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Measures and predictors of varenicline adherence in the treatment of nicotine dependence

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HIGHLIGHTS

- This study compared a biological measure of adherence to a self-report measure.
- Association between drug levels and pill counts was very poor.
- Association between drug levels and pill counts varied little across sub-groups.
- Compared to varenicline levels, pill counts substantially overestimate adherence.
- Use of pill counts in smoking cessation may not be a useful measure of adherence.

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ABSTRACT

Introduction: While adherence to medication in smoking cessation clinical trials is strongly associated with clinical outcome, very few studies have evaluated the validity of pill count as a measure of adherence relative to a biological assay, and evaluated a broad range of correlates of adherence.

Methods: In a smoking cessation clinical trial of varenicline, we compared pill counts collected over 4 different time periods to varenicline salivary levels taken after 2 weeks of treatment, as well as evaluated predictors of adherence to varenicline.

Results: Using a binary measure of adherence based on salivary varenicline levels, adherence was higher among older, white, and more educated participants. Relative to 3, 7, and 14-day pill count, 12-week pill count was the only significant measure able to discriminate adherence as defined by salivary varenicline levels (assessed by area under the receiver operating characteristic curve; AUC = 0.59, $p = 0.004$). Seventy-two percent of participants who indicated adherence on 12-week pill count were classified as adherent based on varenicline saliva levels (sensitivity = 0.80; specificity = 0.40). There was modest variability in the relationship between 12-week pill count and varenicline levels across race and rate of nicotine metabolism. Lastly, General Estimating Equation models demonstrated that longitudinal changes in withdrawal, craving, negative and positive affect, and side effect count and severity were not related to adherence based on salivary varenicline levels.

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Conclusions: These results indicate that 12-week pill count was the best, albeit a relatively weak, measure of varenicline adherence; additional factors associated with treatment adherence need to be identified.

1. Introduction

Cigarette smoking remains the largest preventable cause of morbidity and mortality in the United States (Vital signs: current cigarette smoking among adults aged > / = 18 years–United States, 2005–2010, 2011). Despite substantial reductions in the national rate of adult smoking since the release of the 1964 Surgeon General's report, the current smoking prevalence rate has remained at around 15.1% over the last decade and the need to improve smoking cessation treatments is a public health priority (Jamal et al., 2016). Of the currently approved smoking cessation medications, varenicline is the most efficacious monotherapy (Cahill, Stevens, Perera, & Lancaster, 2013). Varenicline acts as a partial agonist at the α4β2 nAChR subtype and aids in cessation by reducing the reinforcing effects of nicotine and by ameliorating the severity of nicotine craving and withdrawal symptoms (Ebbert, Wyatt, Hays, Klee, & Hurt, 2010). An important predictor of treatment success is medication adherence, or the extent to which individuals use the prescribed amount of varenicline. Greater adherence to smoking cessation pharmacotherapy has been associated with better cessation outcomes in several studies (Killen et al., 2004; Liberman et al., 2013; Schmitz, Stotts, Mooney, Delaune, & Moeller, 2007; Shiffman, 2007; Swan, Javitz, Jack, Curry, & McAfee, 2004). Yet, few studies have examined biological measures of adherence in smoking cessation trials or assessed factors that influence adherence.

