BJPsych | The British Journal of Psychiatry (2022) 221, 702–703.

Correspondence

Edited by Kiriakos Xenitidis and Colin Campbell

Contents

Clozapine initiation in a vacuum

5 May 2022

We read with interest the study by Brodeur et al[1] that makes a case for initiating clozapine in all eligible patients, based on the low absolute risk of subsequent poor adherence. Such a finding is reassuring, especially given the repeated finding that clozapine remains under-prescribed despite strong evidence of its superior efficacy. This is a secondary analysis of pharmacy claims data and as such has all the advantages (representativeness, size) and disadvantages (unmeasured covariates, unstandardised diagnoses, the lack of an *a priori* hypothesis) of any such analysis. There could also be concerns about the use of the MPR (medication possession rate, a measure of pharmacy attendance) as a proxy for treatment adherence, rather than more direct methods.

Other concerns are related to the data and the results themselves. We observe that the sample is heavily skewed towards males (66.3%), which goes against the roughly equal gender ratios that are usually observed in schizophrenia.[2] Although such and similar skews are often found even in previous studies of treatment-resistant schizophrenia,[3] the authors have not delved into this in any depth. Explanations for such a skew might relate to differences in comorbidity rates (e.g. substance use), perceived risk (e.g. aggression) or social support, which may influence the decision to commence clozapine. It is unclear whether or how these factors (that could not be studied in this study) may have influenced patients' treatment adherence, both before and after clozapine initiation. However, most important are the observed rates of adherence before clozapine initiation. Most systematic studies quote an overall treatment adherence of between 40 and 50% for patients with schizophrenia.[4] With this in mind, the observation that the greatest proportion (75.6%) of subjects in this sample fell into the category of those with ≥80% adherence, as measured by the MPR, suggests that this population was quite different in terms of their treatment adherence. It may be that patients are initiated on clozapine only if the treating clinician is confident of future adherence; it might also be that additional measures (e.g. assertive outreach) are provided to those patients who are treatment resistant, and that these factors may be responsible for their improved adherence. In this light, the finding that even those with relatively poor adherence pre-clozapine also show better treatment adherence is heartening.

Overall, it is difficult to conclude from these results alone that clozapine initiation itself is generally associated with an improvement in treatment adherence – any improvements might instead be attributed to factors unrelated to the medication itself, such as patient characteristics or other interventions that were concurrently provided to these patients. We would hope that future studies of this important topic would also adjust for the influence of these factors. This would, of course, entail the planning of a study with an *a priori* hypothesis and outcome measurement.[5]

Declaration of interest

None

References

1 Brodeur S, Courteau J, Vanasse A, Courteau M, Stip E, Fleury MJ, et al. Association between previous and future antipsychotic adherence in patients initiating clozapine: real-world observational study. *Br J Psychiatry* [Epub ahead of print] 27 Jan 2022.

2 Canada PHA. *Schizophrenia in Canada*. 2020. Available from: https://www.canada.ca/en/public-health/services/publications/diseases-conditions/schizophrenia-canada.html [cited 25 Apr 2022].

3 Wesley EW, Kadra-Scalzo G, Pritchard M, Shetty H, Broadbent M, Segev A, et al. Gender disparities in clozapine prescription in a cohort of treatment-resistant schizophrenia in the South London and Maudsley case register. *Schizophr Res* 2021; **232**: 68–76.

4 Valenstein M, Ganoczy D, McCarthy JF, Myra Kim H, Lee TA, Blow FC. Antipsychotic adherence over time among patients receiving treatment for schizophrenia: a retrospective review. *J Clin Psychiatry* 2006; **67**(10): 1542–50.

5 Velligan DI, Weiden PJ, Sajatovic M, Scott J, Carpenter D, Ross R, et al. Adherence problems in patients with serious and persistent mental illness. *J Clin Psychiatry* 2009; **70**(suppl 4): 455.

