Asian Journal of Psychiatry 2 (2009) 106–111

Contents lists available at ScienceDirect

Asian Journal of Psychiatry

journal homepage: www.elsevier.com/locate/ajp

Changes in metabolic syndrome parameters in patients with schizoaffective disorder who participated in a randomized, placebo-controlled trial of topiramate

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ARTICLE INFO

Keywords:
Metabolic syndrome
Schizoaffective disorder–bipolar type
Topiramate
Lithium
Valproate
Antipsychotic agents
Asia

ABSTRACT

This study evaluated changes in the metabolic syndrome (MetS) parameters among patients with schizoaffective disorder–bipolar type who had previously participated in a randomized, placebo-controlled study of topiramate (Chengappa et al., 2007). Topiramate (or placebo) was added to pre-existing mood-stabilizer and/or antipsychotic treatment. Nearly 41% of the 46 participants with fully available data met criteria for MetS at the pre-study baseline, and six (13%) additional subjects met criteria for MetS during the 16-week study. Several subjects (mostly topiramate treated) showed the hypothesized and expected loss in body weight and this correlated with improved glycosylated hemoglobin or systolic and diastolic blood pressure measurements or improvements in lipid levels, whereas a few patients had inconsistent results. Limitations of the study include the lack of targeted treatments for specific components of the metabolic syndrome, and no controls for exercise, diet or concomitant medications. Nevertheless, screening, monitoring and targeted treatment for the metabolic syndrome in psychiatric patients is increasingly becoming the standard of practice. Moreover and especially pertinent to the readership of this journal is that as the prevalence of overweight and MetS have increased worldwide, the World Health Organization has proposed lower cut-off thresholds for obesity in Asia. Furthermore, lower thresholds for waist circumference have also been recommended for Asians.

1. Introduction

Recent reports have consistently indicated that people with schizophrenia, schizoaffective disorder or bipolar disorder have a higher prevalence of metabolic syndrome (MetS) than the general population (Heiskanen et al., 2003; Basu et al., 2004; McEvoy et al., 2005; Fagiolini et al., 2005). These reports used the original criteria described for metabolic syndrome (Ford et al., 2002; Expert Panel, 2001). Recently, changes were made to these criteria, i.e. the fasting blood sugar criterion was lowered from 110 mg/dl to 100 mg/dl (Grundy et al., 2005). Additionally: (1) the low HDL cholesterol (HDL-C) criterion considered as endorsed when HDL-C is normal or if the patient is treated with a drug to improve HDL-C levels and (2) the hypertension criterion is endorsed if either the systolic blood pressure *or* the diastolic blood pressure is elevated ($\geq$130 and/or $\geq$85 mm Hg respectively) or if patients are receiving anti-hypertensive medicines. Finally, the blood sugar criterion of $\leq$100 mg/ml is endorsed if the patient is receiving insulin or oral hypoglycemic agents.

Several factors have been invoked to explain higher prevalence rates of metabolic syndrome in psychiatric patients, including a sedentary lifestyle, unhealthy diets, lack of exercise, excess smoking of cigarettes, and the use of medications that influence appetite, cause weight gain, and impact several other metabolic parameters (Levine et al., 2001).

Efforts to improve various components of MetS in psychiatric patients have attempted to improve eating habits, encouraged exercise and achieve weight loss by behavioral methods (Ganguli, 2007). Other approaches have endeavored to switch psychotropic agents from those that likely cause weight gain to those with less

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doi:10.1016/j.ajp.2009.08.006

potential to do so (Gupta et al., 2004; Meyer et al., 2005; Montes et al., 2007). Yet other approaches have involved adding drugs known to cause weight loss such as topiramate, or sibutramine, or metformin (Egger et al., 2007; McElroy et al., 2007; Wu et al., 2008).

We had conducted a double-blind, placebo-controlled study to evaluate topiramate as an adjunctive treatment for psychotic and mood symptoms in persons with schizoaffective disorder–bipolar type (Chengappa et al., 2007). The results of that study have already been published, and there was no support for efficacy of adjunctive topiramate in ameliorating mood or psychotic symptoms (Chengappa et al., 2007). As topiramate was one of the treatments of the study, and earlier reports had described weight loss or improvements in metabolic parameters in persons receiving topiramate (Chengappa et al., 2001; Bray et al., 2003), one of the secondary hypotheses in the original study (Chengappa et al., 2007) was that there would be potential benefits for those receiving topiramate in patients meeting criteria for the MetS.

2. Methods

A randomized (2:1 in favor of topiramate) double-blind study recruited subjects (receiving care in ambulatory clinics/hospitals affiliated with the University of Pittsburgh, Western Psychiatric Institute and Clinic, or Mayview State Hospital) who provided written informed consent. The study was approved by the Institutional Review Board of the University of Pittsburgh, and by the Office of Mental Health and Substance Abuse Services, Harrisburg, Pennsylvania.

