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LETTER TO THE EDITOR Open Access

Comment on "Opioid antagonists to prevent olanzapine-induced weight gain: A systematic review"

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Dear Editor:

A recent systematic review by Laguado and Saklad highlighted the importance of addressing olanzapine-associated weight gain.[1] While highly efficacious, olanzapine use has been limited by its propensity to cause significant weight gain. The authors considered the role of opioid antagonists in this setting by reviewing efficacy and safety data from the clinical development program of combination olanzapine and samidorphan (OLZ/SAM), concluding in part that samidorphan effectively mitigates olanzapine-associated weight gain. We provide comments on the authors' methodology, as their conclusions may underestimate weight gain mitigation with OLZ/SAM.

We suggest that a more precise estimate of OLZ/SAM's weight mitigation benefit would be obtained by (1) analyzing separately the studies that were of sufficient duration to detect differences in weight gain from those that were not, and (2) weighting these study results before calculating the mitigating effect of OLZ/SAM on olanzapine-associated weight gain.

Trials by Martin et al, Correll et al, and Kahn et al were of adequate duration (12, 24, and 12 weeks, respectively) to evaluate the targeted differences in treatment-associated weight gain between OLZ/SAM and olanzapine.[2-4] In each of these studies, weight gain trajectories for OLZ/SAM and olanzapine were initially similar but then diverged between 4 and 6 weeks of treatment, after which weight gain plateaued in OLZ/SAM-treated patients but continued to increase over time in olanzapine-treated patients. Silverman et al and Potkin et al conducted 3-week and 4-week studies, respectively, that were not of suitable duration to use in calculations of the weight mitigation benefit of OLZ/SAM.[5,6]

Additionally, to obtain a more precise estimate of OLZ/SAM's weight mitigation benefit, the results should be weighted by the sample size of each study. Aggregating outcomes of different studies without considering differences in sample sizes can lead to inaccurate estimates of an intervention's magnitude of effect[7,8] that are avoided by using accepted weighting procedures.[7]

Furthermore, in discerning the true weight mitigation benefit of OLZ/SAM, only studies combining 10 mg of samidorphan with olanzapine are of relevance, as 10 mg is the only dose approved by the United States Food and Drug Administration for use in OLZ/SAM. Last, the description of the number needed to harm (NNH) may be misinterpreted by readers as harm associated with the use of OLZ/SAM because the authors did not present NNH as a negative value. By convention, the use of either a negative NNH or the number needed to treat (NNT), rather than NNH, would communicate more clearly the treatment benefit (ie, the weight-mitigating effect of treatment with OLZ/SAM compared with olanzapine).

Given these considerations and based on studies that were of sufficient duration and designed to evaluate weight gain in patients with serious mental illness, OLZ/SAM's weight mitigation benefit versus olanzapine ranged from −1.33 to −1.9 kg in trials lasting 12 to 24 weeks[2-4]; however, the benefit may be greater over longer treatment durations because weight gain plateaus with OLZ/SAM treatment but continues to increase with olanzapine treatment.

In summary, the methodologies used by the authors may have underestimated the weight-mitigating effect of OLZ/SAM on olanzapine-associated weight gain.[1] To assess the magnitude of this effect accurately, only studies of duration sufficient for assessing this outcome should be included, results of included studies should be weighted, and estimates of effect size should be calculated. Finally, while olanzapine-associated weight gain tends to continue over the long-term, results from open-label studies suggest that weight gain stabilizes during long-term OLZ/SAM treatment.[9,10] Further characterizing the weight gain mitigation effect provided by OLZ/SAM versus olanzapine during treatment courses longer than 6 months' duration may be beneficial to clinicians and to patients, many of whom require long-term and continuous antipsychotic treatment.[11]

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