

# ANTIPSYCHOTIC THERAPY

## Case study 70 report

January 2012

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- ▷ Commentator 1 — Prof Nicholas Keks
- ▷ Commentator 2 — Dr Richard J O'Bryan

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# CASE STUDY 70

## ANTIPSYCHOTIC THERAPY

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### SCENARIO

Emily, 28 years old, was diagnosed with schizophrenia 9 months ago. She was prescribed risperidone and in the last 6 months her dose has been stable at 5mg. During these past 6 months Emily has not experienced a psychotic episode. She does not take any other regular medicines.

Emily has come to see you today as she has been experiencing irregularities in her menstrual cycle for the past 2 months and is concerned about the cause of these.

At this visit Emily mentions that she does not see the point in continuing to take her medicine each day as she has not 'heard voices' in what she describes as 'a long time.'

On examination Emily's body mass index (BMI) is 25 kg/m<sup>2</sup> and blood pressure 120/80 mmHg. Her fasting lipid levels are within normal range. Emily has no family history of diabetes. She has no changes in visual fields and no other neurological abnormality.

**1. Which tests would you request when addressing Emily's concern about menstrual irregularity? (Please indicate all that apply)**

- |   |  |
|---|--|
| <input type="checkbox"/> prolactin        | <input type="checkbox"/> liver function        |
| <input type="checkbox"/> thyroid function | <input type="checkbox"/> fasting blood glucose |
| <input type="checkbox"/> pregnancy test   | <input type="checkbox"/> other (specify) _____ |

**2. List 3 parameters that you would monitor (including the frequency) for Emily after this visit.**

- i. \_\_\_\_\_ Frequency: \_\_\_\_\_
- ii. \_\_\_\_\_ Frequency: \_\_\_\_\_
- iii. \_\_\_\_\_ Frequency: \_\_\_\_\_

**3. List 2 adverse effects (unrelated to her menstrual irregularities) that Emily may experience and your recommendations for their management.**

- i. Adverse effect: \_\_\_\_\_  
Management: \_\_\_\_\_
- ii Adverse effect: \_\_\_\_\_  
Management: \_\_\_\_\_

**4. During your monitoring and investigation Emily's prolactin levels are found to be moderately elevated. What would be your recommendation? (Please select one only)**

- Continue risperidone at the current dose and monitor prolactin level
- Decrease dose of risperidone
- Switch from risperidone to another antipsychotic (specify) \_\_\_\_\_
- Refer to specialist for management
- Other, please specify \_\_\_\_\_

**5. List 2 strategies you would consider to encourage Emily's continued adherence with her medicine**

- i. \_\_\_\_\_  
\_\_\_\_\_
- ii. \_\_\_\_\_  
\_\_\_\_\_

# SUMMARY OF RESULTS

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At the time of publication 1003 responses had been received from all participants, and 200 of those received from doctors have been compiled for feedback in this report.

## CASE SYNOPSIS

Emily, a 28-year-old patient diagnosed with schizophrenia, stable for the last 6 months, and is maintained on risperidone 5 mg/day. She has experienced menstrual irregularity for the past 2 months and is concerned. Emily no longer sees the point in continuing her medicine, as she has not 'heard voices' in a long time. On examination, BMI is 25kg/m<sup>2</sup>. Her blood pressure, fasting lipid levels, neurological examination and visual fields are normal. Emily has no family history of diabetes.

## Investigations for menstrual irregularity on antipsychotic therapy

- ▷ Almost all respondents (98%) would request a serum prolactin test, 89% of respondents would request a pregnancy test, and 88% would request thyroid function test, while only 57% would request blood glucose tests.

## Managing hyperprolactinaemia

- ▷ Respondents suggested dose reduction (46%) and referral to a specialist (33%) as strategies to manage hyperprolactinaemia.

## Monitoring parameters and frequency in antipsychotic therapy

- ▷ The most commonly suggested parameters to monitor were blood glucose (74%); weight, waist circumference and BMI (72%); and blood pressure (44%).
- ▷ Only 33% and 19% of respondents, respectively, suggested annual monitoring of blood glucose and lipids.
- ▷ Most (64%) would monitor weight, waist circumference and BMI every 3 months.
- ▷ Blood pressure monitoring every 6 months was advised by 26%.

