The association of clozapine and haematological malignancies needs to be replicated by other studies and more importantly by analyses of subsamples from VigiBase

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By using a disproportionality analysis in VigiBase, Chrétien et al. (2020) proposed that clozapine is significantly associated with lymphoma, leukaemia and myelodysplastic syndrome. The focus on significance testing instead of replication has led to many false findings in the medical literature (Ioannidis, 2005).

First, assuming that these findings are replicated by better analyses and are not false, the recommendations for clinicians are unclear. Psychiatrists and their patients may not know how to determine exposure to ionising radiation, radon, pesticides, benzene and other organic solvents. On the other hand, many clozapine patients are tobacco smokers and have a history of abusing other substances. It is not clear whether Chrétien et al., recommended clozapine discontinuation, or whether psychiatrists should just 'scare them to death' by describing the increased risk of developing haematological malignancies with clozapine use.

Second, Chrétien et al. did not explain the confounding effect of reporting bias. Clozapine adverse drug reactions (ADRs) in general are vastly overrepresented in VigiBase (De Leon, Sanz, & De Las Cuevas, 2020a; de Leon, Sanz, Norén, & De Las Cuevas, 2020b). This overrepresentation is much worse for clozapine haematological ADRs. In our search on 17 July 2019, for pneumonia we found 144 020 clozapine reports, much more numerous than the reports for risperidone (100 283), quetiapine (80 503) or olanzapine (63 287) (De Leon et al., 2020a). Clozapine is much less frequently prescribed worldwide than risperidone, quetiapine or olanzapine (Hálfdánarson et al., 2017). Due to notoriety bias, VigiBase has considerably more ADR reporting for clozapine than for other antipsychotics much more widely prescribed but much less often reported to VigiBase.

The extraordinary overrepresentation of haematological ADRs for clozapine can be easily understood by remembering that other antipsychotics do not require weekly white blood counts (WBCs). The weekly WBCs may explain (1) the weaker association with haematological malignancies reported by Chrétien et al. and (2) the stronger association of clozapine with leucocytosis that we found and next describe. The VigiBase Bayesian confidence propagation neural network provides a statistical indicator called an information component (IC) and its 97.5% confidence intervals (CIs). An IC_{025} indicates that the lowest value of the 97.5% CI of the IC is higher than expected, based on the background. In their supplementary data, Chrétien et al. listed: for 'malignant lymphoma' 569 reports ($IC_{025} = 1.5$); for leukaemia, 305 reports ($IC_{025} = 0.3$); and for 'myelodysplastic syndrome', 1999 reports ($IC_{025} = 1.3$). Comparing these relatively small numbers with the huge overrepresentation of leucocytosis and similar terms, we found on 17 July: 'WBC increase' had 5025 reports ($IC_{025} = 4.7$); 'neutrophil count increased', 4273 reports ($IC_{025} = 6.3$); and 'leucocytosis', 3486 reports ($IC_{025} = 4.6$). These IC_{025} are much higher and more robust than those reported by Chrétien et al.

Third, the statistical analyses of reports of spontaneous ADRs are not free of controversy (Bate & Evans, 2009). Chrétien et al. used disproportionality analyses without commenting on their limitations. The data for lamotrigine, the negative control, is a concern. The adjusted odds ratio of 1.16 for myelodysplastic syndrome bordered on significance since its 95% CI was 0.99–1.35, which appears to be close to significance, since it was close to 1.0 in the CI. This negative control providing a result bordering on significance suggests the risk of false positives in disproportionality analyses. Rather than using lamotrigine, one should control for the haematological malignancies associated with all other drugs considered together.

Fourth, Bate and Evans (2009) listed as limitations of ADR reporting: (1) missing data in reports (underreporting), (2) reporting changes over time, (3) problems concerning the classification of ADRs using different terminology and (4) duplicated reports. The last three limitations were not discussed by Chrétien et al. Duplications in VigiBase are frequently due to the same case being reported independently by different clinicians or the same clinician reporting more than one ADR for the same case.

Fifth, there are alternatives to disproportionality analysis. As described, VigiBase experts recommend a complex statistical method called Bayesian shrinkage (Bate & Evans, 2009; Norén, Hopstadius, & Bate, 2013) and more importantly, insist that, for ruling out a spurious result, the results should be robust and significant in subgroups (Hopstadius & Norén, 2012). Chrétien et al. did not verify that their results provided significant results in age groups or across continents.

Sixth, Chrétien et al. explored clozapine dose effects in their findings, but they did not explore the effect of duration.

Finally, the prior literature on clozapine and haematological malignancies, which is rather limited, was reviewed by Chrétien et al. and had no prior clinical or pharmacoepidemiological study providing similar findings including three malignancies: lymphoma, leukaemia and myelodysplastic syndrome. Therefore, until Chrétien et al. replicate their results in subsamples and other independent studies providing replication, it may be safer to ignore their results in clinical practice. Chrétien et al. might look back in regret by having contributed to clozaphobia (Cetin, 2014) and having created an additional barrier to the prescription of clozapine (Verdoux, Quiles, Bachmann, & Siskind, 2018).

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