DOI: 10.14744/DAJPNS.2022.00185
Dusunen Adam J Psychiatr Neurol Sci
2022;35:138-140

LETTER TO THE EDITOR

Is samidorphan adjunction a beacon of hope for olanzapine-induced metabolic syndrome?

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Dear Editor,

Antipsychotics have been the mainstay of schizophrenia treatment. The development of second-generation antipsychotic (SGA) drugs and their promotion by the pharmaceutical industry was based on indications that these medications would have a lower risk for movement disorders and, therefore, greater tolerability than first-generation antipsychotics (1). On the other hand, the emergence of obesity and metabolic abnormalities leading to substantial increases in the risk of cardiovascular disease is a serious complication of antipsychotic use, with SGA drugs being particularly implicated (2). The mechanism by which antipsychotics induce weight gain is complicated and determined by various factors. 5-HT2C, H1, H3, and the D2 receptors are associated with antipsychotic-induced weight gain (3). Antipsychotics act as antagonists for these receptors, which may cause a significant elevation in appetite, and a reduced feeling of satiety, thereby increasing food intake (4). Olanzapine, one of the most effective and preferred SGAs in treating schizophrenia and related psychosis and mood disorders, has been reported to increase blood glucose levels robustly (5) and was strongly associated with the development of type-2 diabetes mellitus compared with other SGA drugs (6). The opioid system influences eating patterns and body weight control (7). Therefore, the combination of olanzapine with an opioid receptor antagonist, samidorphan, has been used to reduce olanzapine-related metabolic side effects. This olanzapine/samidorphan combination (OLZ/SAM) was associated with notably less weight gain than olanzapine monotherapy. It was approved for antipsychotic-induced weight gain in schizophrenia and bipolar disorder by the U.S. Food and Drug Administration (FDA) in May 2021 (8).

Samidorphan is an antagonist of μ-opioid receptors with partial agonist activity toward κ- and δ-opioid receptors. It is primarily eliminated by cytochrome P450-3A4 (CYP3A4)-mediated hepatic metabolism and renal excretion and to a lesser extent via CYP3A5, CYP2C19, and CYP2C8 enzymes (9). The adverse effect profile of samidorphan includes somnolence and gastrointestinal side effects such as nausea and constipation. Decreased appetite, dry mouth, anxiety, headache, and orthostatic hypotension were also reported (10). In addition to a preventive role in olanzapine-induced weight gain, samidorphan was investigated in trials for several psychiatric disorders, including alcoholism (11), binge eating disorder (12), and in adjunction with antidepressants in treatment-resistant major depressive disorder (13). However, unlike OLZ/SAM for olanzapine-induced weight gain, these trials were discontinued or remained unapproved by the FDA, mostly due to insufficient evidence of effectiveness.

How to cite this article: Bayraktar I, Balcioglu YH. Is samidorphan adjunction a beacon of hope for olanzapine-induced metabolic syndrome? Dusunen Adam J Psychiatr Neurol Sci 2022;35:138-140.

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Received: April 13, 2022; **Revised:** April 20, 2022; **Accepted:** April 21, 2022

The rationale behind the use of this combination is based on the influence of the opioid system on eating behavior and body weight regulation. Opioid agonists increase food intake and weight gain, while opioid antagonists can induce weight loss (14). μ, κ, and δ receptors are found in central and peripheral nervous systems. Each of the three receptor types plays a role in regulating body weight and metabolic function. In preclinical and clinical research, opioid agonists have been linked to increased food consumption and fat accumulation in rats and humans. Opioid antagonists, on the other hand, have been linked to a decrease in food consumption and fat accumulation. As a result, the opioid system can be used to challenge antipsychotic-related weight gain and metabolic dysregulation (15). However, it is worth mentioning that, as far as we are aware, the relationship between olanzapine-induced appetite increase and weight gain and the opioid system has not been clearly established in the existing body of literature.

A meta-analysis of three clinical trials that compared short-term weight and cardiometabolic alterations between OLZ/SAM and olanzapine monotherapy arms reported that weight changes and cardiometabolic parameters included were not significantly different between the two groups. Srisurapanont et al. (14) concluded that the cardiometabolic parameters may have remained unchanged because samidorphan did not substantially affect weight gain. Furthermore, Yagoda et al. (16) examined the long-term (52 weeks) safety and durability of OLZ/SAM in an open-label study. After approximately six weeks of treatment, the combination therapy was well tolerated and was associated with early stabilization of body weight changes as opposed to olanzapine monotherapy. However, the authors reported that mean increases in body weight stabilized at the early phase of the treatment and showed limited changes until the end of the treatment. The findings of this study suggest that the combination of OLZ/SAM may not be superior to olanzapine monotherapy in weight control as expected when treatment duration is longer.

We also would like to mention potential drug–drug interactions with OLZ/SAM. The main pathway with which olanzapine is metabolized includes UDP-glucuronosyltransferase 1–4 (UGT1A4), CYP1A2 enzymes, and to a lesser extent, CYP2D6 (17). The metabolism of samidorphan is predominantly mediated by CYP3A4 (18). Therefore, the combination of olanzapine with samidorphan does not affect the pharmacokinetic profile of either drug (19). On the other hand, olanzapine is frequently used in combination with mood stabilizers and antidepressants in patients with mood disorders. OLZ/SAM may appear to be safe because valproate, lithium, fluoxetine, and venlafaxine are not theoretically expected to have drug–drug interactions with samidorphan via hepatic CYP-mediated metabolic pathways. Accordingly, a study showed that OLZ/SAM administration did not significantly affect the steady-state pharmacokinetics of lithium or valproate (20). Nevertheless, although pharmacokinetic drug–drug interactions were insignificant between olanzapine and fluoxetine, and venlafaxine (21,22), interactions between samidorphan and antidepressants and other antipsychotics are yet to be investigated.

Previous clinical and physiologically based pharmacokinetic models of co-administration of OLZ/SAM with CYP3A4 inhibitors predicted a weak effect on samidorphan exposure and a negligible effect on olanzapine exposure (23). However, rifampin, a strong inducer of cytochrome CYP3A4, decreased the total systemic exposure of olanzapine and samidorphan by 48% and 73%, respectively (18). Therefore, the concomitant use of OLZ/SAM with strong CYP3A4 inducers, such as rifampin, is not recommended. Taken together, there is an explicit need for further pharmacokinetic data on OLZ/SAM, particularly in the context of cytochrome enzymes other than CYP3A4, to better establish the safety profile of this combination.

Overall, preclinical evidence suggests that the combination of OLZ/SAM may be promising with its positive effects on antipsychotic-induced metabolic dysregulation and weight gain. Nonetheless, clinical evidence is still insufficient to encourage the use of the combination in clinical practice unequivocally. Clinicians should consider the risk of drug–drug interactions while managing antipsychotic-associated metabolic side effects. Future research on the metabolic effects and mechanism of action of OLZ/SAM should be carried out in large patient populations with a focus on the pharmacokinetic profile of this combination. In addition, studies designed to evaluate the longer-term usage of the combination conducted by independent researchers to minimize the influence of industry sponsorship are needed.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors declare that they have no conflict of interest.

Financial Disclosure: The authors declare that they have no financial support.

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