ARTICLE

Stopping and switching antipsychotic drugs

Nicholas Keks
Director[1]
Professor[2]

Darren Schwartz
Senior pharmacist, Research and Drug Information[3]

Judy Hope
Associate professor[2,4]

[1] Centre for Mental Health Education and Research, Delmont Private Hospital, Glen Iris, Victoria

[2] Monash University, Clayton, Victoria

[3] North Metropolitan Health Service Mental Health, WA

[4] Eastern Health, Box Hill, Victoria

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SUMMARY

In general, specialist advice should be sought when stopping or switching antipsychotics.

While antipsychotics are often needed long term, there are circumstances when clinicians, patients and families should reconsider the benefits versus the harms of continuing treatment.

Withdrawal syndromes, relapse and rebound can occur if antipsychotics are discontinued, especially if they are stopped abruptly. Generally, they should be reduced and stopped slowly, ideally over weeks to months.

Relapse of psychosis and exacerbation occur in most patients with psychotic disorders, occasionally with drastic consequences. Sometimes this occurs many months after stopping antipsychotics.

Switching from one antipsychotic to another is frequently indicated due to an inadequate treatment response or unacceptable adverse effects. It should be carried out cautiously and under close observation.

Introduction

Stopping antipsychotic drug therapy is feasible and appropriate in a number of clinical circumstances. For patients who require long-term treatment, switching to another antipsychotic may be needed if their response to treatment has been inadequate, or unacceptable adverse effects have occurred.

For patients with serious psychiatric illness, stopping or switching antipsychotics requires referral to a specialist if possible. However, for patients on small off-label doses of antipsychotics for behavioural disturbance in dementia or for sleep problems, it may be reasonable for the GP to taper the dose and stop treatment with careful monitoring.

Antipsychotics in Australia

There are many drugs with antipsychotic efficacy available, including both oral and depot formulations. They differ in their adverse effects and effectiveness (Table 1). Historically, antipsychotics have been divided into typical (or conventional) and atypical (or novel) types. However, this simple dichotomisation cannot account for the heterogeneity in a range of characteristics with antipsychotic drugs old or new. This includes their likelihood of causing extrapyramidal effects, hyperprolactinaemia, weight gain and metabolic syndrome, sedation versus activation, and cardiac effects (Table 1).

Some antipsychotics are more effective for psychosis than others – clozapine has been recognised as the most effective antipsychotic drug, followed by a mid-efficacy group of amisulpride, olanzapine, risperidone and paliperidone, then the remaining novel and old antipsychotics such as haloperidol and chlorpromazine.[1] Some drugs, such as olanzapine, quetiapine, risperidone, asenapine and ziprasidone, were also found to be effective in mania, mixed states and maintenance treatment of bipolar mood disorder.[2]

Off-label use

Psychiatrists also use some antipsychotics such as olanzapine, quetiapine and risperidone for off-label indications. An example would be adjunctive initial treatment of severe major depression when rapid relief of agitation, insomnia and suicidality is needed while waiting for antidepressants to take effect. As a consequence, GPs are seeing a broad spectrum of patients (not merely those with schizophrenia) who have been started on antipsychotics, often in combination with other psychotropic drugs. It has been common practice to continue these antipsychotics long term, especially when treatment of an acute episode has been reasonably successful. However, long-term antipsychotic use can have serious consequences including tardive dyskinesia, weight gain, metabolic syndrome, diabetes and cardiovascular complications.[3]

Withdrawing antipsychotics

When stopping an antipsychotic, individual circumstances must be carefully considered including illness severity and history, risk of relapse and its consequences, treatment response and prognostic factors, and the patient's social situation (Box 1). If possible, antipsychotics should be stopped very slowly under close medical observation. Abrupt discontinuation can result in rebound psychosis which can be more severe than before treatment

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Table 1 **Antipsychotic drugs available in Australia**

