HHS Public Access

Author manuscript

J Subst Abuse Treat. Author manuscript; available in PMC 2020 September 01.

Published in final edited form as:

J Subst Abuse Treat. 2019 September ; 104: 22–27. doi:10.1016/j.jsat.2019.06.005.

Smokers with Opioid Use Disorder May Have Worse Drug Use Outcomes after Varenicline than Nicotine Replacement

Rosemarie A. Martin, **Damaris J. Rohsenow**, **Jennifer W. Tidey**

Center for Alcohol and Addiction Studies, Brown University School of Public Health, Providence, RI 02912 USA

Abstract

Introduction—Smokers with opioid use disorder (OUD) have little success with smoking cessation, possibly due to interactions between nicotine and opioid receptor systems. Smokers with OUD versus non-opioid substance use disorders (NOUD) have not been compared for response to smoking treatment. Data to make this comparison came from our previous study of 12 weeks (plus dose run-up) of varenicline (VAR) versus 12 weeks of nicotine patch (NRT), in a double-placebo design.

Methods—The current study reports secondary analyses comparing smokers with OUD (n = 47) and NOUD (n = 90) on pretreatment smoking, alcohol and drug use, intolerance of physical discomfort, smoking medication adherence, and 3- and 6-month smoking and substance use outcomes (by VAR versus NRT).

Results—Smokers with OUD did not differ on pretreatment alcohol or smoking measures while reporting significantly more drug use days. Smokers with OUD versus NOUD had significantly fewer days adherent to VAR or placebo capsules but not to patches, and were more tolerant of physical discomfort. While smoking and heavy drinking days at follow-ups did not differ by diagnosis, smokers with OUD had significantly more drug use days in months 4–6 when assigned to VAR (16.4 days) than to NRT (8.1 days).

Conclusions—NRT might be a better choice than VAR for smokers with OUD due to lower adherence and more drug use days with VAR. However, this novel comparison of smoking pharmacotherapy response in smokers with OUD versus NOUD needs to be confirmed with larger numbers of participants.

Keywords

Opioid Use Disorder; Substance Use Disorder; smoking treatment; varenicline; transdermal nicotine; tolerance for discomfort

Corresponding author: Damaris Rohsenow, Ph.D., Center for Alcohol and Addiction Studies, Box S121-5 Brown University, Providence, RI 02912. Phone: 401-864-6648, fax: 401-863-6697, Damaris_Rohsenow@Brown.edu.

Conflict of interest declaration: All authors report no financial interests or potential conflicts of interest.

1. Introduction

About 80–90% of patients with opioid use disorder (OUD) smoke (e.g., Jamal, 2016; Kalman, Morissette & George, 2005). Smokers with OUDs have markedly poor success with smoking cessation, partly because smokers with OUD are notably non-adherent with smoking medications (Miller & Sigmon, 2015; Parker et al, 2018). Smoking increases risk of relapse to substances (Weinberger et al., 2017) while smoking treatment does not increase drug or alcohol use days for smokers with substance use disorder (SUD) (e.g., Prochaska, Delucchi, & Hall, 2004; Anthenelli et al., 2016), so treating smoking among people with SUD may reduce both smoking- and substance-related health risks. Studies have not investigated whether smokers with OUD fare worse in smoking cessation treatment than smokers with non-opioid substance use disorders (NOUD) in terms of adherence with smoking medications, smoking cessation outcomes or substance use outcomes. Any such differences would suggest differential approaches to smoking treatment might be needed. Two possible mechanisms for low cessation rates among smokers with OUD involve intolerance for discomfort and interactions at the neuroreceptor level.

First, pain is reported as a critical motivation for opioid use (Weiss et al., 2014), smoking and pain are highly comorbid (Ditre, Brandon, Zale, & Meagher, 2011), and nicotine has pain-inhibitory effects via actions on α4β2 nicotine acetylcholinergic receptors (nAChR) (Shanti & Shanti, 2014; Shi, Weingarten, Mantilla, Hooten, & Warner, 2010). Smokers with OUD, while abstinent from opioids, may have less tolerance for the discomfort of smoking abstinence than smokers with NOUD. The exception would be if medication-assisted treatment (MAT) for OUD increases their ability to tolerate discomfort. Measures of intolerance for physical discomfort, developed in the context of smoking treatment, include measures of intolerance of both general physical discomfort (breath holding) and discomfort from smoking abstinence. Smokers unable to tolerate holding their breath tend to relapse to smoking more quickly (Brown, Lejuez, Kahler, & Strong, 2002; Hajek, Belcher, & Stapleton, 1987; Hajek, 1991; West, Hajek, & Belcher, 1989), so breath-holding is a relevant measure of intolerance for discomfort. Self-reported intolerance of the discomfort of smoking abstinence on the Intolerance for Smoking Discomfort (IDQ-S) assessment predicted worse smoking outcomes after treatment (Rohsenow et al., 2015). Length of breath holding shares only 9% of variance with the IDQ-S Withdrawal Discomfort scale, and 33% of variance with the IDQ-S intolerance for physical discomfort scale (Sirota et al., 2010; Sirota, Rohsenow, Dolan, Martin, & Kahler, 2013), so these measures assess different aspects of intolerance for physical discomfort. Such measures have not been used to study pain intolerance among people with OUD (except in a study of effects of Hepetitis C, Tsui et al, 2011); studies of pain in that population usually use measures of pain perception instead (e.g., Williams et al., 2014). To date, no study has compared intolerance for discomfort in smokers with OUD versus NOUD, or has investigated the effects of types of smoking cessation medications on intolerance for withdrawal discomfort among smokers with OUD. If smokers with OUD are less able to tolerate the discomfort of smoking cessation, this could have implications for differential use of medication or of cognitive-behavioral strategies to increase acceptance or coping with the discomfort.

