Disentangling relapse and adherence in psychosis


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A defining characteristic of chronic psychotic disorders is their relapsing–remitting nature. Soon after chlorpromazine was discovered as an effective treatment for psychotic disorders, it became apparent that it was not a permanent cure, and that when patients discontinued treatment, symptoms would frequently re-emerge. This finding contributed to the view that long-term therapy was necessary in the treatment of chronic psychoses, and the effectiveness of antipsychotics in preventing relapse have subsequently been viewed as one of their greatest benefits. However, although medication discontinuation is a risk factor for relapse, psychotic disorders are inherently dynamic, and symptomatic fluctuations occur in individuals despite antipsychotic treatment.[1]

Disentangling the effects of medication discontinuation from intrinsic symptomatic variability is challenging, because accurately quantifying medication adherence is not easy.[2] The meta-analysis reported by Jose M Rubio and colleagues[3] in *The Lancet Psychiatry* employs a rigorous approach to address this. The authors systematically collated individual patient data from more than 5000 patients enrolled in 19 treatment cohorts in which patients received treatment with a long-acting injectable antipsychotic. This choice of patient cohort means that it is possible to examine relapse in individuals where adherence is assured. Additionally, the use of clinical trial data means that the data is of sufficient quality and granularity to allow for risk factors for relapse to be systematically investigated.

The authors found that the overall relapse rate in patients receiving a long-acting injectable antipsychotic was 23 per 100 patient-years. They also found that relapse was less common in individuals achieving symptomatic remission prior to trial start (14·8 relapse events per 100 participant-years vs 36·5 relapse events per 100 participant-years), which is in keeping with previous work that suggests early antipsychotic response is predictive of longer-term outcomes.[4] When examining other risk factors, they found that relapse was more frequent in those with a substance use disorder (hazard ratio 1·55, 95% CI 1·15–2·10), and reported that individuals with a diagnosis of tardive dyskinesia were at significantly greater risk of relapse (2·39, 95% CI 1·15–2·10).

These results are important in several respects. From a clinical perspective this study adds to other findings derived from naturalistic studies that show that relapse is relatively frequent and unpredictable, even in individuals with good medication adherence.[5] It also provides further evidence for association between substance use and poor outcomes, although the extent to which this association is causal is hard to fully ascertain.

These findings also have relevance when we consider schizophrenia-spectrum disorders from a neurobiological perspective. There is evidence that chronic D2 receptor blockade is associated with D2 receptor upregulation,[6] and this upregulation might underlie the development of tardive dyskinesia.[7] The association seen between relapse and tardive dyskinesia in Rubio et al is therefore in keeping with the hypothesis that antipsychotic-induced upregulation of D2 receptors is a mechanism underlying breakthrough symptoms in individuals who might have initially responded to treatment.[8]

The study also raises questions about approaches to studying relapse more generally. One issue is highlighted by the lower rates of relapse observed when naturalistic data was used to investigate the same question.[5] This discrepancy likely results in part from inconsistencies in the definition of relapse used between studies,[9] with Rubio and colleagues using a definition based on symptom severity (in contrast to relapse as defined by patient hospitalisation in the naturalistic study). This discrepancy highlights a significant issue; we do not have a clear, operationalised, consensus definition for relapse. Efforts to address this issue, as have been undertaken for definitions of treatment resistance, could advance the field.[10] Another area that would benefit from further exploration is investigation of symptom trajectories in the post-relapse period. Both clinical trials and naturalistic studies frequently end at the first relapse. Although first relapse is a marker of undoubted importance, the longer-term course of the illness has rarely been investigated in large scale systematic studies, and when it has, the results have been discrepant.[9] Although a major challenge to undertake, these methodical long-term studies will help provide the answers we need when trying to take a farsighted perspective in the clinic.

The Lancet Psychiatry, 7 (2020) 722-723. doi:10.1016/S2215-0366(20)30310-2