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Medication adherence and rate of nicotine metabolism are associated with response to treatment with varenicline among smokers with HIV

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Abstract

Introduction: PLWHA who smoke have shown lower cessation rates within placebo-controlled randomized trials of varenicline. Adherence and rate of nicotine metabolism may be associated with quit rates in such clinical trials.

Methods: This secondary analysis of a randomized placebo-controlled trial of varenicline for smoking among PLWHA (N = 179) examined the relationship between varenicline adherence (pill

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6.Contributors

Mackenzie Hosie Quinn, Anna-Marika Bauer, Su Fen Lubitz, and Alex Flitter helped conceptualize this paper, analyze the data, and draft the manuscript. Rebecca Ashare co-drafted the manuscript. Robert Gross and Frank Leone ensured participant safety, helped with participant recruitment, and edited the manuscript. Brian Hitsman edited the manuscript. Robert Schnoll served as the overall study Principal Investigator, conceptualized the present study, handled some of the analyses, and co-drafted the manuscript. All authors reviewed the manuscript for content and have approved the final version.

CRediT authorship contribution statement

Anna-Marika Bauer: Writing - original draft, Writing - review & editing. **Mackenzie Hosie Quinn:** Writing - original draft, Writing - review & editing. **Su Fen Lubitz:** Supervision, Project administration, Writing - review & editing. **Alex Flitter:** Supervision, Project administration, Writing - review & editing. **Rebecca L. Ashare:** Writing - review & editing. **Frank T. Leone:** Supervision, Writing - review & editing. **Robert Gross:** Supervision, Writing - review & editing. **Brian Hitsman:** Conceptualization, Writing - review & editing. **Robert Schnoll:** Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing, Supervision, Funding acquisition.

Conflicts of Interest

Dr. Schnoll and Dr. Hitsman receive medication and placebo free from Pfizer and has provided consultation to Pfizer. Dr. Schnoll has provided consultation to GlaxoSmithKline and CuraLeaf. Dr. Gross serves on a Data and Safety Monitoring Board for a Pfizer drug unrelated to HIV or smoking.

count, ≥80% of pills), nicotine metabolism (based on the nicotine metabolite ratio; NMR) and end-of-treatment smoking cessation (self-reported 7-day point prevalence abstinence, confirmed with carbon monoxide of ≤ 8 ppm, at the end of treatment; EOT).

Results: Combining varenicline and placebo arms, greater adherence (OR = 1.011, 95% CI:1.00–1.02, p = 0.051) and faster nicotine metabolism (OR = 3.08, 95% CI:1.01–9.37, p = 0.047) were related to higher quit rates. In separate models, adherence (OR = 1.009, 95% CI:1.004–1.01, p < 0.001) and nicotine metabolism rate (OR = 2.04, 95% CI:1.19–3.49, p = 0.009) interacted with treatment arm to effect quit rates. The quit rate for varenicline vs. placebo was higher for both non-adherent (19% vs. 5%; $\chi^2[1] = 2.80$, p = 0.09) and adherent (35% vs. 15%; $\chi^2[1] = 6.51$, p = 0.01) participants, but the difference between treatment arms was statistically significant only for adherent participants. Likewise, among slow metabolizers (NMR < 0.31), the varenicline quit rate was not significantly higher vs. placebo (14% vs. 5%; $\chi^2[1] = 1.17$, p = 0.28) but, among fast metabolizers (NMR ≥ 0.31), the quit rate for varenicline was significantly higher vs. placebo (33% vs. 14%; $\chi 2[1] = 4.43$, p = 0.04).

Conclusions: Increasing varenicline adherence and ensuring that fast nicotine metabolizers receive varenicline may increase quit rates for PLWHA.

Keywords

Adherence; Smoking cessation; Varenicline; HIV; Depression; Anxiety

1. Introduction

Survival rates among people with HIV/AIDS (PLWHA) have significantly improved with the widespread use of anti-retroviral therapies (ARTs), with the leading cause of death in this population evolving over the past decade from AIDS-related diseases (e.g., Kaposi sarcoma) to cardiovascular and lung disease (Palella et al., 1998, 2006). As such, there is a critical need to address modifiable risk factors for disease mortality among PLWHA, including tobacco use (Niaura et al., 2000; Benard et al., 2006).

