Commentary

Are Pharmacotherapies Ineffective in Opioid-Dependent Smokers? Reflections on the Scientific Literature and Future Directions

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Abstract

While rates of smoking in the general population have decreased in recent years, dramatic disparities remain among disadvantaged subgroups of smokers, particularly those with concurrent substance abuse. Prevalence rates of smoking among opioid-dependent patients, for example, are fourfold those of the general population. While pharmacotherapies are recommended as a first-line treatment for nicotine dependence, the few studies that have investigated their effectiveness in this population have shown dramatically poorer outcomes compared to the general population. Indeed, these findings have led some researchers to suggest that pharmacotherapies may simply be ineffective in opioid-maintained smokers. In this commentary, we briefly summarize the extant literature on pharmacotherapies in opioid-maintained smokers and contribute new data investigating the contribution of bupropion on smoking outcomes in 81 methadone- and buprenorphine-maintained participants from two randomized trials of financial incentives for smoking cessation. We also discuss several important parameters (ie, timing of the quit attempt, medication adherence, nicotine withdrawal) that may be leveraged to strengthen smoking pharmacotherapy outcomes in opioid-dependent patients. Taken together, an improved understanding of these issues will aid efforts to reduce tobacco-related health disparities in this group of challenging smokers.

Introduction

While smoking in the general US population has decreased steadily over recent decades, tobacco-related health disparities persist, particularly among disadvantaged groups of smokers. This is especially true for those with concurrent substance abuse. Prevalence of smoking among opioid-dependent patients, for example, is fourfold that of non-substance abusers.¹ As a result, up to 50% of substance abusers die from tobacco-related causes, a rate twice that of the general population.² Additionally, while most opioid-dependent smokers report a desire to quit, their success rates are one-fourth that of non-substance abusers.^{3,4} Such dramatic tobacco-related health disparities are of particular concern given the scope of the current opioid abuse epidemic, with 5% of Americans ages 12 and older reporting

recent opioid abuse⁵ and over 345 000 patients receiving methadone or buprenorphine maintenance for opioid dependence annually.⁶ Taken together, efforts to understand and improve the efficacy of smoking interventions in opioid-dependent smokers may reduce the burdens and costs of tobacco-related health consequences.⁷

Pharmacotherapies, such as nicotine replacement therapy, bupropion (Zyban) and varenicline (Chantix), are recommended as first-line approaches to treating nicotine dependence and have been shown to assist smoking cessation in the general population.⁸ However, while approximately half of opioid-dependent smokers report using a pharmacotherapy in a prior quit attempt,³ few studies have directly examined the effects of these medications on smoking outcomes in this group.

Brief Review of Published Studies

We identified four randomized trials in which¹ opioid-maintained patients were randomly assigned to either an active pharmacotherapy versus control/placebo group and² smoking abstinence was evaluated as the primary outcome (Table 1). In the first study, patients enrolled in outpatient substance abuse treatment programs (five methadone maintenance programs, two drug-free clinics) were randomized to receive either smoking cessation (ie, nicotine replacement therapy + counseling) or treatment as usual,⁹ with significantly greater yet still modest abstinence in the smoking cessation versus treatment as usual group throughout Weeks 2–7 of the intervention (10% vs. 0%, respectively). In the second study, opioid-dependent smokers who were stabilized on buprenorphine were randomized to receive bupropion or placebo and no significant differences were found between the two groups, with 13.7% versus 11.4% of participants abstinent during the 10-week study, respectively.¹⁰ Two more recent studies have evaluated the efficacy of varenicline among methadone-maintained smokers.^{11,12} Stein and colleagues¹¹ compared varenicline, placebo, and nicotine replacement therapy on smoking abstinence and found no difference between the three groups, with only 4%, 8%, and 2% of participants assigned to the varenicline, nicotine replacement therapy and placebo groups abstinent at the end of the 6-month study, respectively. Finally, Nahvi et al.¹² compared varenicline to placebo and found significantly greater, though again relatively modest, abstinence in the varenicline versus placebo group at the end of the 3-month intervention period (10% vs. 0%, respectively). Taken together, pharmacotherapy outcomes thus far with opioid-dependent smokers have been disappointing and consistently lower than those typically seen in the general smoker population (eg, approximately 4%–13% vs. 19%–33%, respectively).⁸

Also worth briefly noting is that, in addition to the above trials, a handful of uncontrolled studies have examined the effects of smoking pharmacotherapies in this population either without randomization^{13,14} or as a platform to investigate the efficacy of other smoking cessation or drug abuse interventions.^{15–17} While several reported significant reductions in smoking, abstinence rates were again generally low across those studies with only 7%–15% of participants abstinent at follow-up.

