Off-Label Drug Uses

Zonisamide: Antipsychotic 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. 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} Zonisamide may be beneficial in weight gain due to its activity on several neurotransmitter systems responsible for regulating eating behaviors.³

PATIENT POPULATION

Adults with significant weight gain related to chronic antipsychotic therapy.

DOSAGE AND DURATION

Initial dose of 50 to 100 mg daily (may be administered at night to minimize sedation) and titrated to a maximum of 150 mg (as a single daily dose) to 600 mg daily (in divided doses) for 10 to 16 weeks (maximum duration in a noncontrolled trial was 12 months).³⁻⁶ Titration schedules have varied:

- 100 mg nightly for 7 days, then increased by 100 mg weekly, based on clinical assessment and tolerability, to a maximum of 600 mg daily by the end of the sixth week of treatment.³

- 50 mg daily, titrated to 150 mg daily (as a single dose) over a 2-week period.⁴
- 50 to 100 mg daily, titrated monthly or bimonthly by 50 to 100 mg/day to a maximum of 300 mg daily.⁵
- 50 mg daily for 1 month, titrated monthly by 50 mg/daily to a maximum of 150 mg daily.⁶

RESULTS

Zonisamide for the management/prevention of antipsychotic therapy-induced weight gain has been evaluated in controlled and noncontrolled trials (enrolling fewer than 200 patients) demonstrating beneficial results.³⁻⁶ Controlled trials were short-term (range, 10-16 weeks). Zonisamide was not included in 3 meta-analyses evaluating the efficacy of pharmacological interventions for antipsychotic-related weight gain.^{1,2,7}

Controlled Trials

In a double-blind, placebo-controlled trial, 42 adult patients with a psychotic or bipolar disorder and who were beginning olanzapine therapy (5 to 25 mg daily) were randomized to receive zonisamide or placebo for 16 weeks. Zonisamide was initiated as 100 mg nightly for 7 days and was increased by 100 mg weekly, based on clinical assessment and tolerability, to a maximum of 600 mg daily by the

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end of the sixth week of treatment. The primary outcome measure was change in body weight from baseline; a clinically significant increase in weight was defined as a 7% or greater increase. Secondary outcome measures included changes in body mass index (BMI), waist circumference, and measures of primary and secondary eating behaviors. Twenty-three patients completed the study; 10 (5 in each group) withdrew from the study due to adverse events, and another 9 dropped out for various reasons (eg, loss to follow-up, nonadherence). Outcome measures were analyzed based on comparisons from baseline to last observation carried forward. Longitudinal assessment indicated that zonisamide was associated with a significantly slower rate of BMI and weight increases compared with placebo ($P = .01$). No patients in the zonisamide group experienced significant weight gain, compared with 33% of placebo-treated patients ($P = .009$). Among patients who completed the study, mean changes were significantly smaller in the zonisamide group for weight (+0.6 kg vs +5.3 kg with placebo; $P = .03$) and BMI (+0.2 kg/m² vs +1.9 kg/m² with placebo; $P = .04$). There were no differences between the groups for mean changes in metabolic variables (eg, serum insulin, glucose, triglycerides, cholesterol) and hemodynamics (eg, blood pressure, heart rate). The authors concluded that zonisamide is superior to placebo in mitigating weight gain associated with olanzapine therapy but has no effect on metabolic variables.³

In a double-blind, placebo-controlled trial, 41 patients (age range, 16-65 years) with schizophrenia and stabilized on an atypical antipsychotic were randomized to receive zonisamide or placebo for 10 weeks. Zonisamide was initiated at 50 mg daily and titrated to 150 mg daily (as a single dose) over a 2-week period. The primary outcomes were changes in BMI score and weight. Secondary outcomes included assessment of psychiatric symptoms. Two patients in the zonisamide group withdrew from the study due to exacerbation of symptoms or severe adverse events (eg, arthralgia, insomnia). At the end of the 10-week study period, significant mean reductions from baseline occurred in the zonisamide group for BMI (-0.3 kg/m² vs +2.2 kg/m² with placebo; $P = .0001$), weight (-1.1 kg vs +1.9 kg with placebo; $P = .0001$), and waist circumference (-0.7 cm vs +1.1 cm with placebo; $P = .001$). Secondary outcomes were not specifically reported. The authors concluded that zonisamide promotes modest weight loss in schizophrenic patients treated with atypical antipsychotics.⁴

Noncontrolled Trial

A retrospective review of 82 adult psychiatric outpatients with greater than 5% weight gain related to antipsychotic therapy (duration of at least 3 months) evaluated the effects of zonisamide on weight gain. Zonisamide was administered in flexible dosing regimens but typically was initiated at 50 to 100 mg daily and titrated monthly or bimonthly by 50 to 100 mg/day, to a maximum of 300 mg daily. The final mean dose was 124.6 mg/day for a mean duration of 7.1 months (range, 1-12 months). BMI was assessed prior to zonisamide therapy and at the last treatment point or discontinuation of the drug. Patients were divided into 3 groups based on BMI changes from baseline to endpoint measurements (patients experiencing weight loss [BMI decrease of greater than 5%], 32.9%; patients experiencing no change [BMI did not change within 5%], 53.7%; and patients experiencing weight gain [BMI increase greater than 5%], 13.4%). Thirty patients discontinued treatment due to various causes; 12 (14.6%) discontinued due to adverse events. Mean reduction in BMI was -0.8 kg/m² (range, -2.9 to +4.7 kg/m²; $P < .001$), and mean weight loss was -1.8 kg. Patients in the weight loss group had a mean BMI reduction of 9.8%, patients experiencing no change in weight had a mean BMI reduction of 0.6%, and patients in the weight gain group had a mean BMI increase of 6.5%. The authors concluded that zonisamide is associated with significant weight loss in psychiatric outpatients receiving antipsychotic therapy for various psychiatric disorders.⁵

SAFETY

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

In placebo-controlled trials, cognitive impairment was more frequent with zonisamide than with placebo (25% vs 0%; $P = .02$). Study withdrawal was associated with sedation, cognitive impairment, irritability, or arthralgia/insomnia.^{3,4}

THERAPY CONSIDERATIONS

Based on data from controlled and noncontrolled trials, zonisamide may be beneficial in the management and prevention of weight gain associated with antipsychotic therapy. Larger, controlled trials are needed to determine long-term benefits and clarify optimal dosing.

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