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The association between self-reported varenicline adherence and varenicline blood levels in a sample of cancer patients receiving treatment for tobacco dependence

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ABSTRACT

Introduction: The degree to which smokers quit successfully with varenicline is strongly associated with their adherence to the medication regimen. Thus, measuring varenicline adherence to identify smokers needing additional intervention is a priority. Few studies, however, have examined the validity of self-reported varenicline adherence, using a biological assessment of adherence as a reference. No study has examined this issue among cancer patients trying to quit smoking, who may show unique patterns of adherence given their medical comorbidity.

Methods: This study used data from 76 cancer patients who received varenicline and provided self-reported varenicline adherence data (pill count) and a blood sample to determine varenicline metabolites 4 weeks after initiating varenicline.

Results: Receiver operating characteristic (ROC) curve analyses of plasma varenicline levels showed that 4 ng/ml was the optimal cut-point for differentiating adherence with significant (p's < 0.04) area under the curve values, ranging from 0.73–0.80 for 3-day, 7-day, and 4-week self-reported pill count; specificity values ranged from 0.63–0.78 and sensitivity values ranged from 0.82–0.94. Using this cut-point, adherence was high (88%). However, plasma varenicline levels were weakly correlated with 3-day and 4-week pill count and total pill count (12 weeks) was not correlated with plasma varenicline levels. Patients with head and neck cancer, gastrointestinal cancer, and more advanced disease showed lower varenicline adherence and lower plasma varenicline.

Conclusions: Using the 4 ng/ml cut-point, this study suggests validity of short-term self-reported varenicline adherence among cancer patients undergoing tobacco dependence treatment in contrast to studies in the general population, which supported 12-week pill count.

1. Introduction

Varenicline is one of the most effective medications for tobacco dependence (Cahill, Stevens, Perera, & Lancaster, 2013) even among smokers with psychiatric (Anthenelli et al., 2016) and medical (Price et al., 2017) comorbidities. However, in general population clinical trials, adherence to varenicline rarely exceeds 60% (e.g., Peng et al., 2017), with little known about adherence rates in populations with comorbidities (Pacek, McClernon, & Bosworth, 2017). Across numerous studies, suboptimal adherence significantly reduces the likelihood of successful quitting (Pacek et al., 2017; Peng et al., 2018). Consequently, there is growing recognition for the need to develop interventions to

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increase varenicline adherence. To do so, however, requires valid methods for assessing varenicline adherence.

Despite numerous clinical studies of varenicline, the literature has relied upon self-reported pill count data to determine varenicline adherence with only two exceptions (Buchanan et al., 2012; Peng et al., 2017). Unfortunately, self-reported pill count data are susceptible to response bias and misreporting, which can overestimate adherence (Dunbar-Jacob & Rohay, 2016). While the two studies that have used a biological assay to measure varenicline adherence provide important information about the validity of self-reported varenicline adherence, extension of these results to include important clinical populations, like cancer patients, is needed.

Upwards of 50% of cancer patients who were smokers prior to their diagnosis continue to smoke after diagnosis (Land et al., 2016) and the US Surgeon General concluded that continued smoking by cancer patients is causally associated with a worse cancer prognosis (U.S. Department of Health and Human Services, 2014). Further, relative to the general population of smokers, cancer patients using varenicline may face greater challenges with adherence because of additional medications and treatments for their cancer that already challenge compliance (Kavookjian & Wittayanukorn, 2015; Sawesi, Carpenter, & Jones, 2014). Varenicline's primary side effects, such as nausea, may exacerbate side effects that cancer patients experience, which reduce medication compliance (Roeland, Aapro, & Schwartzberg, 2015). Moreover, given the stigma associated with smoking after a cancer diagnosis (Riley, Ulrich, Hamann, & Ostroff, 2017), patients may be more likely to overstate their level of adherence to medication. Alternatively, to the extent that cancer patients are more motivated to quit smoking, they may be more adherent to medication.

This study compared self-reported pill count measures of varenicline adherence to plasma varenicline levels in cancer patients undergoing tobacco cessation treatment. Participant characteristics related to varenicline adherence were also assessed. Through assessing the validity of self-report measures of varenicline adherence in this important clinical population, we might be able to identify patients who need medication adherence support.