Both male and female patients of any ethnicity over the age of 18 years were recruited. Subjects were required to have a baseline CGI-Severity score (Guy, 1976) of $\geq$4, a PANSS total score of $\geq$60 (Kay et al., 1987), and had received lithium (0.6–1.0 meq/L) or valproate (50–100 mcg/ml) for at least 2 weeks. They could have received one antipsychotic agent but not an antidepressant. Details of the inclusion or exclusion criteria are noted in the earlier publication (Chengappa et al., 2007).

Topiramate was titrated slowly on a weekly schedule to a maximum of 400 mg/day in two divided daily doses over a period of 4 weeks; lower doses were used if patients responded or if they experienced dose limiting side effects. Matching placebo tablets were given in the same dosing schedule as topiramate. Subjects received 8 weeks of double-blinded study medication, and continued for an additional 8 weeks if they were responders ($\geq$20% improvement from baseline on the total scores of the PANSS scale).

One of the secondary hypotheses of this study was to evaluate the impact of topiramate treatment on body weight and metabolic parameters in individual patients. However, it is pertinent for the reader to note that there was no separate randomization for those who met the criteria for metabolic syndrome versus those who did not. As we were enrolling patients into the study, we noted that there was only one published report of metabolic syndrome in patients with schizophrenia (Heiskanen et al., 2003). Therefore, we reviewed the patients who had been recruited at the time (n = 36) into this study to determine the prevalence of metabolic syndrome in this patient population (Basu et al., 2004). In that paper, we used the original NCEP-ATP III criteria to determine the presence or the absence of MetS (Basu et al., 2004). However, in this paper, we applied the revised criteria for MetS (Grundy et al., 2005) with changes noted in the introductory paragraph.

Sitting blood pressure was measured in subjects after they were comfortably seated for about 5 min while discussing neutral topics. Fasting blood (no calorie intake for at least 8–10 h) was drawn to test glucose levels and lipid profiles. Waist circumference was measured at the midpoint between the lowest rib and the iliac crest (which were used as bony landmarks). Height and body weight were measured in light clothing, without jackets or shoes, using the same scale. These measurements were repeated at 8 and 16 weeks.

2.1. Statistical analyses

We did not conduct formal statistical analyses for metabolic outcomes in this study. Due to the small number of subjects in the larger study, and even smaller group who met criteria for the metabolic syndrome, we did not expect sample sizes that would permit comparisons of one group versus another for various parameters (e.g. drug assignment—topiramate vs. placebo, or subjects receiving a specific antipsychotic agent or not, etc.). Instead, we chose a case-based approach to provide specific details in a table format.

3. Results

Forty-eight patients were enrolled for the study, and metabolic syndrome data was available for 46 patients. Among them, 19 (41.3%) subjects met criteria for metabolic syndrome at baseline, and six (13%) developed it during the course of the trial. The mean age of the patients was 45 years, with nearly equal numbers of men (n = 12) and women (n = 13), of whom 14 were Caucasian and 11 were African American (see Table 1). Among the patients who had MetS at baseline, eight subjects satisfied three criteria, three patients met four criteria, and eight patients met all five criteria. The criterion which occurred with the highest frequency was increased waist circumference (96% of subjects), and the next most frequently noted was increased serum triglyceride levels (72%). One subject among the 19 who met the criteria for metabolic syndrome at baseline no longer met the criteria at 8 weeks (ID # 47, Table 1). In this 44-year-old African American male subject, the fasting blood sugar improved, therefore he no longer met the criteria for the MetS. Interestingly, he had been assigned to topiramate during the trial. He had not received treatment for diabetes mellitus and had been counseled to contact his primary care physician. However, we were unable to obtain further follow up as this subject dropped out of the study after 8 weeks. In the rest of the subjects, the number of criteria met at baseline either stayed the same (n = 7, all of whom received topiramate), improved (usually one criterion less, n = 6, of whom five received topiramate), worsened (n = 3, all of whom received topiramate), or could not be determined (n = 3, dropped out, two of whom received placebo).

Twelve (63%) of the 19 subjects who met MetS criteria at baseline received valproate, nine received lithium, and two received both agents (Table 1). Seven of the 19 subjects received risperidone, five received olanzapine, two received quetiapine, and one each received clozapine, or ziprasidone or a first generation antipsychotic agent. At baseline, nine subjects received anti-hypertensive agents, five received oral anti-diabetic agents and/or insulin, and five received statins for hyperlipidemia (Table 1).

As noted earlier, six subjects developed MetS criteria during the course of the study (ID # 3, 4, 37, 45, 25, 48, Table 1). Among these six subjects, serum HDL levels had decreased in four cases, and serum triglyceride levels had increased in three subjects; four received topiramate during the trial and two were assigned to placebo. These subjects received combinations of valproate (n = 4) or lithium (n = 3) with either olanzapine (n = 3) or other antipsychotic agents (quetiapine, n = 1, first generation antipsychotic agent, n = 1). Two of these six subjects received anti-hypertensive agents even prior to meeting the criteria for metabolic syndrome.

During the study there were some unexpected findings. For instance, ID ## 3, 4, and 37 who had developed MetS during the