The second possible mechanism for differential outcomes for smokers with OUD as opposed to other SUDs involves the documented interactions between nicotine and the opioid system. Among patients receiving MAT for OUD, smoking is dose-dependently and temporally-related to MAT dose, suggesting that opioids increase the reinforcing effects of nicotine (Patrick et al., 2014; Richter et al., 2007; Schmitz, Grabowski, Rhoades, 1994; Story & Stark, 1991). In addition, endogenous opioid systems are implicated in nicotine withdrawal and nicotine-reinforced responding (reviewed in D'Souza, 2016). Specifically, blockade of mu opioid receptors has been found to exacerbate nicotine withdrawal symptoms in preclinical and clinical studies and attenuate cue-induced reinstatement of nicotine-reinforced responding (Malin et al., 1993; Krishnan-Sarin et al., 1999; Liu et al., 2009), whereas kappa opioid receptor blockade attenuates withdrawal symptoms and attenuates stress-induced reinstatement of nicotine-reinforced responding (Tejeda, Natividad, Orfila, Torres, & O'Dell, 2012; Grella, Funk, Coen, Li, & Lê, 2014). Preclinical studies have found considerable overlap between the effects of nicotine and opiates in the dopamine (DA) reward pathway (nucleus accumbens), with mu-opioids and nicotinic receptor blockade each similarly inhibiting single-spike firing of DA neurons (Britt & McGehee, 2008).

Given the role of nAChRs in the opioid system, VAR and nicotine replacement therapy (NRT) may have differential success among smokers with OUD. While NRT is a full agonist across nAChRs, VAR is a partial agonist-antagonist at the $\alpha 4\beta 2$ nAChR - it partially substitutes for nicotine effects and partially blocks nicotine effects (Benowitz, 2009). While neither NRT nor VAR provides the burst release of DA that optimally substitutes for the positive reinforcing effects of nicotine from cigarettes, both reduce nicotine withdrawal (Gonzales et al., 2006, Henningfield, 1995). VAR is more effective for smoking cessation than NRT in smokers with or without psychiatric disorders (Anthenelli et al., 2016), is more effective than NRT in smokers in SUD treatment (Rohsenow et al., 2017), and is more effective than placebo but not more effective than NRT in patients on methadone (Nahvi, Ning, Segal, Richter, & Arnsten, 2014). NRT's full agonist effects across nAChRs may provide differential effects from VAR's partial agonist effect on one nAChR so that smokers with OUD may respond differentially from smokers with NOUD, potentially receiving more rewarding DA effects from the full nicotine agonist (NRT). Differential response would help to guide clinicians in the choice of pharmacotherapies for smoking cessation.

In this study we report secondary analyses of our parent trial that compared VAR to NRT in a double-placebo design for smokers in treatment for SUD (Rohsenow et al., 2017) in order to investigate differential responses to smoking cessation intervention by diagnosis. Participants diagnosed with OUD (regardless of comorbid SUDs) were compared to smokers with any NOUD for adherence with study smoking medications, smoking outcomes, and drug and/or heavy drinking outcomes at 3 and 6 months after starting smoking treatment (end of treatment and follow-up). Because VAR and NRT could affect responses of smokers with OUD versus NOUD differentially, interactions with smoking medication condition were investigated for effects on smoking, alcohol use and drug use. In addition, since smokers with OUD versus NOUD may differ in intolerance of physical discomfort, diagnostic groups were compared for the IDQ-S Withdrawal Discomfort scale and length of breath holding. We hypothesized that smokers with OUD would have lower medication adherence, less smoking abstinence, more drug use days after treatment regardless of

smoking medication type, and less tolerance for physical discomfort than smokers with NOUD. Medication effects by diagnosis were exploratory. While VAR did not affect alcohol outcomes in this study (Rohsenow et al., 2017), given interest in effects of VAR on alcohol use (e.g., Litten et al., 2013; O'Malley et al., 2018), percent heavy drinking days was analyzed separately from use of other substances to explore moderation of medication effects by diagnosis.

