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ORIGINAL ARTICLE

Reduced cigarette smoking during injectable extended-release naltrexone treatment for opioid use disorder

An-Li Wang[a], Zhenhao Shi[b], Igor Elman[c], and Daniel D. Langleben[b]

[a]Addiction Institute of Mount Sinai, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [b]Center for Studies of Addiction, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA; [c]Center for Pain and the Brain, Boston Children's Hospital, Boston, MA, USA

ABSTRACT

Background: The prevalence of tobacco cigarette smoking in the US has declined to approximately 15%, yet, it remains over 90% among individuals with opioid use disorder regardless of whether they are currently using opioids illicitly or as opioid substitution therapy. This disparity raises the question of whether opioids facilitate smoking among individuals with opioid use disorder and whether opioid antagonists may reduce it.

Objectives: Determine whether injectable extended-release naltrexone (XR-NTX) treatment of opioid use disorder patients is associated with a spontaneous smoking reduction. We hypothesized that treatment with XR-NTX for would lead to a reduction in smoking in tobacco cigarette smokers with opioid use disorder.

Methods: We analyzed data from 64 tobacco cigarette smokers (38% female) with opioid use disorder who were induced on XR-NTX for prevention of relapse to opioids. The number of cigarettes smoked per day and opioid-related craving and withdrawal were assessed at baseline and during treatment.

Results: Smoking was reduced from 14.4 ± 1.0 to 9.8 ± 1.0($p < 0.001$) cigarettes per day after one month and 8.6 ± 1.1 cigarettes per day after two months of treatment. Daily cigarette consumption was positively correlated with the pre-treatment frequency of opioid use and opioid-related craving during the XR-NTX treatment.

Conclusions: XR-NTX treatment in smokers with opioid use disorder was associated with a 29% decline in daily cigarette consumption. Together with prior evidence of increased smoking during opioid agonist therapy, our finding suggests a pharmacodynamic interaction between nicotine and opioid systems that could influence treatment choices in this population. Our findings merit confirmation in a prospective controlled study. (NCT02324725 and NCT01587196)

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Introduction

Between 2005 and 2017, the prevalence of tobacco cigarette smoking in the US declined from 21% to 15% (1). However, smoking prevalence in individuals with opioid use disorder (OUD) remains extremely high, ranging between 75% and 98% (2,3). Opioid substitution therapy (OST) does not reduce this gap (4,5). Although the prevalence of smoking in all substance use disorders is significantly higher than the population average, smoking in OUD stands out, among other substance use disorders. For example, the odds of being a moderate to heavy smoker are almost double in heroin users, compared to cocaine users (6). Therefore, psychosocial factors such as co-morbid anxiety and depression, poverty, and limited employment and education opportunities that are common to all substance use disorders do not fully explain the extremely high smoking rates among individuals with OUD (7). Such disparity raises the question of whether chronic opioid exposure specifically facilitates smoking among OUD patients. Several lines of observational and experimental evidence point to interactions between opioidergic and nicotine systems that could provide a mechanistic explanation for the co-occurrence of opioid and tobacco use disorder (TUD) (8); For example, methadone treatment of OUD is associated with dose-related increases in smoking (9–12), and conversely, detoxification from methadone has the opposite effect (13). On the molecular level, methadone may have antagonist properties at the a4b2 nicotinic acetylcholine receptors (nAChRs) that could cause a compensatory increase in

CONTACT An-Li Wang anliwang@gmail.com Addiction Institute of Mount Sinai, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, 1399 Park Ave, Room 320-B, New York, NY 10029, USA

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smoking (14). Furthermore, preclinical studies have demonstrated an interaction between endogenous opioid and cholinergic systems and smoking. In rats, the mu opioid receptor (MOR) antagonist naloxone blocked nicotine-induced conditioned place preference. MOR knockout mice showed diminished nicotine reward compared to wild-type mice (15). Together, this literature suggests that opioid agonists might contribute to increased smoking in OUD patients, while opioid antagonists such as naltrexone or nalmefene may have an opposite and, therefore, beneficial effect.