2. Methods

2.1. Participants

Participants were enrolled in a National Cancer Institute-funded randomized clinical trial comparing 12 weeks of varenicline + 12 weeks of placebo to 24 weeks of varenicline (NCT01756885). Only data from the 12-week open-label treatment phase were used for this study. To be eligible for the trial, participants were required to be > age 18 and to have: received a cancer diagnosis or cancer treatment within the past 5 years, reported daily smoking, and reported an interest in quitting smoking. Additional eligibility criteria and exclusion criteria are described elsewhere (Miele et al., 2018; Price et al., 2017). For this study, data from 76 participants who provided blood for varenicline testing were used (only participants from the University of Pennsylvania site were asked to provide samples due to budget constraints). Of the sample characteristics (Table 1), participants who provided a sample had a higher disease stage and carbon monoxide (CO) at study entry (p's < 0.05), vs. participants who did not provide a sample.

2.2. Procedures

The IRBs at the University of Pennsylvania, Northwestern University, and the University of Toronto (which analyzed the blood samples for varenicline levels) approved this study and informed consent was obtained. Following telephone and in-person screening, eligible participants were randomized to 12 vs. 24-weeks of varenicline. Varenicline was provided as per FDA guidelines and all participants received 5 behavioral smoking cessation counseling sessions. Assessments were conducted in-person at Weeks 0 (initiation of medication), 4, and 12. A blood sample (10 ml) was collected at Week 4 from 76 Penn participants who attended the visit; 38 participants either refused the blood draw or did not complete the session in person. Blood was drawn into a tube containing ethylenediaminetetraacetic acid, immediately iced, centrifuged at 4 °C to separate the plasma, and were analyzed in Dr. Tyndale's laboratory following established methods (Peng et al., 2017).

2.3. Measures

2.3.1. Covariates

Demographic, cancer-related (e.g., tumor site/stage), and smoking data were gathered during screening. CO was collected and tobacco dependence was assessed using the Fagerström Test for Cigarette Dependence (FTCD; Heatherton, Kozlowski, Frecker, & Fagerström, 1991).

2.3.2. Pill count measures

Self-reported varenicline adherence was assessed using timeline follow-back (TLFB; Brown, Burgess, Sales, Evans, & Miller, 1998), with participants reporting the number of pills taken each day since the previous visit and returning medication blister packs. Pill count adherence measures were created by dividing the reported number of pills taken by the total number of prescribed pills for each time period (3-day, 7-day, 4-week, 12-week). The 3-day, 7-day, and 4-week pill counts refer to the number of prescribed pills taken during the respective timeframes prior to plasma sample acquisition (Week 4); 12-week pill count is the total number of pills prescribed. Consistent with FDA guidelines for 12 weeks of varenicline treatment, a total of 165 pills were prescribed; for 3-day, 7-day, and 4-week adherence, the prescribed number of pills were 6, 14, and 53 pills, respectively.

2.3.3. Plasma varenicline levels

Plasma samples were collected 4 weeks after initiating treatment (Week 4). Varenicline levels were determined using liquid chromatography-tandem mass spectrometry (Peng et al., 2017). Samples were collected at this time point because it was the first in-person visit when therapeutic levels of varenicline would be reached.

2.4. Data analysis

We followed procedures used in Buchanan et al. (2012) to determine a cut-point for plasma varenicline that differentiated adherent vs. non-adherent participants for the four pill count measures using Receiver Operating Characteristic (ROC) curve analyses. While Buchanan et al. (2012) used 2.0 ng/ml as the cut-point (and Peng et al., 2017 used 4.7 ng/ml, adjusted for saliva vs. plasma), we used the same exploratory approach as Buchanan et al. (2012) to determine a cut-point in this sample given use of a clinical population which may differ in important ways from the general population of smokers studied in Buchanan et al. (2012) and Peng et al. (2017). Using ROC analyses, we examined 2.0, 4.0, 6.0, and 8.0 ng/ml as potential cut-points for adherence using plasma varenicline. Using this approach, we determined how cut-points for plasma varenicline differentiate adherence, which is captured by area under the curve (AUC) values. When the AUC value equals 1.0, the cut-point offers perfect differentiation, but AUC values of > 0.70 are acceptable; AUC values are evaluated using probability testing and 95% confidence intervals.

Next, with a cut-point determined by AUC values, positive and negative predictive value estimates were calculated (with 95% confidence intervals) to assess the accuracy of pill count data vs. plasma varenicline, and we described the sensitivity and specificity of each self-report measure. We used Pearson correlation to assess the relationship between self-reported pill count measures of varenicline adherence and