2. Material and Methods

2.1. Design, Medications, Overview of Procedures

Participants were drawn from a larger study (Rohsenow et al., 2017) in which smokers (10+ cigarettes per day [CPD]) in outpatient SUD treatment were randomized to 12 weeks of VAR along with a placebo patch (n = 77), or of NRT (transdermal) along with capsules containing placebo (n = 60); all started with 1 week of capsules (dose run-up or placebo). The assigned smoking quit day was at the start of the 12 weeks. All were provided Brief Advice to quit smoking, tailored for concerns of smokers in SUD treatment (up to 10 sessions). Motivation to quit smoking was not a criterion. (See Rohsenow et al., 2017, for full inclusionary criteria and methods). Informed consent was followed by physical exam, lab tests, and screening before entry into the study, with baseline assessment followed by urn randomization stratified by gender, Fagerström Test for Cigarette Dependence (FTCD; Fagerström, 2012; Heatherton, Kozlowski, Frecker, & Fagerström, 1991, formerly called Fagerström Test for Nicotine Dependence) and history of major depressive disorder. All procedures were approved by the Institutional Review Board of record.

A compounding pharmacy prepared capsules with VAR and matching placebo. The VAR run-up was 0.5 mg/d for 3 mornings, then 1 mg/d (0.5 mg 2x/d) for 4 days; followed by the full dose of 2 mg/d (1.0 mg 2x/d) for 12 weeks. Capsules with placebo were 1/day for 3 days, then 2/day for the rest of the 13 weeks. NRT was 21 mg/day for 4 weeks, 14 mg/day for 4 weeks, and 7 mg/day for 4 weeks. Matching placebo patches were made by Rejuvenation Labs, Inc., Midvale, UT. Patch use started after the 7-day lead-in, on the assigned Quit Day.

2.2. Assessments

Research assistants conducting interviews were blind to condition. Assessment interviews were conducted at baseline and Quit Day (7 days); within-treatment at 2, 5, and 9 weeks after Quit Day; post-treatment (3 months), and follow-up (6 months) after the first capsule. The subset of assessments used for these analyses are described. Diagnoses (current SUD, current or past major depression) were made according to the Structured Clinical Interview for DSM-IV-Patient version (First, Spitzer, Gibbon, & Williams, 1995). A 6-month Timeline Followback (TLFB) interview (Brown et al., 1998; Ehrman & Robbins, 1994; Sobell & Sobell, 1980) at baseline was scored for number of drug use days, heavy drinking days (defined as ≥6/4 drinks/day for men/women [Flannery et al., 2002]), and CPD. A 30-day drug use questionnaire was given at baseline for details about all illicit drugs used, for description. NRT use was tracked by requiring used patches to be returned, and capsule adherence was tracked by means of MEMSCaps (TM; Aardex) data. Breath carbon

monoxide (CO) was collected using an EC50 Micro III Smokerlyzer® (Bedfont Scientific Ltd, Kent UK). At 3 and 6 months, self-reported 7-day point-prevalence abstinence was confirmed with a CO level ≤ 4 ppm and (if not using NRT) salivary cotinine level ≤ 15 ng/ml (Cropsey et al., 2014; Hughes et al., 2003; Perkins, Karelitz, & Jao, 2013). Missing smoking data was counted as having smoked. Self-reports of drug abstinence required confirmation by a urine drug screener (On Trak® test cups [Roche, Indianapolis, IN, USA) followed by negative results using the enzyme multiplied immunoassay technique (EMIT), gas chromatography and mass spectrometry).

Cigarette dependence pretreatment was based on FTCD score. The reliable and valid Intolerance for Smoking Discomfort Questionnaire (IDQ-S) Withdrawal Intolerance scale (Sirota et al., 2010; 2013), has 12 items Likert-rated from 1 (strongly disagree) to 5 (strongly agree), scored using the mean of ratings. (Examples are “I cannot stand how I feel when I need a cigarette;” “Going through nicotine withdrawal is more stress than I can tolerate.”) Breath holding procedure (Hajek et al., 1987) asked participants to hold their breath as long as possible, with time scored in seconds.

2.3. Statistical Analysis Methods

Variables were investigated for violations of normality. Number of drug use days and of heavy drinking days at 3- and 6 months needed to be log transformed to correct skewness for analyses, but untransformed values are displayed for easier interpretation. Positive imputation was used for missing smoking data (per Higgins & Green, 2011). In the primary outcome report, smoking outcomes, drug use days, and heavy drinking days were also re-analyzed with multiple imputation, but the significance levels did not differ so the analyses without multiple imputation were retained.

First, diagnostic conditions (OUD versus NOUD) were compared for baseline FTCD, CPD, number of days with heavy drinking and number of days with any drug use in the past 180 days using t-tests. Demographic variables, number of counseling sessions, and follow-up completion were also compared. Second, conditions were compared for number of days of adherence with capsules (VAR vs. placebo), and number of days adherent with patch use (nicotine vs. placebo), using two diagnosis by medication condition analyses of variance (ANOVA). Third, smoking outcomes between conditions were compared for CPD at 3 and 6 months using analysis of covariance (ANCOVA) covarying pretreatment CPD. A secondary repeated measures ANOVA was used to determine whether CPD reduced from pretreatment to 3 months. While there was insufficient power to investigate diagnosis as a moderator of medication effects on smoking abstinence, chi square tests were used at 3 and 6 months to compare rates of 7-day confirmed point-prevalence abstinence by diagnostic condition (using Fisher’s exact test if any cell was < 5). Fourth, number of heavy drinking days and number of drug use days were compared by diagnostic and medication conditions using 2 × 2 ANCOVAs at 3 and 6 months, covarying the baseline value of the dependent variable. Simple effects tests within each diagnostic group were used when significant interaction effects were found. Fifth, diagnostic groups were compared for breath holding time and IDQ-S Withdrawal Intolerance scores. Because group differences were found for breath holding time, a t-test by MAT was conducted within OUD, and this time was partially