Himani Mittal, All India Institute of Medical Sciences, Rishikesh, India. Email: himanimittaldr@gmail.com; **Tanmay Joshi**, All India Institute of Medical Sciences, Rishikesh, India; **Vijay Krishnan**, All India Institute of Medical Sciences, Rishikesh, India

doi:10.1192/bjp.2022.122

Authors' reply

27 June 2022

We thank Mittal et al for their interest in our article. Their comments can be summarised into four issues. First, they correctly state that the current study presents limitations that are typical of such studies (unmeasured covariates, unstandardised diagnoses, the lack of an *a priori* hypothesis). However, this is an unlikely explanation for the major finding of the current study, i.e. that the five groups defined according to the medication possession ratio (MPR) before clozapine initiation achieved relatively similar and high MPRs afterward, as the five groups should be affected similarly by these issues.

Second, although MPR has its limitations, it is the recognised method of choice for studies in which other more direct adherence measures (e.g. blood dosages, pill counts) are impossible. In the present study, the validity of the MPRs is reflected in the observation that the relatively high MPR following clozapine initiation was associated with a low mean number of days in hospital (see Fig. 2 in the original article).[1] This is consistent with previous observations that MPR is strongly correlated with clinical outcomes such as hypertension[2] and lower rates of psychiatric hospital admission.[2,3] Finally, this limitation of MPR is unlikely to account for the main conclusion of this paper, as all five groups should be affected similarly.

Third, Mittal et al state that the overrepresentation of men may reflect some unmeasured effects that have influenced the decision to initiate clozapine and adherence to treatment before and after clozapine initiation. As they state, this predominance of males is typical of studies on treatment-resistant schizophrenia, suggesting that the current sample is representative of this population. In addition, as the gender proportion was similar among the five groups, this factor is unlikely to account for the relatively similar levels of adherence after clozapine initiation. Finally, some of these factors (e.g. social support and comorbidities) are unlikely to change as a consequence of clozapine initiation; they are thus unlikely

https://doi.org/10.1192/bjp.2022.123 Published online by Cambridge University Press

explanations for the increase in level of adherence after clozapine initiation. Nevertheless, we agree that these issues might have influenced the decision to initiate clozapine, which makes it difficult to determine to what extent these results would apply in other contexts.

Fourth, Mittal et al correctly point out that the high proportion of patients with relatively high MPRs before the initiation of clozapine reflects the typical inclination of clinicians to preferentially use clozapine in patients judged more likely to adhere to treatment. However, this fact does not explain the most provocative finding of the current study, i.e. that high adherence rates can also be achieved in patients in whom low levels of adherence would have been expected. Moreover, Mittal et al mention that an assertive approach may be responsible for explaining better adherence to treatment. Although this is a possibility, it is reassuring to know that clozapine initiated in the real world setting was maintained, even after 3 year follow-up (Supplementary Fig. 3 and Supplementary Table 2).[1] Clozapine is often managed in Quebec through intensive community outreach teams that routinely monitor treatment adherence. However, these factors have not been measured directly. Therefore, it is reasonable to assume that patients will maintain their treatment once it has been initiated with management that meets current Quebec and Canadian practices. This could be a reflection of the quality of Quebec's public services in long-term follow-up in the community, at least among those willing to initiate best practices, such as the use of clozapine in eligible patients.

In conclusion, although the issues raised by Mittal et al do not invalidate the main findings of the current study, they usefully emphasise the importance of repeating such studies in settings in which clozapine would be introduced more systematically in patients with low levels of adherence and to better assess the impact of clinical interventions aimed at supporting adherence to clozapine.

