BJPsych | The British Journal of Psychiatry (2025)
1–3. doi: 10.1192/bjp.2025.10470

Guest Editorial

Does relapse matter? Insights from new data in schizophrenia

Oliver Howes, Maria Kapi and Bernard R. Bukala

Summary

It is often assumed that relapse leads to poor long-term outcomes, but new data question this in regard to symptoms, social function, quality of life and, possibly, employment. We consider this together with other impacts, risks and costs and how individual circumstances all influence decisions about antipsychotic maintenance treatment to prevent relapse.

Keywords

Psychotic disorders/schizophrenia; antipsychotics; evidence-based mental health.

Substantial evidence shows that maintenance treatment with antipsychotic medicine reduces the risk of relapse in schizophrenia. This includes the results from more than 90 randomised controlled trials,[1] plus large pharmaco-epidemiological studies,[2] showing that the risk of relapse is roughly halved in people continuing on antipsychotic treatment relative to those who discontinue antipsychotics. The number needed to treat (NNT) to prevent one relapse is around three,[1] which compares favourably with many other interventions in medicine.

However, does preventing relapse matter? This is an important question because antipsychotic maintenance treatment is not a zero-sum game. Some antipsychotic treatments have been shown in randomised controlled trials to induce cardiometabolic side-effects.[3] Tardive dyskinesia remains a risk even with newer dopamine D2/3 receptor-blocking drugs, and is irreversible in some people.[4] Sedation, sexual impairment, motor dysfunction, prolactin elevation and other side-effects affect quality of life.[5] D2/3 receptor blockade may also induce secondary negative symptoms and impair functioning.[4] It is not surprising, then, that many patients want to discontinue maintenance antipsychotic treatment. A further consideration is the health service costs of maintenance treatment: the direct cost of the medicine, the clinician and pharmacist time monitoring treatment and the costs of investigations to monitor side-effects and interventions required to address these. These all divert resources from other uses. On top of this, there is the psychosocial impact on the patient and their carers of maintenance treatment: the implicit message that they remain unwell and in need of care, and the time they spend on taking treatment.

These factors highlight how important it is to understand whether relapse matters. There are two aspects to this: the impact of relapse itself and the consequences of relapse. There is substantial evidence that the duration of untreated psychosis is associated with poorer long-term outcomes.[6] This could suggest that relapse of psychosis is also associated with lasting effects, including higher long-term symptom severity and poorer long-term social and occupational function.[7] However, it is surprising how few studies have investigated the long-term impact of relapse, particularly given the number of studies that have investigated whether antipsychotic treatment reduces the risk of relapse. Moreover, most studies have used convenience samples to compare outcomes in patients who have relapsed with those who have not. Consequently, a major issue with many of these studies is sampling bias: effects could be driven by baseline differences in the severity of illness, for example. In this context, a recent randomised trial provides an important addition to the evidence base on the long-term outcomes following relapse.[8]

The report by Moncrieff et al[8] is a secondary analysis of data from the RADAR trial, which recruited over 250 chronically ill patients taking antipsychotic treatment for recurrent psychosis or schizophrenia. Patients were randomised to either (a) gradual, flexible antipsychotic dose reduction with the aim of stopping treatment (the discontinuation group) or (b) continuing on the current dose of antipsychotic treatment (the maintenance group). Social functioning was the primary outcome measure, but the authors also collected data on symptom severity, quality of life and employment status. They compared change in these measures from baseline to 24-months follow-up. Importantly, a large proportion of patients (190/253, 75%) completed the 24-month follow-up, 82 of whom experienced at least one relapse during the follow-up period. The study found no significant difference in any of the outcome measures at 24 months between patients who relapsed and those who had not. However, there was a significantly higher risk of relapse in the discontinuation group relative to the maintenance group. Nevertheless, the results of the long-term outcomes were essentially the same after adjusting for whether patients were randomised to maintenance or discontinuation group. Moreover, there was no significant change in any of the measures when the baseline data were compared with the follow-up data in those patients who had experienced a relapse.

Clinicians and experts by experience (see Box 1) often report that a patient's illness does not respond as well to treatment following a relapse as it did before relapse. Real-world evidence also indicates that the dose of antipsychotic increases following each relapse.[2] However, one of the most striking findings of the study by Moncrieff et al is that symptom severity at 24 months was not significantly different from baseline levels in those whose illness had relapsed. This is not compatible with the hypothesis that relapse is associated with poorer subsequent response to treatment on average, although information on antipsychotic dose at follow-up is not reported and so it is unclear whether this changed following relapse relative to baseline – in future studies it would be important to establish the effect of relapse on the antipsychotic treatment required which, as discussed, comes with significant costs. Nevertheless, overall these data indicate that relapse is not associated with long-term effects on social function, symptom severity or quality of life.

