

## Efficacy of Varenicline for Smoking Cessation in Bipolar Disorder

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**R**isk of early death in people with bipolar disorder has long been recognized, but systematic studies documenting its occurrence not just from suicide or accidents but also from medical comorbidities have only recently begun to appear in the literature. Observational studies<sup>1,2</sup> identify at least a 2-fold increased risk of death from natural causes in people with bipolar disorder, most often relating to cardiovascular, cerebrovascular, respiratory, or endocrine diseases. This doubling in risk of premature death—about the same risk as that caused by smoking itself<sup>1</sup>—reduces life expectancy among people with bipolar disorder by about 10 years as compared to the general population.<sup>2</sup> But, despite widespread awareness among mental health professionals about links between bipolar disorder and increased mortality, nearly all patient intervention research to date has mainly targeted the treatment of psychiatric symptoms rather than the common medical comorbidities that contribute to overall lethality. Indeed, effective treatment of mood symptoms in bipolar disorder—even with some metabolically risky atypical antipsychotics—has been shown to lower overall mortality risk by 60%.<sup>3</sup> Among modifiable contributors to premature death in people with bipolar disorder, cigarette smoking is likely the most obvious and prevalent.

In this issue of *The Journal*, the randomized study of varenicline by Chengappa and colleagues<sup>4</sup> comes auspiciously at a time of renewed national interest in smoking cessation, particularly in people with chronic and severe forms of mental illness, who collectively still remain overrepresented among adult tobacco smokers. A recent report<sup>5</sup> analyzing national trends in smoking cessation found that, while Americans overall today smoke significantly less than in previous years, reduction has been evident only among adults without mental illnesses; reductions in smoking behavior have been only slight among people with serious mental illnesses.

From a public health standpoint, the findings by Chengappa and colleagues<sup>4</sup> are compelling: varenicline is 8 times more likely than placebo to help bipolar patients stop smoking at 3 months, and 3 times more likely to sustain those benefits after 6 months. Of particular importance, varenicline showed no increased risk over placebo for causing a significant worsening of mood symptoms or the development of suicidal features. These efficacy findings compare favorably with another recent large randomized trial<sup>6</sup> of varenicline for smoking cessation in bipolar disorder or schizophrenia patients, which found a 6-fold advantage for smoking cessation with varenicline over placebo at 52 weeks—although in the latter study, bipolar disorder subjects comprised less than 10% of the study group.

Other known treatment options for smoking cessation either have been studied only preliminarily in small groups of bipolar patients (such as bupropion<sup>7</sup>), and can pose psychiatric safety limitations (eg, bupropion would be contraindicated during manic or mixed episodes), or have not been systematically studied to establish their safety and efficacy in bipolar disorder patients (eg, nicotine replacement therapy). The present study by Chengappa et al<sup>4</sup> represents the largest controlled trial dataset documenting both the safety and efficacy of any intervention for smoking cessation in this clinical population.

This line of research should prompt 2 central issues for practicing psychiatrists:

First, how often and how systematically do we screen and counsel our own patients about smoking cessation? Do psychiatrists even recognize counseling about smoking cessation (alongside other lifestyle factors that jeopardize physical health and longevity) as falling within their purview and scope of practice? An extensive review<sup>8</sup> of cigarette smoking and bipolar disorder observed that, while most surveyed psychiatrists were aware of smoking status among their patients, counseling or intervention was provided during no more than 12% of visits. This marked disparity is especially troubling given the relevance of smoking to mental health management, including known links between smoking and depression, smoking and other substance misuse, the need to gauge metabolic risk factors when prescribing medications that can adversely affect weight or glycemic and lipid levels, and, not least of all, anticipating pharmacokinetic interactions between tobacco smoke and certain antipsychotics or serotonin reuptake inhibitors.<sup>8</sup>

Second, psychiatrists must feel knowledgeably equipped to guide their patients as well as other physicians and health care providers about the psychiatric safety of varenicline as a treatment option for smokers with psychiatric illnesses. How do we place into proper context the handful of case reports linking varenicline with iatrogenic psychosis or adverse mood effects alongside the US Food and Drug Administration's 2009 black box warning of an 8-fold increased risk for suicidal or self-injurious behavior? And to what extent have psychiatrists and other physicians curtailed prescribing varenicline in recent years because of such safety concerns? Gibbons and Mann<sup>9</sup> used propensity score matching to reanalyze psychiatric adverse events in the existing industry-controlled trial database, as well as in a much larger randomized Department of Defense database, and found no evidence of an increased risk for suicidal behaviors, depression, or aggression/agitation. Does this make concerns about reported psychiatric adverse effects a nonissue?

One might consider the possibility that *if* varenicline carries any genuine increased risk for adverse psychiatric reactions among vulnerable subgroups, perhaps the hazard depends on whether such susceptible individuals are effectively treated

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psychiatrically before exposure to varenicline. That would be a take-away message suggested by another recent multisite randomized comparison of varenicline or placebo in over 500 remitted major depression patients whose mood disorder had been stabilized before starting varenicline.<sup>10</sup> Wise management may thus point to a sequence of clinical events: identify and treat mood disorders in known or at-risk patients, and then consider varenicline as a safe and effective adjunctive treatment option for patients who smoke.

Two-thirds or more of adults with bipolar disorder are smokers,<sup>8</sup> many of whom neglect physical health concerns and may seldom see a primary care doctor<sup>11</sup>—and, when they do, the presence of bipolar disorder often may be overlooked or misidentified.<sup>12</sup> For these reasons, psychiatrists are perhaps ideally poised to recognize and address smoking cessation as part of comprehensive mental health treatment. Amid calls for psychiatrists to play an increasingly active role in monitoring and managing the overall physical health of our patients,<sup>13</sup> it is hard to ignore data showing a relatively simple intervention that could meaningfully help save our patients' lives.

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