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Vitamin B_{12} Deficiency Risk During Metformin Treatment for Weight Management in Second-Generation Antipsychotic Recipients:

Reply to Mulsant et al

To the Editor: We thank Mulsant et al[1] for their response to our recent publication in JCP.[2]

We echo and agree that vitamin B_{12} deficiency is a well-recognized adverse effect of long-term metformin treatment and that patients receiving second-generation antipsychotics (SGA) may be susceptible to developing, or not being screened for, this deficiency due to a combination of medical, psychiatric, and social factors. We appreciate the authors' letter to the readers, of the mechanism by which B_{12} deficiency occurs in metformin recipients and might possibly cause irreversible peripheral neuropathy. Our goal with this letter is to further clarify the treatment side effects associated with metformin prescription and the scope for supplementing the same.

In our study, we concluded the improvement in adherence to SGA in nondiabetic patients prescribed metformin for the treatment or prevention of antipsychotic-induced weight gain during 180-/365-day follow-up period.[2] Previous studies have identified the risk of B_{12} deficiency in long-term metformin users further accentuated by diabetes status, increasing the risk of peripheral neuropathy.[3] The mean duration of metformin exposure ranged around 5.3 years for the onset of neurological symptoms.[4] However, our study included only nondiabetic patients, primarily for weight management rather than for diabetes, and the duration of exposure was generally short. From our subsequent studies, we identified that the mean (SD) duration of exposure of metformin in nondiabetic SGA recipients was 217.07 (175.46) days. Therefore, prolonged use and the associated risk of B_{12} deficiency is less relevant in this specific population, and we do not consider it a major safety concern in the context we examined. Potential risk factors from previous studies included elderly patients, preexisting depleted reserves of cobalamin to as low as 5%–10%, longer duration of diabetes, and longer duration and larger dose of metformin.[5]

That said, we fully agree that B_{12} supplementation is safe, inexpensive, and effective, and it may be considered when metformin use is intended for longer durations or in populations at higher risk for deficiency. Prophylactic supplementation represents a practical and low-risk approach to mitigate potential neuropsychiatric or neurological complications associated with B_{12} deficiency. We appreciate the authors' emphasis on this important consideration and agree that awareness of B_{12} status is a valuable aspect of patient care when metformin treatment is prolonged. The recommendations provide useful guidance for clinicians who may use metformin for extended periods in vulnerable populations.

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