correlated with number of drug use days and CPD at 3 and 6 months while entering the baseline value of the same dependent variable as a covariate, to see breath holding predicted these outcomes.

3. Results

3.1. Baseline Differences and Medication Adherence by Diagnosis

All pretreatment variables by diagnostic condition are shown in Table 1. Criteria for more than one substance of abuse were met by 90% of people with OUD, 47% of people with NOUD (see Table 1 for details). Diagnostic groups did not differ significantly in proportion receiving each study medication, in smoking variables or number of heavy drinking days. Participants with OUD had significantly more drug use days pretreatment, were older, and were more likely to be White, attended one fewer counseling sessions, and were less likely to complete follow-up. Among those with OUD, in the 30 days pretreatment 23 (49%) used heroin while 18 (38%) used other opiates (7 [15%] used no illicit drugs. Of people with OUD, 7 (15%) were using methadone and 2 (4%) suboxone as MAT. Amphetamines, hallucinogens or inhalants were used on less than 1 day across the sample, while tranquilizers were used on $M = 3.6$ days ($SD = 8.8$) out of the last 30 days.

Smokers with OUD had significantly fewer days using the capsules (VAR or placebo) than smokers with NOUDs, with no significant interaction with the content of the capsules. (See Table 1.) However, diagnostic conditions did not differ significantly in number of days of using the patches (NRT or placebo patches), again with no significant interaction with whether the patches contained nicotine or not. In the parent trial (Rohsenow et al., 2017), capsule use was collinear with patch use, $r = .89$, with no medication differences.

3.2. Smoking and Substance Use Outcomes

CPD did not differ significantly by diagnostic condition at 3 or 6 months. The repeated measures ANOVA showed a significant reduction at 3 months, $F(1,84) = 144.42$, $p < .001$, 3 month $M = 6.3$ CPD (SD = 6.7). At 3 months, while only 2 out of 47 participants with OUD were abstinent from smoking compared to 10 out of 77 participants without OUD, this difference was not significant by Fisher's Exact Test ($p < .13$).

Alcohol and drug use data were obtained from 93 participants at 3 months (25 with OUD, 68 with NOUD), and from 80 participants at 6 months (20 with OUD, 60 with NOUD). Heavy drinking occurred on $M = 2.4$ days ($SD = 0.8$) at 3 months and $M = 3.4$ days ($SD = 1.3$) at 6 months. No significant main or interaction effects of diagnosis with medication were found for heavy drinking. For number of drug use days, no significant effects were found 1–3 months, but for 4–6 months the interaction of diagnosis with medication was significant, $F(1,75) = 4.11$, $p < .046$, partial $\eta^2 = .052$. Simple effects tests showed a significant medication effect only within the OUD condition, $F(1,76) = 5.18$, $p < .026$; those on VAR reported M = 16.4 days (SD = 32.0) while those on NRT reported 0.1 (SD = 5.7) days of drug use from 4–6 months of follow-up. Participants with NOUD reported M = 3.8 (SD = 2.9) days of drug use.

3.3. Intolerance for Discomfort

Participants with OUD held their breath significantly longer than participants with NOUD (see Table 1) but did not differ significantly in IDQ-S Withdrawal Intolerance scores ($t < 1$). Partial correlations of breath holding time with drug use days at 3 and 6 months, covarying baseline drug use days, was not significant (trend at 3 months $pr = -.16$). Partial correlations of breath holding time with CPD, covarying pretreatment CPD, were significant in the expected direction at 3 months, $pr = -.21$, $p < .036$, but not at 6 months. Because it was unexpected that participants with OUD held their breath about 6 s longer than other participants, we explored whether use of MAT could account for these results. However, that possibility was not supported, M = 40.1 s (SD = 21.4) for participants on MAT, M = 41.7 s (SD = 16.7) for participants with OUD not on MAT, $t(45) < 1$.

4. Discussion

Smokers with OUD versus those with NOUD did not differ significantly in smoking abstinence or cigarettes per day 3 and 6 months after starting smoking treatment. The non-significantly greater abstinence after NRT than VAR is consistent with the same non-significant differences found by Stein et al. (2013) in smokers with OUD. Studies reporting less success with smoking treatment by smokers with OUD have used smokers with no SUD as the comparison so this is the first study to find that smokers with OUD have similar smoking treatment outcomes to smokers with other SUDs. Smokers with OUD versus NOUD also did not differ significantly in pretreatment smoking rates or dependence.

