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A Preliminary Feasibility Study of Varenicline for Smoking Cessation in Bipolar Disorder

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TO THE EDITOR

Our review of studies examining smoking cessation interventions among persons with bipolar disorders (George, Wu, and Weinberger, 2012, in this issue), shows the need for safe and efficacious smoking cessation treatments for these patients. Only one study has been published thus far: a trial of 5 bipolar smokers treated with sustained-release (SR) bupropion (Weinberger, 2008) showed promise for tobacco treatment in this group.

Varenicline is the latest FDA-approved first-line pharmacotherapy for tobacco addiction. A partial agonist for the alpha4beta2 subtype of nicotinic acetylcholine receptors (nAChRs) (Nides, 2008), varenicline may be more efficacious than bupropion SR (Gonzales, 2006). While varenicline has a generally acceptable safety profile, neuropsychiatric symptoms have emerged in post-marketing reports including mood alterations, aggression and psychosis (Kohen, 2007; Tonstad, 2010). Therefore, the aim of the current pilot study was to investigate the safety and efficacy of varenicline in smokers with bipolar disorder.

Using a double-blind, randomized, placebo-controlled 10-week design, nicotine dependent bipolar smokers were randomized to receive varenicline (1mg po BID) or placebo, and weekly smoking cessation counselling based on the study of Weinberger and colleagues (Weinberger, 2008). Subjects were adult outpatients with a SCID derived DSM-IV diagnosis

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DISCLOSURES

Dr. George reports that, in the past two years, he has received contract support from Pfizer, speaker's bureau fees from Janssen, Astra-Zeneca and Pfizer, and has served on a Data Monitoring Committee for Novartis. Drs. Weinberger, Levinson and Wing, and Ms. Wu, Ms. Mancuso and Ms. Haji-Khamneh have no financial disclosures to report.

of Bipolar I or II disorder, who smoked at least 10 cigarettes/day; were on a stable dose of a mood stabilizer for at least a month; and were deemed psychiatrically stable through clinical evaluations prior to enrolment. Psychiatric stability was operationalized as a score of less than 12 on the Young Mania Rating Scale (YMRS; Young, 1978), and a score of less than 24 on the Hamilton Depression Scale (HDRS; Hamilton, 1960). Individuals were not eligible if they were using smoking cessation medication; diagnosed with a major medical condition; or diagnosed with drug abuse or dependence in the last 3 months. Subjects provided written informed consent, which was approved by the Centre for Addiction and Mental Health Research Ethics Board.

In total, 169 phone screens were conducted, from which 164 subjects were found ineligible due the following reasons: low smoking levels ($n=33$), current alcohol or drug abuse ($n=31$), not interested ($n=24$), not on mood stabilizers ($n=18$), other psychiatric diagnosis ($n=14$), psychiatrically unstable ($n=10$), current bupropion treatment ($n=7$), past varenicline use ($n=7$), exclusionary medical conditions ($n=5$), and logistics problems which prohibited participation ($n=15$).

Amongst the five randomized subjects, 3 were randomly assigned to receive active varenicline while 2 received placebo in a standard titration (Weinberger, 2008). The target quit date was set at day one of week three. Subjects were required to attend weekly appointments for medication pick-up and assessments. In addition to monitoring physical side effects, manic and depressive symptoms were closely assessed throughout the trial using standardized measures. The primary study outcome was biochemically verified smoking abstinence at trial endpoint by expired breath carbon monoxide levels of less than 10 ppm).

All five subjects (2 males, 3 females) were chronic, heavy smokers of Caucasian ancestry. All three subjects assigned to the varenicline treatment condition (Subjects 1, 2 and 5) completed the 10-week trial, and both placebo-treated subjects (Subjects 3 and 4) dropped out by Week 3.

Subject 1 met the criteria for endpoint smoking abstinence. Subjects assigned to varenicline smoked fewer cigarettes per day than those assigned to placebo (varenicline 7.3 ± 2.2 vs. placebo 20.5 ± 5.0 cigarettes), and this was confirmed biochemically by a reduction in carbon monoxide levels from baseline (% change: varenicline $-52.93 \pm 50.3\%$ vs. placebo $+41.1 \pm 6.3\%$). At the 6-month follow-up, all subjects had returned to baseline smoking levels.

Study medication was well-tolerated. Nausea and insomnia were the main adverse events associated with varenicline treatment. Mood symptoms were reported by Subjects 1 and 4, who endorsed passive suicidal ideation at weeks 10 (varenicline) and 2 (placebo), respectively. Both events were temporary and associated with situational stressors. Overall, psychiatric symptoms (mania and depression ratings) were not significantly changed in any subject from baseline to endpoint.

In summary, in this small study of five bipolar patients, treatment with varenicline was tolerated and associated with reductions in smoking. Future studies should use multi-center designs to overcome problems with recruiting stable bipolar smokers.

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