TOPIRAMATE - INDUCED WEIGHT LOSS IN SCHIZOPHRENIA: A RETROSPECTIVE CASE SERIES STUDY

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ABSTRACT

Objective
Atypical antipsychotics have been associated with weight gain. This study examines the efficacy of adjunctive topiramate in patients with schizophrenia and schizoaffective disorder with antipsychotic-induced weight gain.

Methods
A 2-year retrospective case analysis was performed in all 300 patients of the outpatient Special Follow-up Clinic for chronic schizophrenia and related psychoses at the Allan Memorial Institute, McGill University Health Centre (Montreal, Canada), a tertiary care University teaching hospital.

Results
10 patients met study inclusion criteria. Mean daily topiramate dose was 197.5mg (±77) (range, 125-400mg). Topiramate produced continued weight loss throughout the study duration without tolerance. Patients treated for 6 months and more had significantly higher Body Mass Index (BMI) differences than those treated for shorter durations ($BMI\text{-}d_{6\ months}$=-4.7±2.4; $BMI\text{-}d_{2\ months}$=-3.2±2.3; P=0.015). BMI changes were similar across genders.

Conclusion
This study supports topiramate use to target weight loss in stable overweight schizophrenic patients as a potential therapy that requires further investigation.

Key words: *Antipsychotics, schizophrenia, topiramate, weight gain, obesity*

In schizophrenia, the estimated prevalence of overweight (body mass index [BMI] 25–29 kg/m^2) and obese (BMI>30kg/m^2) individuals is 2 to 3-fold that of the general population.[1] Patients with schizophrenia are predisposed to becoming overweight through lifestyle factors, including sedentary lives, unhealthy diet and socioeconomic status.

Alternatively, antipsychotic medications have been correlated with a further increase in the prevalence of excess body weight.[2] Antipsychotic-induced weight gain is one of the leading causes of treatment non-compliance.[3,4] Furthermore, excess body weight may lead to numerous *de novo* chronic diseases (diabetes, hypertension, dyslipidemias) or worsen preexisting medical comorbidity, increasing morbidity among schizophrenic patients.[5,6] Prevention of weight gain and treatment of obesity among schizophrenic patients taking atypical antipsychotics have become a priority in clinical practice and represent a major public health problem. Low-calorie diet and behavioural methods can be efficacious, but benefits are rarely maintained.[7] Pharmacotherapy

may be a helpful option. Unfortunately, the use of anorexiants, such as fenfluramine, may exacerbate psychotic symptoms.[8] Topiramate is an anticonvulsant used in a wide variety of disorders (bipolar disorder, migraine, neuropathic pain). Weight loss by reduced appetite was reported during topiramate use.[9-11] For this reason, interest in topiramate as a treatment for antipsychotic-induced weight gain arises. Although the mechanism of topiramate-induced weight loss likely involves potentiation of GABAergic transmission and antagonism of AMPA glutamate receptors, its precise mechanism remains under investigation.[12]

This study examines the efficacy of adjunctive topiramate therapy in patients with schizophrenia with antipsychotic-induced weight gain in a naturalistic, retrospective case series. We hypothesized that adjunctive topiramate would significantly induce weight loss in those with a history of antipsychotic-induced weight gain.

METHODS

Patients

Data were obtained from 300 medical records of patients followed in 2003-2004, in the outpatient Special Follow-up Unit for chronic schizophrenia and related psychoses, at the Allan Memorial Institute, McGill University Health Centre (Montreal, Canada) a tertiary care University teaching hospital.

In this outpatient clinic, all subjects met DSM-IV criteria for schizophrenia or schizoaffective disorder. Patients were selected based on chart review. Each patient was required to meet the following criteria for inclusion:

1. overweight as defined by BMI$\geq$25kg/m^2;
2. adjunctive topiramate treatment initiated to achieve weight loss, based on informed consent between patients and treating psychiatrists;
3. at least two months of topiramate treatment.

