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# Patients need reliable facts and figures about antipsychotics†

EDITORIAL

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## SUMMARY

The results of Wunderink *et al*'s trial support the experience of most practising psychiatrists: guided discontinuation of antipsychotics works for some patients, but most stay in remission only with carefully tailored and monitored maintenance treatment at the 'lowest effective dose'. It is important to review maintenance annually and to discuss with patients whether dose reduction/discontinuation should be attempted.



## DECLARATION OF INTEREST

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The introduction of chlorpromazine for the treatment of schizophrenia was 'one of the twelve definitive developments in modern medicine' (Le Fanu 2011), and antipsychotic medication remains one of the most effective treatments in medicine (Leucht 2012a). We know from randomised controlled trials (RCTs) that antipsychotic drugs are effective in treating acute psychosis and reducing relapse (Leucht 2012b), and long-term observational studies suggest that they reduce violence (Fazel 2014) and overall mortality (Tiihonen 2009). On the other hand, they undoubtedly have a range of unpleasant adverse effects and many patients do not like taking medication.

Current guidance published by the National Institute for Health and Care Excellence (NICE 2014: section 1.3.6.3) states that 'Treatment with antipsychotic medication should be considered an explicit individual therapeutic trial'. It goes on to say: 'Record the rationale for continuing, changing or stopping medication, and the effects of such changes'. This is not quite an assumption that 'most people with schizophrenia will need long-term antipsychotic treatment', as claimed by Moncrieff (2015, this issue) – although other treatment guidelines do suggest that medication should be maintained for up to 2 years or even longer in chronic illness (Barnes 2011; Hasan 2013; Scottish Intercollegiate Guidelines Network 2013).

## The known benefits and harms of antipsychotics

In a recent systematic review and meta-analysis of 65 RCTs involving 6493 patients, antipsychotic drugs reduced relapse rates at 1 year from 64% on placebo to 27% on medication (Leucht 2012b). This is an absolute benefit increase of 37% and taking the reciprocal gives a number needed to treat to benefit (NNTB) of three patients. There are hardly any treatments in modern medicine with NNTBs of three! This does not mean that two patients out of three do not benefit – the average benefit is, of course, about a one-third reduction in the risk of relapse. Indeed, Leucht *et al* (2012b) reported that there were fewer patients with unimproved or worse disease severity in drug-treated groups. The lack of a difference in relapse rates comparing studies with abrupt versus gradual discontinuation argues against relapse being confused with cessation reactions (and also argues against a putative 'supersensitivity psychosis'). Antipsychotic medication also reduced hospital admissions, improved quality of life and reduced the frequency of aggressive acts. Data on employment were of low quality and too scarce from these RCTs to allow significant differences to be identified.

If one consults the Cochrane Library, there are even RCTs showing similar benefits over 2 years or more, as well as benefits in other outcomes such as increased 'global improvement' (Adams 2014). There is also strong evidence that these advantages are not simply attributable to conflicts of interest such as pharmaceutical company sponsorship of the trials (Adams 2013).

On the downside, Leucht *et al* (2012b) reported that antipsychotic drugs were associated with movement disorders (16% of treated patients *v.* 9% on placebo), sedation (13% *v.* 9%) and weight gain (10% *v.* 6%). Nevertheless, as indexed by the numbers of patients who stay in the studies, patients consistently seem to prefer antipsychotic medication to placebo treatment (Leucht 2012b;

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Adams 2013, 2014). Longer-term harms are more difficult to quantify, but may include increased cardiovascular and other health risks (Young 2014). The possible association between exposure to antipsychotic medication and loss of brain volume is of unclear clinical relevance, but could reflect, for example, sedation-exacerbated inactivity (Fusar-Poli 2013).

## What did Wunderink *et al* actually do and show?

The effects of treatment in practice require long-term observational studies such as that by Wunderink and colleagues. They completed a trial of guided dose reduction/discontinuation versus maintenance treatment involving 128 patients receiving antipsychotics after a first episode of psychosis. It should be noted, however, that 157 were originally randomised and that they came from a still larger group of those who were assessed (Wunderink 2007). The patients had been in remission for 6 months before randomisation. Allocation list concealment was carried out, but the trial was not masked ('blind') and we know very little about how the patients were treated otherwise. At the 18-month assessment (2 years into the study), there were twice as many relapses in the discontinuation group (43% *v.* 21%, NNTB = 5) and the authors concluded at that time that 'only a limited number of patients can be successfully discontinued'. The subsequently reported 7-year follow-up data (Wunderink 2013) come from an impressively successful endeavour to re-contact 103 (80%) of the group who completed the original trial. The unsettling finding is that those originally in the dose reduction/discontinuation arm were now twice as likely to have achieved recovery in terms of both symptomatic and functional remission (40% *v.* 18%, absolute risk reduction ARR = 22%, NNTB = 5).

A close reading of the methods and results sections of the paper reveals some important detail. At baseline, the dose reduction/discontinuation group had non-significantly less psychotic symptoms and for less time before treatment, a better occupational history and more co-habitees than the maintenance treatment group, more of whom had a diagnosis of schizophrenia. The strongest predictor of recovery was actually living together with someone at baseline (OR = 4.4), followed by the trial arm treatment strategy (OR = 3.5). Only about 20% of those in the dose reduction/discontinuation group actually managed to discontinue their antipsychotic medication at all. There were no actual differences between the dose reduction/discontinuation and maintenance treatment groups in social function or quality of life, and the mean dose of antipsychotic over the previous 2 years was only about 1.5 mg different in haloperidol equivalents (~2 mg *v.* ~3.5 mg daily). In the final analysis, only 8 individuals in the dose reduction/discontinuation group and 3 in the maintenance treatment group had sustained antipsychotic discontinuation during the 7-year follow-up (Wunderink 2013).

## Conclusions

The job of clinicians caring for patients with schizophrenia is to treat them to the best of their ability, to give them the best available information about the likely benefits and harms of various treatment strategies, to share any uncertainties about this evidence and to help them to decide on the best management strategy for them. Most clinicians I know do therapeutic trials of slowly withdrawing medication after patients have been well for a year or two. Most patients who have ongoing contact with psychiatric services tend to receive the 'lowest effective dose' that keeps them well and adverse effects to a tolerable minimum. Wunderink *et al*'s non-masked RCT is therefore unlikely to dramatically alter clinical practice, although it should encourage us all to review annually the rationale for continuing antipsychotic medication and to consider with patients whether dose reduction/discontinuation should be attempted. What it actually shows is that antipsychotic discontinuation is rarely feasible and that slow tapering of the dose down to an average of about 2 mg haloperidol equivalents is associated with some measures of functional improvement. Indeed, the results are entirely in keeping with treatment guidelines which suggest that antipsychotic medication should be maintained for 2 years and then phased withdrawal attempted (Barnes 2011). What the trial suggests we really need is not new strategies for managing antipsychotic treatment after a first episode, but a way of identifying the small number of patients who can manage without antipsychotics.

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