The injectable extended-release form of the opioid antagonist naltrexone (XR-NTX) has been an important treatment alternative to agonist maintenance in OUD since it was approved by the FDA in 2010. Unlike OST, XR-NTX blocks the MORs without significant agonist activity, producing pharmacological abstinence from opioids for approximately 4 weeks after each injection. Thus, it obviates the daily compliance concerns. We previously reported a spontaneous reduction in the number of cigarettes smoked per day (CPD) in a small sample of OUD patients receiving XR-NTX treatment (16). Here we report results of a retrospective analysis of CPD data collected during two consecutive clinical trials of 12 weeks of XR-NTX for the prevention of relapse to opioids in OUD (clinical trials number: NCT02324725 and NCT01587196).

Materials and methods

Seventy-two treatment-seeking OUD patients (27 Females (38%), age 29.22 ± 8.59 (Mean ± SD) years, education 13.66 ± 2.06 years, 64 Caucasian (89%), 6 African American (8%), 2 Asian (3%)) were recruited through local advertising between November 2011 and March 2013. All gave written informed consent to participate in the University of Pennsylvania Institutional Review Board approved protocol.

A DSM-IV-TR diagnosis of opioid dependence was established using best estimate format, based on all available sources of information, including history, clinical interview, the Mini–International Neuropsychiatric Interview for DSM-IV (17) and the Addiction Severity Index (ASI) 5th Edition (18). Inclusion criteria were: 1) between 18 and 55 years of age; 2) DSM-IV-TR diagnosis of opioid dependence; 3) active opioid use, confirmed by urine toxicology screen and self-reported daily heroin or prescription opioid use for more than 2 weeks in the past 3 months; 4) urine toxicology screen negative for opioids after detoxification; 5) good physical health as determined by history and physical examination and screening blood work-up. Exclusion criteria were: 1) current chronic medical illnesses; 2) current use of anti-dopaminergic agents, anti-depressants, anticonvulsants, mood stabilizers, and beta-blockers; 3) current DSM-IV-TR Axis I psychiatric disorders with the exception of opioid and nicotine dependence, non-dependent cocaine abuse and depressive disorders; 4) lifetime history of concurrent IV cocaine and heroin (speedball) administration; 5) pregnancy or breast-feeding; 6) history of clinically significant head trauma; 7) contraindications for XR-NTX treatment including medical conditions requiring opioid analgesics, e.g. chronic pain or planned surgery, obesity, elevated liver enzymes (> 3 times upper limit of normal) and failure to complete opioid detoxification. Prior to the first XR-NTX injection, a challenge with 0.6 mg of naloxone HCL intravenously, was performed for all subjects to ascertain the pharmacodynamic completeness of their detoxification. Participants could receive up to three monthly intramuscular injections of XR-NTX (Vivitrol, manufactured by Alkermes, Cambridge, MA, USA). In this formulation, 380 mg of naltrexone is gradually released from dissolvable polymer microspheres. The weekly Timeline Followback (TLFB) questionnaire, which assessed the number of cigarettes smoked per day (CPD), was collected at baseline and during treatment (19). Participants rated their opioid-related craving and withdrawal on a 0–10 scale (0 = not at all, 10 = very much) at each injection session. A paired t-test was used to examine the change in CPD before and after the XR-NTX treatment. A repeated ANOVA was applied to examine the effect of XR-NTX on CPD during the treatment period, using XR-NTX treatment as a within-subject variable (baseline, weeks 4, weeks 8, and weeks 12) and gender (male vs. female) as a between-subject variable. Furthermore, we examined the relationships between CPD, days of opioid use in the last 30 days (preceding XR-NTX), opioid-related craving, and withdrawal using Pearson correlations.

Results

Sixty-four out of 72 OUD patients (89%) were daily tobacco cigarette smokers (CPD 14.38 ± 1.02, mean ±SE). None were enrolled or planning to enroll in a smoking cessation program at screening. Patients' primary misused substance was either heroin (55%) or prescription opioids (45%). The route of administration was intravenous in forty-five percent of participants, intranasal or oral in 50% and unknown in 5%. In the past thirty days, 31 (48%) of the participants reported also using cannabis, 20 (31%) used cocaine, 3 (5%) used amphetamines, and 40 (63%) used more than one substance. Participant characteristics are summarized in Table 1.