Declaration of interest

E.S. received funding from Lundbeck Canada Inc. and Otsuka Canada Pharmaceutical Inc. He has served on the advisory boards and been a lecturer for Lundbeck Canada Inc, Otsuka Canada Pharmaceutical Inc, and Janssen. M.-A. R. reports grants from Mylan Canada, Janssen Canada, Mylan Canada and Otsuka-Lundbeck Alliance Canada during the conduct of the study. Outside the submitted work, he has also received personal fees from Boehringer Canada (research contracts), Lundbeck Canada (research contracts), Otsuka-Lundbeck Alliance (advisory honoraria; speaker honoraria), HLS Canada (advisory honoraria), Mylan Canada (advisory honoraria; speaker honoraria) and Janssen Canada (speaker honoraria). M.-F.D. reports grants from Mylan Canada, Janssen Canada and Otsuka-Lundbeck outside the submitted work. Outside the submitted work, she has also received personal fees from Otsuka-Lundbeck Alliance (advisory honoraria; speaker honoraria) and Janssen Canada (speaker honoraria). Except for the grants mentioned above, the authors declare no other competing interests.

References

1. Brodeur S, Courteau J, Vanasse A, Courteau M, Stip E, Fleury M-J, et al. Association between previous and future antipsychotic adherence in patients initiating clozapine: real-world observational study. *Br J Psychiatry* [Epub ahead of print] 27 Jan 2022. Available from: https://doi.org/10.1192/bjp.2022.1.
2 Valenstein M, Copeland LA, Blow FC, McCarthy JF, Zeber JE, Gillon L, et al. Pharmacy data identify poorly adherent patients with schizophrenia at increased risk for admission. *Med Care* 2002; **40**(8): 630–9.
3 Valenstein M, Blow FC, Copeland LA, McCarthy JF, Zeber JE, Gillon L, et al. Poor antipsychotic adherence among patients with schizophrenia: medication and patient factors. *Schizophr Bull* 2004; **30**(2): 255–64.

Sebastien Brodeur, M.D., M.Sc., Département de Psychiatrie et Neurosciences, Université Laval, Québec (QC), Canada. Email: sebastien.brodeur.2@ulaval.ca; **Josiane Courteau**, Ph.D., Groupe de recherche PRIMUS, Centre de recherche du Centre hospitalier universitaire de Sherbrooke (CRCHUS), Sherbrooke (QC), Canada; **Alain Vanasse**, M.D. Ph.D., Groupe de recherche PRIMUS, Centre de recherche du Centre hospitalier universitaire de Sherbrooke (CRCHUS), and Département de médecine de famille et de médecine d'urgence, Université de Sherbrooke, Sherbrooke (QC), Canada; **Mireille Courteau**, M.Sc., Groupe de recherche PRIMUS, Centre de recherche du Centre hospitalier universitaire de Sherbrooke (CRCHUS), Sherbrooke (QC), Canada; **Emmanuel Stip**, M.D., M.Sc., Département de Psychiatrie et d'Addictologie, Université de Montréal, Montréal (QC), Canada, and Department of Psychiatry and Behavioral Science, College of Medicine and Health Science, United Arab Emirates University, Al Ain, United Arab Emirates; **Marie-Josée Fleury**, Ph.D., Institut universitaire en santé mentale and Département de Psychiatrie, Université McGill, Montréal (QC), Canada; **Alain Lesage**, M.D., M.Phil., Département de Psychiatrie et d'Addictologie, Université de Montréal, Montréal (QC), Canada, and Centre de Recherche, Institut universitaire en santé mentale de Montréal (IUSMM), Montréal (QC), Canada; **Marie-France Demers**, B.Pharm. M.Sc., Centre de Recherche CERVO, Québec (QC), Canada, and Faculté de pharmacie, Université Laval, Québec (QC), Canada; **Olivier Corbeil**, Pharm.D. M.Sc., Faculté de pharmacie, Université Laval, Québec (QC), Canada; **Laurent Béchard**, Pharm.D., M.Sc., Faculté de pharmacie, Université Laval, Québec (QC), Canada; **Marc-André Roy**, M.D., M.Sc., Département de Psychiatrie et Neurosciences, Université Laval, Québec (QC), Canada, and Centre de Recherche CERVO, Québec (QC), Canada

doi:10.1192/bjp.2022.123