Original Data

Our group has an established line of research investigating the efficacy of a behavioral intervention for promoting smoking abstinence among methadone- and buprenorphine-maintained patients.^{18–20} We examined the contribution of bupropion to those outcomes by combining data across two randomized trials, both of which offered bupropion as an optional pharmacotherapy. In the first, we examined the efficacy of abstinence-contingent financial incentives to produce initial (2-week) smoking abstinence in opioid-maintained smokers and found significantly increased abstinence in the Contingent versus Noncontingent experimental group.¹⁹ In the second, all participants received a 2-week contingent incentive intervention and were then randomized to an additional 10 weeks of contingent versus noncontingent incentives to examine the efficacy of incentives in sustaining abstinence. Again, we found significantly increased abstinence among the extended Contingent versus Noncontingent group.²⁰

As noted above, all participants were offered the opportunity to receive bupropion (300mg), provided at no cost and dispensed according to the published guidelines. We examined data from participants who received the Contingent intervention for the first 2

weeks ($n = 99$) to examine whether bupropion use would be associated with biochemically-verified smoking abstinence. Abstinence was defined as a breath carbon monoxide ≤ 6 ppm on Study Days 1–5 and as a urine cotinine ≤ 80 ng/mL on Days 6–14. Eighteen participants were excluded from the analyses (eight participated in both studies and thus only their first quit attempt was included, three terminated bupropion prior to their quit date, one participant's significant other was also in the study, and six received varenicline treatment outside of the study).

Participants were on average 33 years old, 38% male and smoked 18.6 ± 9.5 cigarettes per day. With regard to their opioid treatment, 68% and 32% were maintained on methadone or buprenorphine, respectively. Thirty-two participants received bupropion during the study and 49 did not. There were no significant differences in baseline demographic, smoking history or opioid treatment characteristics between those electing to take bupropion compared to those who did not. When urinary cotinine and expired breath carbon monoxide data were examined, we found no significant effect of bupropion on either percent of smoking-negative samples when collapsed across all study visits [$t(79) = -1.20, P = .23$] or participants' smoking status at the final visit [$X^2(1, N = 81) = 1.61, P = .20$]. While we may have been limited in power to detect an effect of bupropion, these data are largely consistent with prior studies showing no marked benefit of pharmacotherapy among opioid-dependent smokers.

Considerations for Pharmacotherapy Use in Opioid-Dependent Smokers

The underwhelming outcomes from the studies to date have prompted researchers to question whether pharmacotherapies may be ineffective in opioid-maintained smokers.^{10,21} However, before ruling out the utility of first-line pharmacotherapies in this group of smokers, we believe it is prudent for researchers and clinicians to consider several important parameters in their future efforts to evaluate or use pharmacotherapies with opioid-dependent smokers.

Consider the Timing of the Quit Attempt

There has been debate over when to recommend smoking cessation for individuals enrolled in opioid treatment.^{22,23} Indeed, changes in opioid dose are associated with corresponding changes in smoking,^{24–26} and ongoing illicit opioid and other drug use can also influence smoking rates.²⁷ Both of these may undermine the cessation effort. While several of the above published studies limited enrollment to patients who were in opioid treatment for at least a minimum length of time,^{9,11} only one required participants to have no recent change in opioid dose prior to the quit attempt.¹² Indeed, in one study patients initiated opioid-maintenance treatment and smoking cessation therapy concurrently.¹⁰

It is important to consider the appropriate timing for an opioid-maintained patient to undertake a quit attempt. This is likely to be when the patient is stable on their opioid dose and demonstrated abstinence from illicit drug use for a meaningful period. Also worth noting is that smoking cessation, when initiated by patients who are stable in their opioid treatment, does not destabilize their progress with opioid or other illicit drug abstinence^{9,28} and may even be associated with improved substance abuse treatment outcomes.²⁹

Support Medication Adherence

Prior studies in the general smoker population,^{30,31} as well as among opioid-dependent smokers,^{16,32–34} have shown that adherence to

Table 1. Randomized Trials of Smoking Cessation Pharmacotherapy in Opioid-Dependent Smokers

Reference	N	Opioid medication	Pharmacotherapy	Adjunct treatments	Primary outcomes ^a	Effect sizes ^b
Reid et al. ⁹	225	Methadone	Nicotine patch (14 mg or 21 mg) vs. treatment as usual	Mood management and cognitive behavioral therapy	1	$d = 0.39$
Mooney et al. ¹⁰	40	Buprenorphine	Bupropion (300 mg) vs. placebo	Skills training; contingency management	2	$d = 0.17$
Stein et al. ¹¹	315	Methadone	Varenicline (2 mg) vs. placebo vs. nicotine patch (21 mg or 42 mg)/gum (4 mg)	National Cancer Institute's 5A's	2	$d = 0.07$ – 0.21
Nahvi et al. ¹²	112	Methadone	Varenicline (2mg) vs. placebo	Brief individual counseling	1	$d = 0.48$

^a1 = Significantly better smoking abstinence outcomes in pharmacotherapy condition versus control, 2 = No different in smoking abstinence outcomes in pharmacotherapy versus control.

