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Commentary

Clozapine, relapse, and adverse events: a 10-year electronic cohort study in Canada: commentary: author response

Shawn Halayka and Lloyd Balbuena

Reply

We agree with Kikuchi that the diversity of diagnoses may have obscured clozapine's risk–benefit balance in our paper.[1] Hence, our findings may have reflected the lower range of the overall benefit of clozapine. Table 1 shows the expected count of re-hospitalisation events stratified by index diagnosis in adult patients. These were calculated using flexible survival models implemented in the stpm3 Stata package.[2]

The figures in Table 1 show that clozapine had fewer relapse events compared with other drugs in patients with schizophrenia and schizoaffective disorders. In patients with bipolar disorder, the relapse events were the same, but clozapine had higher adverse event counts. The reverse was true in those with schizoaffective disorders: lower relapse event counts for clozapine but the same adverse event counts as other drugs. The child and youth cohort could not be stratified by diagnosis because of low numbers.

We agree with Kikuchi that the adverse events analysis was tilted in favour of other antipsychotics. Suicide attempts and deaths were not available in the data, so clozapine's benefit is probably underestimated,[3] while adverse events more specific to other drugs are probably underestimated.

The decision to exclude unmedicated periods was deliberate, since our objective was a head-to-head comparison of medications. In a previous paper[4] we found that over a 5-year period, people with schizophrenia, on average, spent 11 months without medication and only 17 days on clozapine. Within-person analysis was considered, but this technique discards the records of people who did not switch from other drugs to clozapine or *vice versa*. In our data, these patients made up the majority.

In summary, our register-based study shows that clozapine is an effective medication, with benefits and risks that require balancing.

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Data availability

The data supporting Table 1 are available from the Canadian Institute of Health Information. Restrictions apply to the availability of these data, which were used under licence for this study. Data are available from the authors with the permission of the Canadian Institute of Health Information, which can be obtained by writing to help@cihi.ca.

Author contributions

S.H. wrote C++ code for the data in Table 1. L.B. created the statistical model and wrote the paper. Both authors approved the content.

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Declaration of interest

None.

Analytical code availability

The code for reproducing Table 1 is publicly available at https://github.com/lloydxeno/antipsychotics/blob/main/correspondence

References

1 Balbuena L, Halayka S, Lee A, Ahmed AG, Hinz T, Kolla N, et al. Clozapine, relapse, and adverse events: a 10-year electronic cohort study in Canada. *Br J Psychiatry* [Epub ahead of print] 18 Sep 2024. Available from: https://doi.org/10.1192/bjp.2024.140.

2 Lambert PC. *STPM3: Stata Module to Fit Flexible Parametric Survival Models. Statistical Software Components. 21 Feb 2024 edn*. Boston College Department of Economics, 2023.

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4 Peters E, Shamloo A, Lodhi RJ, Marcoux G, Jackson K, Halayka S, et al. Medication gaps and antipsychotic polypharmacy in previously hospitalized schizophrenia patients: an electronic cohort study in three Canadian provinces. *Front Psychiatry* 2022; **13**: 917361.

Table 1 Re-hospitalisation counts by drug group and diagnosis per 1000 person-months

	Relapse events, mean (95% CI)		Adverse events, mean (95% CI)	
Index diagnosis	Other drugs	Clozapine	Other drugs	Clozapine
Bipolar disorder, $n = 20\,786$	42.96 (40.41–45.68)	45.91 (37.59–56.14)	1.46 (1.22–1.76)	2.41 (1.32–4.53)
Schizophrenia, $n = 17\,422$	43.14 (40.15–46.38)	34.87 (31.37–38.80)	1.12 (0.91–1.39)	1.49 (1.09–2.05)
Schizoaffective disorder, $n = 6050$	52.05 (47.14–57.52)	41.03 (35.35–47.67)	1.23 (0.91–1.67)	1.53 (0.93–2.55)

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