## Managing adverse effects of risperidone

- ▷ Respondents listed weight gain (72%), extrapyramidal symptoms (56%) and daytime sedation (30%) as the most common adverse effects of risperidone.
- ▷ More than half of respondents (68%) recommended providing lifestyle advice to manage weight gain.
- ▷ Half (50%) recommended reducing the dose of risperidone to manage daytime sedation, while 44% recommended reducing the dose to manage extrapyramidal symptoms.

## Strategies to increase adherence to antipsychotic therapy

- ▷ Respondents listed regular follow-up and medicines review (66%) and patient education (40%) to encourage adherence to medicine prescriptions.

# RESULTS IN DETAIL

## Investigations in patient with menstrual irregularity on antipsychotic therapy

Table 1 summarises respondents' recommendations on laboratory investigations, given Emily's concern about menstrual irregularities.

TABLE 1: SUGGESTED INVESTIGATIONS FOR MENSTRUAL IRREGULARITIES

Investigations	% of respondents (n = 200)*
Prolactin	98
Pregnancy	89
Thyroid function	88
Liver function	47
Blood glucose	57
Others†	31

\* Respondents may have more than one response

† Includes hormone levels (LH, FSH, progesterone, testosterone, androgen, oestrogen, TSH), gynaecological tests (Pap smear, chlamydia testing, vaginal/pelvic ultrasound), and blood chemistry (electrolytes, urea and creatinine, iron, ferritin, FBC and haemoglobin).

### Practice points

- ▷ Be aware that menstrual irregularities due to hyperprolactinaemia are an adverse effect of antipsychotic use.<sup>1</sup> Consider other signs of hyperprolactinaemia, which include gynaecomastia, galactorrhoea, decreased libido and sexual dysfunction.<sup>2</sup>
- ▷ Exclude other causes such as pregnancy or metabolic dysfunction as part of differential diagnosis in patients with menstrual irregularities.<sup>3</sup>

## Managing hyperprolactinaemia

TABLE 2: MANAGEMENT OF HYPERPROLACTINAEMIA

Management	% of respondents (n = 129)*
Decrease dose of risperidone	46
Refer to specialist for management	33
Continue risperidone at current dose and monitor prolactin level	23
Switch from risperidone to another antipsychotic	6

\* Respondents may have more than one response

### Practice points

- ▷ Manage symptomatic hyperprolactinaemia with the following strategies<sup>4</sup>:
  - exclude other causes such as pregnancy, hypothyroidism and other medicines
  - reduce the dose of antipsychotic gradually if the patient's mental state is stable
  - switch antipsychotic therapy, in consultation with a specialist or a mental health team, to an antipsychotic with a low propensity to elevate prolactin (e.g. aripiprazole).

## Monitoring parameters and frequency

- ▷ Respondents were asked to list three parameters that they would monitor (including frequency) for Emily after her visit. Table 3 outlines the responses.

TABLE 3: PARAMETERS MONITORED AND THEIR FREQUENCIES\*

Parameters	% Monthly to 3-monthly monitoring (n = 110)	% 6-monthly monitoring (n = 189)	% 12-monthly monitoring (n = 189)
Adherence to medicine	14	—	0.5
Blood glucose	20	25	33
Blood pressure	27	26	22
Electrocardiogram	—	—	11
Extrapyramidal symptoms	4	8	—
Gynaecological status†	22	1	—
Lipid	2	13	19
Prolactin	9	7	6
Weight, waist circumference and BMI	64	12	3
Others‡	9	1	2

\* Respondents may have more than one response

† Gynaecological status pertains to menstrual cycle and sexual problems, breast and vaginal examinations, Pap smears and pelvic ultrasound

‡ Includes blood chemistry and mental wellbeing

## Practice points

- ▷ Recognise that people with mental illnesses often have poor physical health and can develop adverse effects from using antipsychotics.<sup>5</sup>
- ▷ Monitor at every visit:
  - weight and waist circumference
  - adverse effects
  - lifestyle activities such as smoking status, alcohol and illicit drug consumption.<sup>2,4,6–8</sup>
- ▷ Monitor annually:
  - blood pressure
  - fasting blood glucose
  - electrocardiogram
  - menstrual irregularities
  - lipids
  - galactorrhoea
  - gynaecomastia.

