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# Guide to when and how to safely withdraw antipsychotics

Martin Livingston MD, FRCPsych

- change of diagnosis: patient does not have a psychotic illness
- prolonged remission after a first episode of psychosis
- bipolar illness: switching from mania to depression
- bipolar illness: switching to alternative mood-stabilising agents, eg from quetiapine to sodium valproate or valproic acid
- drug-induced psychoses: psychosis has remitted on drug withdrawal
- depressive illness: antipsychotic added to an antidepressant is no longer required
- off-label uses: where no benefit is evident, eg use of a sedative antipsychotic in anxiety disorders

**Our series on stopping drugs provides practical advice on why, when and how to withdraw drug therapy. Here the author discusses the issues arising from discontinuing antipsychotics.**

**Table 1.** Indications for withdrawing antipsychotics

Antipsychotic medication is effective in the treatment and prophylaxis of psychotic illness. In addition, some antipsychotics, eg olanzapine, quetiapine and risperidone, have a role as mood stabilisers in bipolar illnesses, and quetiapine is a useful addition to the treatment of bipolar depression.

Longer-term use of antipsychotics carries significant risks to physical health and well-being and has to be weighed carefully against the potential benefits in managing the mental disorder.

Drugs such as clozapine, olanzapine, quetiapine and risperidone may induce the onset of the metabolic syndrome,<sup>1</sup> resulting in the development of type 2 diabetes and early-onset cardiac disease. Movement disorders, drug-induced parkinsonism, dystonias, akathisia and tardive dyskinesia may occur, especially with higher doses of the more potent dopamine-blocking antipsychotics such as haloperidol and pimozide (Orap).

Neuroleptic malignant syndrome (NMS), an uncommon but potentially fatal side-effect of antipsychotics, presents with muscle rigidity, fever, autonomic instability and delirium and an elevated creatine phosphokinase.<sup>2</sup> Torsade de pointes is a potentially fatal ventricular arrhythmia that results from QT interval prolongation.<sup>3</sup>

## Indefinite treatment with antipsychotics

Many patients ask to come off antipsychotic medication because of concerns over stigma, drug intolerance and impaired insight resulting from their illness. It is important to state the case for continuation of the prescription where this is indicated. Often a change of drug is helpful. Examples include swapping aripiprazole (Abilify) for olanzapine in patients concerned about weight, or switching from aripiprazole to quetiapine in patients complaining of agitation and sleeplessness.

In some cases mental health legislation may have to be invoked

because an insight-impaired patient is placing himself or others at significant risk by failing to adhere to essential antipsychotic medication. There are some patients for whom lifelong medication with antipsychotics is essential as the risk of relapse never disappears. Even with optimal antipsychotic and psychosocial therapy programmes around 45 per cent of patients with schizophrenia will experience an exacerbation or major recurrence after an acute episode.<sup>5</sup>

Lifelong antipsychotic medication may also be necessary in delusional and schizoaffective disorders. In the case of patients who have bipolar illness the alternatives to antipsychotics prescribed as mood stabilisers are lithium and some anticonvulsants, eg valproic acid (Depakote). In depressive illness with psychotic features or treatment-resistant depression, electroconvulsive therapy (ECT) remains a safe and highly effective alternative to antipsychotics.<sup>5</sup>

<i>Motor</i>	acute – dystonia, dyskinesia, akathisia later onset – tardive dyskinesia, tardive dystonia
<i>Neurovegetative</i>	acute – nausea, insomnia, anxiety later onset – paraesthesia, disturbed temperature regulation, hyperalgesia more chronic (up to 6 months duration) – dysthymia, impaired concentration

**Table 2.** Discontinuation symptoms

**Candidates for anti-psychotic withdrawal**

There is an urgent need to stop antipsychotic medication in patients who are suspected of developing NMS. Unfortunately, it is usually the case that patients who have suffered NMS will need such medication in the future and alternative antipsychotics will have to be prescribed, preferably from among those without high affinity to dopamine blockade, *eg* chlorpromazine or clozapine.

Other reasons for rapid withdrawal include cardiac side-effects of a potentially life-threatening nature and rare drug idiosyncratic problems such as cholestatic jaundice, most commonly found with chlorpromazine.

More planned withdrawal may be attempted for the indications

shown in Table 1. Many patients and their doctors feel that a trial off antipsychotic medication is warranted for patients who have a sustained remission following a first episode of psychosis. Unfortunately there is no evidence-based guidance on the issue and a recent randomised controlled trial indicated twice the rate of relapse in a group of patients on placebo following a one-year remission after a first episode of psychosis.<sup>6</sup>

**How to withdraw**

The patient’s consent should be sought following explanation of the intended programme of withdrawal and the likely withdrawal effects. The decision to withdraw is often difficult. It is helpful to consult a carer, if the patient agrees, as

well members of the multidisciplinary team involved in the patient’s care. GPs may feel it is helpful to ask for a psychiatric opinion on whether withdrawal is appropriate in some cases.

The actual course of drug withdrawal is generally problem free – at least in the short term. Recurrence of illnesses such as schizophrenia may take months and the risk does not disappear with time. The absence of an early relapse, after discontinuation, causes patients to minimise the risk of nonadherence to antipsychotic regimens. Patients who notice no difference in their mental state for some weeks after stopping antipsychotics may continue off their medication. Problems then escalate if there is a relapse of an insight-impairing illness.

Nonadherence to antipsychotic regimens is common, with as many as 74 per cent of subjects stopping oral medication.<sup>7</sup> Nonadherence is frequently missed by the clinician, another indicator that short-term severe withdrawal effects are relatively unusual.

