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Low incidence of adverse events following varenicline initiation among opioid dependent smokers with comorbid psychiatric illness

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ABSTRACT

Background: Most drug treatment patients smoke cigarettes, yet few data exist on the prevalence and outcomes of varenicline treatment among smokers with comorbid substance use and psychiatric disorders.
Methods: We reviewed all patient charts of opioid-dependent smokers prescribed varenicline between May 2006 and December 2009 in two urban methadone clinics that also provide on-site medical and psychiatric care. We assessed prevalence, adverse events, and effectiveness of varenicline treatment in this cohort.
Results: We identified 575 smokers among 690 patients (83.3%), and assessed 82 courses of varenicline treatment prescribed to 70 smokers. Both cardiovascular risk factors and psychiatric illness were highly prevalent among those prescribed varenicline: hypertension, 51%; hyperlipidemia, 23%; diabetes, 20%; depression, 53%; anxiety, 30%; psychotic disorders, 10%; bipolar disorder, 8.6%. Of 82 varenicline courses, nine (11%) were discontinued due to adverse events and two due to depressive symptoms. One patient initiated new psychiatric medications within six months of initiating varenicline, but did not discontinue varenicline. There were no reports of suicidal ideation, agitation prompting clinical intervention, or psychiatric hospitalization. There were no incident cardiac or vascular events within six months of varenicline prescription. Some (8.6%) varenicline-treated smokers quit smoking, and cessation was significantly associated with varenicline treatment duration.
Conclusions: Despite substantial comorbidity, opioid-dependent smokers receiving integrated substance abuse, medical and psychiatric care had few documented adverse events with varenicline treatment. Methadone patients will likely experience little harm and a great deal of benefit from treatment with varenicline for smoking cessation.

1. Introduction

Both tobacco use and tobacco-related disease among persons with alcohol or drug use disorders are highly prevalent (Hser et al., 1994; Hurt et al., 1996; Lasser et al., 2000; Richter and Arnsten, 2006), but multiple studies have shown limited smoking cessation treatment provision in substance abuse treatment programs (Friedmann et al., 2008; Fuller et al., 2007; Hunt et al., 2012; Richter et al., 2004). In particular, smoking cessation pharmacotherapy is underutilized in these settings, partly because the safety of varenicline in patients with comorbid psychiatric illness has been questioned.

The psychiatric risks of varenicline are not well characterized. Reports of behavior change, agitation, depression, suicidal ideation and suicide among patients taking varenicline led to an FDA warning in February 2008. A subsequent "boxed warning" in July 2009 advised providers to monitor patients taking varenicline for the development of psychiatric symptoms, including agitation, depression, and suicidal ideation (U.S. Food and Drug Administration). While phase III trials of varenicline had stringent eligibility criteria that excluded persons with medical and psychiatric comorbidity, including substance users (Gonzales et al., 2006; Jorenby et al., 2006), the results of post-marketing surveillance demonstrating adverse psychiatric events highlight the need to evaluate varenicline safety in patients with psychiatric comorbidity and substance abuse disorders.

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Varenicline may also be associated with a small increase in risk of cardiovascular events (Rigotti et al., 2010; Singh et al., 2011). In one randomized clinical trial among patients with cardiovascular disease, there were slightly higher rates of nonfatal myocardial infarction, need for coronary revascularization, and peripheral vascular disease among varenicline-treated compared to placebo participants, though these differences were not statistically significant (Rigotti et al., 2010). In addition, a meta-analysis of selected varenicline clinical trials critiqued for trial selection and statistical methods that could bias toward false-positive findings (Prochaska and Hilton, 2012; Squire, 2011; Takagi and Umemoto, 2011) described a small absolute increase in the risk of serious adverse cardiovascular events among varenicline arm participants (Singh et al., 2011). By contrast, a subsequent meta-analysis, including all published randomized trials of varenicline, and focused on the period of varenicline exposure, found no significant increase in serious cardiovascular events associated with varenicline (Prochaska and Hilton, 2012).

Because varenicline is more efficacious than bupropion (Gonzales et al., 2006; Jorenby et al., 2006) or nicotine replacement therapy in the general population (Stapleton et al., 2008), it is particularly important to determine its risk profile among substance abuse treatment patients. Cessation approaches evaluated to date among opioid-dependent smokers have included bupropion or nicotine replacement therapy in combination with behavioral therapy, but these treatments have not been effective over control conditions (Mooney et al., 2008; Reid et al., 2008; Shoptaw et al., 2002; Stein et al., 2006b). Trials are currently underway to assess varenicline's efficacy in this population, but concerns remain regarding adverse events.

Our objective was to assess prevalence, adverse events, and effectiveness of varenicline treatment among opioid-dependent smokers receiving substance abuse treatment. Our setting is uniquely suited for this study as we provide comprehensive, longitudinal primary care in combination with methadone treatment to patients with opioid dependence.

2. Methods

2.1. Study setting and participants

We reviewed paper medical charts of all patients receiving methadone maintenance treatment at two of the clinics in the Einstein Division of Substance Abuse (DoSA). DoSA offers treatment through a network of 11 closely linked clinics in the Bronx, NY. The two clinics were selected because of the high volume of patients receiving on-site primary medical care. All DoSA patients are opioid-dependent and >80% smoke cigarettes (Nahvi et al., 2006). Each DoSA clinic offers integrated on site general and HIV-related medical, gynecologic, and mental health services, co-located with substance abuse treatment. Patients receive methadone from nurses up to six times weekly, meet with counselors at least monthly for structured psychosocial assessment, and meet with medical providers for annual physical exams and mandatory visits following hospitalization, incarceration or other clinic absence. Psychosocial and clinical concerns, including changes in behavior, are discussed in weekly interdisciplinary meetings including clinic leadership, counselors, nurses, physician assistants and physicians. Subjects for this analysis included cigarette smokers prescribed varenicline for smoking cessation by DoSA providers at any point during a 3.5-year period from May 2006 through December 2009. Patients reporting varenicline prescription from outside providers were excluded from analysis because exact dates of treatment initiation and duration were unavailable.