However, when provided with VAR, the smokers with OUD had worse drug use outcomes from 4 to 6 months than smokers with NOUD. Differences at outcome were not due to the pretreatment differences in drug use (controlled in analyses), particularly since an interaction with medication type was found. While preliminary due to the small number of participants, this suggests that VAR may be a less favorable choice for smokers with OUD, particularly in the absence of greater benefit to smoking cessation. Given known interactions between nicotine and the opioid system at the receptor level, and given that NRT binds to more types of nAChRs than VAR does, it is possible to speculate that NRT dampens desire to use opiates compared to VAR by stimulating more nAChRs. If so, then increasing the dose of nicotine (e.g., double patches, adding spray) may be better for smokers with OUD. Results need to be replicated with larger samples before treatment recommendations can be made.

Differences in drug use outcomes are not due to less ability to tolerate physical discomfort since smokers with OUD had significantly greater ability to tolerate physical discomfort than smokers with NOUD, and because ability to tolerate the discomfort of breath holding did not predict drug use outcomes, similar to the lack of predictive value of intolerance of anxiety (Baxley, Weinstock, Lustman, & Garner, 2019). However, greater breath holding predicted a lower 3-month smoking rate, as found in studies of smokers in general (e.g., Hajek, 1991). The greater tolerance of breath-holding discomfort by smokers with OUD was not accounted for by use of MAT. However, they could have had opioids in their systems at baseline – they only needed to report no drug use starting the day before baseline and not appear impaired. The results suggest that smokers with OUD are not in greater need of behavioral approaches to help them tolerate discomfort as part of their smoking treatment.

Patients with OUD are known to have poor adherence with medications in general (Miller & Sigmon, 2015). In the present study, this effect was found to be specific to adherence to the capsules (VAR or placebo), with which smokers with OUD were significantly less adherent than smokers with NOUD. This was not accounted for by pharmacologic effects, since the low adherence occurred across VAR and placebo capsules. Resistance to taking capsules that might contain medication is possibly a form of “treatment fatigue”, which has been noted in populations with chronic medical conditions (Claborn, Meier, Miller, & Leffingwell, 2015). Since this resistance did not apply to patches, this may be another reason why NRT may be preferable for smokers with OUD. It is possible that patch counts, being less reliable than use of MEMS for the capsules, resulted in inflated estimates of adherence, although it is not clear why this would be the case only for the patients with OUD not with other SUDs.

Limitations include that the number of smokers with OUD in this secondary analysis was low so that some effects may not have been detected due to low power, most abused other substances as well, and the results are limited to smokers with SUD recruited from the community in one urban area. While this novel comparison of medications and intolerance for discomfort between smokers with and without OUD is suggestive, it needs repeating with a larger number of patients and in other regions of the country.

5. Conclusions

Results of this study suggest that it may be preferable to offer smokers with OUD NRT rather than VAR, given their lower adherence and more illicit drug use days during follow-up when given VAR compared to NRT. However, given the small number of participants, replication is needed with a larger number of patients before such recommendations can be made. Smokers with OUD as opposed to non-opiate SUDs otherwise did not differ significantly in smoking outcomes after smoking treatment. The fact that smokers with OUD were more, rather than less, able to tolerate physical discomfort indicates that providers do not need to fear that the discomfort of nicotine withdrawal is likely to precipitate relapse in these smokers. Given that smokers with OUD have not previously been compared to smokers with NOUD for any of these outcomes, this line of research bears further investigation.

Acknowledgments

Appreciation is expressed to Suzanne Sales for her data analyses.

Funding: This work was supported by the National Institute on Drug Abuse (grant number 1R01DA024652) and by a Senior Career Research Scientist Award from the Department of Veterans Affairs to DJR. The funding agencies had no further role in study design, in the collection, analysis and interpretation of the data, in the writing of the report, or in the decision to submit the paper for publication. The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or of the National Institutes of Health.

Non-standard abbreviations

NOUD	non-opioid substance use disorders
MAT	medication-assisted treatment

VAR	varenicline
CPD	cigarettes per day
IDQ-S	Intolerance for Smoking Discomfort
FTCD	Fagerström Test for Cigarette Dependence
TLFB	Timeline Followback
CO	Breath carbon monoxide

References

Anthenelli RM, Benowitz NL, West R, St Aubin L, McRae T, Lawrence D, … Evins EA (2016). Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): A double-blind, randomized, placebo-controlled clinical trial. The Lancet, 387, 2507–2520.

Baxley C, Weinstock J, Lustman PJ, & Garner AA (2019). The influence of anxiety sensitivity on opioid use disorder treatment outcomes. Experimental and Clinical Psychopharmacology, 27, 64–67. [PubMed: 30080059]

Benowitz NL (2009). Pharmacology of nicotine: Addiction, smoking-induced disease, and therapeutics. Annual Review of Pharmacology and Toxicology, 49, 57–71.