Antipsychotic drug *	Formulation	Drug half-life	Notes on adverse effects
Amisulpride	Tablets	12 hours	Low sedation risk, can be activating, dose-dependent EPS, hyperprolactinaemia, low risk of metabolic syndrome, high risk QTc prolongation (very dangerous in overdose)
Aripiprazole	Tablets	75 hours (95 hours for dehydroaripiprazole)	Initially activating, initial akathisia risk, low sedation, low risk of metabolic syndrome, very low risk of increasing prolactin
	Long-acting injection	46 days for 400 mg every 4 weeks	
Asenapine	Wafers	24 hours	Mildly sedative, dose-dependent EPS, low–moderate risk of metabolic syndrome
Brexpiprazole	Tablets	91 hours	Initially activating with possible akathisia, low sedation, low risk of metabolic syndrome
Chlorpromazine	Tablets, oral liquid, injection	15–30 hours, multiple metabolites	Sedative and tranquillising, anticholinergic, moderate risk of EPS, postural hypotension, photosensitivity, moderate risk of metabolic syndrome, hyperprolactinaemia
Clozapine	Tablets, oral liquid	12 hours (4–66 hours)	Sedative, anticholinergic, postural hypotension, paralytic ileus, agranulocytosis, convulsions, high risk of metabolic syndrome, cardiac effects, nocturnal hypersalivation, urinary incontinence
Flupentixol	Long-acting injection	3 weeks – 3 months	Moderate–high risk of EPS, moderate risk of metabolic syndrome, hyperprolactinaemia
Haloperidol	Tablets, oral liquid, injection	21 hours	High risk of EPS, hyperprolactinaemia, low risk of metabolic syndrome
Haloperidol decanoate	Long-acting injection	3 weeks	
Olanzapine	Tablets, wafers, injection	33 hours	Moderately sedative and tranquillising, high risk of weight gain and metabolic syndrome, moderately anticholinergic, low risk of hyperprolactinaemia
Olanzapine pamoate monohydrate	Long-acting injection	30 days	
Lurasidone	Tablets	18 hours	Mildly sedative, low risk of metabolic syndrome, low–moderate risk of dose-dependent EPS, low–moderate risk of hyperprolactinaemia, low risk of QTc prolongation, nausea
Paliperidone	Tablets, injection	23 hours	Low risk of sedation, low risk of dose-dependent EPS, high risk of hyperprolactinaemia
Paliperidone decanoate	1-monthly long-acting injection	25–49 days	
	3-monthly long-acting injection	84–95 days with deltoid injection, 118–139 days with gluteal injection	
Periciazine	Tablets	12 hours	Moderately sedative and tranquillising, moderate risk of dose-dependent EPS
Quetiapine	Conventional tablets	7 hours, first active metabolite norquetiapine 12 hours	Sedative and tranquillising, low risk of EPS, low risk of hyperprolactinaemia, moderate–high risk of weight gain and metabolic syndrome, anticholinergic
	Modified-release tablets		Drug effects longer lasting so used once daily
Risperidone	Tablets, oral liquid, injection	3-17 hours, 9-hydroxy-risperidone 24 hours	Mild–moderate sedation, risk of initial postural hypotension, low risk of dose-dependent EPS, high risk of hyperprolactinaemia
	Long-acting injectable microspheres	Approximately 11 days (steady state occurs after 4 x 2-weekly injections)	

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Table 1 **Antipsychotic drugs available in Australia (continued)**

Antipsychotic drug *	Formulation	Drug half-life	Notes on adverse effects
Ziprasidone	Capsules, injection	6–10 hours	Mild–moderate sedation, initial risk of activation and akathisia, low risk of dose-dependent EPS, low risk of metabolic syndrome, high risk of QTc prolongation, low risk of hyperprolactinaemia
Zuclopenthixol	Tablets	20 hours	Mild–moderate sedation, moderate–high risk of EPS
Zuclopenthixol acetate	Intermediate-acting injection	Approximately 2 days	
Zuclopenthixol decanoate	Long-acting injection	19 days	

* Droperidol and ziprasidone mesylate injection are omitted as they are only used acutely.
EPS extrapyramidal symptoms (dystonia, akathisia, pseudo-parkinsonism, tardive dyskinesia)

Box 1 **When to consider stopping antipsychotics**

Psychiatrist review may not be required

- Antipsychotic (e.g. low-dose quetiapine) has been used for anxiety or sleep disturbance, and ongoing treatment is not needed or desired.
- Antipsychotic has been used for disturbed behaviour in dementia but may no longer be needed because of behavioural or environmental interventions.
- Antipsychotic has been trialled for off-label indications and has proven ineffective.

