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A Preliminary Study of Sustained-Release Bupropion for Smoking Cessation in Bipolar Disorder*

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To the Editors

Individuals with bipolar disorder smoke cigarettes at higher rates (31%-67%) than the U.S. general population (~20%) (1, 2), have a more difficult time with smoking cessation (1), and smoking is related to greater severity of both manic and depressive symptoms (2, 3). However, there have been no controlled studies of nicotine dependence treatments in this subset of psychiatric smokers.

The sustained release (SR) formulation of bupropion (BUP) is a weak catecholamine reuptake inhibitor (4) and a potent non-competitive ion channel site antagonist at the nicotinic acetylcholine receptor (nAChR), which was approved as an aid to smoking cessation in the U.S. in 1997 (5). While bupropion is safe and improves smoking cessation rates for smokers with schizophrenia [e.g., (6)], this agent has not been tested for smokers with bipolar disorder. This report describes the first controlled evaluation of bupropion in smokers with bipolar disorder on short-term smoking abstinence rates.

Participants in this pilot study were clinically stable outpatients with DSM-IV diagnoses of bipolar I disorder and nicotine-dependent cigarette smokers consuming at least 10 cigarettes per day (cpd), with expired breath carbon monoxide (CO) levels ≥10 parts per million

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Location of Work: This study was conducted at the Connecticut Mental Health Center, Department of Psychiatry, Yale University School of Medicine, New Haven, CT

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(ppm). Subjects were recruited from the outpatient clinics of Connecticut Mental Health Center (CMHC) or other mental clinics in the Greater New Haven, Connecticut area. Written informed consent was obtained from all participants, and the protocol was approved by the Yale School of Medicine's Human Investigation Committee.

A total of N=204 patients with bipolar I disorder were screened by phone. The primary reasons for ineligibility (n=199) were: current antidepressant medication (n=57), not taking or not being stabilized on a mood stabilizer (n=42), current drug use (n=32), low levels of smoking (n=9), medical exclusions (n=14), refusal to participate (n=12), dropping out during the screening sessions (n=25) or logistic reasons (n=8). Five participants were determined to be eligible, attended the first group therapy session, and received study medication.

Two participants were randomly assigned to receive bupropion and three to placebo. Bupropion (BUP; Wellbutrin or Zyban™; GlaxoSmithKline) as the intermediate-release (IR) formulation (or PLA) was initiated on Day 1 of the 10 week trial at 75 mg po qd × 3 days, then increased to 150 mg [as BUP SR formulation] qd × 4 days, and then increased to a final dose of up to 150 mg po bid (300 mg/day) by Day 15 (target quit date; TQD) as tolerated. This dose was continued for an additional eight weeks at up to 150 mg po bid as tolerated. All participants received weekly sessions of manualized group behavioral therapy as described previously (7). Smoking abstinence at study endpoint was determined by self-reported cigarette smoking (8) verified objectively by CO level < 10 ppm. Non-completers were judged as smoking. Mood symptoms were assessed using the Young Mania Rating Scale (YMRS,(9)), the Beck Depression Inventory (BDI, (10)) and Hamilton Depression Rating Scale (HDRS, (11)).

Participants were an average age of 57.2 years (SD=6.8; 60% female, 100% Caucasian). Four participants were stabilized on Lithium (600-900 mg/day) and one participant received divalproex sodium (1000 mg/day); each of the subjects had therapeutic plasma levels of these mood-stablizers. Participants smoked an average of 20.1 cpd (SD=9.2). Number of study weeks completed was comparable between medication groups (BUP M=7.0, SD=4.2; PLA M=9.7, SD=0.6). See Table 1 for demographic, smoking, and psychiatric variables.

Two participants receiving placebo discontinued medication. One participant (Participant 3) took the full dose of the study medication for 6 weeks without problems and was observed to have hypomanic symptoms including increased distractibility and sexual inappropriateness at his 7th weekly appointment. As a safety measure the study medication was discontinued. The participant's hypomanic symptoms decreased over the next two study appointments. A second participant (Participant 4), also randomized to placebo medication, was observed to have hypomanic symptoms (e.g., difficulty sleeping, increased energy) at her 4th weekly appointment. Study medication was stopped at this time and restarted the initial dose (75 mg/day, placebo) two weeks later after her hypomanic symptoms resolved. The subject was maintained on this dose of study medication for the duration of the study. Participant 5, who received placebo medication, reported one minor spike in mood symptoms (YMRS score = 5 at the 4th week as compared to a baseline score of 0.5) and a dose change of lithium during the second week of the study (a decrease from 600 mg/day to 450 mg/day). No changes were made to study medications. No participant receiving placebo medication quit smoking during the trial

The two participants receiving BUP reported no problems tolerating study medication. Participant 1 completed the study and was CO-confirmed abstinent at EOT. She reported no significant mood changes or side effects. Participant 2 dropped out of the study after the 4th

week due to transportation and schedule-related issues. He reported that he quit smoking on his TQD but abstinence was not confirmed by CO.

