Off-Label Drug Uses

Topiramate: Antipsychotic-Induced Weight Gain

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This *Hospital Pharmacy* feature is extracted from *Off-Label Drug Facts*, a publication available from Wolters Kluwer Health. *Off-Label Drug Facts* is a practitioner-oriented resource for information about specific drug uses that are unapproved by the US Food and Drug Administration. This new guide to the literature enables the health care professional or clinician to quickly identify published studies on off-label uses and determine if a specific use is rational in a patient care scenario. References direct the reader to the full literature for more comprehensive information before patient care decisions are made. Direct questions or comments regarding *Off-Label Drug Uses* to jgeneral@ku.edu.

BACKGROUND

Excessive weight gain is a known complication of long-term administration of typical and atypical antipsychotics.^{1,2} Weight gain is typically significant, may affect compliance, and can be associated with changes in insulin resistance. Several possible mechanisms have been suggested, including increased appetite related to neuronal receptor activity, disruption of metabolic-endocrine weight regulation, or changes in insulin resistance and glucose tolerance.^{1,2} Documented weight loss associated with topiramate use in patients with seizure or bipolar disorder^{3–5} has prompted its use in reducing or preventing weight gain associated with antipsychotics. The proposed mechanism of topiramate in promoting weight loss is via improvement in insulin sensitivity related to reduction in leptin concentrations and visceral fat.⁶

PATIENT POPULATION

Adult patients with significant weight gain related to chronic antipsychotic therapy.

DOSAGE AND DURATION

Initial oral dose is 25 mg/day with various titration schedules to a maximum of 300 mg/day.

RESULTS

Topiramate in the treatment and prevention of antipsychotic weight gain has been evaluated in several meta-analyses and controlled and noncontrolled

trials enrolling over 500 patients.^{1–11} The majority of trials have been short term (approximately 12 weeks) but some have been as long as 18 months, and they suggest a modest weight loss in most patients (approximating 1.27 to 3.95 kg).

Meta-analyses

A meta-analysis of available controlled trials (January 1, 1990 through June 30, 2011) evaluated the efficacy of pharmacological interventions for antipsychotic or mood stabilizer–related weight gain. In a review of 4 randomized, double-blinded, placebo-controlled trials with topiramate, the overall effect supported the use of topiramate for management of antipsychotic-related weight gain with a mean difference of 3.95 kg (95% CI, 1.77 to 16.12; $I^2 = 86\%$) in weight loss with topiramate over placebo. In general, limitations of data in this meta-analysis include a lack of long-term follow-up, analysis only from completers, a high degree of heterogeneity among studies, and a focus on the use of olanzapine.²

A meta-analysis of all controlled clinical trials for pharmacological and/or behavioral management of second-generation antipsychotics (SGA)–induced weight gain included an evaluation of 3 trials using topiramate. Based on the results of these studies, there is preliminary evidence that the use of at least 200 mg of topiramate may contribute to weight loss in schizophrenic patients who have been treated with SGAs other than clozapine. However, the use of

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topiramate as adjuvant therapy was not recommended for patients starting SGA therapy. Studies with long-term follow-up were recommended to determine whether this drug was an effective weight loss agent in schizophrenia.¹

A meta-analysis of published randomized controlled trials (up to July 2011) evaluating the effect of topiramate on weight gain associated with atypical antipsychotics included 8 trials ($N = 336$ patients). The mean change in body weight was calculated for each trial as the difference in mean body weight between topiramate and control from baseline to follow-up and calculated as the weighted mean difference (WMD). The target topiramate dose in these studies ranged from 100 to 300 mg daily. Five trials enrolled patients who had gained weight related to atypical antipsychotics. Three trials included patients not yet taking atypical antipsychotics prior to randomization. This meta-analysis found that topiramate was associated with weight loss or attenuated weight gain when compared to controls (-2.83 kg; 95% CI, -4.62 to -1.03). A significant heterogeneity ($I^2 = 70\%$) was identified between these trials. Subgroup analyses revealed that adults only were associated with a higher WMD (-3.07 kg; 95% CI, -5.05 to -1.09). Trials included in this meta-analysis evaluated atypical antipsychotics with at least a moderate risk of weight gain (eg, olanzapine, risperidone, clozapine, and quetiapine), but there were not sufficient available data to allow assessment of differential effects on weight gain among the various antipsychotics.⁶

Controlled Trials

In a 12-week, double-blinded, placebo-controlled, parallel group trial, 72 first-episode adult schizophrenia patients (drug-naïve) were randomized to receive olanzapine with topiramate (100 mg daily) or placebo. The dose of olanzapine ranged from 5 to 20 mg daily in both groups. Topiramate was initiated at 50 mg daily, titrated to 100 mg daily at 1 week, and continued at this dose for the remaining 11 weeks. By the end of the 12 weeks, there was a significant reduction in mean weight for the topiramate group (-1.27 kg; $P = .003$) and a significant gain for the olanzapine-only group ($+6.03$ kg; $P < .001$). Significant decreases were also observed in the topiramate group for leptin, glucose, cholesterol, triglycerides, and blood pressure measurements. The olanzapine-only group had significant increases in the same parameters with the exception of blood pressure. The authors suggested that the addition of topiramate to

olanzapine therapy was effective in preventing olanzapine-related weight gain and metabolic effects.⁷

SAFETY

This is a limited safety profile. Refer to package labeling for complete prescribing information (eg, Warnings/Precautions, Adverse Reactions, Drug Interactions).

The use of topiramate to promote weight loss has been associated with few adverse events, including mild hand tremors, sedation, nausea, impaired concentration, fatigue, cognitive impairment, blurred vision, headache, myalgia, increased/decreased appetite, and tingling/weakness in the extremities.¹⁻¹¹

THERAPY CONSIDERATIONS

Topiramate in the treatment and prevention of antipsychotic weight gain has been studied in several meta-analyses and controlled trials, suggesting a modest weight loss in most patients.

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