug, respondents would recommend the following drugs (Table 5).
- Chosen dosages varied greatly. For example, risperidone doses ranged from 1–10 mg daily.

Table 5

Alternative antipsychotic drug	% of respondents (n = 200)
Risperidone (Risperdal)	49.5
Quetiapine (Seroquel)	17.5
Ziprasidone (Zeldox)	10.0
Amisulpride (Solian)	7.5
Haloperidol (Serenace)	4.5
Aripiprazole (Abilify)	4.0
Miscellaneous*	7.0

* Includes chlorpromazine (2%), clozapine (1.5%), trifluoperazine, pericyazine, flupenthixol (1% each) and fluphenazine (0.5%)

- Table 6 summarises the main advantages of switching from olanzapine to an alternative antipsychotic drug.

Table 6

Advantage of switching to alternative drug	% of respondents recommending alternative antipsychotic drug*					
	Risperidone (n = 99)	Quetiapine (n = 35)	Ziprasidone (n = 20)	Amisulpride (n = 15)	Haloperidol (n = 9)	Aripiprazole (n = 8)
Less tendency for:						
• weight gain	85.9†	77.1	100.0	73.3†	77.8	100.0†
• increased blood glucose concentration	37.4	22.9	25.0	40.0†	55.6†	38.0†
• adverse effects (overall)	12.1	5.9	5.0	6.7	—	—
• metabolic disturbance	11.1	11.8	15.0	26.7	—	25.0
• sedation	—	—	—	13.3	—	—
May help compliance	6.1	2.9	—	—	—	12.5
Different strengths allow small dosage increments	—	11.8	—	—	—	—

* Respondents may have more than one response

† Some respondent stated that the alternative drug does not cause this particular adverse effect

- Table 7 summarises the main disadvantages of switching from olanzapine to an alternative antipsychotic drug.

Table 7

Disadvantage of switching to alternative drug	% of respondents recommending alternative antipsychotic drug*					
	Risperidone (n = 99)	Quetiapine (n = 35)	Ziprasidone (n = 20)	Amisulpride (n = 15)	Haloperidol (n = 9)	Aripiprazole (n = 8)
Potential loss of control or relapse of symptoms	51.5	68.6	55.0	46.7	11.1	62.5
May not be as effective for this patient	35.4	34.3	65.0	26.7	11.1	50.0
(Greater) risk of:						
• extrapyramidal symptoms	33.3	11.4	40.0	6.7	100.0	25.0
• increased prolactin levels	15.2	—	—	—	—	—
• neuroleptic malignant syndrome	—	—	—	6.7	11.1	12.5
May cause other adverse effects	12.1	8.6	10.0	20.0	—	12.5
May decrease compliance	7.1	2.9	5.0	13.3	—	12.5
Unsure what dose is needed for this patient	4.0	8.6	—	6.7	—	12.5

* Respondents may have more than one response

Practice points

Selecting and initiating antipsychotic drug treatment

- Select an antipsychotic drug based on the properties of the drug and the clinical needs of the patient. Note that there may be great individual variability in response, tolerability and preference.[1]
- All antipsychotic drugs competitively block dopamine D_2 receptors — this is the basis of their antipsychotic efficacy but also the mechanism by which they induce extrapyramidal adverse effects and increase prolactin concentrations.[2] Hence, successful treatment depends on a balance between effectiveness and adverse effects.
- In general, start with a low dose and titrate upwards at a rate and to a level that best suits the patient.[1] Maintain treatment using the lowest effective dose.[3]
- Common adverse effects of antipsychotic drugs are summarised in the Appendix (page 14).
- Atypical antipsychotic drugs are preferred because of their lower risk of extrapyramidal adverse effects at therapeutically effective doses, compared with the typical antipsychotic drugs.[4,5] However, this advantage lessens as the dose of the atypical antipsychotic drug is increased.[2] Also, the lower risk of extrapyramidal adverse effects needs to be balanced against the problems of metabolic adverse effects.[2]