It is important to consider several factors in the study design and patient population to identify the patients to which these results are most applicable. Importantly, the authors note that the majority of participants in the RADAR trial were 'male, white, single and unemployed', so the results must be generalised with caution to other patient populations. Patients entering the trial consented to randomisation and follow-up, and individuals were excluded if they were legally required to take antipsychotic

https://doi.org/10.1192/bjp.2025.10470 Published online by Cambridge University Press

Box 1 The impact of relapse: a personal perspective

I have lived with schizophrenia for the past 20 years and have had six relapses during this time. After each relapse, my antipsychotic medicine has not been as effective as it was before the relapse and the dose has had to be increased. Every relapse has also had great effect on my self-esteem and it takes considerable time to return back to normal and smile from my heart again. For me, relapse is a devastating experience each time. An important long-term consequence of my relapses has been the loss of some friends who couldn't accept me when I had psychosis. This has narrowed my friendship circle. Not all relapses have had the same long-term consequences on my life. Ten years ago, I had a relapse and lost my employment, and professional registration. I recovered and got a different job 3 months later. However, my professional registration was only restored 9 years later, which affected my career progression as I couldn't apply for jobs that required a licence to practice as a doctor. I consider this an important consequence. In contrast, I had another relapse almost 2 years ago and my employer treated me with great care and respect, provided me with the time to recover and I didn't lose my job. In my experience, the impact of relapse varies, and it is very much dependent on your circumstances at the time, your place in your patient journey and how well you can manage a relapse.

Dr Maria Kapi, expert by lived experience and training

treatment. We can speculate that this is likely to have enriched the sample for people who were relatively well engaged with mental health services and who, consequently, would re-engage with treatment quickly following a relapse to maximise the chance of recovery. This may limit the applicability of the findings to patients who do not engage well with services. The patients entering the trial also showed relatively low symptom severity at baseline. While we do not have any information on the severity of symptoms prior to entering the study, this suggests that their illnesses had responded well to prior treatment. Similarly, we have limited information on the relapse history of patients prior to entry into the trial but, given that baseline symptom ratings were low, it seems they had recovered well following their previous relapse. The findings of this study may, thus, be less applicable to patients where their illness has shown only a partial response to treatment.

Another important characteristic of the RADAR study population is the chronicity of their condition, and that patients had mostly had multiple previous relapses (on average, three previous hospital admissions). Evidence from other studies suggests that antipsychotic treatment response is lower following the second (and subsequent) relapse relative to the first, hinting that prevention of the second relapse is particularly important.[2] Therefore, it would valuable for RADAR and future similar studies to include subgroup analyses comparing long-term outcomes in patients with one prior relapse with those who have had two or more prior relapses.

Around 25% of the sample was in employment, education or training at baseline. This is fairly representative for people with schizophreniform disorders in the UK, but means that the study was probably underpowered to detect differences in employment status between those who experienced a relapse relative to those who did not. For example, to detect a 10% difference in employment rates at $P < 0.05$ (two-tailed) requires a sample size of 490 with 80% power when the baseline employment rate is 25% (two-sample test of independent proportions using G*Power 3.1; Heinrich Heine University Düsseldorf, Düsseldorf, Germany; https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower). It is interesting to note that, in numerical terms, the proportion of people in employment, education or training had dropped more in the relapse group than in the group that had not relapsed. Thus, the finding of no significant difference between groups in this outcome measure should be treated with caution. It is also important to note that relapse may have other long-term consequences that were not measured in this study, such as loss of friends and self-esteem, and effects on career progression (see Box 1).

Notwithstanding the issues discussed above, the finding that there is no evidence that relapse is associated with long-term effects across multiple measures is a reassuring outcome for patients and clinicians alike. Perhaps relapse is not so terrible after all? However, patients and clinicians also need to consider the effects of relapse itself. Acute deterioration in mental state can present serious risks to self and others, and damage social relationships (see Box 1). Relapse also increases health service costs, particularly if it leads to admission to hospital (which occurred in 25% of participants in the antipsychotic reduction group in the RADAR trial).[8]

In conclusion, while it is clear that antipsychotic maintenance treatment reduces the risk of relapse in schizophrenia, the decision to take maintenance treatment depends on multiple factors, including the impact of side-effects and the direct consequences of relapse, as well as its long-term effects. New data from Moncrieff et al[8] add important evidence on key elements of the latter in patients with chronic illness, low risk and low levels of symptoms. There are also outstanding issues, including whether employment was affected, the health economic effects and whether findings will generalise to other patient groups, particularly those who are more unwell prior to discontinuation. This highlights the need for further studies into the long-term risks and benefits of antipsychotic maintenance treatment. Finally, it is important to recognise the large number of factors that may influence the risk–benefit analysis and the importance given by an individual to make the decision to continue maintenance treatment – a complex and highly personal choice. Decision aids may help by supporting patients and clinicians to identify what is important to the individual.[9] Clinicians and patients should also recognise that the balance may shift with changing circumstances and values, meaning that the decision needs to be both individualised and revisited. One size does not fit all, all the time!