Discussion

This is the first placebo-controlled trial to evaluate bupropion SR for smoking cessation in bipolar I disorder. Though the sample was small, bupropion was well-tolerated. Interestingly, patients who developed hypomania had all been assigned to placebo medication. Factors relating to increased hypomania may have included psychosocial stressors, stress related to attempting to quit smoking, and nicotine withdrawal; active bupropion treatment may have provided some reduction of nicotine withdrawal and craving symptoms. Bupropion has been safely used to treat the depressed phase of bipolar I and II illness (12). There is anecdotal clinical evidence that bupropion is less likely than SSRI and tricyclic antidepressants to induce a switch from depression to mania or hypomania in patients with a bipolar history (13), although one prospective follow-up study has questioned this (14). There are known polymorphisms in the long (“l”) form of the 5-HT transporter gene (5-HTTLPR) which appear to predispose patients to antidepressant-induced mania (15, 16) and could explain why bupropion (a dopamine and norephinephrine reuptake inhibitor) is less likely to induce mania or hypomania. Thus, bupropion may be a promising treatment for smokers with bipolar disorder as an aid for smoking cessation with a lower probability of increasing manic or hypomanic symptoms. It should be noted that co-administration of bupropion with certain antidepressant and antipsychotic medications may increase blood levels through CYP2D6 inhibition (17) so administration of this medication to patients with bipolar disorder should be monitored carefully.

Bipolar smokers were extremely difficult to recruit into this smoking cessation study with only 4% of patients who went through the initial phone screen reaching randomization. A large proportion of bipolar patients were taking an antidepressant medication (an exclusion due to concerns of combining bupropion with existing antidepressant therapy in bipolar I subjects) while another large group of participants were not taking a mood stabilizer. These factors may limit the utilization of bupropion in bipolar smokers. Our results provide the first preliminary evidence this agent may be well-tolerated in bipolar smokers and useful in smoking cessation treatment. Further studies with larger sample sizes recruited using multi-site trials are warranted to determine the safety and efficacy of bupropion in this subset of psychiatric smokers.

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Table 1

Medication assignment, demographic and baseline psychiatric variables for bipolar smokers (n=5).

	Participant 1	Participant 2	Participant 3	Participant 4	Participant 5	Full Sample (n=5)
Study Medication Assignment	BUP	BUP	PLA	PLA	PLA	--
Number of study weeks completed (max. 10)	10	4	9	10	10	8.6 ± 2.6
Endpoint abstinence	Quit	Not Quit	Not Quit	Not Quit	Not Quit	1 Quit/4 Not Quit
Gender	Female	Male	Male	Female	Female	2M/3F
Race	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	5 C
Age (years)	54	60	61	47	64	57.2 ± 6.8
Baseline CPD	20	20	35.29	13.29	12.14	20.1 ± 9.2
Endpoint CPD	0	1.42*	35**	13.57	4.29	10.9 ± 14.5
Baseline CO level (ppm)	25	16	26	13	10	17.4 ± 8.1
Endpoint CO level (ppm)	0	20*	29**	10	7	13.2 ± 11.4
Mood Stabilizer	Lithium 900 mg/day	Lithium 600 mg/day	Valproate Sodium 1000 mg/ day	Lithium 600 mg/day	Lithium 600 mg/day	4 Lithium/1 Valproate
FTND	7	7	10	4	4	6.4 ± 2.5
Age of Smoking Onset	13	18	12	15	15	14.6 ± 2.3
Duration of Smoking (years)	41	42	49	25	49	41.2 ± 9.8
Pack-years	59	42	86	19	78	56.8 ± 27.2
Number of Lifetime Quit Attempts	5	4	6	2	5	4.4 ± 1.5
Contemplation Ladder	8	5	6	6	8	6.6 ± 1.3
BDI	0	6	20	12	12	10.0 ± 7.5
HDRS 17 item	6	2	9	6	2	5.0 ± 3.0
HDRS 21 item	8	2	12	9	2	6.6 ± 4.5
Young Mania Rating Scale	4.5	5.5	4.5	3.0	0.5	3.6 ± 2.0

Key: BUP, bupropion; PLA, placebo; M, male; F, female; C, Caucasian; CPD, cigarettes per day; CO, carbon monoxide; FTND, Fagerström Test of Nicotine Dependence; BDI, Beck Depression Inventory; HDRS, Hamilton Depression Rating Scale.

*CPD and CO from last week of participation in the study (Week 4)

**CPD and CO from last week of participation in the study (Week 9)