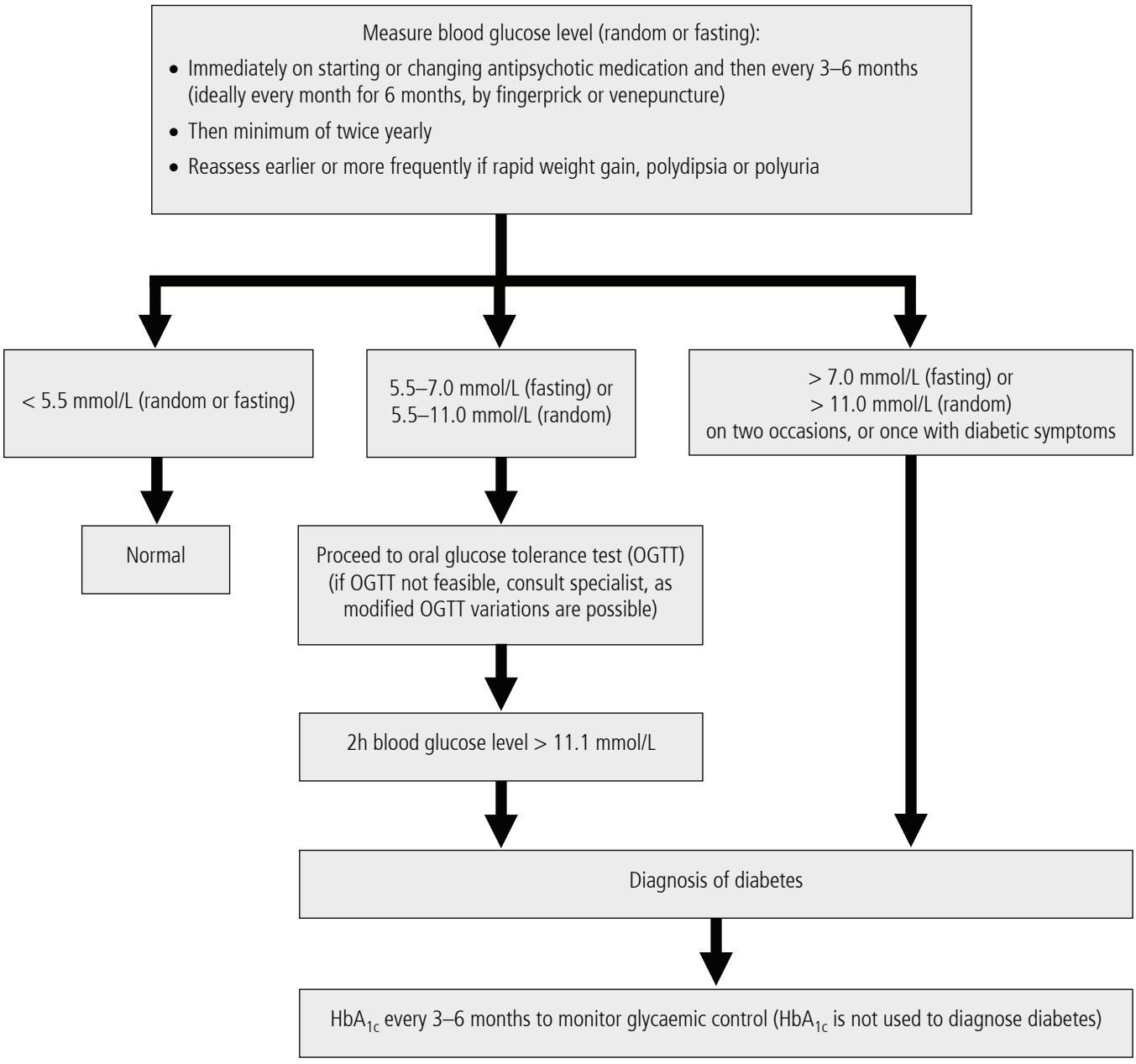
Preventing and managing metabolic disturbances

- Monitor for potential metabolic disturbances (weight gain, type 2 diabetes, dyslipidaemia) when starting or changing antipsychotic drug treatment, when increasing the dose of the drug, and during ongoing treatment.[6]
- Monitoring parameters should include fasting (or random) blood glucose concentration (see Figure 1 for detailed guidelines), fasting lipids, weight, waist and hip circumference, body mass index and blood pressure.[6,7]
- Educate the patient, family and carer(s) about potential metabolic disturbances and provide lifestyle advice regarding diet and physical activity.[8]
- In managing weight gain, consider the following:[8]
  - set realistic goals
  - provide highly structured interventions
  - provide support (intensive support at the start; may be less intensive over time).
  - focus on reducing caloric intake (changing types of food and reducing portion sizes) rather than complex dietary changes
  - recommend gradual increase in physical activity to 30–60 minutes of moderate physical activity on most days of the week.
- If there is significant weight gain or metabolic effects, reassess the risk and benefit of the antipsychotic drug choice and concurrent medications from both a psychiatric and a metabolic perspective.[8]

Switching to a different antipsychotic drug

- Consider a crossover phase of 1–2 weeks for non-acute patients. Reduce the dose of the first medication (or stop depot preparation) and gradually increase the dose of the second medication.[1]
- Educate the patient and carer(s) about the risks (potential relapse, temporary exacerbations of adverse effects) and potential benefits (improved symptom reduction, eventual reduction in adverse effects) of switching.[1]

Figure 1. Screening for hyperglycaemia in people treated with antipsychotic medication. (Adapted from: Lambert TJR, Chapman LH. Diabetes, psychotic disorders and antipsychotic therapy: a consensus statement. Med J Aust 2004;181:544–8. ©Copyright 2004. The Medical Journal of Australia. — reproduced with permission.)