Britt JP & McGehee DS (2008). Presynaptic opioid and nicotinic receptor modulation of dopamine overflow in the nucleus accumbens. The Journal of Neuroscience, 28, 1672–1681. [PubMed: 18272687]

Brown RA, Burgess ES, Sales SD, Whiteley JA, Evans DM, & Miller IW (1998). Reliability and validity of a smoking timeline follow-back interview. Psychology of Addictive Behaviors, 12, 101–112.

Brown RA, Lejuez CW, Kahler CW, & Strong DR (2002). Distress tolerance and duration of past smoking cessation attempts. Journal of Abnormal Psychology, 111, 180–185. [PubMed: 11866171]

Claborn KR, Meier E, Miller MB, & Leffingwell TR (2015). A systematic review of treatment fatigue among HIV-infected patients prescribed antiretroviral therapy. Psychology, Health & Medicine, 20, 255–265.

Cropsey KL, Trent LR, Clark CB, Stevens EN, Lahti A, & Hendricks PS (2014). How low should you go? Determining the optimal cutoff for exhaled carbon monoxide to confirm smoking abstinence when using cotinine as a reference. Nicotine & Tobacco Research, 16, 1348–1355. [PubMed: 24891552]

Ditre JW, Brandon TH, Zale EL, & Meagher MM (2011). Pain, nicotine, and smoking: Research findings and mechanistic considerations. Psychological Bulletin, 137, 1065–93. [PubMed: 21967450]

D'Souza MS (2016). Neuroscience of nicotine for addiction medicine: Novel targets for smoking cessation medications. Progress in Brain Research, 223, 191–214. [PubMed: 26806777]

Ehrman RN & Robbins SJ (1994). Reliability and validity of 6-month timeline reports of cocaine and heroin use in a methadone population. Journal of Consulting and Clinical Psychology, 62, 843–850. [PubMed: 7962889]

Fagerström KO (2012). Determinants of tobacco use and renaming the FTND to the Fagerström Test of Cigarette Dependence. Nicotine and Tobacco Research, 14, 75–78. [PubMed: 22025545]

First MB, Spitzer RL, Gibbon M, & Williams JBW (1995). Structured clinical interview for DSM-IV axis I disorders - patient edition SCID-I/P, version 2.0. Biometrics Research Department, New York State Psychiatric Institute, New York, NY.

Flannery BA, Allen JP, Pettinati HM, Rohsenow DJ, Cisler RA, & Litten RZ (2002). Using acquired knowledge and new technologies in alcoholism treatment trials. Alcoholism, Clinical and Experimental Research, 26, 423–429.

Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, Billing CB, … Reeves KR (2006). Varenicline phase 3 study group. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist vs sustained-release bupropion and placebo for smoking cessation: A randomized controlled trial. Journal of the American Medical Association, 296, 47–55. [PubMed: 16820546]

Grella SL, Funk D, Coen K, Li Z, & Lê AD (2014). Role of the kappa-opioid receptor system in stress-induced reinstatement of nicotine seeking in rats. Behavioural Brain Research, 265, 188–197. [PubMed: 24583188]

Hajek P (1991). Individual differences in difficulty quitting smoking. Addiction, 86, 555–558.

Hajek P, Belcher M, & Stapleton J (1987). Breath-holding endurance as a predictor of success in smoking cessation. Addictive Behaviors, 12, 285–288. [PubMed: 3661283]

Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO (1991). The Fagerström test for nicotine dependence: A revision of the Fagerström tolerance questionnaire. British Journal of Addiction, 86, 1119–1127. [PubMed: 1932883]

Henningfield JE (1995). Nicotine medications for smoking cessation. The New England Journal of Medicine, 333, 1196–1203. [PubMed: 7565976]

Higgins JPT & Green S, editors. (2011). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. Available from www.cochrane-handbook.org.

Hughes JR, Keely JP, Niaura RS, Ossip-Klein DJ, Richmond RL, & Swan GE (2003). Measures of abstinence in clinical trials: Issues and recommendations. Nicotine & Tobacco Research, 5, 13–25. [PubMed: 12745503]

Jamal A (2016). Current cigarette smoking among adults – United States, 2005–2015. Morbidity and Mortality Weekly Report, 65.

Kalman D, Morissette SB, & George TP (2005). Co-morbidity of smoking in patients with psychiatric and substance use disorders. The American Journal on Addictions, 14, 106–123. [PubMed: 16019961]

Krishnan-Sarin S, Rosen MI, & O'Malley SS (1999). Naloxone challenge in smokers. Preliminary evidence of an opioid component in nicotine dependence. Archives of General Psychiatry, 56, 663–668. [PubMed: 10401515]

Litten RZ, Ryan ML, Fertig JB, Falk DE, Johnson B, Dunn KE, … Sarid-Segal O (2013). A double-blind, placebo-controlled trial assessing the efficacy of varenicline tartrate for alcohol dependence. Journal of Addiction Medicine, 7, 277. [PubMed: 23728065]

Liu X, Palmatier MI, Caggiula AR, Sved AF, Donny EC, Gharib M, & Booth S (2009). Naltrexone attenuation of conditioned but not primary reinforcement of nicotine in rats. Psychopharmacology (Berl), 202, 589–598. [PubMed: 18807246]

Malin DH, Lake JR, Carter VA, Cunningham JS, & Wilson OB (1993). Naloxone precipitates nicotine abstinence syndrome in the rat. Psychopharmacology (Berl), 112, 339–342. [PubMed: 7871039]

Miller ME & Sigmon SC (2015). Are pharmacotherapies ineffective in opioid-dependent smokers? Reflections on the scientific literature and future directions. Nicotine & Tobacco Research, 955–959. [PubMed: 26180219]

Nahvi S, Ning Y, Segal KS, Richter KP, & Arnsten JH (2014). Varenicline efficacy and safety among methadone maintained smokers: A randomized placebo-controlled trial. Addiction, 1099, 1554–1563.