Psychiatrist review required

- Full recovery after first episode of psychosis and patient has been well for 12 months.
- Recurrent psychosis when:
  - patient has fully recovered and been well for 12–24 months
  - illness severity and other risk factors allow
  - patient and family wish to re-evaluate the benefits and harms of ongoing treatment.
- Bipolar mood disorder when antipsychotic is no longer necessary, especially when lithium monotherapy is appropriate.
- Full recovery after drug-induced psychosis and evaluation suggests treatment may no longer be needed (e.g. illicit drug use has stopped).
- Psychotic depression that has responded to treatment and psychosis is no longer evident.
- Patient has responded to early treatment with sedating antipsychotic (e.g. quetiapine and olanzapine) for severe agitated depression and adjuvant antipsychotic therapy is no longer necessary.

was started. This is not uncommon when stopping clozapine as a result of complications such as agranulocytosis or myocarditis.[4] Depending on the pharmacological action of the antipsychotic, several withdrawal syndromes can occur (Table 2).

Some antipsychotics (particularly depot injections) have long half-lives and are unlikely to be associated with significant withdrawal symptoms (Table 1).

After a first episode of psychosis in schizophrenia and related disorders, stopping antipsychotics is considered when the patient has made a full recovery and been well for at least 12 months.[5] Up to 40% of patients who have experienced a single episode of psychosis may remain well after stopping their antipsychotics or at least require only low doses.[6]

If there have been a number of episodes of psychosis, or recovery is incomplete, ongoing antipsychotic treatment is usually recommended as the chance of exacerbation or relapse is high if the drug is stopped. In patients who have experienced more than one episode but have fully recovered and been well for at least 12 months with antipsychotics, gradual dose reduction accompanied by close observation can be considered. Illness severity, treatment complications (e.g. obesity), previous pattern of relapse, risk to self and others, and the psychosocial consequences of relapse should be carefully considered in the harm–benefit assessment. Repeated episodes of psychosis worsen longer term prognosis. As the risk of relapse after a second episode is high, most clinicians would recommend long-term treatment.[6]

Patients who have experienced psychotic depression and have responded to a combination of antidepressants and antipsychotics with or without electroconvulsive therapy, can often be continued on antidepressant drugs alone. There are no clear guidelines for when antipsychotics can be withdrawn in these patients. However, after the patient has been recovered for some time, it is often possible to gradually reduce the dose while continuing to monitor the patient's mental state (especially if serious risk factors like suicidality were present initially).

Patients who have been started on sedating antipsychotics for severe agitated depression, anxiety or insomnia can often be taken off them, especially if there has been significant clinical improvement.

Antipsychotics for behavioural disturbance associated with dementia and other brain diseases should be reviewed and deprescribing should be considered due to the serious adverse effects and lack of evidence for long-term use.[7]

Switching antipsychotics

There are a number of clinical situations in which switching from one antipsychotic to another is considered. Review by a psychiatrist is indicated before switching, particularly in complex clinical situations or when urgent switching is necessary (Box 2). When choosing a drug to switch to, it helps to know which antipsychotics have a lower risk of the common adverse effects associated with long-term therapy. Table 3 lists antipsychotics that have lower risks of adverse effects such as extrapyramidal and anticholinergic symptoms, weight gain, postural hypotension and hyperprolactinaemia.[1,8]

Switching is not necessarily a panacea. Illness exacerbation may occur during the switch, and new adverse effects may emerge. When switching is being undertaken due to an inadequate response, it is important to ensure the dose of the first antipsychotic has been optimised, the patient has been treated for an adequate amount of time, and that they are adhering to treatment.[9]

The choice of the new drug will be partly determined by the reasons for the switch, but probable efficacy, adverse effects, dosing regimen and patient or carer preferences also need to be taken into account. Broad characteristics of antipsychotics are given in Table 1, but more details may be necessary and expert advice could be valuable in making drug choices.

