Concurrent Metformin and Second-Generation Antipsychotics: The Need to Add Vitamin B_{12}

To the Editor: We read with interest the article by Daggolu and Chen[1] discussing improved adherence to, and potentially effectiveness of, second-generation antipsychotics coprescribed with metformin. Their findings extend the results of previous clinical trials and meta-analyses demonstrating the effectiveness of metformin to mitigate antipsychotic-induced weight gain.[2] However, Daggolu and Chen[1] do not mention an important safety consideration: the association between metformin and vitamin B_{12} deficiency. Metformin impairs B_{12} absorption, partly through calcium-dependent mechanisms, with overt deficiency emerging after months to years as hepatic stores decline.[3,4] To our knowledge, the prevalence of B_{12} deficiency in patients coprescribed antipsychotics, and metformin has not been studied, but it has been reported in 6%–50% of patients with diabetes receiving long-term treatment with metformin.[4]

B_{12} deficiency can cause an irreversible peripheral neuropathy relatively quickly,[3] and it also contributes to cognitive changes and other neuropsychiatric symptoms, including mood or psychotic symptoms.[3,5] Published guidance on how to manage the risk of B_{12} deficiency in patients taking metformin is inconsistent. An expert consensus guideline on mitigating antipsychotic-induced weight gain recommended that B_{12} levels be checked annually in patients prescribed metformin (or every 6 months in those with additional specified risk factors for B_{12} deficiency—for example, a vegan diet or a prescription of a proton pump inhibitor[6]). Another expert opinion endorses a more cost-effective approach consisting of B_{12} testing when metformin is started, with selective follow-up testing based on individualized risk.[4] However, B_{12} testing alone fails to detect about one-third of individuals with B_{12} deficiency.[3,7] Furthermore, it is expensive and unavailable in many low- and middle-income countries (LMICs).

In this context, we agree with an expert consensus on diagnosing and managing B_{12} deficiency published by Obeid et al in 2024,[7] which cautions against routine B_{12} monitoring in at-risk individuals, noting that testing incurs unnecessary costs compared with B_{12} supplementation. Given the risk of early neuropathy, this consensus recommends prophylactic vitamin B_{12} supplementation, suggesting the use of either 1,000 µg intramuscularly every 1–3 months or 1,000–1,500 µg orally daily.[7] This oral dosage should be enough given that individuals with B_{12} malabsorption still absorb B_{12} through passive diffusion that allows the absorption of 1% of an oral dose.[4,8] The use of oral supplementation is supported by a recent meta-analysis that found no significant difference in effectiveness among oral, sublingual, and intramuscular administration routes for vitamin B_{12} deficiency.[8] While an oral dosage of 1,000–1,500 µg with a 1% absorption more than exceeds the recommended daily allowance for healthy adults of 2.4 µg per day,[3] it is safe since B_{12} is a water-soluble vitamin excreted in the urine when present in excess.[4,7]

In conclusion, clinicians who decide to coprescribe antipsychotics and metformin based on the study of Daggolu and Chen[1] need to consider the associated risk of B_{12} deficiency and its neuropsychiatric sequelae. The expert consensus of Obeid et al[7] offers them a practical approach that mitigates this risk: prophylactic oral supplementation. This approach is particularly attractive in LMICs where access to B_{12} testing is limited.

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