Six participants dropped out before the 1st XR-NTX injection, 36 received 1 injection, 6 received 2 injections, and 16 received 3 injections. There was

Table 1. Participant characteristics.

N	64
Age (years)	29.35 ± 8.90
Gender (N/%)	
Female	24 (37.5%)
Male	40 (62.5%)
Education (years)	13.64 ± 2.03
Race (N/%)	
Caucasian	57 (89%)
African American	5 (8%)
Asian	2 (3%)
Drug use in the past 30 days (days)	
Heroin	9.42 ± 1.40
Other Opioids	6.16 ± 1.19
Cocaine	2.00 ± 0.59
Cannabis	5.84 ± 1.27
Lifetime opioid use (years)	
Heroin	3.93 ± 0.83
Prescription Opioids	3.44 ± 0.41
Route of opioid use	
IV injection	29 (45%)
Non-IV injection	32 (50%)
Missing	3 (5%)

a significant decrease in CPD after the 1st XR-NTX injection ($t(54) = 5.70$, $p = 0.0000005$, paired t-test). The decline in cigarette consumption was sustained throughout the treatment ($F(3, 29) = 17.908$, $p = 0.000007$, one way repeated ANOVA with Greenhouse-Geisser correction). Post-hoc tests showed that participants smoked significantly fewer cigarettes per day during the XR-NTX treatment, compared to the baseline CPD (baseline vs. weeks 4, $p = 0.0001$, baseline vs. weeks 8, $p = 0.00007$, baseline vs. weeks 12, $p = 0.002$, weeks 4 vs. weeks 8, injection $p = 0.04$, Figure 1). There was no XR-NTX by gender interaction ($F(1, 30) = 0.404$, $p = 0.624$) nor overall gender effect ($F(1, 30) = 0.031$, $p = 0.861$). Baseline CPD were positively correlated with self-reported days of opioid use in the last 30 days ($r = 0.373$, $p = 0.003$). During XR-NTX treatment, CPD was positively correlated with symptoms of opioid-related craving ($r = 0.319$, $p = 0.021$) but not with opioid-related withdrawal ($r = 0.212$, $p = 0.132$).

Discussion

Extended-release opioid antagonist treatment (XR-NTX) for OUD was associated with a spontaneous reduction in cigarette smoking in patients who were not seeking smoking cessation. Smoking has

