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Missed opportunities to test the neuropsychiatric safety--and efficacy--of varenicline among smokers with substance use disorders

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1. Introduction

Tobacco control gains have not been universally shared. Though tobacco use prevalence in the U.S. is declining overall, 15% of U.S. adults (36 million people) continue to smoke (Jamal et al., 2016). The burden of tobacco use is disproportionately concentrated in select populations, including persons with substance use disorder (SUD). Over 75% of individuals in treatment for SUD smoke cigarettes (Guydish et al., 2011) and smokers with SUD face a disproportionate burden of tobacco-related disease and death (Aldridge et al., 2017; Apollonio, 2016; Hurt et al., 1996). Additionally, smokers with SUD who are in recovery have an increased risk of relapse, compared to non-smokers (Weinberger et al., 2017). Without identification and implementation of efficacious tobacco treatment interventions, smokers with SUD may enter treatment, achieve recovery, and remain at risk for relapse or death from tobacco-related causes.

Despite this marked burden of tobacco use, there is a limited evidence base to guide smoking cessation treatment among persons with SUD. Though, among smokers without SUD, varenicline is more efficacious for smoking cessation than bupropion, nicotine replacement monotherapy, or placebo, early varenicline trials excluded smokers with SUD. Case reports and the FDA boxed warning of neuropsychiatric risk potential of varenicline added additional questions about varenicline safety among persons with SUD.

2. The EAGLES trial: contributions

The Evaluating Adverse Events in a Global Smoking Cessation Study (EAGLES) trial was a large, multi-site, randomized, placebo controlled, double-blind, triple dummy trial of 12 weeks of varenicline, bupropion, and nicotine patch (Anthenelli et al., 2016). Participants

were smokers, motivated to quit, with (n=4116) and without (n=4028) current or past psychiatric disorders. There was no difference in the incidence of moderate or severe neuropsychiatric adverse events among the four treatment groups: varenicline 4%, bupropion 4.5%, nicotine patch 3.9% and placebo 3.7%. The definitive findings from the EAGLES trial, in combination with results from other trials among persons with mental health and SUD, paved the way for the FDA removal of the boxed warning in December 2016.

3. The EAGLES trial: missed opportunities

The most salient limitation of the EAGLES trial was the exclusion of smokers with substance use disorders. Subjects had to have been in sustained full remission for the last 12 months; even those in sustained remission who were receiving medication assisted treatment with opioid agonists or partial agonists (i.e., methadone, buprenorphine) were excluded. With common exclusion criteria, clinical trials yield results that generalize to only approximately half of the daily smoking population (Motschman et al., 2016), leaving gaps in the evidence base for tobacco treatment among people disproportionately impacted by tobacco use. This missed opportunity is of particular concern given the escalating prevalence of opioid use disorder in the U.S. With over 2 million persons in the U.S. with opioid use disorder (Center for Behavioral Health Statistics and Quality, 2015), over three-quarters of whom smoke cigarettes (Guydish et al., 2011), there is a time-sensitive need to reduce tobacco-related disease in this group.

4. Do we need trials to evaluate the neuropsychiatric risk potential of varenicline among smokers with SUD?

Given the EAGLES trial results, what are the questions that remain about neuropsychiatric outcomes with varenicline among smokers with SUD? First, it is important to differentiate the specific outcomes of potential clinical concern. Are smokers with SUD treated with varenicline at risk for neuropsychiatric adverse events, such as changes in behavior, depressed mood, or suicidal ideation? Or, alternately, is the risk of relapse to SUD of concern?

4.1. Varenicline does not increase neuropsychiatric adverse events among smokers with SUD

Neuropsychiatric adverse events associated with varenicline have been quantified in multiple randomized trials among smokers with alcohol- (Litten et al., 2013; McKee et al., 2009; Meszaros et al., 2013), opioid- (Nahvi et al., 2014a; Stein et al., 2013), cocaine- (Plebani, 2012; Poling et al., 2010) and mixed substance use disorders (Rohsenow et al., 2017). The results of these trials are consistent: there is no difference between varenicline and nicotine replacement therapy or placebo control conditions with respect to rates of depressive symptoms (Litten et al., 2013; McKee et al., 2009; Plebani, 2012; Poling et al., 2010; Rohsenow et al., 2017), incident major depressive disorders (Nahvi et al., 2014a) or suicidal ideation (Meszaros et al., 2013; Mitchell et al., 2012; Nahvi et al., 2014a; Stein et al., 2013).

The EAGLES trial reinforced these findings: a subset of patients receiving smoking cessation medications experience neuropsychiatric adverse events; more events are reported among those with psychiatric illness than those without; and these events occur irrespective of the treatment method used. In the EAGLES trial, those participants with current or past psychiatric disorders reported more moderate and severe neuropsychiatric events than those in the non-psychiatric cohort: 238/4074 vs 84/3984. These adverse events occurred irrespective of treatment method, in the psychiatric cohort, the non-psychiatric cohort, and overall. Taken together, these results suggest that it may not be the varenicline, or other smoking cessation medications, but the process of smoking cessation itself that enhances risk of neuropsychiatric events.

