



# Managing the metabolic adverse effects of antipsychotics

Guidance to support the multidisciplinary team manage a patient stopping and switching antipsychotics

Empowering decision-making in mental health



**Psychotropic Drug Directory**

Available through

 **Medicines  
Complete**



# Guidance for a patient stopping and switching antipsychotic drugs

Empowering decision-making in mental health



**Tom is a 28-year-old man with a diagnosis of schizophrenia. He has been stabilised on olanzapine 20 mg daily; however, his cholesterol, blood glucose, and weight have increased significantly over the past year.**

Weight gain, high blood glucose, and high cholesterol are common side-effects from olanzapine. As a preventative measure, dietary advice has been given to Tom in every follow-up appointment; however, this has proved insufficient for him. Nevertheless, the consultant psychiatrist consults PDD to see if any other behavioural interventions could be tried to help Tom at this stage.

In the **Management of side-effects** section, Psychotropic Drug Directory includes evidence-based management strategies found in published literature to help aid the next course of action for the individual patient. These strategies can range from behavioural to medication interventions such as switching drugs or adjunctive therapies.

The psychiatrist looks at the behavioural interventions for managing weight gain due to antipsychotics in Psychotropic Drug Directory, and decides to refer Tom to attend a regular weight management group.

The screenshot shows the Medicines Complete website interface. At the top, there is a search bar containing '6.6 Endocrine effects'. Below the search bar, there are several navigation icons. The main content area is titled 'Psychotropic Drug Directory' and shows a list of search results. The first result is 'Polyuria and renal impairment (often a symptom of diabetes insipidus)'. The second result, which is highlighted, is 'Weight gain (see also metabolic syndrome)'. Below this, there are other results: 'Antidepressants \*', 'SSRIs', and 'Mirtazapine'. To the right of the search results, there is a section titled 'Behavioural interventions' with the sub-heading 'Dietary interventions and nutritional education may be effective, e.g:'. This section contains a list of bullet points with references to clinical studies.



Tom's attendance at the weight management group has been erratic over the last 8 weeks, and his weight and other metabolic parameters have not improved. Nevertheless, Tom continues well-established on olanzapine, so the psychiatrist consults Psychotropic Drug Directory to see if decreasing the olanzapine dose could be an effective strategy to improve the metabolic side-effects that Tom is experiencing.

The psychiatrist finds in Psychotropic Drug Directory several strategies for managing olanzapine-related hyperglycaemia and weight gain.

The screenshot shows the 'Medicines Complete' website interface. At the top, there is a search bar containing '6.6 Endocrine effects'. Below the search bar, the 'Psychotropic Drug Directory' section is visible. On the left, there is a sidebar with 'Subsections' and 'Related Content'. Under 'Subsections', 'Olanzapine' is highlighted. The main content area displays the title 'Olanzapine' followed by several key management strategies:

- Discontinue** (although it may not always resolve, see Koller and Doraiswamy, *Pharmacotherapy* 2002; 22: 841-52).
- Reduce dosage** – may help as the effect seems to be dose-related (n = 49 946, Ulcickas Yood *et al*, *BMC Psychiatry* 2011; 11: 197; FFT).
- Switch** to an alternative antipsychotic, e.g. quetiapine, risperidone, cariprazine, aripiprazole or ziprasidone.
- Rosiglitazone** 4-8 mg/d improved glycaemic control in olanzapine metabolic disturbance but had no effect on HbA1c or lipids (n = 30, RCT, d/b, p/c, 12/52, Baptista *et al*, *Pharmacopsychiatry* 2009; 42: 14-9).

Evidence suggests that hyperglycaemia and weight gain are dose-related, therefore the psychiatrist decides to try a lower dose of Olanzapine 15 mg daily.

Four weeks later, Tom's blood glucose has decreased very slightly but he has started to report hearing voices, and claims that his olanzapine is not working as always. Therefore, the psychiatrist increases the olanzapine dose back to 20 mg daily.

The psychiatrist is now considering switching olanzapine to another antipsychotic and rings the pharmacy medicines information department seeking advice about other suitable antipsychotics for Tom, such as one with less risk of metabolic side-effects.

