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Letter to the editor: the longitudinal effect of antipsychotic burden on psychosocial functioning in first-episode psychosis patients: the role of verbal memory

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Ballesteros et al. (2020) investigated the relationship between antipsychotic medication dosage, anticholinergic burden and psychosocial functioning in patients with first-episode psychosis over time and whether cognitive deficits, a core feature of the disease, mediated this relationship. Despite important contributions to the existing literature, including a new method of calculating anticholinergic burden, we write to express our concerns and to offer some suggestions regarding the statistical analysis and theoretical framework.

This study followed 157 first-episode psychosis patients over two years. Several mediation models were performed to test the relationship between medication and psychosocial functioning, with six different cognitive domains as potential mediators. Mediation models were performed using 10 000 bootstrap samples. From this, a 95% confidence interval was obtained, and if zero was not included, the mediation was considered significant (Shrout & Bolger, 2002). For example, one of the models had attention as a mediator, symptom severity as a parallel mediator, antipsychotic dosage as the independent variable, psychosocial functioning as the dependent variable and anticholinergic burden as a covariate. Two models were found to be significant: model 1 with the mediator attention and model 5 with the mediator verbal memory. Despite the quality of the statistical method and the robustness of the performed tests, several points must be raised. Although zero is not included in the two significant models, the values obtained are very close to zero, indicating a minimal effect size. After correcting for multiple testing, these statistical results would likely be non-significant (Chaubey, 1993; Dai, Stanford, & LeBlanc, 2022). Indeed, the more tests performed, the more likely it is to find a significant effect that is not significant, also known as Type II Error (Chaubey, 1993). For each test performed, the researchers had a 5% chance of being wrong and finding a significant effect that was not there, which after six mediation models resulted in a non-negligible 26.5% probability of being wrong (Benjamini & Hochberg, 1995).

We also identified some key elements regarding medication. In reality, patients with psychosis present with multiple comorbidities and take several medications, such as antidepressants (Eum et al., 2017). The Drug Burden Index is an innovative way to measure anticholinergic burden. It is a valuable contribution to the literature as it is the only anticholinergic burden scale considering daily medication dosage. We also wonder whether the authors calculated the anticholinergic burden for all drugs taken by the patients, not just the antipsychotics (as suggested by the title). If not, we suggest calculating the total Drug Burden Index for all medications, as they are also likely to have an anticholinergic burden (Gerretsen & Pollock, 2011).

In addition, it might be beneficial to include more details on how the Drug Burden Index was calculated to facilitate reproducibility. We also noted that data on medication adherence were not provided, although they could offer useful information on treatment compliance.

It is also worth mentioning that patients with suicidal ideation and substance use disorders were included in this study. Although 40–50% of patients with schizophrenia have suicidal ideation, it is of interest to include them as it represents a strong ecological validity and provides data on this subgroup of patients who are often excluded from similar studies (Kovaszny et al., 1997; Skodlar, Tomori, & Parnas, 2008). Nevertheless, the inclusion of patients with substance abuse disorders may be a potential bias, as interaction may occur between the substance used and the medications taken in treatment, creating noise regarding the actual link between medications and psychosocial functioning (Baigent, Holme, & Hafner, 1995; Green, Noordsy, Brunette, & O'Keefe, 2008; Wilkins, 1997). We also observed that no information was provided as to whether this subgroup of patients had to abstain from substance use to participate in the study. We suggest conducting analyses with and without this subgroup to determine whether the results would differ, as substance misuse can affect psychosocial functioning and cognitive performance.

This study aimed to examine the effects of antipsychotic medication dosage and anticholinergic burden on psychosocial functioning in patients with early psychosis after two years of

follow-up while considering cognitive impairments as a potential mediator. We note that the authors did not correct for multiple tests after running six mediation models, did not provide complete documentation on medication and overlooked the rationale for including patients with substance use disorders. We look forward to your response and hope some of our suggestions can be considered.

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