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RE: Longitudinal effect of clozapine-associated sedation on motivation in schizophrenia: naturalistic longitudinal study

Beyond the specifics of clozapine: a call for broader sample replication

We read with interest the article by Wolpe et al (2023),[1] in which the researchers study the association between negative symptoms and sedation secondary to antipsychotics. This is an important topic to advance clinical knowledge in the field.

This article raises two important topics. On the one hand, the researchers used patient-reported sleep hours as an indirect proxy for sedation produced by an antipsychotic. Although the authors provided ample and convincing reasoning for this choice in the article's supplementary materials, we believe it would also be interesting to analyse the relationship between negative symptoms and sleep hours produced exclusively during the day, since it is reasonable to think that they may have a greater impact on motivation and pleasure (MAP) than total sleep hours. One factor that could support this possibility is pharmacological treatment with modafinil, which has considerable evidence in the treatment of negative and cognitive symptoms of schizophrenia through an increase in daytime arousal.[2]

On the other hand, and more importantly, we believe that studying patients treated with clozapine restricts the sample to a very specific subgroup: individuals with treatment-resistant schizophrenia. Such individuals have, at a group level, more prominent symptoms in the positive, negative and cognitive spheres, longer duration of illness, greater cumulative exposure to other antipsychotics and greater functional impairment.[3] All of this may have a direct as well as an indirect impact on the severity of negative symptoms, which is not convincingly studied in this article. Moreover, clozapine is one of the few drugs (and arguably the only one) that has consistently demonstrated improvement in negative symptoms[4] (as corroborated by this article). This opens the door to postulate that, if this sedation could be effectively combatted, the beneficial effects of clozapine in this regard could be much broader, but it remains unclear whether the findings of this article might be exclusive of people with treatment-resistant schizophrenia or, rather, generalisable.

Another interesting aspect is that, according to the results of the linear mixed-effects model estimating the predictors of MAP, there is a statistically significant inverse correlation between the daily dose of clozapine and negative symptoms. As sedation associated with clozapine is a dose-dependent adverse effect,[5] this could suggest that there are other mediating factors in the relationship between these variables in this subgroup of patients.

For the above reasons, we believe it is highly relevant to replicate this study in a more representative sample, in order to study this relationship in a broad and generalisable way. This would also allow clarification as to whether the effectiveness of other more recent drugs that have shown evidence in the treatment of these symptoms (such as cariprazine[6]) could also be mediated by the (relative lack of) sedation they produce. If this were the case, the implications of this finding could be significant and open the door to the development of new pharmacological treatment strategies for these symptoms.

Declaration of interest

None.

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Author's Reply. RE: Longitudinal effect of clozapine-associated sedation on motivation in schizophrenia: naturalistic longitudinal study

We thank Aymerich et al for their comments and important suggestions for future research. We agree that excessive daytime somnolence (as contrasted with total sleep duration) may have specific relevance for the motivation and pleasure (MAP) domain of symptoms in schizophrenia. There are additional difficulties in measuring daytime sleep duration, including the potential for circadian phase shift to be associated with both schizophrenia[1] and antipsychotic medication.[2] Our study[3] adopted the widely used approach of self-reported total sleep duration, which is readily amenable to use in routine clinical practice. However, both detailed sleep diaries and actigraphy hold promise for future research in this field.

Although patients with treatment-resistant schizophrenia (TRS) taking clozapine are an important and common subgroup of those with schizophrenia,[4] we agree that it is important to study factors affecting MAP in broader groups of patients, as well as the effects of other medications and mediators. Whether the potential benefits of clozapine extend beyond those with TRS as postulated by Aymerich et al is an open question; clozapine

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remains underused for TRS.[4] Although there are limitations when studying patients taking the same principal antipsychotic, this approach also has key advantages, as clinical and basic researchers strive to account for confounding variables such as medications, which may in fact have contrasting effects on negative symptoms.[5]

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