In the US, studies show that 50–74% of PLWHA are regular smokers (Burkhalter et al., 2005; Crothers et al., 2005; Feldman et al., 2006; Miguez-Burbano et al., 2005; Webb et al., 2007). This rate greatly exceeds the 15% prevalence rate of smoking in the general population (Norris et al., 2018) and exceeds rates reported for other notable clinical populations, such as cancer (xxxx), cardiovascular (Rigotti et al., 2006), and depressed (Grant et al., 2004) patients. Thus, ensuring that PLWHA who smoke receive effective cessation treatment is a vital priority.

While there is limited support for the use of behavioral interventions, bupropion, or nicotine replacement therapies (NRTs) to treat tobacco use for PLWHA, varenicline has been tested with PLWHA in four studies. A study with 36 smokers found a quit rate of 42% (Cui et al., 2012). A non-randomized study found a quit rate of 26% for varenicline vs. 12% for nicotine patches (Ferketich et al., 2012). Two randomized, placebo-controlled trials found that, compared to placebo, varenicline significantly increased EOT quit rates, with cessation rates of 28–29% (Mercié et al., 2018; Anthenelli et al., 2016), compared to 12–13% for

placebo treated participants. However, the quit rates yielded by varenicline for PLWHA are considerably lower than the general population's (38%) (Pacek et al., 2018). These studies highlight the need to identify factors associated with responsiveness to varenicline that can be targeted by interventions to improve the efficacy of varenicline treatment for PLWHA.

There is a growing literature, in the general population and among PLWHA, that adherence to smoking cessation medication is a critical determinant of treatment efficacy (Niaura et al., 2012; Fagerström, 2012). In our varenicline trial with PLWHA, 58% of smokers were adherent to varenicline (Anthenelli et al., 2016), and non-adherence reduces quit rates (Niaura et al., 2012). Likewise, several studies have shown that an individual's rate of nicotine metabolism, measured by the ratio of two nicotine metabolites derived from smoking (3′hydroxycotinine [3HC]/cotinine) and referred to as the nicotine metabolite ratio (NMR), is associated with varenicline response (Brown et al., 1998). We have found that HIV + smokers are more likely to be fast nicotine metabolizers, vs. the general population (Crawford et al., 2018), and high NMR among PLWHA correlates with smoking more cigarettes per day (Hughes et al., 2003), underscoring the importance of evaluating the association between NMR and varenicline efficacy among PLWHA.

Therefore, this study used data from a previous clinical trial that tested varenicline for tobacco dependence among PLWHA to examine varenicline adherence and nicotine metabolism as factors related to varenicline response. Determining the influence of these factors on varenicline responsiveness in this community of smokers can help guide the design interventions to improve treatment response and offer new methods to reduce tobacco-related morbidity among PLWHA.

2. Methods

We used data from a completed clinical trial (NCT01710137; N = 179) that compared placebo to varenicline for tobacco use among PLWHA for the present analyses. The methods and primary results of this trial, which was approved by the University of Pennsylvania IRB and was conducted between October 2012 and June 2018, have been reported elsewhere (Anthenelli et al., 2016).

2.1. Participants

We recruited participants through Penn medical clinics, media advertisements, and through a community-based HIV clinic. To be eligible, participants had to be ≥ age 18, had to have a confirmed HIV diagnosis and were receiving treatment with ART, and had to have HIV viral loads < 1000 copies/ml. Participants were excluded for a life-time history of psychosis or a suicide attempt, self-reported current or planned pregnancy, self-reported current use of smoking cessation medications, and indications of unstable or untreated alcohol/substance abuse. The characteristics of the sample (N = 179) have been reported previously (Anthenelli et al., 2016).

2.2. Procedures

Participants provided written informed consent. Varenicline was given for 12 weeks based on U.S. Food and Drug Administration dosing guidelines: Day 1-Day 3 (0.5 mg once daily);

Day 4–7 (0.5 mg twice daily); and Day 8-Day 84 (1.0 mg twice daily). All participants were offered six standardized, Public Health Service guideline-based smoking cessation counseling sessions at Weeks 0, 1, 3, 5, 7, and 9, in-person or by phone (SRNT Subcommittee on Biochemical Verification, 2002; Shelley et al., 2015; Gross et al., 2014), which included a quit day at week 1.