Depending on the pharmacology of the antipsychotic, switching may result in withdrawal syndromes, particularly anticholinergic withdrawal with drugs such as quetiapine, clozapine, chlopromazine and olanzapine. Changing from one antipsychotic to another (when, for example, seeking a drug with a lower risk of weight gain) can result in loss of efficacy and withdrawal symptoms. It is essential for patients and carers to be informed about the possible consequences of switching, and an action plan for how to deal with any difficulties should be formulated.

Clozapine

When a patient is being switched from clozapine to another antipsychotic, rebound psychosis and other serious withdrawal effects may occur irrespective of which drug is substituted. Clozapine discontinuation should be done under the guidance of a psychiatrist. The dose should be gradually tapered, not stopped suddenly.[10] However, sometimes this may be unavoidable if, for example, agranulocytosis has occurred.

Switching strategies

In contrast to switching antidepressants, a drug-free period between stopping the first antipsychotic and starting the second is not recommended due to the risk of relapse. Table 4 lists the different methods of changing from one antipsychotic or formulation to another. Whether switching from an oral to a depot antipsychotic, depot to depot, or depot to oral, specific instructions need to be followed (Table 4).

Direct switch

While it is possible to stop the first drug and start the second drug the next day, this may result in withdrawal symptoms and possible drug interactions. When the first antipsychotic is aripiprazole or brexpiprazole, a direct switch can be made as both these drugs have very long half-lives and no anticholinergic effects.

Table 2 **Withdrawal syndromes associated with antipsychotic drugs**

Type of withdrawal syndrome	Causative antipsychotics	Clinical manifestations
Cholinergic syndrome	Chlopromazine, clozapine, olanzapine, quetiapine	Nausea, vomiting, headache, restlessness, anxiety, insomnia, fatigue, malaise, myalgia, diaphoresis, rhinitis, paraesthesia, loose bowels
Dopaminergic syndrome	All antipsychotics in Table 1	Withdrawal dyskinesia, akathisia, dystonia, tardive dyskinesia
Rebound psychosis	Clozapine	Psychosis above pre-treatment levels, illusions, hallucinations, catatonia

Box 2 **When to consider switching from one antipsychotic to another**

Psychiatrist review required if possible

- Inadequate clinical response for acute symptoms despite dose optimisation and adequate duration of treatment trial.
- Poor control of chronic symptoms and persistence of functional disabilities during maintenance therapy.
- Relapse despite adequate prophylactic or maintenance treatment of a psychotic illness.
- Persistence of certain symptoms of psychotic illness (e.g. negative symptoms and cognitive dysfunction) despite adequate doses of one antipsychotic, which may respond better to an alternative drug.
- Unacceptable adverse effects at low therapeutic doses before a clinical response in susceptible individuals (e.g. extrapyramidal effects in Asian patients). Consider switching to an antipsychotic with a lower risk for the adverse effect.
- Emergence of unacceptable adverse effects during treatment with one antipsychotic (e.g. increased appetite and problematic weight gain), which may improve with an antipsychotic that has a lower risk.
- Need to change the antipsychotic drug due to a physical complication (e.g. ziprasidone is contraindicated in cardiovascular illness, antipsychotics that cause significant hyperprolactinaemia are contraindicated in breast cancer).
- Request from patient or carer to change drugs due to unacceptable adverse effects (e.g. sexual dysfunction with an antipsychotic that has caused hyperprolactinaemia).
- Poor treatment adherence – consider changing from an oral antipsychotic to a long-acting depot injectable form.