Commentary 1

Professor David Castle
Chair of Psychiatry
St Vincent's Hospital, Melbourne
The University of Melbourne

Key points

- People with mental disorders such as schizophrenia carry a high burden of medical morbidity, including diabetes, hypertension, smoking and obesity; these comorbidities are often unrecognised and suboptimally treated.[9]
- Most people with schizophrenia (about 80% in a recent Australian survey[10]) do have contact with general practitioners, who have a key role in the treatment of the individual's mental and physical health.
- Some of the antipsychotic medications have a greater propensity to cause weight gain, hypertriglyceridaemia and emergent diabetes than others; patients using these agents need to be monitored regularly.
- Decisions about switching medications are complex and require a full and detailed discussion of risks and benefits with the patient and (where appropriate) his or her family and carers.

Respondents to the case scenario clearly recognised that olanzapine is one of the antipsychotics that has a particular propensity for causing weight gain, but they appeared to be reluctant to necessarily switch to another medication despite the patient expressing concern about his weight gain. In addition, the family history of type 2 diabetes should alert GPs to a potential risk in this patient of the emergence of type 2 diabetes, which is well recognised in the setting of weight gain as well as probably a direct effect of olanzapine on the insulin cascade.[11]

Obviously the decision to switch medication is a complex one and requires full discussion of risks and potential benefits with both the patient and (when appropriate) his or her family and carers. The clinical situation (such as the current scenario) is a difficult one — the patient is well controlled, in terms of his/her psychotic symptoms, with a particular agent, but the agent is causing side effects that the patient is unhappy with. However, the ongoing risks of obesity and, potentially, diabetes are extremely worrying in terms of medical morbidity and mortality in people with schizophrenia and related disorders and this also needs to be taken into account. Furthermore, obesity is well recognised as a side effect associated with non-adherence to medication[12] and there is potential for the patient, who is clearly expressing a desire to stop his olanzapine, to do so anyway, with the very real risk of psychotic relapse. On balance, it is much better that any switch is performed in a controlled manner, with appropriate monitoring.

Respondents recognised that certain psychosocial interventions might be helpful in minimising weight gain associated with olanzapine. There is indeed an evidence base in this regard,[8] and concerted interventions looking at diet and exercise can be effective in weight loss.[13] However, these need to be ongoing and sustained and are usually associated with fairly modest weight loss.

Some of the modern (atypical) antipsychotics are associated with much less propensity for weight gain than others and it might be worth considering a switch to one of these agents (for example, aripiprazole or ziprasidone seem to carry little risk of weight gain).[14] These might be worth considering in this patient's case. Having said this, there is always the risk of a non-response, which would require careful discussion as well as close monitoring during the switch.

Any switch should be performed over a matter of some weeks, with slow reduction in dosage of the current drug (i.e. olanzapine) and a slow incremental dose of the new agent.[15] The patient and carers should be carefully apprised of the potential warning signs of psychotic relapse, and appropriate intervention plans need to be put in place ahead of time to deal with these.

Commentary 2

Dr Richard J O'Bryan
General Practitioner
Melbourne

Paranoid schizophrenia

The current case study of Zac illustrates the following key points concerning paranoid schizophrenic psychosis:

- the common onset of schizophrenia in early adult life (often during the late teens or early 20s)
- the propensity for schizophrenia to episodically relapse
- the therapeutic benefits and the potentially harmful effects of antipsychotic medication
- the frequent patient requests to cease antipsychotic medication because of restoration of wellbeing, or because of real, anticipated or perceived deleterious side effects.

Zac's case

Zac has requested cessation of his prescribed medication (olanzapine 15 mg daily) because he is symptom free and concerned about his excessive weight gain and the possibility of developing diabetes mellitus (given a family history of type 2 diabetes).

Because of the apparent beneficial effects of olanzapine, about two-thirds of respondents recommended that Zac continue taking this medication, either in the same dose or in a reduced dose but allied with measures to address the side effects of weight-gain and potential diabetes. About one-third would have recommended ceasing olanzapine and substituting it with an alternative antipsychotic medication.