The pharmacist consults Psychotropic Drug Directory to find out about the risk of hyperglycaemia, hypercholesterolemia, and weight gain of other antipsychotics to support the choice of a new antipsychotic for Tom. Psychotropic Drug Directory contains dedicated tables that offer a quick snapshot of the side-effect profile of psychotropic drugs, which can be used to compare drugs and aid prescribing in the individual patient. For example, relevant tables for this case would include table 6.6.1 (Risks of raised glucose), table 6.6.2 (Risks of raised cholesterol), and table 6.6.3 (Relative risk of weight gain and increased BMI).



Medicines Complete

6.6 Endocrine effects

Psychotropic Drug Directory

Highlight search

Subsections Related Content

- Diabetes
- Diabetes insipidus
- Diabetes mellitus
- Clozapine
- Olanzapine
- Risperidone
- Hepatotoxicity

Table 6.6.1: Risks of raised glucose

Drug	Risk
Clozapine	0.97
Iloperidone	0.73
Cariprazine	0.70
Olanzapine	0.67
Haloperidol	0.59

Medicines Complete

6.6 Endocrine effects

Psychotropic Drug Directory

Highlight search

Subsections Related Content

- Diabetes
- Diabetes insipidus
- Diabetes mellitus
- Clozapine
- Olanzapine
- Risperidone
- Hepatotoxicity
- Valproate

Table 6.6.2: Risks of raised cholesterol

Antipsychotics	LDL cholesterol	Antipsychotic	HDL	Antipsychotic	Total
Olanzapine	0.96	Amisulpride	0.83	Clozapine	0.97
Quetiapine	0.91	Olanzapine	0.76	Olanzapine	0.91
Brexpiprazole	0.66	Quetiapine	0.59	Quetiapine	0.82
Risperidone/pal	0.54	Risperidone/pal	0.51	Amisulpride	0.64
Aripiprazole	0.48	Cariprazine	0.47	Haloperidol	0.59
Lurasidone	0.27	Lurasidone	0.45	Risperidone/pal	0.55
Ziprasidone	0.12	Aripiprazole	0.25	Brexpiprazole	0.52

Medicines Complete

6.6 Endocrine effects

Psychotropic Drug Directory

Highlight search

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Table 6.6.3: Relative risk of weight gain and increased BMI

Relative risk of weight gain		Relative risk of increased BMI	
Antipsychotic	Weight gain	Antipsychotic	BMI gain
Olanzapine	0.92	Olanzapine	0.93
Clozapine	0.90	Clozapine	0.85
Quetiapine	0.65	Quetiapine	0.68
Risperidone/pal	0.58	Risperidone/pal	0.56



Evidence suggests that aripiprazole has less impact on weight, dyslipidaemia, and diabetes. Hyperlipidaemia seems to be resolved after switching to aripiprazole, and a mean 2.55 Kg (+1.5Kg) weight loss has been seen.

**Medicines Complete**  
6.6 Endocrine effects

Psychotropic Drug Directory

**Medication interventions**

**Reduce the dose.** There is evidence that weight gain with clozapine and olanzapine is related to **plasma** levels, and reducing the dose may reduce plasma levels. However, there is insufficient evidence on other newer antipsychotics (Simon *et al*, *J Clin Psychiatry* 2009; **70**: 1041–50).

- **Slower introduction** has been postulated to lead to a lower final weight gain.

**\* Switching drugs**  
(see *Table 6.6.1* for the relative risks; review *s* = 4, *n* = 636, Mukundan *et al*, *Cochrane Database Syst Rev* 2010; **12**: CD006629).