Patients were informed of the most common and clinically relevant side effects of topiramate and the decision to proceed forward was documented in the hospital chart. Chart review exclusion criterion was: topiramate used to target psychiatric symptoms (i.e., topiramate used to alleviate mood and/or psychotic symptoms). Patients with comorbid conditions, such as diabetes, were not excluded. Information regarding age, sex, diagnoses, BMIs, antipsychotic treatment, concomitant medication use, and duration and dosage of topiramate were obtained from charts.

Efficacy Assessments

Nurses or physicians weighted patients at the clinic and recorded the weight in patients' charts. While no specific efforts were made to achieve inter-rater reliability on measuring body weight, the same scale was used every time. Efficacy measures were 1) BMI variations after 2 months of topiramate treatment and 2) BMI variations after 6 months of topiramate treatment. Standardized rating scales of psychiatric psychopathology, quality of life or adverse events were not available for all patients. Therefore, psychiatric data collected from this chart review are quantified in a non-standardized fashion.

Statistical Analysis

Patients' BMIs before and after topiramate use (BMI-d) was compared using a paired t-test. A t-test was used to compare BMI-d between genders and BMI-d between patients treated for longer ($\geq$6 months) versus shorter duration (<6 months).

RESULTS

Ten patients met study inclusion criteria. Baseline demographic data, clinical characteristics, and antipsychotic medications are shown in Table 1. All patients were treated with at least one atypical antipsychotic (clozapine, olanzapine or risperidone), and for 80%, treatment included 2 or 3 antipsychotics. Adjuvant treatment included mood-stabilizers (mainly valproic acid, mean daily dose 833 mg [±276mg]), anticholinergic agents for drug-induced parkinsonism and benzodiazepines for anxiety. Two patients had type-II diabetes (diet controlled) and one was treated for hypertension. All patients had been referred to a dietician for nutritional counseling prior to commencing topiramate (one refused).

The duration of topiramate treatment ranged from 2 to 24 months (mean duration=10 months [±7.7]). Six patients received topiramate for a period of 6 months or more. Mean daily dose of topiramate was 197.5mg [±77] (range, 125-400mg). As can be seen in Figure 1, patients' BMIs decreased after

topiramate use. After > 2 months (n=10), mean BMI-$d_{2\ months}$ was -3.2 kg/m^2 [±3.1] (P=0.009). One patient kept gaining weight (BMI-d=+2.9 kg/m^2) and adjunctive topiramate therapy was discontinued. After >6 months of treatment (n=6), a significantly greater weight loss occurred (BMI-d_{6} months=-4.7 kg/m^2 [±2.4], P=0.005). Hence, patients treated for longer periods had significantly greater BMI-d decreases than those treated for shorter periods (P=0.015). BMI-d decreases were similar across genders (P=0.998).

To determine whether the change in BMI increases with the duration of topiramate use, we correlated the change in BMI with the duration of treatment. We found that BMI change is positively correlated (r=0.66) with duration of treatment and that this correlation is statistically significant (p=0.019). This finding supports the notion that BMI will be reduced with longer treatment periods, and that the duration of treatment is a major contributor to weight loss since, 44% of the variance (R^2=0.44) in BMI change is attributable to the duration of treatment.

During topiramate therapy, 3 patients noted improved social functioning (increased pleasure in activities, increased motivation, began exercising); 2 had decreased positive symptoms, despite stable antipsychotic dosage; 1 noted reduced anxiety; and none reported worsening of psychosis or cognitive dulling. Drug-induced movement disorders, measured by the extrapyramidal symptom rating scale[13], were found in one patient with objective worsening of tremors, and another had objective reduction in tardive dyskinesia severity.