O'Malley SS, Zweben A, Fucito LM, Wu R, Piepmeier ME, Ockert DM, … Jatlow P (2018). Effect of varenicline combined with medical management on alcohol use disorder with comorbid cigarette smoking: A randomized clinical trial. The Journal of the American Medical Association: Psychiatry, 75, 129–138. [PubMed: 29261824]

Patrick ME, Dunn KE, Badger GJ, Heil SH, Higgins ST, & Sigmon SC (2014). Spontaneous reductions in smoking during double-blind buprenorphine detoxification. Addictive Behaviors, 39, 1353–1356. [PubMed: 24845165]

Perkins KA, Karelitz JL, & Jao NC (2013). Optimal carbon monoxide criteria to confirm 24-hr smoking abstinence. Nicotine & Tobacco Research, 15, 978–982. [PubMed: 22990219]

Prochaska JJ, Delucchi K, & Hall SM (2004). A meta-analysis of smoking cessation interventions with individuals in substance abuse treatment or recovery. Journal of Consulting and Clinical Psychology, 72, 1144. [PubMed: 15612860]

Richter KP, Hamilton AK, Hall S, Catley D, Cox LS, & Grobe J (2007). Patterns of smoking and methadone dose in drug treatment patients. Experimental and Clinical Psychopharmacology, 15, 144–153. [PubMed: 17469938]

Rohsenow DJ, Tidey JW, Kahler CW, Martin RA, Colby SM, & Sirota AD (2015). Intolerance for withdrawal discomfort and motivation predict voucher-based smoking treatment outcomes for smokers with substance use disorders. Addictive Behaviors, 43, 18–24. [PubMed: 25531536]

Rohsenow DJ, Tidey JW, Martin RA, Colby SM, Swift RM, Leggio L, & Monti PM (2017). Varenicline versus nicotine patch with brief advice for smokers with substance use disorders with or without depression: Effects on smoking, substance use and depressive symptoms. Addiction, 112, 1808–1820. [PubMed: 28498504]

Schmitz JM, Grabowski J, & Rhoades H (1994). The effects of high and low doses of methadone on cigarette smoking. Drug and Alcohol Dependence, 34, 237–242. [PubMed: 8033762]

Shanti BF & Shanti IF (2014). Updates on smoking and low back pain. Practical Pain Management Journal, 14.

Shi Y, Weingarten TN, Mantilla CB, Hooten WM, & Warner DO (2010). Smoking and pain: Pathophysiology and clinical implications. Anesthesiology, 113, 977–992. [PubMed: 20864835]

Sirota AD, Rohsenow DJ, MacKinnon SV, Martin RA, Eaton CA, Kaplan GB, Monti PM, Tidey JW, & Swift RM (2010). Intolerance for smoking abstinence, physical and emotional discomfort questionnaires: Psychometric properties and relationship to tobacco dependence and abstinence. Addictive Behaviors, 35, 686–693. [PubMed: 20381260]

Sirota AD, Rohsenow DJ, Dolan SL, Martin RA, & Kahler CW (2013). Intolerance for discomfort among smokers: Comparison of smoking-specific and non-specific measures to smoking history and patterns. Addictive Behaviors, 38, 1782–1787. [PubMed: 23254229]

Sobell LC & Sobell MB (1980). Convergent validity: An approach to increasing confidence in treatment outcome conclusions with alcohol and drug abusers In Sobell LC, Sobel MB, & Ward E, Eds. Evaluating alcohol and drug abuse treatment effectiveness: Recent advances, pp. 177–183. Elmsford, NY: Pergamon Press.

Stein MD, Caviness CM, Kurth ME, Audet D, Olson J, & Anderson BJ (2013). Varenicline for smoking cessation among methadone-maintained smokers: A randomized clinical trial. Drug and Alcohol Dependence, 1332, 486–493.

Story J & Stark MJ (1991). Treating cigarette smoking in methadone maintenance clients. Journal of Psychoactive Drugs, 23, 203–215. [PubMed: 1765893]

Tsui JI, Herman DS, Ketavong M, Anderson B., Stein M (2011). Chronic Pain and Hepatitis C Virus Infection in Opioid Dependent Injection Drug Users. Journal of Addictive Disease, 30, 91–97.