2.2. Design, procedures, and measures

2.2.1. Data collection. A physician and trained research assistants used structured data collection forms to conduct medical record reviews. Among all patients, we extracted data regarding demographic characteristics, smoking status, and prescribed smoking cessation treatment. Ninety-four percent of charts from the two clinics were available for review. Among patients prescribed varenicline, we extracted data regarding medical and psychiatric comorbidity, concomitant substance use, methadone dose, and adverse events and tobacco use following varenicline prescription. Charts were re-reviewed to resolve discrepancies or correct omissions as necessary; 25 (36%) charts were reviewed at least twice. The research protocol was approved by the Einstein Committee on Clinical Investigations.

2.2.2. Smoking status and smoking cessation treatment. Smoking status is recorded by medical providers during annual physical exams on a standard form used in all DoSA clinics. Only one reviewed chart was missing this information. Biochemical assessment of tobacco use is not standard practice in DoSA.

Medical provider notes and patient medication lists were reviewed to determine whether nicotine replacement therapy, bupropion, or varenicline were prescribed. If varenicline was prescribed, the maximum treatment duration was estimated based on the following three categories: (1) single four-week course without refills, (2) four-week course and two refills (twelve-week course), or (3) four-week course without documentation of whether or not refills were prescribed (four weeks or more). Prescriptions were filled at commercial pharmacies of patients' choosing; pharmacy records were unavailable for verification of prescription filling.

2.2.3. Comorbidity. Self-reported and/or clinically verified medical and psychiatric diagnoses are recorded by DoSA medical providers during history and physical exam visits conducted annually with all patients. Medical providers' notes were reviewed to ascertain whether patients were receiving psychiatric treatment, and, if so, whether it was on- or off-site.

2.2.4. Substance use and methadone dose. Unannounced urine toxicology tests are routinely performed in all DoSA clinics. Urine testing is conducted using the Enzyme Multiplied Immunoassay Technique (EMIT) at a commercial laboratory, and evaluates for presence of opiates, cocaine, or benzodiazepines. We extracted data regarding: (1) number of toxicology tests performed and (2) number of tests positive for cocaine, opiates, or benzodiazepines, in the six months prior to and the six months following each varenicline prescription. Methadone dose at the time of varenicline prescription was also recorded.

2.2.5. Adverse events following varenicline prescription. We reviewed medical and psychiatric providers' notes and patient medication lists to assess adverse events: (1) in the six months following each varenicline treatment course and (2) beyond the six months following each varenicline course, but specifically attributed to varenicline. We collected data on all potential adverse events that have been reported by ≥5% of participants receiving varenicline in published research, including: nausea, vomiting, headache, irritability, fatigue, insomnia, difficulty concentrating, and changes in dreams. We also collected data on neuropsychiatric events outlined in the 2008 and 2009 FDA warnings regarding varenicline. To characterize neuropsychiatric events, we assessed: (1) whether varenicline was discontinued due to specific side effects; (2) whether new antidepressant, antipsychotic, anxiolytic or mood-stabilizing medications were prescribed; (3) whether new psychiatric treatment was initiated; (4) occurrence of suicidal ideation, documented on standard annual physical exam forms used throughout DoSA or medical or psychiatric progress notes; (5) incident agitation or aggression, documented in ad hoc meetings with patients and administrative, counseling, and medical staff to address disruptive behavior, or in mandatory medical visits following incarceration; (6) medical or psychiatric hospitalizations, documented in mandatory medical visits to resume methadone dosing following clinical absence or hospitalization; and (7) mortality. A physician re-reviewed charts of all patients with documented neuropsychiatric symptoms to ascertain patients' baseline clinical status, psychotropic medication history, and whether patients or providers attributed symptoms to varenicline treatment.

Following the FDA drug safety communication in June 2011 warning of potential cardiovascular risks with varenicline use, charts were re-reviewed to ascertain whether patients experienced incident cardiovascular events. These included: myocardial infarction, cardiac arrhythmia, peripheral vascular disease, cerebral vascular disease, or cardiac or vascular procedures in the six months following varenicline prescription. Cardiovascular events are documented in annual physical exams, medical progress notes, or mandatory medical visits following hospitalization. Nearly all (98.5%) charts were available for re-review.

2.2.6. Tobacco use following varenicline prescription. We ascertained self-reported tobacco use status following varenicline prescription from annual physical exam forms and provider notes. Since smokers are advised to quit one week after starting varenicline, duration of abstinence was estimated from one week after the date of varenicline prescription to the date at which tobacco abstinence was last documented in the medical record. This estimation may overestimate duration (if onset of abstinence lagged more than one week following varenicline initiation) or underestimate duration (if relapse occurred later than last date of recorded abstinence). If the chart had no documented assessment of smoking status following varenicline ($n = 4$), smoking was assumed.

2.3. Analysis

Analyses were performed using STATA (StataCorp, College Station, TX). Descriptive data include patient characteristics (described by means and standard deviations, medians and interquartile ranges, or percentages) and the proportion of patients experiencing each outcome. Associations between patient characteristics and smoking cessation were tested using *t*-tests, Wilcoxon rank sum tests, Chi-square tests, or Fisher's exact tests, as appropriate. In a subgroup of 53 patients for whom complete varenicline treatment course information was available, we