2.3. Measures

Participant demographic (e.g., age, income, education), smoking-related (e.g., baseline smoking rate, age started smoking, nicotine dependence measured by the Fagerström Test for Cigarette Dependence (FTCD) (Ledgerwood and Yskes, 2016), and disease-related (e.g., baseline viral load, type of anti-retroviral medication) information was collected prior to initiating treatment.

Varenicline adherence was assessed at Weeks 0, 1, 3, 5, 7, 9, and 12 using the timeline follow-back method (Cinciripini et al., 2017) and blister-pack collection as done previously (SRNT Subcommittee on Biochemical Verification, 2002; Chen et al., 2015). We assessed the total number of pills taken out of the total pills prescribed and computed an overall proportion of medication adherence (adherence defined by taking ≥ 80% of prescribed medication) (Anthenelli et al., 2016). If a discrepancy regarding the number of pills taken arose between blister-packs and what was reported during timeline follow-back, the amount in the blister-pack was recorded and used.

For the parent trial, 128/179 enrolled participants provided blood for NMR analyses. Providing a blood sample was optional and not all attempts at collecting the sample were successful, most often due to complications resulting from past injection drug use. For a description of this sub-sample, see Anonymous (Peng et al., 2017). Plasma samples were examined for nicotine, cotinine, and 3-hydroxycotinine (3-HC), to identify NMR, using liquid chromatography-tandem mass spectrometry (SRNT Subcommittee on Biochemical Verification, 2002). Participants were classified as slow metabolizers of nicotine if their NMR was < 0.31 and were classified as fast metabolizers if their NMR was ≥ 0.31 (SRNT Subcommittee on Biochemical Verification, 2002).

Smoking behavior was assessed using the timeline follow-back procedure as done previously (SRNT Subcommittee on Biochemical Verification, 2002; Shelley et al., 2015) and cessation was determined using 7-day point-prevalence abstinence at Week 12 based on no self-reported tobacco use during the 7 days preceding the assessment and exhaled carbon monoxide (CO) ≤ 8 ppm [31,32]. The 8 ppm cutoff was used in the past varenicline trials, so was used here to allow for the comparison of data.

2.4. Analyses

We used chi-square and ANOVA to determine if smoking cessation rate was related to any demographic, smoking-related or disease-related characteristic, which would be treated as covariates in subsequent analysis. We used a single logistic regression model to assess the relationship between medication adherence, nicotine metabolism, and week 12 abstinence (controlling for treatment arm), evaluating the predictors using odds ratios, 95% confidence intervals, and p-values. We used chi-square tests to describe variation in quit rates between

adherence groups and nicotine metabolism groups. We then explored separate logistic regression models of the adherence and nicotine metabolism groups by treatment arm interaction terms, respectively, and used chi-square tests to describe the nature of any interactions. Analyses for adherence used the entire sample (N = 179) but analyses for NMR used participants with NMR samples (N = 128).

3. Results

None of the demographic, smoking-related or disease-related characteristics were related to smoking cessation rate (p's > 0.05). Controlling for treatment arm (placebo vs. varenicline), the relationship between medication adherence and quit rate was marginally significant (OR = 1.011, 95% CI:1.00–1.02, p = 0.051). Across both treatment arms, the quit rate for non-adherent participants was 13.6% (8/59), vs. 23.3% (28/120) for adherent participants (χ^2[1] = 2.48, p = 0.12). Likewise, controlling for treatment arm, the relationship between rate of nicotine metabolism and smoking cessation rate was significant (OR = 3.08, 95% CI:1.01–9.37, p = 0.047). Across both treatment arms, the quit rate for slow metabolizers was 10.4% (5/48), vs. 22.5% (18/80) for fast metabolizers (χ^2[1] = 3.17, p = 0.08).