Test prolactin levels when hyperprolactinaemia is suspected.<sup>2,4,6–8</sup>
- ▷ Monitor 6 monthly: extrapyramidal symptoms.<sup>2,4,6–8</sup>
- ▷ Assess adherence to antipsychotic therapy regularly and systematically.<sup>6</sup>
- ▷ Maintain physical health by promoting preventive health checks such as Pap smears.
- ▷ For suggested monitoring and review frequency for people taking antipsychotics long term, refer to *NPS News 74 Balancing benefits and harms of antipsychotic therapy* ([www.nps.org.au/news\\_74](http://www.nps.org.au/news_74)).

## Managing adverse effects of risperidone

Respondents were asked to list two adverse effects of risperidone other than menstrual irregularities. Table 4 outlines responses.

TABLE 4: ADVERSE EFFECTS OF RISPERIDONE LISTED BY RESPONDENTS

Adverse effects	% of respondents (n = 200)*
Weight gain	72
Extrapyramidal symptoms	56
Sleep disturbances (daytime sedation / insomnia)	31
Metabolic disturbances (increased blood glucose and lipids, unspecified metabolic disturbances)	31
Others†	9
Increased prolactin level	4

\* Respondents may have more than one response

† Includes high blood pressure, headache, hypotension, behaviour problems and anticholinergic adverse effects

Table 5 summarises the three most listed adverse effects of risperidone and the suggested management strategies.

TABLE 5: THREE MOST COMMON ADVERSE EFFECTS OF RISPERIDONE, WITH SUGGESTED MANAGEMENT STRATEGY

Adverse effect	Management strategy	% recommending (n=200)*
Weight gain	Advise lifestyle change (diet and exercise)	68
	Reduce dose of antipsychotic therapy	14
	Refer to other health professionals (specialist/allied health)	9
	Switch antipsychotic therapy	7
	Medicine review	3
Extrapyramidal symptoms	Reduce dose	44
	Switch antipsychotic therapy	33
	Monitor extrapyramidal symptoms	5
	Refer to other health professionals (specialist/allied health)	5
	Discontinue antipsychotic therapy	4
	Add benztropine	2
	Medicines review	2
Advise lifestyle change (diet and exercise)	1	
Sleep disturbances†	Reduce dose of antipsychotic therapy	50
	Adjust dose of antipsychotic therapy	18
	Switch antipsychotic therapy	16
	Refer to other health professionals (specialist/allied health)	8
	Discontinue antipsychotic therapy	3
	Advise lifestyle change (diet and exercise)	2
	Medicines review	1

\* Respondents may have more than one response

† Sleep disturbances include daytime sedation (98.8%) and insomnia (1.2%)

## Strategies to increase adherence to antipsychotic therapy

Respondents were asked to list two strategies to encourage Emily's continued adherence to her antipsychotic therapy. Table 6 outlines the responses.

TABLE 6: STRATEGIES TO INCREASE ADHERENCE TO ANTIPSYCHOTIC THERAPY

Strategies	% of respondents (n=200)*
Regular follow-up and medicines review	66
Educate patient on the condition and importance of adherence to antipsychotic therapy	40
Counselling	20
Involve family/support group	18
Advise lifestyle change (diet and exercise)	18
Refer to other health professionals (specialist/allied health)	16
Reduce or adjust dose to minimise side effect	12
Others <sup>†</sup>	9

\* Respondents may have more than one response

† Includes the use of aids and contraceptive measures

### Practice points

- ▷ Provide information on the antipsychotic's effects and address the issues that are perceived as problems.<sup>2</sup>
- ▷ Encourage the patient to attend regular visits and assess how well they are tolerating the antipsychotic therapy.<sup>2</sup>
- ▷ Plan and request for a home medicines review to identify any medicine-related issues and to improve adherence.<sup>12</sup>

# COMMENTARY 1

## Key points

- ▷ Menstrual dysfunction is a frequent and challenging complication of some antipsychotic medications. There are no easy answers.
- ▷ Adherence to treatment is critical for prevention of further illness, which will lead to worse outcomes.
- ▷ Schizophrenia is not a comprehensive diagnosis. Work out the patient's illness phase and treatment needs in an overall life context.