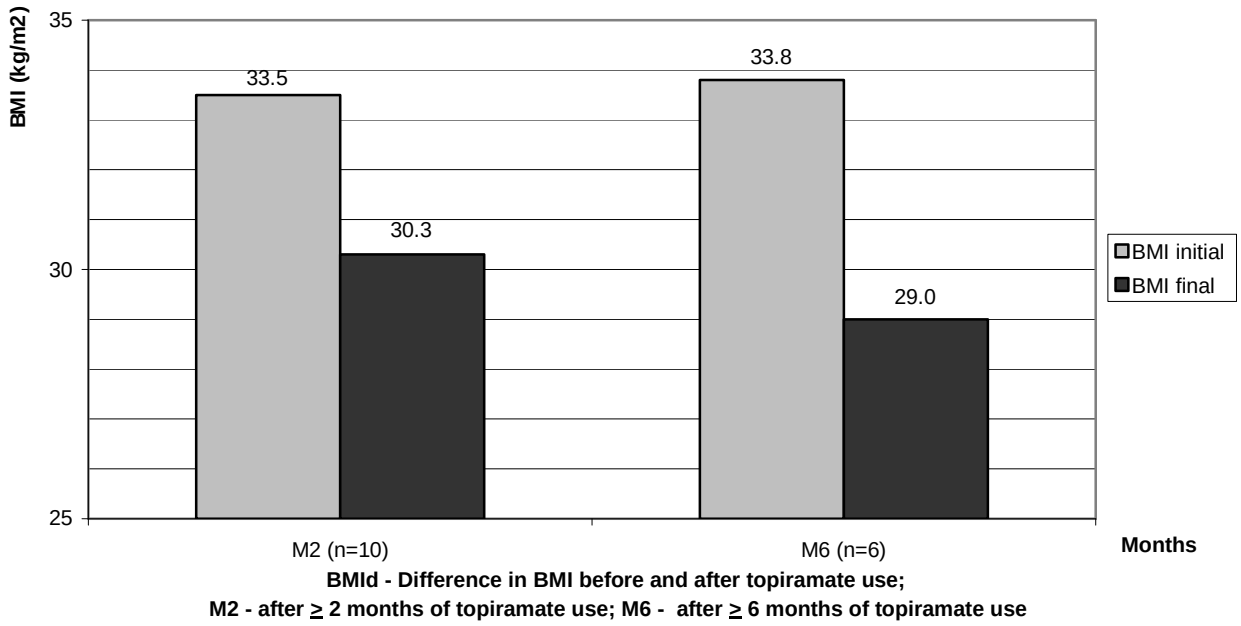
The patient who gained weight, a 30-year-old male, differed as he only took topiramate for 2 months, the shortest of any study patient, and underwent several other medication changes during that time (risperidone 6mg/day discontinued, zuclopenthixol decanoate increased from 50 to 100mg IM q2week, and quetiapine initiated and slowly tapered to 100mg/day). In the other nine patients antipsychotics were maintained constant (n=5) or increased (n=4, olanzapine increased in 3, clozapine initiated in 1).

TABLE 1 Demographic Data, Clinical Characteristics and Antipsychotic Medications (baseline data)

Variable	n	Mean	SD
Age, y	10	35.6	7.4
Baseline			
Weight, kg	10	93.7	26.2
Height, m	10	1.71	0.13
BMI, kg/m^2	10	33.5	5.6
Sex			
Men	7	--	--
Women	3	--	--
DSM-IV diagnosis			
Schizophrenia	9	--	--
Schizoaffective disorder	1	--	--
Daily dose of topiramate, mg/day	10	197.5	77.7
Duration of topiramate treatment, months	10	10	7.3
Antipsychotic medications			
Olanzapine, mg/day	8	16.6	6.7
Risperidone, mg/day	4	4.5	0.9
Clozapine, mg/day	1	200	---
Haloperidol, mg/day	2	15	5
Haloperidol decanoate, mg/4 weeks	4	310	160
Fluphenazine decanoate, mg/4 weeks	1	100	--
Zuclopenthixol decanoate, mg/4 weeks	1	100	--

BMI: Body Mass Index; DSM-IV: Diagnostic Statistical Manual of Mental Disorders– 4th edition; SD: Standard deviation.