^bEffect sizes for primary smoking outcomes based on Cohen's d .

smoking cessation pharmacotherapies is highly correlated with abstinence. However, opioid-maintained patients have notoriously poor rates of adherence to non-opioid medications,^{35,36} including smoking cessation medications.^{9,11,14} In prior studies this may have also been compounded by a lack of monitoring and clinic contact. For example, in several of the above trials the medication was dispensed to patients in large quantities, there was limited staff observation of medication ingestion, and participant self-report was used as the primary measure of adherence.^{14,17}

Enhancing medication adherence through increased monitoring may aid efforts to investigate the efficacy of pharmacotherapies in this population. Several approaches are worth considering. First, directly-observed ingestion can increase opioid-maintained patients' adherence to other intensive medication regimes, such as Hepatitis C and HIV treatments.^{37,38} While this approach may be too intensive for the general population, opioid patients often visit their treatment clinic frequently for staff-observed opioid administration. Thus, observation of smoking pharmacotherapy ingestion may be a practical method to increase adherence and permit more rigorous evaluations of efficacy in this population.³⁹ A second possibility is to leverage incentive-based approaches, wherein patients receive monetary or clinic-based incentives (eg, take-home doses, clinic privileges) contingent upon medication adherence. In a recent review, incentive-based interventions increased medication adherence by at least 20%–30% across a range of challenging clinical populations.⁴⁰

Consider the Possibility of a Unique Pattern of Nicotine Withdrawal

Nicotine withdrawal is a hallmark of nicotine dependence and is one of the strongest predictors of relapse following a quit attempt.⁴¹ Withdrawal symptoms in most smokers typically peak within the first two days of abstinence and last for 2–4 weeks.⁴² However, there is a lack of research on nicotine withdrawal in this population. In the only two studies to our knowledge that have examined nicotine withdrawal in opioid-maintained smokers, an atypical withdrawal pattern emerged that suggested no clear peak but rather a gradual decrease in withdrawal following cessation.^{9,19} One possible reason may be a pharmacological interaction between opioids and nicotine. Elkader and colleagues,⁴³ for example, investigated the interactions between methadone and nicotine during abstinence and reported that opioids may attenuate nicotine withdrawal. Given the important role of withdrawal in smokers' success with quitting, an improved understanding of it in opioid-dependent smokers may aid efforts to improve outcomes in this group.

Additional Considerations

Several additional details warrant brief mention. First, opioid administration may be associated with a unique pattern of cue-induced craving. Indeed, Richter and colleagues⁴⁴ used digital cigarette packs to monitor smoking patterns as a function of methadone dosing and found that smoking rates peaked in the first 2 hours post methadone administration. As such, it may be beneficial to recommend a short-acting pharmacotherapy (eg, nicotine gum) during this interval. Second, substance abuse is often associated with high rates of psychiatric comorbidity, a vulnerability uniquely related to poorer cessation outcomes.⁴⁵ Ensuring that patients' concomitant psychiatric problems are adequately addressed may aid smoking outcomes. Third, amount and quality of social support has been shown to influence smoking cessation outcomes, self-efficacy and desire to quit.⁴⁶ However, opioid-maintained smokers report low levels of perceived social support and small social networks.^{47,48} Interventions that include a peer-support component may increase perceived self-efficacy, aiding in adherence to the program. Finally, a number of important factors may influence the successful dissemination of smoking cessation programs (pharmacological or otherwise) in drug abuse clinics. These include the training provided to treatment staff, staff attitudes toward smoking cessation, and policies that support the incorporation of cessation services.⁴⁹

Conclusion

The literature to date suggests that smoking pharmacotherapies may have limited effectiveness in opioid-dependent patients, at least under the conditions in which they have been evaluated. However, it is possible that methodological details may have undermined prior investigations of pharmacotherapy efficacy. Greater attention to several important parameters—particularly the timing of the quit attempt, medication adherence and the possibility of an atypical nicotine withdrawal profile—may strengthen future scientific and clinical efforts to use pharmacotherapies with opioid-dependent smokers. Efforts are also needed to elucidate other biological, social, and environmental factors that may influence pharmacotherapy efficacy in these patients. Considering the staggering economic and public health costs of smoking-related health disparities, an improved understanding of the efficacy of pharmacotherapies for treating nicotine dependence in opioid-dependent smokers is important.

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Declaration of Interests

None declared.

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