BJPsych | The British Journal of Psychiatry (2017)
211, 127–129. doi: 10.1192/bjp.bp.117.201103

Editorial

Do antipsychotic drugs lose their efficacy for relapse prevention over time?†

Stefan Leucht and John M. Davis

Summary
There is a debate about long-term treatment of schizophrenia with antipsychotic drugs, with some experts suggesting that these drugs should be discontinued. In this issue, Takeuchi *et al* demonstrated by a meta-analysis of 11 trials that antipsychotic drugs maintained their efficacy for relapse prevention for 1 year, whereas patients on placebo kept getting worse. We consider these findings in the light of the current discussion about possible dose-related brain volume loss, supersensitivity psychosis, the high variability of results in long-term follow-up studies and recent approaches to discontinue antipsychotics in patients with a first-episode. The new findings speak in favour of continuing antipsychotics at the same dose, at least in patients whose condition is chronic, but the topic is complex.

Declaration of interest
In the past 3 years S.L. has received honoraria for consulting from LB Pharma, Lundbeck, Otsuka, Roche, and TEVA, for lectures from AOP Orphan, ICON, Janssen, Lilly, Lundbeck, Otsuka, Sanofi, Roche, and Servier, and for a publication from Roche.

Stefan Leucht (pictured) is a Professor of Psychiatry at the Department of Psychiatry and Psychotherapy at the Technische Universität München. His main research interests are systematic reviews, clinical trials, trial methodology, and pharmacogenetics in schizophrenia. John Davis is Professor of Psychiatry at the University of Illinois at Chicago. He is interested in meta-analysis (with publications dating back to the first meta-analysis in psychiatry, published in 1975), the biogenic hypothesis of depression, and the molecular biology of schizophrenia.

There is a new debate about long-term treatment with antipsychotics stimulated by data suggesting a dose-related brain volume loss,[1] supersensitivity effects of long-term treatment with antipsychotics[2,3] and some follow-up studies showing that patients who do not receive antipsychotics in the long-term have better outcomes than treated patients.[4]

In this context Takeuchi *et al* present an analysis of the symptom trajectories in relapse prevention studies over 1 year.[5] In the placebo-treated groups they find a continuous worsening of approximately 50% over baseline of the mean Positive and Negative Syndrome Scale (PANSS)/Brief Psychiatric Rating Scale (BPRS) scores at 1 year, compared with an only 10% worsening of these scores in the antipsychotic group. This finding is important because it means that antipsychotic efficacy is maintained over time and should not be discontinued. At first glance, this contrasts with our meta-analysis of relapse prevention studies where 64% of placebo-treated *v.* 27% of drug-treated patients experienced a relapse within 1 year.[6] When we summarised the relapse rates of only the 11 studies included by Takeuchi *et al*, the results were more similar 55% *v.* 22% relapsed. The drug–placebo difference became smaller over time in our analysis, but we discussed that this was likely because of statistical artefacts, among others because most studies did not use survival analyses (Fig. 3 in Leucht *et al*[6]). To understand better how it is possible that the average PANSS/BPRS scores remained relatively stable over 1 year on the drug, despite some patients relapsing, one needs to know that in many studies the patients are not necessarily symptom free at baseline and therefore patients can improve, as well as get worse. For example, in Pigott *et al* 2003,[7] the average PANSS at baseline was about 82 and at the end-point the drug-treated group improved by two points. Or, in our meta-analysis 30% of drug-treated patients improved at the end-point (Fig. 1 in Leucht *et al*[6]). Some patients relapsed in the drug-treated group but this was balanced by those patients that improved.