In many cases, pill count through daily diaries, or assessment of used blister packs, is widely used as a reference standard of adherence in smoking cessation trials as it is both convenient and easy to assess. In a 2015 Cochrane review summarizing interventions to increase adherence to smoking cessation medication, 5 out of 8 included studies used pill count to assess adherence while the remaining studies used self-report or electronic monitoring systems (Hollands et al., 2015). However, pill count may not be accurate in estimating adherence; it tends to overestimate medication adherence and yield an imprecise metric of the total dose taken (Farmer, 1999; Haynes, Ackloo, Sahota, McDonald, & Yao, 2008; McDonald, Garg, & Haynes, 2002; Pullar, Kumar, Tindall, & Feely, 1989). A biological measure, derived from blood, saliva, or urine concentrations of medication, is generally considered to be the most accurate measure of adherence and is commonly used in other research fields such as epilepsy (Dutta & Reed, 2006; Herkes & Eadie, 1990; Landmark, Rytter, & Johannessen, 2007; Malone, Eadie, Addison, Wright, & Dickinson, 2006; Mitchell, Scheier, & Baker, 2000; Specht, Elsner, May, Schimichowski, & Thorbecke, 2003; Vermeire, Hearnshaw, Van Royen, & Denekens, 2001; Williams et al., 2001). Given varenicline's pharmacokinetic attributes such as minimal metabolism and long half-life (approximately 24 h) (Faessel et al., 2010), assessment of varenicline is a valid method for biologically assessing varenicline adherence. However, biological measures are not routinely used as part of drug monitoring in smoking cessation trials due to challenges of collection, analysis, and cost, resulting in a lack of information regarding the use of biological measures to determine adherence. As such, remarkably few studies have examined the validity of pill count compared to a biological assay (Buchanan et al., 2012). There is a need to validate pill count measures of varenicline use against biological measures of adherence in treatment-seeking smokers, as well as in subgroups of smokers (e.g. different gender, race and rate of nicotine metabolism).

In addition, given that adherence rates are often sub-optimal (Catz et al., 2011; Shelley et al., 2015), another priority in this area is the development of interventions designed to enhance adherence. Examining longitudinal predictors of adherence to varenicline could help inform such intervention development. In the present study, we expand the investigation of correlates of adherence by examining how psychological variables (e.g., positive and negative affect), cessation-related variables (e.g., craving and withdrawal), and medication side effects may be associated with a biological measure of adherence. By designing interventions that specifically target these variables during the early stages of a quit attempt, there may be an opportunity to improve adherence to varenicline and ultimately increase smoking cessation rates.

Thus, the present study was designed to: 1) evaluate pill count measures of medication use against varenicline levels, 2) assess the relationship between pill count measures of adherence and varenicline levels across subgroups of smokers (e.g., gender, race, and rate of nicotine metabolism), and 3) examine changes over time in withdrawal, affect, craving and side effects between adherent and non-adherent participants.

2. Methods

2.1. Participants

This study is a secondary analysis of data from a placebo-controlled, randomized clinical trial that compared the efficacy of varenicline and transdermal nicotine for treating nicotine dependence among slow and fast metabolizers of nicotine (ClinicalTrials.gov Identifier: NCT01314001). A full list of the inclusion and exclusion criteria can be found in Lerman et al. (2015).

Given our interest in assessing the validity of pill count measures of adherence compared to a biological measure of varenicline use, only the 421 participants randomized to the varenicline arm of this trial were included. Further, the present analyses were restricted to 376 of the 421 participants who provided saliva samples for varenicline level testing.

2.2. Procedures

Detailed clinical trial procedures are published elsewhere (Chenoweth et al., 2014; Lerman et al., 2015; Schnoll et al., 2014). Subjects randomized to varenicline remained on medication for a total of 12 weeks at the following doses: 0.5 mg once daily for Days 1–3, 0.5 mg twice daily for Days 4–7, and 1.0 mg twice daily for Days 8–84. Assessments, described below, occurred on weeks 0, 1, 4, 8, and 12 (end of treatment, EOT).

2.3. Measures

2.3.1. Covariates

Basic demographic and smoking-related data were collected during the intake visit. To assess subjects' levels of nicotine dependence, the Fagerström Test for Nicotine Dependence was administered (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991). Blood samples for NMR assessment were evaluated using liquid chromatography-tandem mass spectrometry (LC-MS) with a limit of quantification of ≤ 1 ng/ml for both compounds (St. Helen et al., 2012).

2.3.2. Pill count adherence measures

Medication adherence was assessed using a timeline follow-back measure (Brown, Sales, Whiteley, Evans, & Miller, 1998), with participants reporting the number of pills taken each day since the previous visit. To calculate pill count adherence measures (3-day, 7-day, 14-day, and 12-week pill count), the reported number of pills taken was divided by the total number of prescribed pills for that time period. The 3-, 7-,