Varenicline may in fact mitigate the negative affect and depressive symptoms experienced by smokers trying to quit. Varenicline-treated patients in the EAGLES trial, both with and without psychiatric illness, experienced decreases in Hospital Anxiety and Depression Scale scores over time (Anthenelli et al., 2016). In clinical trials of varenicline among smokers with and without SUD, varenicline has been associated with suppression of depression (Cinciripini et al., 2013; Foulds et al., 2013; Plebani et al., 2013; Stein et al., 2013), reduced smoking reward (Cinciripini et al., 2013), and decreased negative affect (Cinciripini et al., 2013; Patterson et al., 2009). In one trial of smokers with opioid use disorder, compared to those receiving nicotine replacement therapy, significantly fewer varenicline-treated subjects reported depressed mood (Stein et al., 2013). Similarly, in a trial of persons with alcohol dependence, compared to placebo, varenicline treated subjects had greater improvements in mood (Plebani et al., 2013).

4.2. Smoking cessation treatment does not increase risk of relapse to SUD

Despite historical concerns, data from clinical trials and meta-analyses consistently show that treating tobacco use among persons in treatment for SUD, or in recovery, does not adversely impact SUD treatment outcomes (Apollonio, 2016; Prochaska et al., 2004; Thurgood et al., 2016). Though the majority of these trials predate the use of varenicline and evaluated interventions including behavioral treatments, nicotine replacement therapy or bupropion, their results consistently demonstrate no association between tobacco cessation interventions and relapse to alcohol or other drugs. In one trial of varenicline among persons in outpatient SUD treatment, there was no association between varenicline treatment and heavy drinking or drug use (Rohsenow et al., 2017).

It is likely that *tobacco use* rather than tobacco cessation interventions, increases risk of relapse to alcohol or other SUD. Two tobacco cessation intervention trials show an association between periods of tobacco abstinence and abstinence from alcohol (Cooney et al., 2015) or opioids and cocaine (Shoptaw et al., 2002). These findings are also seen in epidemiologic data: compared to non-smokers, smokers with SUD who are in recovery have an increased risk of relapse (Weinberger et al., 2017).

5. What gaps remain in treatment of tobacco use among smokers with SUD?

There are many remaining research questions with regard to varenicline use among smokers with SUD. Though it is disappointing that this group was excluded from participation in the EAGLES trial, results of clinical trials among smokers with psychiatric illness and SUD have been reassuring and consistent. As a result, our research questions no longer hinge on the neuropsychiatric safety of varenicline. This eliminates prior barriers to varenicline use, and opens important new research opportunities.

First, how can we enhance implementation of evidence-based smoking cessation treatment in SUD treatment programs? Only 18–38% of SUD treatment programs offer smoking cessation counseling (Friedmann et al., 2008; Richter et al., 2004), and 30% offer smoking cessation medication (Eby et al., 2015; Knudsen and Roman, 2015; Knudsen and Studts, 2011; Muilenburg et al., 2014; Rothrauff and Eby, 2011). Policy-based approaches may help—for example, in 2008, the NY Office of Alcoholism and Substance Abuse Services mandated that all substance use disorder treatment programs be tobacco-free and offer tobacco cessation treatment. Compared to substance use disorder counselors outside of NY, one year after the regulations, NY-based counselors reported greater provision of guideline-recommended cessation counseling, and greater availability of pharmacotherapy (Eby and Laschober, 2013). Unfortunately, five years after regulations, tobacco prevalence rates among patients were unchanged (Pagano et al., 2016), highlighting the dual challenges of providing evidence-based care and ensuring that the evidence base is appropriate to the population served.

Next, we must enhance the efficacy of standard cessation interventions. Varenicline treatment among smokers with SUD has resulted in substantially lower quit rates than in smokers without SUD (Nahvi et al., Nov 2015; Nahvi et al., 2014a; Rohsenow et al., 2017; Stein et al., 2013). Are strategies that optimize pharmacotherapy efficacy among smokers without SUD, such as pre-cessation pharmacotherapy prior to target quit date (Hajek et al., 2011), or extended medication treatment (Evins et al., 2014; Hall et al., 2017; Schlam et al., 2016; Schnoll et al., 2015; Schnoll et al., 2010; Tonstad et al., 2006), applicable to smokers with SUD? Can strategies that address key barriers to cessation among smokers with SUD, such as poor medication adherence (Nahvi et al., 2014b), or nicotine-opioid interactions (Richter et al., 2007; Winhusen et al., 2016), boost cessation rates? Can the addition of varenicline enhance the efficacy of contingency management approaches (Shoptaw et al., 2002; Sigmon et al., 2016)?

Standard cessation interventions have largely failed to reach smokers with SUD, and their effects have been modest. To improve cessation intervention outcomes and reduce the burden of tobacco-related disease, novel approaches are needed. The large body of literature describing the safety of varenicline, among persons with and without SUD, presents an important opportunity to optimize both its efficacy and delivery among smokers with SUD.

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