

EDITORIAL

Long-term effects of antipsychotics[†]

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[†]See related editorials on pp. 80–84 and 85–87, this issue.

SUMMARY

Antipsychotics are useful at reducing acute symptoms, but recent evidence calls into question their long-term efficacy and raises concern about adverse effects on the brain.

DECLARATION OF INTEREST

None

Antipsychotic drugs have been the mainstay of treatment for people diagnosed with schizophrenia or psychosis since they were introduced in the 1950s. They are recommended for acute psychosis, and routinely prescribed on a long-term basis for the amelioration of ongoing symptoms and the prevention of relapse. The National Institute for Health and Care Excellence (NICE) clinical guideline assumes that most people with schizophrenia will need long-term antipsychotic treatment (NICE 2014). New evidence suggests that psychiatric practice may need to change, however.

Evidence for long-term treatment

The evidence base for the long-term use of antipsychotic drugs consists of randomised controlled trials in which people already established on treatment are randomised to continue with maintenance treatment or to have their antipsychotics discontinued. These trials find higher rates of relapse among people randomised to discontinue antipsychotics (Leucht 2012).

Problems with this evidence base have been recognised for some time. First, follow-up has mostly been short, with few trials lasting longer than a year. Second, relapse has been defined in a wide variety of ways, and many definitions have not specified the presence of psychotic symptoms. Third, discontinuation has usually been abrupt, with the consequence that antipsychotic withdrawal symptoms may have been misdiagnosed as relapse in placebo-treated patients, especially in studies in which relapse was defined as a small increase in general symptoms. Fourth, few studies have evaluated outcomes other than relapse (Leucht 2012).

Meta-analyses suggest that studies with longer follow-up tend to find smaller differences in

relapse rates than those lasting for shorter periods (Leucht 2012). Consequently, the lack of longer-term follow-up of the outcome of antipsychotic discontinuation presents a major obstacle to the evaluation of antipsychotic therapy.

The Wunderink *et al* study

In 2013, data from a 7-year follow-up of a randomised antipsychotic discontinuation trial were published (Wunderink 2013). The original study (Wunderink 2007), conducted in The Netherlands, involved 131 people who had recovered from a first episode of psychosis and had been in remission for 6 months. Participants were randomised to antipsychotic maintenance treatment or to a gradual and flexible antipsychotic reduction strategy. At the 18-month follow-up (128 participants), only 54% of the discontinuation group had completely discontinued antipsychotics, and only 22% discontinued and remained off. Thirty-two per cent stopped and then restarted their antipsychotic medication and the rest did not manage to discontinue at all. At 18 months, relapses were twice as common in the discontinuation group than in the maintenance group (43% *v.* 21%), although time spent in hospital was not increased. There were no differences in measures of social functioning between the groups, but there was a non-significant trend towards more people being in work in the discontinuation group (Wunderink 2007). A neurocognitive substudy also showed better performance in the discontinuation group (Faber 2011). Despite this, Wunderink *et al* concluded that antipsychotic discontinuation is a strategy that should be reserved for people who are unwilling to adhere to maintenance treatment.

At 7-year follow-up, however, the situation had changed. Rates of relapse had evened out, with 62% of the discontinuation group experiencing a relapse *v.* 69% of the maintenance group. Although symptomatic recovery was the same in the two groups, people randomised to the antipsychotic discontinuation strategy were twice as likely to show 'functional remission' than those randomised to maintenance (46% *v.* 20%). At this point, 21% of the discontinuation group were off antipsychotics completely, and a further 21% were taking very low doses (less than 1 mg haloperidol

equivalent per day) (Wunderink 2013). A *post hoc* analysis according to actual treatment received showed that 56% of patients who discontinued antipsychotics or reduced to a very low dose showed functional remission compared with 22% of those who continued antipsychotics (Wunderink 2013). Although this study recruited only people with first-episode psychosis, a recent meta-analysis found no difference in the outcome of antipsychotic discontinuation between studies involving patients with a first episode of psychosis and those with recurrent illness (Leucht 2012).

Antipsychotics and the brain

Other important developments include emerging evidence about the effects of antipsychotics on brain matter. In 2005, a study with macaque monkeys showed that these drugs reduce brain matter by around 10% over 18 months of treatment (Dorph-Petersen 2005). Evidence in patient populations is complex, but some studies indicate decreases in brain matter associated with antipsychotic treatment levels (Moncrieff 2010), including results of the largest and longest cohort study of first-episode schizophrenia published to date (Andreasen 2011).

Whether these structural effects are reflected in intellectual functioning is uncertain. Some studies suggest not, but others have found an association between reduced brain matter and cognitive capacity (Moncrieff 2010).

Conclusions

Antipsychotics can effectively reduce acute psychotic symptoms in many people, but evidence on the benefits of long-term treatment is more

equivocal, and recent evidence underlines their potentially negative effect on brain volume, alongside other serious physical complications.

NICE (2014) recommends more research into long-term outcomes of antipsychotic discontinuation. In the meantime, recent evidence suggests that a trial of supported antipsychotic discontinuation should be considered as one option in the routine treatment of people with psychotic conditions. This strategy may help some people to improve their functioning and quality of life, and reduce the risks to their physical health.

References

- Andreasen NC, Nopoulos P, Magnotta V, et al (2011) Progressive brain change in schizophrenia: a prospective longitudinal study of first-episode schizophrenia. *Biological Psychiatry*, **70**: 672–9.
- Dorph-Petersen KA, Pierri JN, Perel JM, et al (2005) The influence of chronic exposure to antipsychotic medications on brain size before and after tissue fixation: a comparison of haloperidol and olanzapine in macaque monkeys. *Neuropsychopharmacology*, **30**: 1649–61.
- Faber G, Smid HG, Van Gool AR, et al (2011) Neurocognition and recovery in first episode psychosis. *Psychiatry Research*, **188**: 1–6.
- Leucht S, Tardy M, Komossa K, et al (2012) Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. *Lancet*, **379**: 2063–71.
- Moncrieff J, Leo J (2010) A systematic review of the effects of antipsychotic drugs on brain volume. *Psychological Medicine*, **40**: 1409–22.
- National Institute for Health and Care Excellence (2014) *Psychosis and Schizophrenia in Adults: Treatment and Management* (Clinical Guideline CG178). NICE.
- Wunderink L, Nienhuis FJ, Sytema S, et al (2007) Guided discontinuation versus maintenance treatment in remitted first-episode psychosis: relapse rates and functional outcome. *Journal of Clinical Psychiatry*, **68**: 654–61.
- Wunderink L, Nieboer RM, Wiersma D, et al (2013) Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation or maintenance treatment strategy: long-term follow-up of a 2-year randomized clinical trial. *JAMA Psychiatry*, **70**: 913–20.