Diagnosing schizophrenia is not particularly helpful. It is more useful firstly to assess the patient's illness profile in terms of positive and negative symptoms, cognitive dysfunction, mood elevation and/or depression and anxiety.<sup>13</sup> Secondly the patient's illness phase needs to be recognised. Is this first-episode or early relapsing psychosis and its aftermath? Is it acute illness or is this chronic illness? In about one-third of patients it will be relapsing illness with relative wellness between episodes.<sup>13</sup>

In this case I will assume Emily has experienced her first psychotic episode, which had responded to antipsychotic medication (as is the case with more than 90% of such patients) and has been well for a few months while taking risperidone. The dose of risperidone is rather high: patients having a first-episode would be taking about 2 mg on average. As Emily does not have extrapyramidal side effects and is well, the dose is in the therapeutic range (although it may well be that Emily will tolerate substantial dose reduction without relapse).

Unfortunately Emily has developed menstrual irregularities with risperidone. As risperidone frequently causes substantial hyperprolactinaemia, about one-third of women on long-term treatment with risperidone experience this complication. Reducing the dose is not always helpful, as risperidone has a ceiling effect on prolactin secretion at quite modest doses. Changing to other atypical antipsychotics, especially quetiapine, aripiprazole, ziprasidone

and asenapine (olanzapine to a lesser extent) should help, but there is the risk of precipitating a relapse. Some clinicians have suggested use of a suitable oral contraceptive in appropriate circumstances.

Why persist with risperidone for Emily? It is an effective medicine with only a mild to moderate effect on metabolic parameters, such as weight gain, in most patients. There are no anticholinergic side effects and the drug can often be taken long term without any extrapyramidal side effects. Also, medication change should not be undertaken lightly, as psychotic relapse can worsen prognosis, result in traumatising hospitalisation or catastrophic complications, including suicide.

Of greatest concern in this case is Emily's apparent enthusiasm for stopping the antipsychotic medication. It is true that, if Emily's case is that of recovered first-episode psychosis, she has a 20-30% chance of staying well. But that means more than a 70% chance of relapse, with consequences as noted above.<sup>14</sup> Some patients have quite mild illness and may regard relapse of psychosis as an acceptable risk. Most patients, if fully informed about the nature of the illness and implications of relapse, choose to continue with treatment and minimise risk of relapse.

The most common cause of illness relapse is failure to adhere to treatment. Each relapse during the first 5 or so formative years during which the long-term illness pattern is established tends to worsen outcome. Negative symptoms become more prominent and positive symptoms are less reversible with treatment, as well as taking longer to respond. The dose requirement of antipsychotic medication virtually doubles.

In some patients poor insight is a key factor in non-compliance, so a good therapeutic relationship, supportive therapy and psycho-education about the illness and treatment are crucial. For many patients side effects lead to poor adherence. Antipsychotics are quite challenging, as side effects are frequent and often distressing with these drugs.

The degree of understanding patients can attain about their illness may be influenced by factors such as partial recovery and ongoing psychosis, intelligence, education, psychopathy, sociocultural factors and so on. But most often the key factor is the quality of the therapeutic relationship between patient and doctor. Good psycho-education for the patient and their family takes empathy, time and effort, as well as an appreciation by the health professional of the challenges of treating psychosis.

### **Conflict of interest**

I have no current conflicts of interest.

During my career I have received research support, and/or acted as consultant to, and/or received honoraria from, Astra Zeneca, Eli Lilly, Novartis, Wyeth, Bristol Myer Squibb, Janssen, Sanofi Aventis, Organon, Lundbeck, Servier and Pfizer. During my career I have been employed by Government services and acted as consultant to Governments.