- **Aripiprazole** (see also adjunctive) – a mean 2.55 (+1.5) kg weight loss occurs when switching to aripiprazole from other antipsychotics (M-A, *s* = 9, *n* = 784, Barak and Aizenberg, *J Obes* 2011; **2011**: 898013; FFT). A systematic review concluded aripiprazole had less impact on weight, dyslipidemia and diabetes than other newer antipsychotics (SR, *s* = 22, Citrome *et al*, *Curr Med Res Opin* 2014; **30**: 1629–41), albeit with higher drop-outs. Having said that, in another study aripiprazole had the same incidence of MetS and a higher drop-outs than olanzapine and haloperidol (*n* = 300, RCT, one year, Parabiaghi *et al*, *Acta Psychiatr Scand* 2016; **133**: 63–75)
- **Asenapine** only causes a mean weight gain of less than 1 kg over a year (Potkin, *J Clin Psychiatry* 2011; **72** [suppl 1]: 14–18) and a switch to it from olanzapine gave a 7% drop in weight with no deterioration (*n* = 1, Okazaki *et al*, *Neuropsychiatr Dis Treat* 2017; **13**: 2837–40; FFT)
- **Cariprazine** – switch to (Halans and Wuest, *J Clin Psychopharmacol* 2019; **39**: 413–6)

**Medicines Complete**  
6.6 Endocrine effects

Psychotropic Drug Directory

**Hyperlipidaemia**

**Antipsychotics**

Hyperlipidaemia has been reported with all antipsychotics (decreasing incidence from clozapine, olanzapine, risperidone, quetiapine, ziprasidone to first generation) except aripiprazole, cariprazine and lurasidone.

**Manage risk factors**, e.g. weight gain, dietary changes and glucose intolerance.

**Discontinue any beta-blockers**, which may enhance the effects on lipids (*n* = 50, Batmiller *et al*, *Schizophr Res* 2003; **59**: 49–57).

**Lipid-lowering therapy**, e.g. rosuvastatin (*n* = 100, 3/12, De Hert *et al*, *J Clin Psychiatry* 2006; **67**: 1889–96).

**Switch drugs**

- **Amisulpride, lurasidone, ziprasidone, risperidone** (*n* = 15, Su *et al*, *Psychopharmacology [Berl]* 2005; **183**: 383–6) and cariprazine may be alternatives if olanzapine or clozapine-induced, as may be:
- **Aripiprazole** has resolved hyperlipidaemia from clozapine (*n* = 1, Ball *et al*, *Ann Pharmacother* 2005; **39**: 1570–2) and olanzapine-induced hyperlipidaemia (*s* = 3, *n* = 546, RCT, Newcomer *et al*, *Schizophr Res* 2008; **106**: 300–7; FFT) and may be the best option (*n* = 13 133 vs 17 240, Olsson *et al*, *Am J Psychiatry* 2006; **163**: 1821–5), but not all improve and the switch has a significant risk of worsening symptoms (*n* = 52, 52/52, Chen *et al*, *J Psychopharmacol* 2012; **26**: 1201–10)



Based on the available information on Psychotropic Drug Directory, the pharmacist recommends aripiprazole to Tom's psychiatrist. To ensure that the switch from olanzapine to aripiprazole is safe and effective, the pharmacists can also find on Psychotropic Drug Directory the latest evidence-based recommendations.

## Type of switches

A dedicated section on **Switching or discontinuing psychotropic drugs** contains detailed information about the different switching strategies, their risks, and their rationale.

2.2 Switching or discontinuing ps

Psychotropic Drug Directory

Subsections

Switch 1: Medicine-free interval

Switch 2: No interval

Switch 3: Partial overlap

Switch 4: Full overlap

Switch 5: Incomplete

### Switch 3: Partial overlap

(Add new medicine, either at standard dose or titrated upwards, while slowly tapering the first medicine down)

**Switch 3a: Partial overlap**  
(usually acceptable)

**Switch 3b: Abrupt partial overlap**  
(tapered stop, abrupt start)

**Advantages**

1. Appropriate when symptom control is needed but there is a high risk of relapse or deterioration.
2. No abrupt potentially destabilising changes
3. May be unavoidable for LAI/depot to oral switches, where plasma levels will decline slowly. †
4. Useful where cholinergic rebound may occur. Anticholinergic cover can be retained for several weeks. †

**Disadvantages**

1. Two medicines may be given at sub-therapeutic doses.
2. Combined ADRs may occur.
3. Potential for drug interactions, especially with antidepressants.
4. Potential for medication errors if not planned fully in advance – involve patient and carers if the patient is at home.
5. High potential for polypharmacy if the switch is never completed (see Switch 5). †



## Specific antipsychotic switches

Evidence-based information about switching to/from specific antipsychotics and other psychotropic drugs is also included in Psychotropic Drug Directory, and the pharmacist specifically looks at the information for switching olanzapine to aripiprazole.

