Varenicline for Smoking Cessation in the Bipolar Patient

To the Editor: I commend Chengappa and coauthors for their recent NIMH-funded, non–industry supported article[1] revisiting the use of the selective $\alpha_4\beta_2$ nicotinic acetycholine receptor partial agonist varenicline in patients with bipolar disorder. The accompanying thoughtful commentary by Goldberg[2] is similarly appreciated.

The Food and Drug Administration (FDA) does appear to hand out apparently damning black box warnings with alacrity, witness the citalopram and zolpidem edicts. These can be counterbalanced by strong research.[3] But in the case of varenicline, the FDA warning is, in my opinion, fully justified.

Chengappa et al wisely used only euthymic bipolar disorder patients in their research, versus unstable bipolar patients. How they chose or defined this cohort is uncertain, as is whether comorbid substance abuse was screened out. The authors have helpfully presented useful information (albeit with a limited number of subjects) suggesting reasons for the high-risk nature of varenicline in psychiatric patients who are attempting smoking cessation. These include:

1. Insomnia (45.2% vs 27.6% placebo)—confirmed by other industry-supported research (reference 4 and the March 9, 2015, FDA Safety Announcement), albeit in much lower numbers
2. Abnormal dreams (58.0% vs 31.0% placebo)
3. Suicidal ideation (6.5% vs 3.4%, 1 case with placebo)—a nonsignificant difference, (but 96.8% of their patients already had experienced pretreatment suicidal ideation, in other words a universal high-risk group for potential suicidality)
4. Depressed mood (25.8% vs 6.9% placebo)

Brief case presentation. Ms A was a 32-year-old woman with chronic unstable bipolar I disorder with psychotic features (*DSM-IV-TR*) and polysubstance abuse including chronic nicotine dependence, which was partially controlled on medication. She had been requesting varenicline—after seeing advertising on television—for several years, which had been frequently denied by the psychiatrist. After starting with a busy new internist, she again requested a varenicline trial, which was granted. Within 3 days, she had completed a tragic suicide. There were no other overt precipitants to the suicide other than the varenicline trial.

In patients with unstable bipolar disorder, and especially those with psychotic features or comorbid substance abuse, *any* acute increase in insomnia could push them into an acute manic episode or aggravate comorbid symptomatology including psychosis and impulsive suicidality. It is also possible that varenicline may have a unique proimpulsivity, prosuicidality, or deliriogenic action.

The authors, supported by Goldberg's commentary,[2] state that the use of varenicline (and varenicline with bupropion) in the bipolar group should be implemented "in this highly vulnerable patient population."[1(p771)] Goldberg states that varenicline is "a relatively simple intervention that could meaningfully help save our patients' lives."[2(p774)] They both attempt to whitewash and minimize a potentially problematic intervention.

In conclusion, while supporting the public health sentiments that all smoking cessation interventions should be strongly encouraged in this population, I would provide a major caveat that in the bipolar population, if indicated, varenicline should be commenced inpatient with monitored supervision for at least a week, so that discontinuation can be instituted immediately in a structured setting. Internists should refer these patients first to a psychiatrist as the implications and potential risks are high.

References

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Dr Chengappa and Colleagues Reply

To the Editor: First, as reported by Dr Tofler, the death of a young woman (32 years) with bipolar illness by suicide is tragic. Second, we would like to address some of the queries raised about our study[1] by Dr Tofler. Stability of the bipolar illness course for subjects participating in the study was defined by total scores of ≤8 on the Young Mania and Montgomery-Asberg Depression Rating Scales, maintenance medications for bipolar illness being used in stable doses (≥8 weeks), and no recent (≤6 months) hospitalization, emergency room visit, suicidal attempt, or aggressive or violent acts. Furthermore, clinicians were requested to refer patients whom they knew well and opined to be clinically stable in the past 6 months. Current or recent (3 months) substance or alcohol dependence was exclusionary.

As noted by Dr Tofler, certain adverse event (AE) frequencies for varenicline are higher than those reported in cessation studies done in other populations of smokers; however, the baseline for some AEs is relatively high in our study (see the Placebo AE column, Table 2).[1(p769)] Among other explanations, one is that frequency distributions of AEs can change considerably between treatments with just small numbers of subjects (in our case, N = 60) reporting an AE versus not. Moreover, the study was not statistically powered to test small to moderate effects for AEs, eg, depressed mood, as we point out in the discussion in the main paper.

As Dr Tofler underscores, this population of smokers is at high risk for potential suicidality, and only 6 of 60 bipolar

subjects (10%) in our study did not have a life-time history of suicidal ideation/behavior, consistent with studies that have assessed this illness characteristic in smokers versus nonsmokers with bipolar illness (referenced in the discussion section[1]).

We have not attempted to "whitewash and minimize a potentially problematic intervention," but in fact have recommended the opposite: being prudent and maintaining clinical vigilance for emergent psychiatric side effects (including suicidality) when initiating and continuing varenicline for smoking cessation (abstract and discussion sections[1]). All bipolar patients in our study were outpatients, and the recommendation by Dr Tofler that if varenicline were indicated for smoking cessation, it should be commenced in an inpatient setting (for at least a week) seems rather extreme, and in our opinion, cannot guarantee that this will prevent suicidality in bipolar patients.

Reference

1. Chengappa KNR, Perkins KA, Brar JS, et al. Varenicline for smoking cessation in bipolar disorder: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2014;75(7):765–772.

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