When some long-acting injections are discontinued such as fluphenazine decanoate and flupentixol decanoate (Depixol Injection), the drug does not fully leave the body for some months after discontinuation, prolonging the time to a relapse related to drug withdrawal. Planned withdrawal should be carried out over a period of months to minimise drug withdrawal problems and to ensure that any signs of relapse are spotted before it becomes entrenched.

**Role of the GP**

It is common for GPs to either initiate or monitor antipsychotic medication. In those patients who suffer from an enduring psychosis such as schizophrenia or are

**Case 1. Patient wishes to stop medication**

AD is a 38-year-old man who was started on antipsychotic medication when he developed a schizophrenia-like psychosis involving thought process disorder, persecutory delusions and auditory and visual hallucinations. This took place 15 years ago when AD was taking LSD and cannabis. He stopped taking street drugs and remained on antipsychotics, usually at low dose without further relapse. He tended, however, to be somewhat circumstantial in his thinking and struggled to complete course work at university, his degree taking several years longer than normal. He seemed overly introspective and has never gained employment.

The treating psychiatrist advised remaining on medication but AD was keen to discontinue. The risk-benefit profile of discontinuation in his case was explained and it was agreed to reduce his aripiprazole from 10mg to 5mg and six months later to stop it altogether. Twelve months after discontinuation concerns about his thought processing remain, but on follow-up at OPD no relapse has occurred. It is planned to keep him under review for at least another year.

prone to frequent relapse, as in brittle bipolar illnesses, the need for specialist review of the treatment plan and multidisciplinary team input usually mandates referral to the secondary-care mental-health services.

GPs should be able to supervise gradual antipsychotic withdrawal in their patients, especially if specialist input is rapidly and readily available in the event of major withdrawal effects or incipient relapse. Good communication between primary and secondary care facilitates smooth withdrawal and it is helpful for patients, those involved in treatment and carers to have a plan in the event of relapse or other problems in withdrawal.

### Symptoms in withdrawal

When symptoms emerge during withdrawal of antipsychotics there are several possible causes. These are that symptoms of the underlying illness are emerging, unmasked by drug withdrawal, that a new episode of illness has developed, that a withdrawal or discontinuation syndrome is taking place or a rebound or supersensitivity psychosis has developed. It is often difficult to distinguish clinically between these possibilities.

#### *Discontinuation syndrome*

This term is used to describe withdrawal illnesses in individuals who are coming off medication that does not induce dependence. Some of the symptoms shown in Table 2 are nonspecific, *eg* impaired concentration and dysthymia, and may feature as side-effects in the placebo arm of controlled drug studies. More objective indicators of a discontinuation syndrome are dyskinesias, dystonias and disturbed temperature regulation.

### Case 2. Problems with an antipsychotic switch

SM, 53, has been suffering from a schizoaffective disorder for over 20 years, during which there have been several admissions and regular outpatient review at psychiatric clinics with CPN input. Her GP contacted the psychiatrist to point out that the patient was now more concerned about the worsening pronation-supination tremor of both hands as she was spilling liquids. On clinic review SM was noted to have a rather stiff, immobile facial expression as well as the tremor, and on examination had cog-wheeling evident in both wrists.

The prescription at that time was haloperidol 6mg per day, lithium carbonate 800mg per day and citalopram 20mg per day with occasional use of temazepam 20mg for night sedation. The patient agreed to try a cross titration with quetiapine substitution for haloperidol over a three-month period and warned that the movement disorder might take some time to resolve. About four months later, now off haloperidol and taking 600mg per day of quetiapine SM was noted to be telephoning the psychiatric resource centre several times per week complaining of not feeling as well, poor sleep and agitation. When seen at the outpatient clinic she was noticeably irritable and atypically challenging but not depressed.

A diagnosis of hypomania was made, thought to be due to reduced antipsychotic potency with the switch. SM would not consider any other option but a return to haloperidol, now back at a dose of 5mg per day. Sleep has improved and she is now less irritable.

Most antipsychotics have multiple neuroreceptor actions; for example, chlorpromazine and clozapine, which have significant anticholinergic activity, may provoke nausea, vomiting, insomnia and disturbing dream-laden sleep on withdrawal.<sup>8</sup> These symptoms are treatable with the prescription of an antipsychotic agent such as procyclidine. The release from dopamine blockade, which is present in every antipsychotic medication, may cause nausea and vomiting.

#### *Rebound psychosis*

This is a rapid-onset psychosis occurring within days of stopping antipsychotics, characterised by paranoid delusions, grandiosity, elation, hallucinations and hostility. It usually follows abrupt withdrawal of antipsychotics and is sometimes termed a supersensitivity psychosis.<sup>9</sup> Evidence for such an entity is most compelling following

clozapine withdrawal but it may occur with other antipsychotic drugs.

It represents a very serious hazard in the treatment of people who have severe treatment-refractory mental illnesses associated with antisocial behaviour, especially if they stop their clozapine covertly and abruptly. It is difficult to know clinically whether what is being observed is a relapse or a new type of psychotic disorder induced by coming off antipsychotics. The phenomena of a rebound psychosis suggest it is more akin to a stimulant-induced psychosis involving overactivity of dopaminergic and noradrenergic systems.

#### *Relapse of the original mental illness*

Obviously this may arise due to the removal of the prophylactic effect of the antipsychotic and in effect provides a vindication for the prescription of the medication in the

first place. Symptoms may have been suppressed by the antipsychotic, unleashed by withdrawal leading to a new episode of illness

### Conclusion

Withdrawal of antipsychotics requires careful consideration. It may be attempted in primary care or the specialist mental health services. It is best performed on a gradual basis following discussion with the patient and all of the parties involved in his or her care.

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### Declaration of interests

Dr Livingston has received consultancy fees from Janssen and Servier.

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