Psychotropic Drug Directory

Subsections

5. Switching to/from clozapine

15. Switching to/from paliperidone palmitate (PPIM, Xeplion<sup>®</sup>, PP3MTrevicta<sup>®</sup>, see also 2.2.4)

### Table 2.2.2: Switching antipsychotics

Swipe or scroll within the table to navigate

To	Phenothiazines	D2 blockers	FGA depots/LAIs	Aripiprazole <sup>15</sup>	Asenapine <sup>15</sup>	Cariprazine	Clozapine <sup>15</sup>
From							
Phenothiazines	RT (1)	RT (2)	RT (3)	RT (4)	RT (12)	RT (17)	CC
D2 blockers	RT (10)	RT (11)	RT (3)	RT (4)	RT (12)	RT (17)	CC
FGA depot/LAIs	RT (3)	RT (3)	RT (3)	RT (3, 4)	RT (3,12)	RT (17)	CC (5)
Aripiprazole <sup>15</sup>	RT (4)	RT (4)	RT (3,4)	-	RT (12)	RT (17)	CC
Asenapine <sup>15</sup>	RT (12)	RT (12)	RT (3,12)	RT (4,12)	-	RT (17)	NC
Cariprazine	RT (17)	RT (17)	RT (17)	RT (17)	RT (17)	-	RT
Clozapine <sup>15</sup>	Care (5)	Care (5)	Care (3,5)	RT (4,5)	NOP (5,12)	RT (17)	-

For switching to aripiprazole, evidence suggests that a long cross-tapering from olanzapine to aripiprazole would be more successful, but that it needs to be flexible and tailored to the individual.

Psychotropic Drug Directory

Subsections

5. Switching to/from clozapine

15. Switching to/from paliperidone palmitate (PPIM, Xeplion<sup>®</sup>, PP3MTrevicta<sup>®</sup>, see also 2.2.4)

### 4. Switching to aripiprazole oral or LAI \*

a. Any to oral aripiprazole: \*

Abrupt switching to oral aripiprazole can often be poorly tolerated, especially in people with milder rather than more severe symptoms (n = 77, RCT, open, 12/52, Pae *et al. Clin Drug Invest* 2010; **30**: 187–93). Aripiprazole has a high affinity to dopamine receptors, with a long half-life, displacing almost every other antipsychotic, and stimulating D2 receptors to about 30% activity. This abrupt change from minimal dopamine activity to 30% within hours can lead to abrupt worsening and akathisia (acutely distressing), possibly via a dopamine supersensitivity and particularly after high doses of other antipsychotics (n = 264, Takase *et al. J Psychopharmacol* 2015; **29**: 383–9).

A cross-taper is most likely to be successful, starting aripiprazole at 5 mg/d (UK SmPC mentions 10 mg/d, which is too high if switching), then increasing stepwise to 15 mg/d, and then reducing the previous antipsychotic by 25% twice a week (n = 53 [c = 48], RCT, open, 14/52, Takeuchi *et al. J Clin Psychopharmacol* 2008; **28**: 540–3; n = 77, RCT, open, 12/52, Pae *et al. Eur Neuropsychopharmacol* 2009; **19**: 562–70). Dual administration for 2/52 then stopping the first antipsychotic over one week (fast switch) or four weeks (slow switch) has been reported to be equally effective (n = 79, RCT, open, 8/52, Hwang *et al. J Clin Psychopharmacol* 2015; **35**: 635–44). In a further investigation in chronic schizophrenia, add-on switching to



The pharmacist then suggests starting aripiprazole 5 mg daily, increasing the dose weekly by 5mg up to 15 mg daily, then decrease olanzapine by 5 mg over the following four weeks.

Tom is then counselled about his new medication and monitored for therapeutic progress and tolerability. After four weeks of treatment with aripiprazole, there is a marked improvement in Tom's metabolic parameters, and his psychotic symptoms are well-controlled.



## Psychotropic Drug Directory

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