FIG. 1 Mean BMI Before and After Topiramate Use



BMId - Difference in BMI before and after topiramate use;
M2 - after ≥ 2 months of topiramate use; M6 - after ≥ 6 months of topiramate use

DISCUSSION

Atypical antipsychotics have been associated with greater weight gain compared to classical antipsychotics.[2] The mechanism of antipsychotic-induced weight gain is still unknown. Antagonism of histamine H_1[14] and serotonin 5-HT_{2C}[15] receptors or leptin dysregulation has been postulated. Younger age, ethnicity (African-American, Asian, and Hispanic individuals), and low BMI when commencing treatment have been found to increase the risk of antipsychotic-induced weight gain.[16] Gender has also been reported but results are conflicting. The prevalence of overweight schizophrenic patients requires that all patients taking antipsychotics be actively screened and treated if needed. The National Institutes of Health (NIH)[17] recommends weight reduction therapy for individuals with a BMI≥25kg/m^2. Basic principles in managing weight gain and obesity in schizophrenia are similar to those used in general population. NIH guidelines include three major components: low-calorie diet, exercise, and behavioral strategies to alter lifestyle changes. Pharmacotherapy is recommended in combination with behavioral management if BMI>30 kg/m^2. It is also recommended in patients with a BMI≥27 kg/m^2 and medical comorbidities (e.g., diabetes, dyslipidemia, hypertension), in whom no weight loss has been achieved within 6 months with diet and behavioral methods.

Despite the small sample size and the naturalistic approach, the present study supports using adjunctive topiramate to promote weight loss in stable overweight schizophrenic patients, with greater BMI decreases for longer treatment periods. These findings are consistent with previously reported results. Several case reports[18-20], one case series[21], one open-labeled study[22], and one randomized placebo-controlled study[23] have reported on adjunctive topiramate to target weight loss in schizophrenia.

Summarizing the results, these publications involved a total of 113 schizophrenic patients, with mean treatment duration of 19 weeks [±13]. Daily doses of topiramate studied ranged from

75mg to 400mg. All previous publications[18-23] concluded that topiramate contributes to weight loss throughout the study duration. Interestingly, a dose-ranging study[23] found that topiramate's weight loss effect was dose dependent (BMI-$d_{200mg/day}$ > BMI-$d_{100mg/day}$). Topiramate was safe and relatively well tolerated. Adverse effects were generally mild to moderate, and tended to resolve over time. Most frequently reported were: paresthesias, anorexia, dyspepsia, psychomotor slowing, dizziness, diarrhea, and nausea. While psychotic symptoms[24,25] and cognitive side effects[26,27] have been described with topiramate treatment of epilepsy, no cognitive dulling, psychotic exacerbation, or behavioral effects were noted in the schizophrenia studies. This may be attributable to the use of lower doses in schizophrenia compared to epilepsy.

The present study has several limitations. First, this is a naturalistic retrospective study with a small sample size. Lack of a control group impairs the ability to account for the effects of usual treatment on weight. In addition, there was no evaluation of the impact of diet and behavioral methods in the weight loss. Furthermore, there was a lack of standardized psychopathologic, neurocognitive, and quality of life assessments.

In the present study, the observed changes in weight were not due to a concomitant decrease in antipsychotic use, as in the 9 out of 10 patients who lost weight, antipsychotics were either maintained constant (n=5) or increased (n=4). For the remaining patient, antipsychotics were altered and no change in weight was observed.

In addition to dietetic and behavioral approaches, topiramate provides a useful option for clinicians facing clinically significant antipsychotic-induced weight gain in stable schizophrenic patients. However, to evaluate the broader perspective of adjunctive topiramate as a weight-controlling method in schizophrenia, long term, randomized, placebo-controlled, dose-ranging clinical trials that include standardized psychopathologic, neurocognitive, and quality of life assessments, are required. Furthermore, the possibility of withdrawal symptoms or rebound weight gain when topiramate is discontinued should be investigated.

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