Real-world effectiveness studies of low doses of antipsychotics

The recent study by Heidi Taipale and colleagues[1] raises the crucial question of what we can really learn from real-world effectiveness studies about the real-life use of low doses of antipsychotics. In their analysis of a nationwide database, Taipale and colleagues[1] report an increased risk of rehospitalisation associated with time periods when patients receive low doses of antipsychotics (<4·5 mg per day equivalent risperidone) or doses lower than standard dose compared with time periods when patients receive standard doses (4·5–5·5 mg per day of equivalent risperidone; ie, 1·0 [SD 0·1] defined daily dose). Taipale and colleagues[1] suggest that a low efficacy of low doses could account for increased risk of rehospitalisation.[1] We would be more cautious with this interpretation. In patients who did not relapse during the 5-year follow-up, the proportion of time periods when patients received low doses or doses lower than standard dose was not reported.

See Online for appendix

In patients with one or two relapses, lower and higher defined daily doses were associated with a significant increase in rehospitalisation. Because real-world observational data cannot rule out confounding factors—the most important being the patient and the psychiatrist, and the complex interaction between the two—it could be interpreted from these results that psychiatrists adapt the dose for their patients on the basis of their clinical status. This interpretation aligns with the fact that almost all ongoing trials investigating the benefit–risk ratio of antipsychotic dose reduction include only stabilised patients with residual symptoms (eg, NCT02307396, EudraCT 2016-000709-36, EudraCT 2016-000565-23, and EudraCT 2017-002406-12).

With the knowledge that the mean dose given to patients with one or more relapse was higher than 1·2 defined daily doses (6 mg per day equivalent risperidone; ie, higher than doses with the best benefit–risk ratio for acute episodes or for remitted patients),[2] Taipale and colleagues[1] suggest identifying subgroups of patients likely to benefit from low doses. They show that 2309 (43·0%) of 5367 patients never relapsed, 1931 (35·9%) had one or two relapses, and 1127 (21·1%) had three or more. A trivial interpretation could be that not all patients are the same. This view speaks against the classic staging model of schizophrenia (appendix), but it aligns with the idea that schizophrenia spectrum might include multiple phenotypes with specific courses and responses to treatment.[3] Of these, cycloid psychoses are validated psychotic phenotypes of lifelong relapsing-remitting course. Cycloid psychoses represent 15–20% of all endogenous psychoses, and they are easily differentiated from relapsing progressive and purely progressive phenotypes over a 30-year follow-up (appendix).[3] For example, in an observational study done 13 years after a first psychotic episode, patients with cycloid psychoses were treated with low doses (2·1 mg [SD 1·8] equivalent risperidone, or 0·42 defined daily doses), and 6 (18·2%) of 33 had discontinued antipsychotics.[4] A meta-analysis by Tani and colleagues[5] has shown that both negative symptoms and cognition improved following dose reduction. Thus, Taipale and colleagues'[1] observations should not be interpreted as evidence against dose reduction, but they suggest that patient stratification approaches for dose reduction, in which lifelong phenotypes like cycloid psychoses, might be of interest.

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Authors' reply

We thank Fabrice Berna and colleagues[1] for their interest in our Article.[2] We fully agree that the schizophrenia spectrum is a heterogeneous group of disorders,[3] but we disagree with their claim that heterogeneity is inconsistent with the staging concept because homogeneity has never been postulated within stages. Additionally, we would like to clarify other issues that were raised. Our definition for low dose was less than 0·6 defined daily doses per day, corresponding to 3·0 mg per day equivalent risperidone (not less than 4·5 mg per day as reported by Berna and colleagues). The number of person-years and hospitalisations during use of each dose category are reported in the appendix of our original Article. People who did not relapse during the follow-up were included and contributed to the between-individual analyses of the first relapse.