Supersensitivity psychosis

The symptom trajectories presented by Takeuchi *et al* are also important in the context of rebound or supersensitivity psychosis, a possibility suggested in the 1970s by Chouinard and colleagues[2] based on an observation of ten patients. This is pharmacologically plausible as dopamine supersensitivity is observed in animals. (For reviews, see Murray *et al*[8] and Moncrieff.[3]) Takeuchi *et al* found a gradual worsening of symptoms rather than an initial peak as would be expected for withdrawal symptoms. In our meta-analysis we examined rebound psychosis by comparing abrupt and gradual withdrawal of antipsychotics in the placebo groups, but we did not find any difference. However, the minimum duration of tapering was only 3 weeks,[5] which may have been too short. We also compared the relapse rate of drug *v.* placebo, in patients who were relapse free on either drug or placebo for 3 months, 6 months and 9 months, and then followed up until the end of the studies. The differences in relapse rates between drug and placebo were similar (Fig. 4 in Leucht *et al*[6]). If the difference in relapse rates were simply explained by supersensitivity psychosis, the relapse rate should have been lower in those patients who had been relapse free for 9 months. A similar observation has been reported in a meta-analysis of antidepressants.[9] It is possible after some time on the drug that patients might have been 'cured', and would not need antipsychotics any longer. In a third analysis we therefore examined whether the drug–placebo difference in relapse rates became smaller in patients who had been stable on antipsychotics for up to 3–6 years before they were randomised to either stay on antipsychotics or to be switched to placebo. We found that even those patients who had been stable for 3–6 years and then were randomised to drug or placebo, those on placebo relapsed at a higher frequency than those who stayed on antipsychotics, and

†See pp. 137–143, this issue.

https://doi.org/10.1192/bjp.bp.117.201103 Published online by Cambridge University Press

the drug–placebo difference was not influenced by the time patients were stable on antipsychotics before randomisation (Fig. 2 in Leucht *et al*[6]). However, the limitation was, again, that drugs were withdrawn abruptly.

Very long-term follow-up

Takeuchi *et al*'s data were restricted to 1 year and ours to 2 years, but the very long-term outcome of schizophrenia is complex. Some examples: according to a methodologically sound systematic review on average only 13.5% of patients achieve a full recovery.[10] In contrast, in both studies from the pre-antipsychotic era[11] and in recent studies a considerable proportion of patients with a first psychotic episode were in remission at follow-up, with wide variability in diagnostic criteria, remission criteria and frequency (for example 32% in Aastrup *et al*,[11] 20% in Robinson *et al*[12] and 40% in the AESOP study[13]). But we cannot identify them in advance and full (social and symptomatic) recovery over a long period may be rare.[10] Harrow *et al*[4] reported a 20-year follow-up of a Chicago cohort of 70 patients with schizophrenia, drawn in large part from a psychoanalytic hospital, where affluent, mainly first- or second-episode patients, were admitted to hospital for long-term psychoanalysis. In total, 50% (approximately 7 out of 15) of untreated patients compared with about 15% of treated patients were recovered at 20 years. Patients with a better prognosis might not have needed antipsychotics, thus not taking antipsychotics was not necessarily causal for the better outcome (which epidemiologists call 'confounding by indication'). As an analogy, people who survived a cancer without treatment might also do better than those who underwent chemotherapy. In contrast, at the 14-year follow-up of a well-designed epidemiological study from a defined catchment area in China more untreated patients had died, had higher unemployment rates and fewer were in remission.[14] Although there are some predictors of non-relapsing patients, they are not accurate enough to be fully confident of correct identification. We would hope that more data on imaging, cognition and genetics will provide robust criteria in the future.

Brain volume loss

The evidence suggesting that antipsychotics cause brain volume loss in a dose-related fashion is worrying, but equivocal, because it is difficult to disentangle whether this is because of the illness or the medication. Higher doses of medication are required for more severely ill patients. In six macaque monkeys olanzapine and haloperidol led to more brain volume loss than placebo.[15] In an observational 15-year follow-up study higher antipsychotic doses were associated with more brain volume loss,[16] but in the same sample there was more brain volume loss in those patients who spent most time in exacerbation of psychosis, which would mean that relapses need to be prevented.[17] Moreover, the clinical relevance is unclear, because in one study treated patients performed better on cognitive tests than untreated patients despite more brain volume loss.[18]

