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An Association between the use of hypnotics and quit status in the treatment of Nicotine Dependence with Varenicline in Bipolar Disorder

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People with mental illnesses such as schizophrenia, bipolar or depressive disorders and substance abuse smoke nearly half of all cigarettes sold in the USA; are more addicted than the general population of smokers, and among the least likely to quit.^{1,2} Importantly, persons with severe mental illness die significantly younger than their peers mainly due to medical conditions such as cardiovascular or respiratory disorders or cancer.^{3,4} Smoking cessation offers one of the best opportunities to reverse the excess mortality among the mentally ill.⁵

During cessation efforts, smokers struggle with symptoms of nicotine withdrawal such as insomnia, anxiety, and irritability. Insomnia, anxiety and irritability are symptoms associated with bipolar disorder, and so make it even harder to quit smoking. Moreover, all three approved smoking cessation aids (nicotine replacement therapies NRT, bupropion and varenicline) can cause insomnia, abnormal dreams and anxiety.^{6,7} Therefore, efforts to better manage insomnia and anxiety will likely increase the odds of heavily addicted smokers, such as those with bipolar illness to quit. A secondary aim in a recently completed randomized, controlled trial of varenicline for smoking cessation in bipolar disorder⁸ was to assess whether concomitant medications (sedative-hypnotic agents, anxiolytics, anti-psychotic agents, anti-depressants or mood stabilizers) were correlated with quit status, and those results form the basis of this report.

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METHODS

A randomized, double-blind, placebo controlled study of varenicline to aid 60 consenting smokers with bipolar disorder (DSM-IV) motivated to quit indicated that varenicline was significantly more efficacious (7-day point prevalence of self-reported no smoking verified by expired carbon monoxide < 10 ppm at 3 months, i.e. end of treatment; (15/31, 48.4%) than placebo (3/29, 10.3%).⁸ Medications used to treat bipolar disorder were continued unchanged (mood stabilizers, second-generation antipsychotic agents, and anti-depressants). During smoking cessation, anxiolytics or hypnotics could be continued, initiated or adjusted as clinically appropriate to manage nicotine withdrawal symptoms. Initial statistical comparisons using the Fisher's exact test assessed differences in receipt of various psychotropic drug classes by quit status. Only hypnotic drug use differed between quitters (50%, 9/18) and non-quitters (21%, 9/42), Fisher's exact $p = 0.035$. A logistic regression analysis was run with quit/not-quit as the primary outcome, and medication assignment (varenicline/placebo) and hypnotic drug usage as the two independent predictor variables (Table). An interaction term (study medication $\times$ hypnotic drug) was introduced to assess if it contributed to the model.

Among adverse events, nicotine-withdrawal related symptoms (insomnia, abnormal dreams, anxiety and irritability) were especially reviewed by treatment-assignment and quit status; as these symptoms are likely targets of treatment (i.e. hypnotics or anxiolytics).

RESULTS

We were interested in differences (if any) for five psychotropic drug categories (mood stabilizers, antipsychotic agents, anti-depressants, anxiolytics or hypnotic drugs) among those who quit ($n = 18$) vs not ($n = 42$). As noted earlier, only the use of hypnotic drugs emerged as significantly different between quitters (9/18, 50%) and non-quitters (9/42, 21%). Of the 18 subjects who received hypnotic medications, 14 subjects were prescribed these drugs at baseline and continued, and 4 were initiated during the treatment phase. The hypnotic medications included trazodone ($n=11$), zolpidem ($n=4$), temazepam ($n = 2$), low dose doxepin ($n=1$), hydroxyzine ($n = 1$), and trazodone and zolpidem ($n = 1$). Varenicline/placebo, ($\beta = 2.23$, $p = 0.003$) and hypnotics/no-hypnotics ($\beta = 1.5$, $p = 0.032$) were significant independent predictors of quit status, with the following odds ratios – (β) of 9.3 (95% CI = 2.1, 40.9) and 4.5 (95% CI = 1.1, 17.6), respectively. Although the interaction was not statistically significant, there appeared to be a meaningful differential effect of the treatment between those taking and not taking a hypnotic, with the odds ratio of quit with varenicline compared to placebo being nearly eight times greater among those taking a hypnotic. This finding warrants further study.

Among the sleep-related adverse events, insomnia was reported by 8/10 (80%) of patients who received varenicline and quit vs 2/8 (25%) assigned to placebo (Fisher's exact $p = 0.054$). Among those who quit with varenicline ($n = 8$), insomnia ranged from 1 to 30 days, and 1 to 14 days in the two placebo-assigned patients neither of whom quit. In both treatment groups, insomnia began 3 to 4 days after the target quit date, and in a few subjects lasted 3 to 5 weeks. Twice the percentage of varenicline-treated patients who received

hypnotic agents complained of abnormal dreams (5/10, 50%) vs 2/8 (25%) who received placebo (not statistically significant). The demographic, illness and smoking characteristics of this subgroup (n=18 who received hypnotic agents) was not significantly different (data not shown) from that reported in the parent study for the entire cohort.⁸

DISCUSSION

These data suggest that the concomitant use or initiation of hypnotic agents with varenicline was more likely to be associated with quit status in smokers with bipolar illness desirous of quitting, however, it is pertinent to note this result does not suggest cause and effect. Another limitation is the relatively small number of subjects who used hypnotic agents (also openly and not randomly) in the parent study. As noted above, during the smoking cessation efforts, varenicline-treated patients experienced treatment-emergent insomnia and abnormal dreams more often than those assigned to placebo.

Symptoms of nicotine withdrawal include among others sleep disturbance, anxiety and irritability, and such symptoms can precipitate relapse to smoking.⁹ Furthermore, treatment with smoking cessation agents such as NRT, bupropion and varenicline are associated with sleep disturbances.^{6,7} Moreover, sleep disturbances in persons with bipolar illness may precede illness exacerbations (i.e. depressive and manic episodes) and may persist in the euthymic phase.¹⁰ Therefore, among euthymic individuals with bipolar illness (as was the case in this study) efforts to manage sleep disturbance may be especially relevant in achieving abstinence from smoking. Among smokers attempting to quit, sleep disturbances contribute significantly to relapse.^{7,11} Separately, in smokers with schizophrenia, it has been shown that they experience more intense cigarette craving and nicotine withdrawal symptoms during smoking abstinence than smokers without psychiatric disorders.¹² Patients with bipolar illness share some of the same smoking characteristics as those with schizophrenia, and therefore mitigating nicotine withdrawal symptoms especially insomnia may be especially relevant in promoting long-term smoking cessation.¹³

Future work concentrating specifically on the management of nicotine withdrawal symptoms such as insomnia, irritability and anxiety especially in highly addicted smokers may provide more definitive guidance for clinicians on the use of hypnotic agents. The hypothesis that hypnotic agents may aid in quitting by managing nicotine withdrawal symptoms requires to be tested in prospective trials.

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Table

	Varenicline		Placebo	
	Hypnotics	No Hypnotics	Hypnotics	No Hypnotics
Quit	8	7	1	2
Not Quit	2	14	7	19