## COMMENTARY 2

### Clinical presentation

A patient, Emily, aged 28 years, presents with menstrual irregularities of 2 months' duration in the context of having been diagnosed with schizophrenia 9 months previously, and of being treated with a stable dose of risperidone 5 mg/day for the past 6 months. She has been free of auditory phenomena for what she describes as a 'long time', and would like to discontinue taking risperidone.

### Clinical problems

#### Menstrual irregularity

Emily's menstrual irregularity may or may not be related to her taking risperidone. A non-iatrogenic cause of her menstrual irregularity must be excluded. This will involve a:

- ▷ gynaecological physical examination (including a cervical Pap smear)
- ▷ pelvic ultrasound
- ▷ pregnancy test
- ▷ survey of her sex-hormone profile.

Twenty-eight years of age is very early for the onset of climacteric symptomatology, but this may occur in women whose menarche was of late onset.

The exclusion of any other cause of menstrual irregularity raises the likelihood that it is of iatrogenic origin and due to hyperprolactinaemia secondary to use of risperidone. An abnormally high prolactin level in the absence of other detectable clinical cases of menstrual irregularity would strongly support a diagnosis of a risperidone side effect.

Among antipsychotic (atypical) medications, risperidone has the highest profile of inducing hyperprolactinaemia and, as a consequence, menstrual irregularities.

#### Diagnosis of schizophrenia

The diagnosis of schizophrenia has been made, as far as the clinical history reveals, on the sole symptomatology of Emily's 'hearing voices'. It is not known whether Emily has any:

- ▷ other positive symptoms (e.g. delusions or thought disorder)
- ▷ negative symptoms (e.g. flat affect, poverty of thought, lack of motivation or volition, or social withdrawal)
- ▷ cognitive symptoms (e.g. distractibility, impaired working memory, impaired executive function)
- ▷ mood symptoms (e.g. depression or mania or hypomania).

Nor is it known whether Emily may be affected by alcohol or drug abuse, particularly cannabis or amphetamine.

The diagnosis of schizophrenia is entirely symptomatology based, and can be made only for a complex (or combination) of symptoms, persisting over a prolonged period of time, exceeding 6 months. Schizophreniform and schizo-affective disorders exist as discrete clinical entities, and present with distinct symptomatic profiles that require specific psychopharmacological treatment modalities.

In the case of Emily a careful retrospective clinical history needs to be made to elicit and/or exclude all positive, negative, cognitive and mood symptoms associated with schizophrenia. The symptomatology must then be correlated with the categories of Psychotic disorders in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) to obtain a diagnostic classification of Emily's mental disorder.

#### Non-adherence to antipsychotics

The problem of non-adherence or cessation of medication is commonly seen in all long-term medication, whether antipsychotic or otherwise. This problem is compounded in the psychotically disturbed patient for the following reasons.

##### *Lack of insight as to the need for antipsychotic medication*

This problem is particularly common in the paranoid or hypomanic/manic (i.e. mood-elevated) patient, for whom subjective

symptoms are not distressing and who perceive themselves as OK and the rest of the world as not OK.

#### *Apathy and lack of volitional motivation*

Patients taking antipsychotics may fail to comply with or maintain continuity in taking prescribed medication simply through development of apathy and lack of volitional motivation.

#### *Feeling of wellbeing and invulnerability in the patient relieved of subjectively distressing symptomatology after use of antipsychotic medication*

Relapse of psychosis is very common in patients who stop antipsychotic medication or reduce their antipsychotic dose to suboptimal levels below the threshold of therapeutic efficacy. Relapse in these situations can result in a recrudescence of psychosis that may be more difficult to restabilise than it was when originally medicated.

#### *Intolerability of antipsychotic side effects*

Side effects from antipsychotic medication are not uncommon and may be long lasting and of serious importance. All antipsychotics have a spectrum of side effects, which vary in frequency and severity. Among the atypical antipsychotics the common and clinically important side effects include:

- ▷ induced obesity (with all its attendant complications such as diabetes mellitus, hyperlipidaemia, hypertension, degenerative arthritis in weight-bearing joints)
- ▷ extrapyramidal neurological disorders (sometimes resulting in refractory or permanent tardive dyskinesia)
- ▷ hypersomnia or insomnia
- ▷ hyperprolactinaemia (resulting in menstrual disorders, gynaecomastia, lactation)
- ▷ blood dyscrasias
- ▷ cardiovascular damage
- ▷ severe constipation.