Oliver Howes, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK; **Maria Kapi**, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK; **Bernard R. Bukala**, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK

Correspondence: Oliver Howes. Email: oliver.howes@kcl.ac.uk

First received 24 Feb 2025, final revision 7 Aug 2025, accepted 22 Sep 2025

Author contributions

O.H., M.K. and B.R.B contributed equally to the writing and editing of the manuscript.

Funding

For the purpose of open access, this paper has been published under a CC-BY licence to any Accepted Author Manuscript version arising from this submission. The work developing this paper was funded by Medical Research Council UK (nos MC_U120097115, MR/W005557/1 and MR/V013734/1), UK Research and Innovation (no. 10039412), the European Union (nos 101028661 and 101026235), Margaret Temple, the King's Challenge Fund and the Wellcome Trust (nos 094849/Z/10/Z and 227867/Z/23/Z); and by the National Institute for Health and Care Research (NIHR) Biomedical Research Centre at South London and Maudsley National Health Service Foundation Trust and King's College London (grants to O.H.). The views expressed here are those of the authors and they do not represent the views of their employers or funders.

Declaration of interest

O.H. has received research funding from and/or participated in advisory/ speaker meetings organised by Abbvie, Alkermes, Angellini, Autifony, Biogen, BMS (Karuna), Boehringer-Ingelheim, Delix, Eli Lilly, Elysium, Heptares, Global Medical Education, Invicro, Jansenn, Karuna, Lundbeck, Merck, Neumora, Neurocrine, Ontrack/ Pangea, Otsuka, Sunovion, Teva, Recordati, Roche, Rovi and Viatris/ Mylan. He was previously a part-time employee of Lundbeck A/v. M.K. is an employee of Otsuka Pharmaceuticals Europe Ltd. B.R.B. has received consulting honoraria from Relation Therapeutics and Candesic.

https://doi.org/10.1192/bjp.2025.10470 Published online by Cambridge University Press

References

1 Ostuzzi G, Bertolini F, Tedeschi F, Vita G, Brambilla P, del Fabro L, et al. Oral and long-acting antipsychotics for relapse prevention in schizophrenia-spectrum disorders: a network meta-analysis of 92 randomized trials including 22,645 participants. *World Psychiatry* 2022; **21**: 295–307.

2 Taipale H, Tanskanen A, Correll CU, Tiihonen J. Real-world effectiveness of antipsychotic doses for relapse prevention in patients with first-episode schizophrenia in Finland: a nationwide, register-based cohort study. *Lancet Psychiatry* 2022; **9**: 271–9.

3 Pillinger T, McCutcheon RA, Vano L, Mizuno Y, Arumuham A, Hindley G, et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. *Lancet Psychiatry* 2020; **7**: 64–77.

4 Kaar SJ, Natesan S, McCutcheon R, Howes OD. Antipsychotics: mechanisms underlying clinical response and side-effects and novel treatment approaches based on pathophysiology. *Neuropharmacology* 2020; **172**: 107704.

5 Lobo MC, Whitehurst TS, Kaar SJ, Howes OD. New and emerging treatments for schizophrenia: a narrative review of their pharmacology, efficacy and side effect profile relative to established antipsychotics. *Neurosci Biobehav Rev* 2022; **132**: 324–61.

6 Howes OD, Whitehurst T, Shatalina E, Townsend L, Onwordi EC, Mak TLA, et al. The clinical significance of duration of untreated psychosis: an umbrella review and random-effects meta-analysis. *World Psychiatry* 2021; **20**: 75–95.

7 Emsley R, Chiliza B, Asmal L. The evidence for illness progression after relapse in schizophrenia. *Schizophr Res* 2013; **148**: 117–21.

8 Moncrieff J, Pillai E, Marston L, Lewis G, Barnes TRE, Johnson S, et al. The association between relapse and the outcome of schizophrenia and recurrent psychotic disorders. *Br J Psychiatry* 2025; **227**: 673–9.

9 Kaar SJ, Gobjila C, Butler E, Henderson C, Howes OD. Making decisions about antipsychotics: a qualitative study of patient experience and the development of a decision aid. *BMC Psychiatry* 2019; **19**: 309.

https://doi.org/10.1192/bjp.2025.10470 Published online by Cambridge University Press