First-episode studies

The final line of evidence is the open randomised controlled trial by Wunderink and colleagues[19] in which patients in a first-episode in remission were either continued on antipsychotics or were gradually withdrawn. The major difference, in comparison with the classical relapse intervention studies, was that if withdrawal was not possible, medication was reinstituted or the dose re-increased. This strategy is actually quite similar to what many physicians do when following the wishes of their patients. Gradual dose reduction did not prevent relapse in that there were 22% more relapses in the discontinuation group (43%) compared with the continuation group (21%). But most of the 13 patients who could be successfully discontinued initially remained relapse free, and, in the 7-year follow-up patients in the gradual discontinuation group had a significantly better functional outcome. The major limitation was that after the initial 2 years the study was no longer randomised, meaning that patients did not follow the treatment that they had been initially assigned to any longer. Much can have happened in 5 years. This makes it impossible to derive a causal relationship between the initial attempt to withdraw antipsychotics and better functional outcome at 7 years. We find a causal relationship unlikely, in particular because the doses in both groups were similarly low at the end of 2 years (in the attempted withdrawal group 2.8 mg/day haloperidol equivalent and in the maintenance group 2.9 mg/day).

Implications

There have been many attempts to stop medication, closely monitor early warning symptoms of relapse and reinstitute treatment rapidly, but these have failed to prevent relapse.[20] Attempts to identify the minimum effective doses for relapse prevention with dose–response studies have also proven to be difficult.[21,22] But the side-effects of antipsychotic drugs such as movement disorders, sedation, hormonal changes and particularly weight gain can produce significant physical comorbidities that can contribute to the documented excess mortality of schizophrenia.[23] Therefore, an approach to identify the patients with a first-episode who do not need maintenance treatment would solve a major problem. But replications are needed, because the stakes are high when doses are down-titrated with relapse as the lower limit. In the meantime, Takeuchi *et al*'s results speak in favour of continuing antipsychotics at the same dose, at least for chronic illness, because the superiority of antipsychotics compared with placebo was large and increased even further over time.

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First received 11 May 2017, accepted 14 Jul 2017

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https://doi.org/10.1192/bjp.bp.117.201103 Published online by Cambridge University Press

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psychiatry in pictures

Up and Away by Isobel Prescott (1935–2013)

Lucy Alexander

Citation: Press release for the 2009 Parkinson's Disease Society Mervyn Peake Award for Art

Cambridge woman wins Parkinson's Disease Society award for art

Isobel Prescott, from Cambridge, has won this year's Mervyn Peake Award for Art. Isobel won with her painting *Up and Away* and her award was presented by Richard Briers and Fabian Peake at an awards ceremony at Westminster Central Hall in London on 3 July [2009].

Launched by the Parkinson's Disease Society (PDS) and the Peake family 7 years ago, the awards celebrate the creative achievements of people with Parkinson's in art, poetry and photography. The awards are held in memory of the late illustrator, writer and poet Mervyn Peake (1911–1968), whose works included *Gormenghast* and the *Alice in Wonderland* illustrations, and who developed Parkinson's in later life.

This is the first year Isobel has entered the awards. Isobel, who was diagnosed with Parkinson's in 2005 said: 'I chanced to see the competition advertised in *The Parkinson* magazine and as I had a painting underway based on sketches made of *Event Horizon* (Anthony Gormley's London rooftop exhibition) I decided to enter considering it apposite – the straight and stiff human figures representing the stiffness of Parkinson's disease; the ''up and away'' being a fanciful flight from that lack of fluent mobility. Only later did I realise that this splendid prize founded by the Peake family, which I was delighted (of course) to receive, rightly embraces any subject thus encouraging sufferers to think and do beyond the brain malfunction of Parkinson's.'

Isobel was posthumously diagnosed with multiple system atrophy. Lucy Alexander is her daughter.

The British Journal of Psychiatry (2017) 211, 129. doi: 10.1192/bjp.bp.117.199067

https://doi.org/10.1192/bjp.bp.117.201103 Published online by Cambridge University Press