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Effects of Topiramate on Smoking in Patients with Schizoaffective Disorder, Bipolar Type

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To the Editors:

It has been suggested that topiramate (Topamax®; Ortho-McNeil Neurologics, Inc.; Titusville, New Jersey USA) may have use for treating addictions including nicotine dependence due to its modulation of dopaminergic activity in the corticomesolimbic axis through actions on GABAergic and glutamatergic systems¹. Topiramate has been shown to increase abstinence from alcohol² and led to higher levels of spontaneous abstinence from smoking in participants receiving topiramate as treatment for alcohol dependence³. Few trials have examined topiramate specifically for smoking cessation and findings from these studies have been mixed. Khazaal et al⁴ reported that six out of 13 smokers given topiramate (maximum dose 50–225 mg/day for n=11, 500 mg/day for n=1, and 800 mg/day for n=1) were abstinent from smoking after two months with two additional participants reducing their smoking significantly (>50%). In contrast, Anthenelli et al⁵ found a trend (p=0.10) towards differences in smoking abstinence with topiramate (200 mg/day) versus placebo in male adult smokers (n=38); however, there was no difference in smoking abstinence rates for female smokers (n=49) by treatment group. Additional questions about the usefulness of topiramate for smoking cessation have been raised by studies reporting increased subjective report of nicotine withdrawal⁶ and enhanced rewarding effects of IV nicotine⁷ and smoked cigarettes⁶ with topiramate. Examining new medications for the treatment of tobacco dependence is important especially in groups of smokers with high prevalence of smoking and difficulty with smoking cessation (e.g, smokers with psychiatric conditions⁸). The purpose of the study was to report data on smoking behavior from a placebo-controlled trial of topiramate which primarily evaluated psychiatric symptoms (mood and psychotic symptoms) in patients with schizoaffective disorder, bipolar type.

This report is based on a secondary analysis of an eight-week placebo-controlled, randomized clinical trial examining the safety and efficacy of topiramate for patients with schizoaffective disorder, bipolar type⁹. Patients in the study were randomly assigned to

topiramate (TOP, 100–400 mg/d) or placebo (PLA) using a 2:1 ratio in favor of topiramate. Participants were not provided with any specific pharmacological or behavior treatment for smoking. Participants were included in this analysis if they reported that they were current smokers as defined by an expired breath carbon monoxide (CO) level ≥ 10 ppm at baseline. CO levels were assessed at baseline, week 4, and week 8 (end of study). Self-reported cigarette smoking was only assessed at the beginning of the trial, prior to medication randomization. The study protocol and consent forms were reviewed and approved by the Institutional Review Board of the University of Pittsburgh, and the Research Review Committee of Mayview State Hospital, and the Office of Mental Health and Substance Abuse Services, Harrisburg, PA. All participants gave their consent to participate after procedures and possible side effects were explained to them.

Thirty-one out of the full sample of 48 participants (65%) reported daily smoking consistent with the high rates of smoking in this population¹⁰. The current analyses were conducted on the twenty-four participants (50% of the full sample; TOP $n=13$, PLA $n=11$) who both reported daily smoking and had a baseline CO level of at least 10 ppm. Participants were 50% male and 54% Caucasian (42% African-American, 4% Other) and reported smoking an average of 20.2 (SD=13.4) cigarettes per day. There were no baseline differences between the treatment groups on gender ($p=0.68$), race/ethnicity ($p=0.52$), age ($p=0.22$), weight ($p=0.48$), CO level (TOP $M=24.6$, $SD=11.3$; PLA $M=24.6$, $SD=10.6$; $p=0.99$) or number of cigarettes smoked per day (TOP $M=23.2$, $SD=14.5$; PLA $M=16.6$, $SD=11.8$, $p=0.24$).

No differences were found in CO levels at week 4 (TOP $M=21.6$, $SD=11.3$; PLA $M=25.6$, $SD=9.7$; $p=0.44$) or week 8 (TOP $M=23.7$, $SD=8.2$; PLA $M=21.4$, $SD=10.39$; $p=0.62$) between treatment groups. A repeated measure analysis of variance (ANOVA) showed no effect of Time ($p=0.56$) and no Group $\times$ Time interaction ($p=0.22$), suggesting that CO levels remained generally unchanged for participants on topiramate and placebo during the course of the trial. There was no effect of Time ($p=0.32$) and no Group $\times$ Time interaction ($p=0.38$) on weight. No differences were found when the analyses were rerun including gender as a variable suggesting that CO did not change over the course of the study for male or female participants; however, these results should be interpreted with caution due to the low power to detect differences among these small groups. Both treatments (TOP and PLA) reduced scores on psychotic or mood symptoms and there were no significant differences in the reduction of psychiatric symptoms by treatment group (see Chengappa et al, 2007⁹).

Discussion

This secondary analysis examined the potential efficacy of the anticonvulsant topiramate on a surrogate measure of smoking (CO levels) in patients with schizoaffective disorder, bipolar subtype. The relationship between topiramate and smoking has not, to our knowledge, been previously investigated for this group of smokers. Our findings are consistent with a lack of an effect as reported by Anthenelli et al⁵ but contrast the higher rates of abstinence and reduced smoking found by Johnson et al³ and Khazaaal et al⁴. Interestingly, psychotic and mood symptoms in these smokers with schizoaffective disorder were also unaffected (see Changappa et al., 2007⁹). Limitations of this study include a small sample size and assessment of smoking by CO level only. In addition, the purpose of this study was to examine the impact of topiramate on psychiatric symptoms and not specifically on smoking. Therefore, no smoking cessation counseling or assessment of smoking-related variables (e.g., cravings and withdrawal, interest in smoking cessation) occurred during the course of the trial and our results may not generalize to smokers who are actively attempting to quit smoking. Johnson et al³ reported higher levels of spontaneous abstinence from smoking in a sample of alcohol-dependent patients who did not receive counseling related to smoking cessation; however, our analyses did not provide evidence for spontaneous

cessation or reduction in schizoaffective, bipolar type smokers in this study. Although mixed, studies^{4,5} that reported some evidence or trend for smoking reduction with topiramate involved smokers who were seeking assistance for smoking cessation and motivation level has been suggested to make a critical difference in the efficacy of medication for smoking cessation¹¹. Future studies assessing motivation to quit and providing smoking cessation counseling would provide a stronger test of topiramate's effects with smokers who have psychiatric disorders who are interested in smoking cessation. Although topiramate has shown some promise for smoking cessation in non-psychiatric and alcohol dependent smokers, these analyses do not support the idea that this medication would help patients with schizoaffective disorder reduce their smoking spontaneously.

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