Table 3 **Switching antipsychotics based on risk of adverse effects**

Adverse effect	Recommended order of replacement drug (listed from lower to higher risk of adverse effect)
Extrapyramidal effects	Clozapine Quetiapine Olanzapine (low-dose) Aripiprazole Brexpiprazole Ziprasidone
Anticholinergic effects	Risperidone Paliperidone Ziprasidone Asenapine Lurasidone Haloperidol Aripiprazole Brexpiprazole
Weight gain	Haloperidol Ziprasidone Lurasidone Aripiprazole Amisulpride Asenapine
Postural hypotension	Haloperidol (oral and decanoate) Periciazine Flupentixol Amisulpride Aripiprazole
Hyperprolactinaemia	Aripiprazole Asenapine Quetiapine Clozapine Ziprasidone Olanzapine (low-dose)
QTc prolongation	Lurasidone Aripiprazole Paliperidone Haloperidol
Sedation	Amisulpride Paliperidone Aripiprazole Brexpiprazole
Sexual dysfunction	Aripiprazole Brexpiprazole Quetiapine (conflicting evidence)

Source: references 1 and 8

Cross titration

Evidence indicates there may be little difference in the risk of relapse with immediate and gradual antipsychotic stopping or switching.[11] Most psychiatrists use the cross-titration strategy. This involves a reduction of the first antipsychotic while introducing the second drug.

Continuation with slower titration and discontinuation

A slower approach to titration is to continue the first antipsychotic for a period at its usual dose while gradually increasing the therapeutic dose of the second antipsychotic. The first antipsychotic can then be gradually reduced and stopped. The risk of relapse is minimised with this approach, but there may well be additive adverse effects during the process.

Interactive switching tool

An interactive tool provides specific switching guidelines for different antipsychotics, including from one oral antipsychotic to another and from one depot antipsychotic to another.

Conclusion

There are a variety of clinical circumstances in which stopping an antipsychotic should be considered and undertaken if appropriate. When it is necessary to switch from one antipsychotic to another during the course of treating psychoses, clinicians need to have some understanding of the pharmacokinetics and dynamics of antipsychotic drugs in order to plan and carefully monitor a switching regimen. This usually involves a period of both drugs being used simultaneously.

Stopping and switching antipsychotics can result in serious consequences, particularly a relapse of psychosis which may entail serious risks and worsen long-term prognosis. Withdrawal syndromes related to cholinergic and dopaminergic effects may occur depending on the characteristics of the antipsychotics involved. <

Conflict of interest: none declared

Antipsychotic switching tool

Nicholas Keks, Darren Schwartz and Judy Hope

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Go online to use this interactive tool.

Table 4 **Techniques for changing from one antipsychotic or formulation to another (psychiatrist review required)**

Change	Comment
Direct switch: First antipsychotic is stopped and next antipsychotic is started on the following day	Simplest strategy but expertise is required and may be best carried out in an inpatient setting. Risk of discontinuation symptoms from first antipsychotic may be substantial. There may be a significant risk of drug interactions depending on individual drug characteristics. Should be avoided if possible when switching from clozapine.
Cross titration: First antipsychotic is gradually reduced while second antipsychotic is gradually increased to therapeutic dose	Most common strategy used in clinical practice. Provides some balance between minimising risk of relapse and minimising risk of adverse effects during overlap. Expertise required due to differing pharmacokinetics and possibility of drug interactions.
Continuation with slower titration and subsequent discontinuation: First antipsychotic is continued at usual dose, second antipsychotic is gradually titrated up to near therapeutic dose, then first antipsychotic is gradually reduced and stopped, while dose of second antipsychotic is increased to its therapeutic dose	Most conservative strategy suitable for patients with a high risk of relapse. However, there will be significant overlap of the two antipsychotics with a likelihood of adverse effects during switch. There is also the risk that the planned discontinuation of the first antipsychotic never takes place or therapeutic dose of second antipsychotic is not reached.
Formulations	
Oral to depot	Specific instructions need to be followed for each particular depot. Continuation of oral antipsychotic may be required for some time after injecting depot depending on the characteristics of depot drug.
Depot to depot	Need to follow instructions with new depot for changing from previous depot drug. This is most commonly undertaken as a direct switch but, because of the long half-lives, it is in effect a cross titration.
Depot to oral	Because of the long half-lives, depot formulations can be stopped immediately. For all oral antipsychotics except clozapine, the oral drug should be started on the date that the depot antipsychotic was due. Clozapine requires a very slow titration at the start of therapy. As the effective dose of clozapine varies so much between patients, it is common to continue the depot antipsychotic until clozapine has reached therapeutic plasma concentrations or has shown significant clinical effect.

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