Tejeda HA, Natividad LA, Orfila JE, Torres OV, & O'Dell LE (2012). Dysregulation of kappa-opioid receptor systems by chronic nicotine modulate the nicotine withdrawal syndrome in an age-dependent manner. Psychopharmacology (Berl), 224, 289–301. [PubMed: 22659976]

Weinberger AH, Platt J, Esan H, Galea S, Erlich D, & Goodwin RD (2017). Cigarette smoking is associated with increased risk of substance use disorder relapse: A nationally representative, prospective longitudinal investigation. The Journal of Clinical Psychiatry, 78, e152–e160. doi: 10.4088/JCP.15m10062. [PubMed: 28234432]

Weiss RD, Potter JS, Griffin ML, McHugh RK, Haller D, Jacobs P, … Rosen KD (2014). Reasons for opioid use among patients with dependence on prescription opioids: The role of chronic pain. Journal of Substance Abuse Treatment, 47, 140–5. [PubMed: 24814051]

West RJ, Hajek P, & Belcher M (1989). Severity of withdrawal symptoms as a predictor of outcome of an attempt to quit smoking. Psychological Medicine, 19, 981–985. [PubMed: 2594893]

Williams BA, Ahalt C, Stijacic-Cenzer I, Smith AK, Goldenson J, & Ritchie CS (2014). Pain behind bars: The epidemiology of pain in older jail inmates in a county jail. Journal of Palliative Medicine, 17, 1336–1343. [PubMed: 25265035]

HIGHLIGHTS

- Smokers with opiate vs. other substance use disorders had similar smoking rates after treatment.
- Smokers with opiate use disorder were less adherent to medication capsules but not to patches.
- Smokers with opiate use disorder had more drug use after treatment if they took varenicline vs. patch.
- Patch may be a better choice than varenicline for smokers with opiate use disorder for these reasons.

Table 1:

Baseline Participant Characteristics and Treatment Adherence by Diagnostic Group: Opioid Use Disorder (OUD) versus Any Other Substance Use Disorder (Non-OUD). Mean (SD) or N (Percentage)

	Total (n = 137)	OUD (n = 47)	Non-OUD (n =90)
	N* (%) or *M (SD)	***N* (%) or *M (SD)***	***N* (%) or *M (SD)***
Randomized to varenicline/placebo patch (*n,* %)	77 (56%)	26 (55%)	51 (57%)
Male	72 (53%)	27 (57%)	45(50%)
Race			
White/Caucasian [1]	113 (83%)	43 (92%)	70 (78%)
Black/African American	21 (15%)	2 (4%)	19 (21%)
Asian/Pacific Islander or Multi-racial	3 (2%)	2 (4%)	1 (1%)
Hispanic [2]	7 (5%)	4 (8%)	3 (3%)
Age [3]	39.6 (10.1)	35.6 (10.1)	41.7 (9.5)
Years of education	12.3 (2.2)	12.2 (2.3)	12.4 (2.2)
Cigarettes per day	19.5 (7.4)	19.2 (9.4)	19.7 (10.9)
Fagerström Test for Cigarette Dependence	5.5 (1.9)	5.26 (1.88)	5.56 (1.94)
Opiate use disorder	47 (34%)	47 (100%)	0 (0%)
Alcohol use disorder	99 (72%)	26 (55%)	73 (81%)
Marijuana use disorder	32 (23%)	15 (32%)	17 (19%)
Cocaine use disorder	83 (61%)	33 (70%)	50 (55%)
No. heavy drinking days [4]	33.9 (4.3)	25.1 (43.0)	38.5 (52.9)
No. drug use days [4,5]	21.9 (29.3)	60.4 (58.4)	28.7 (46.4)
Breath holding time (s) [6]	37.3 (15.8)	41.4 (17.4)	35.1 (14.4)
Days of capsules taken out of 91 possible [7]	42.5 (33.7)	34.8 (32.6)	47.0 (33.9)
Days of patches used out of 84 possible	34.4 (32.8)	28.6 (32.4)	37.7 (31.6)
Counseling sessions completed [8]	4.2 (2.5)	3.6 (2.6)	4.5 (2.3)
Lost to follow-up or withdrew (3 months) [9, 10]	48 (35%)	24 (51%)	24 (27%)
Lost to follow-up or withdrew (3 months) [9, 11]	57 (42%)	27 (57%)	30 (33%)

[1] White vs. non-white: $\chi^2(1) = 4.02$, $p < .045$.

[2] Per requirements of the National Institutes on Health, Hispanicity is an ethnic, not racial grouping, so Hispanics can be of any race.

[3] $t(135) = 3.50$, $p < .001$.

[4] Number of days out of 180 pretreatment days, using Timeline Followback.

[5] $t(76.97) = 3.23$, $p < .002$.

[6] $t(135) = 2.27$, $p < .028$.

[7] $F(1,132) = 4.06$, $p < .046$, partial $\eta^2 = .03$

[8] $t(135) = 2.21$, $p < .025$.

[9] For point-prevalence abstinence, positive imputation resulted in data from all participants being included in analyses

[10] $\chi^2(1) = 8.07$ $p < .004$.

[11] $\chi^2(1) = 7.39$ $p < .007$.