An interaction term for adherence and treatment arm was significant (OR = 1.009, 95% CI: 1.004–1.01, p = 0.001). As shown in Fig. 1 (top panel), for non-adherent participants (N = 59), the difference in quit rates between varenicline and placebo was not significantly different (19% vs. 5%; χ^2[1] = 2.80, p = 0.09). However, among those who were adherent (N = 120), the quit rate for varenicline was significantly higher than for placebo (35% vs. 15%; χ^2[1] = 6.51, p = 0.01). Likewise, an interaction term for rate of nicotine metabolism and treatment arm was significant (OR = 2.04, 95% CI:1.19–3.49, p = 0.009). As shown in Fig. 1 (bottom panel), among slow metabolizers (N = 48), the quit rate for varenicline was not significantly higher than for placebo (14% vs. 5%; χ^2[1] = 1.17, p = 0.28). However, among those who were fast metabolizers of nicotine (N = 80), the quit rate for varenicline was significantly higher than for placebo (33% vs. 14%; χ^2[1] = 4.43, p = 0.04).

4. Discussion

The results from the present analyses underscore the importance of varenicline adherence and rate of nicotine metabolism on quit rates in PWLHA. Increasing adherence to varenicline along with considering nicotine metabolism rate may be potential targets of interventions to increase quit rates in PLWHA treated with varenicline.

Previous studies have documented the important role of medication adherence in determining cessation outcomes (Niaura et al., 2012) but the present results strengthen this literature. As we (Anthenelli et al., 2016) and others [33] have reported, close to 40% of smokers with HIV do not take a sufficient proportion of their prescribed varenicline. As such, testing interventions designed to improve varenicline adherence is an important priority. One potential novel method for increasing varenicline adherence is Managed Problem Solving (MAPS), which is a behavioral intervention found to be successful at increasing ART adherence among PLWHA [34]. MAPS represents a potential intervention for varenicline adherence since the focus of the intervention is on barriers to adherence (e.g.

difficulties with tolerability, forgetfulness and beliefs) that generalize to other medications where adherence can be challenging.

The present results continue to document the need to consider a smoker's NMR when selecting a treatment approach. Faster metabolizers of nicotine showed substantially improved response to varenicline than slow nicotine metabolizers in this study. Importantly, PLWHA who smoke may be more likely to be fast metabolizers of nicotine than smokers without HIV (Crawford et al., 2018) and this may be why past studies have shown that HIV + smokers show low quit rates when using transdermal nicotine [35]. A previous study with the general population of smokers found that the effect of metabolism rate in response to varenicline was significantly enhanced among smokers who are adherent to medication, compared to those who were non-adherent [36]. Future research is needed to better understand why smokers with HIV show increased NMRs compared to the general population of smokers (including the possibility that ARTs may increase nicotine metabolism) (Peng et al., 2017), if a tailored approach to smoking cessation treatment selection improves treatment response, and if methods to decrease NMR among PLWHA reduce smoking rates.

4.1 Limitations

These results should be considered in the context of study limitations. First, the analyses are underpowered especially for the models examining the interaction terms. Although underpowered, exploratory analyses of factors associated with medication treatment response has been done in past studies to generate hypotheses that can be tested in subsequent studies [37,38]. Second, since the present data were taken from a randomized controlled clinical trial, which included relatively stringent eligibility criteria, the sample may not be representative of the population of PWLHA who are regular smokers. Taking the low statistical power and potential unique sample characteristics together, the present results should be replicated in a larger and more representative population of smokers with HIV. Lastly, the present data on varenicline adherence was based on self-reported pill counts, which may have limited validity. While these data were compared to returned blister packs and previous research has shown that the 12-week pill count data used here correlates with salivary varenicline levels [39], future studies like this one should consider more rigorous measures of adherence.

4.2. Conclusions

In this study of factors related to varenicline response among PLWHA, our results suggest that boosting medication adherence and selecting fast metabolizers of nicotine for varenicline may increase quit rates from varenicline treatment for PLWHA. Ongoing studies are formally testing factors that may increase nicotine metabolism among smokers with HIV, compared to the general population (R01 HL151292), and examining adherence and nicotine metabolism optimization strategies that could be integrated into the clinical care for PLWHA in order to increase rates of tobacco cessation (R01 CA243914).

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HIGHLIGHTS

- Adherence and NMR interacted with treatment arm to effect quit rates.
- Higher quit rates were found for fast metabolizers using varenicline than placebo.
- Adherence and nicotine metabolism optimization may increase quit rates for PLWHA.