These latter side effects occur particularly in the context of clozapine medication.

Occasionally perceived side effects of antipsychotic medication are due to the patient

having somatic delusions of harm attributable to the medication. In these situations, side effects may be thought to be derived from the inert excipient of the medication (e.g. magnesium, cellulose, etc). It can be very difficult to shift these delusions, and successful management is achieved only by careful selection of medication with the patient's concordance and understanding.

#### *Failure of regular follow-up and monitoring of patient's compliance with, and response to, antipsychotic medication*

The treating clinician must carefully schedule the patient's time for follow-up appointments, according to the severity of the patient's psychosis, the response to treatment, and the reliability of the patient to self-medicate or be administered medication by a third party. The patient should be contactable if a follow-up appointment is missed, and the treating clinician should maintain a record of future appointment fixtures in the eventuality of a missed appointment.

## **Appropriate management of Emily**

Menstrual irregularity is a symptom, not a disease, and requires an aetiological diagnosis.

Presuming that other possible causes have been eliminated, it is reasonable to conclude that risperidone is the aetiological factor causing the menstrual irregularity. This conclusion would be strongly supported by the presence, on blood testing, of hyperprolactinaemia, a recognised side effect of risperidone and a cause of menstrual irregularity.

Withdrawal of risperidone would be appropriate treatment because of:

- ▷ its unacceptable side effect of menstrual irregularity, which may be the precursor of amenorrhoea and infertility in a patient of childbearing age.
- ▷ the patient's concern about her menstrual irregularity (sufficient for her to seek medical advice).
- ▷ the doubt of its therapeutic necessity (given the vague and incomplete history of 'schizophrenia'). Withdrawal should be done slowly.

After withdrawal of risperidone one of three clinical options could be invoked:

- ▷ if a careful retrospective history cannot establish an unequivocal diagnosis of schizophrenia, no further antipsychotic medication is given, but careful follow-up of the patient at regular intervals, at least once monthly, is maintained for two years to assess any relapse into psychosis.
- ▷ if a careful retrospective history establishes an unequivocal diagnosis of an isolated auditory–hallucinatory past event induced by a specific and non-repeatable stressor (e.g. drug- or illness-induced), no further management need be given, and the patient may be advised to voluntarily present herself if symptoms recur.
- ▷ if a careful retrospective history establishes unequivocal schizophrenia, an alternative antipsychotic medication (one other than risperidone), should be instituted. In that situation it would be the toss of a mental coin as to whether quetiapine, amisulpride or aripiprazole should be used. I would favour aripiprazole because of its:
  - predictable efficacy
  - relative freedom from side effects
  - once-daily need for administration
  - simple stepwise dose adjustment
  - affordability (being available on the Pharmaceutical Benefits Scheme).

Wholistic management of this patient cohort involves not only the administration of antipsychotic medication, but attention to comorbid organic illnesses and to lifestyle, particularly:

- ▷ housing
- ▷ nutrition
- ▷ clothing
- ▷ hygiene
- ▷ recreational outlets
- ▷ exercise and interests
- ▷ relationships and relinkage to families of origin
- ▷ legal and financial matters
- ▷ spiritual and religious issues (especially those surrounding death and suicide).

### Conflict of interest

None.

Dr O'Bryan has practised as a GP in the inner suburb of Melbourne, St Kilda, for the past 36 years. During that time he has managed a high caseload of patients with psychosis, most of whom have had associated socioeconomic deprivations to a marked degree.

Dr O'Bryan has a postgraduate Masters degree in General Practice Psychiatry; this and long-time experience in general medicine has enabled him to manage the psychiatrically ill patient in a comprehensive and wholistic way.

He is a contributor to the chapter on Psychosis in General Practice Psychiatry (McGraw Hill 2007).

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