In evaluating the recommendations offered by the respondents, the following issues should be considered:

- The strong likelihood of schizophrenic relapse if antipsychotic medication is ceased in this particular patient. This factor has obviously been recognised by most respondents, as only one recommended ceasing the antipsychotic medication.
- The relative beneficial efficacies; the possible deleterious side effects; the drug compliance profiles; GP familiarity with, and confidence in, prescribing; and the availability and cost of the various antipsychotic medications proposed for Zac's continuing pharmacotherapeutic management.
- The likelihood, or not, of successfully addressing and overcoming intolerable or harmful side effects of prescribed medication. In particular, weight gain (olanzapine), sedation (quetiapine and olanzapine), and hyperprolactinaemia (risperidone and amisulpride), may be difficult, if not impossible, to manage adequately.
- Typical antipsychotic medications (e.g. haloperidol) are outmoded and their use should be strongly discouraged except in cases of extreme non-compliance, where depot medication is indicated and depot risperidone (Risperdal Consta) is not tolerated. This is because of their greater propensity (compared with atypical antipsychotic medications) to cause seriously disabling and often irreversible extrapyramidal side effects, including tardive dyskinesia. Possible medicolegal implications of initiating or continuing them should not be forgotten.
- GPs should use only medications with which they are familiar and which they can prescribe with confidence.
- A surprisingly high number of respondents (10%) chose to substitute olanzapine with ziprasidone. Ziprasidone is relatively new on the Australian market and has only recently been listed on the Pharmaceutical Benefits Schedule. Reported adverse reactions include somnolence, nausea and vomiting, and postural hypotension.[16] There are also concerns about QT prolongation.[16]

Summary

Zac's case is a common and challenging clinical problem which requires sensitive and skillful GP management. The important management issues involve:

- empathy with the patient's wish to cease taking antipsychotic medication
- firmness in insisting on continued medication
- skillful discernment in choosing appropriate continuing medication, and preparedness to switch to an alternative medication if deemed necessary
- supportive psychotherapeutic skills to facilitate and ensure ongoing patient compliance with the chosen medication regimen
- education and encouragement of patient towards his own self-care and co-operation in holistic management, including diet, exercise, hygiene, social and recreational pursuits, etc
- collaboration with significant others, (consultant psychiatrist and/or physician, mental health care workers, dietitian, family, friends, etc), to optimise management outcomes.

Appendix

Common adverse effects of antipsychotic drugs* at usual therapeutic doses[3,17]

Drug	Common adverse effects	Relative frequencies of some adverse effects (not related to intensity)				
		Sedation	Postural hypotension	Anti-cholinergic	Extra-pyramidal	Weight gain
Atypical antipsychotic drugs						
Amisulpride (Solian)	Dose-related EPSE (including acute dystonia and tardive dyskinesia), insomnia, anxiety, agitation, somnolence, amenorrhoea, galactorrhoea, hypersalivation, constipation	+	+	0	++†	+
Aripiprazole (Abilify)	Headache, somnolence, akathisia, light-headedness, nausea, vomiting, constipation	++	+	0	+	+
Clozapine (Clopine, CloSyn, Clozaril)	Drowsiness, seizures, headache, dizziness, orthostatic hypotension (especially at start of treatment), tachycardia, hyperpyrexia, hepatitis, neutropenia, hypersalivation, weight gain, nausea, vomiting, constipation, urinary retention, urinary incontinence	+++	+++	+++	+	+++
Olanzapine (Zyprexa)	Hyperglycaemia, type 2 diabetes, weight gain, dizziness, peripheral oedema, orthostatic hypotension, dry mouth, constipation, drowsiness	+++	+	++	+	+++
Quetiapine (Seroquel)	Drowsiness, dizziness, orthostatic hypotension, tachycardia, dry mouth, constipation	+++	++	+	+†	++
Risperidone (Risperdal)	Orthostatic hypotension (especially early in treatment), tachycardia, insomnia, agitation, anxiety, headache, akathisia, hyperprolactinaemia	++ (initially)	+++ (initially)	0	++	++
Ziprasidone (Zeldox)	Headache, somnolence, dizziness, dyspepsia and nausea	++	+	+	+	+
Typical antipsychotic drugs						
Chlorpromazine (Largactil)	Sedation, orthostatic hypotension, tachycardia, dry mouth, blurred vision, mydriasis, constipation, nausea, urinary retention, sexual adverse effects, EPSE, weight gain, hyperprolactinaemia (may result in galactorrhoea, gynaecomastia, amenorrhoea or infertility)	+++	+++	+++	++	+++
Haloperidol (Serenace)		+	+	+	+++	++
Pericyazine (Neulactil)		+++	++	+++	+	++
Thioridazine (Aldazine)		+++	+++	+++	+	+++
Trifluoperazine (Stelazine)		+	++	+	+++	++

Approximate frequencies (not the intensity with which adverse effects occur) of adverse effects:
0 = negligible or absent (< 2%); + = infrequent (> 2%); ++ = moderately frequent (> 10%); +++ = frequent (> 30%)

* Only PBS-listed drugs with an immediate-acting formulation are included

† Rarely a problem at usual therapeutic doses

EPSE = extrapyramidal side effect

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