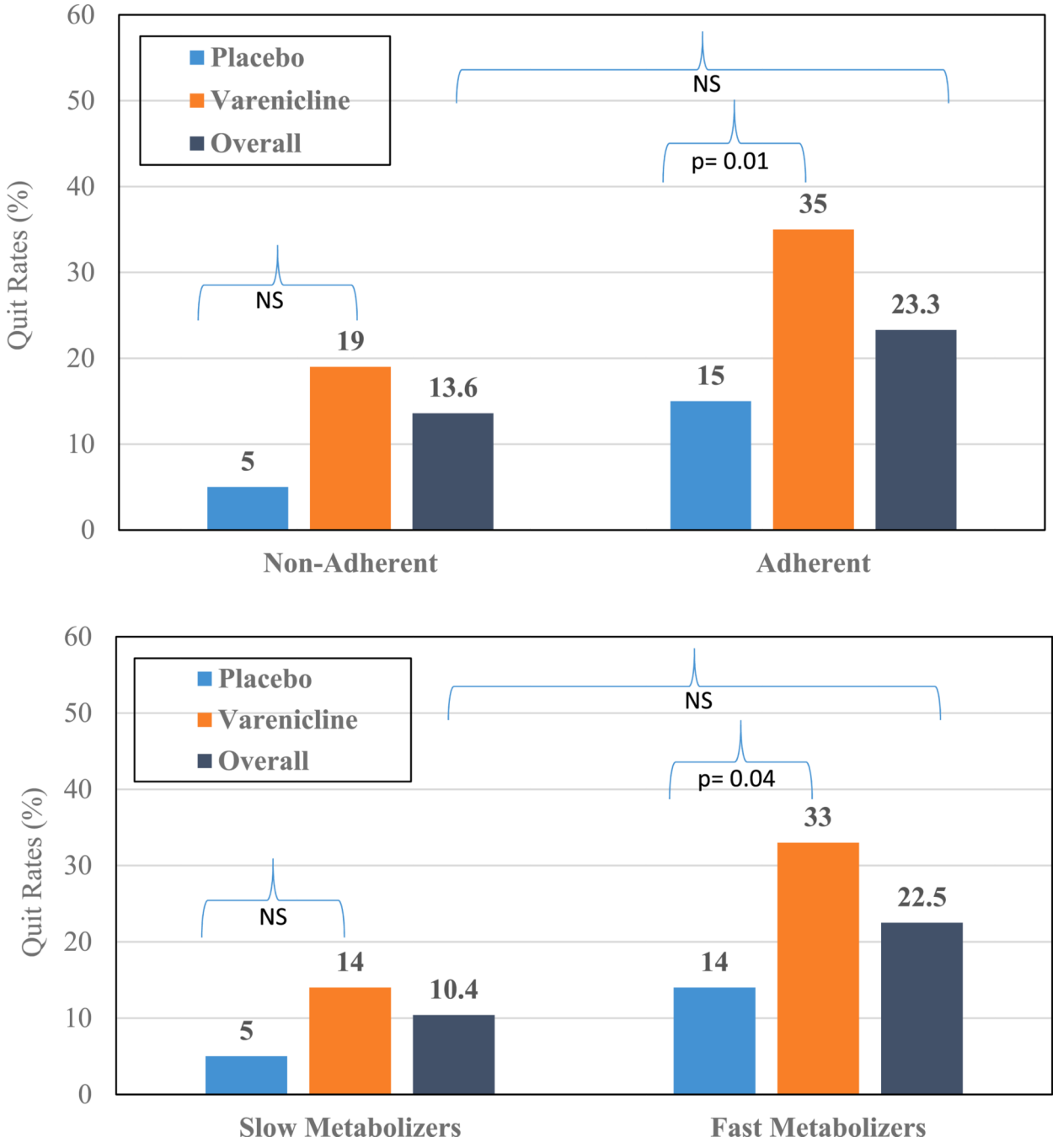

Fig. 1.

Rates of smoking cessation by placebo and varenicline arms overall across medication adherence (Top) and across nicotine metabolism (Bottom) groups. *Note.* Sample size for analyses for adherence was 179 but 131 for NMR.