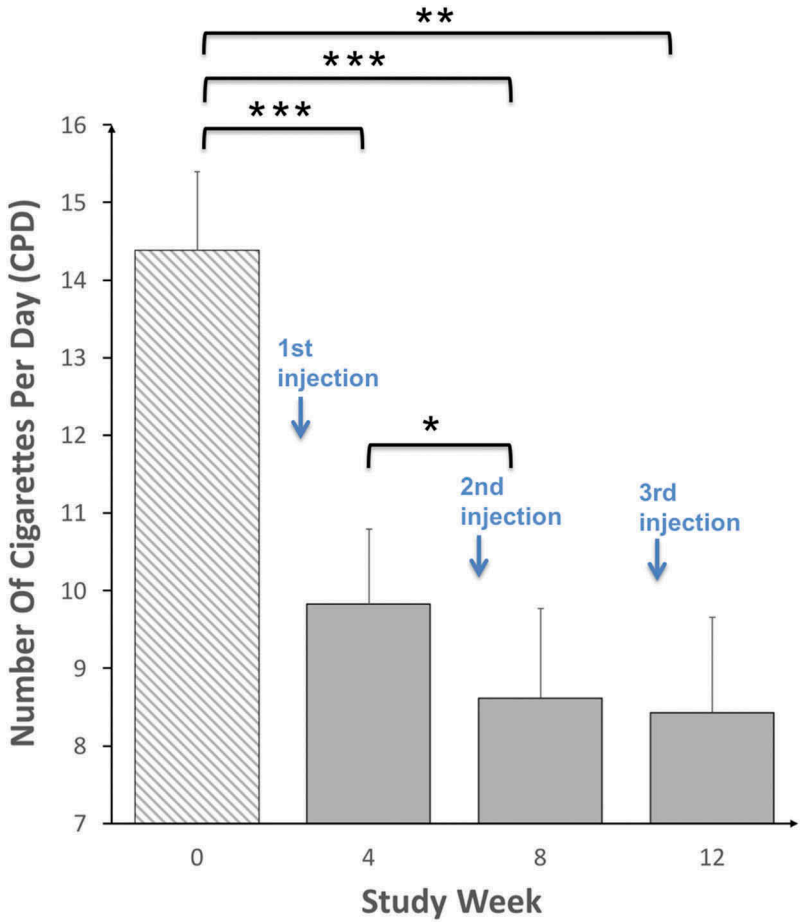

Figure 1. Change in number of cigarettes per day (CPD) during XR-NTX treatment in OUD patients who were cigarette smokers. Study week 0 = baseline, before the 1st injection. Error bars represent standard error of mean. *** <0.001, **<0.01, *<0.05.

historically been overlooked among the harm reduction goals of OST (5). However, the dramatic rise in the numbers of individuals exposed to both illicit and therapeutic opioids, along with the decline in the overall smoking prevalence in the US, calls for a re-examination of the public health significance of smoking in OUD (20,21).

Our observation is consistent with some, but not all, previous studies of opioid antagonists in human smokers without OUD. In a double-blind drug-placebo study, Wewers et al. (1998) found lower plasma nicotine levels, lower number of cigarettes smoked daily (CPD), and decreased satisfaction from smoking in smokers on oral naltrexone compared to placebo (22). Studies by other groups also reported a reduction in CPD after oral naltrexone administration (23–28). Although oral naltrexone showed acute or short-term benefits on changing smoking behaviors, including reduced CPD in smokers, it has had little to no success in promoting long-term smoking abstinence (29–31). The lack of efficacy in achieving long-term abstinence could be due to not accounting for gender differences (32), comorbidities (33), or disparate outcome measures (34). Moreover, the well known poor adherence to oral naltrexone (35) could have further reduced the reliability of the results.

As mentioned in the Introduction, pharmacodynamic interactions between opioid agonists and nicotine receptors could provide a mechanism for cross-sensitization, cross-tolerance, and opioid augmentation of nicotine reward (36). Indeed, our findings show a positive relationship between the frequency of opioid use and CPD at baseline and between opioid-related craving and CPD during the XR-NTX treatment. It could be that XR-NTX reduces the rewarding effects of nicotine directly or indirectly through the blockade of endogenous opioid neurotransmission (37). In OUD patients, XR-NTX also counters the effect of exogenous opioids, both illicit and prescribed, that increase nicotine reward.

Many smoking-related illnesses are, at least in part, dependent on the cumulative lifetime cigarette consumption. Thus an incremental reduction in the number of tobacco cigarettes smoked per day without cessation would be a meaningful harm reduction intervention. Although the effect may be limited to individuals with OUD whose endogenous opioidergic system is dysregulated, it is worthwhile to test whether it may generalize to smokers without co-morbid OUD. A potential limitation of excluding individuals with chronic medical illnesses that required medical monitoring and treatment could have created sampling bias against heavier smokers who may have been more likely to have smoking-related illnesses, such as chronic obstructive pulmonary disease (COPD). However, participants in our studies were 29 ± 9 years old, an age group in which the prevalence of clinically diagnosed COPD in smokers is less than 15%, reducing the possible impact of sampling bias (38–40). Future studies could use spirometry to screen for subclinical COPD in all participants (40).

Our observations come with a number of caveats. A secondary retrospective analysis of a within-subjects design can point to associations, but cannot establish causality. Another limitation of the retrospective analysis is the restricted number of smoking assessments. Our assessment of smoking was limited to self-reported number of CPD and did not include other standard instruments such as the Fagerstrom Test of Nicotine Dependence (FTND) or biochemical measures such as urine cotinine levels. Adding these measures to future studies could provide a useful additional perspective on the potential changes in nicotine dependence severity in response to treatment and subjective measures of smoking. Lastly, future studies may consider more advanced forms of data collection in participants' regular environment e.g. ecological momentary assessments (EMA) (41).

In summary, we observed a significant reduction in the number of cigarettes smoked per day during extended-release opioid antagonist treatment in smokers with OUD who were not seeking smoking cessation. Though our study design can only identify associations, our observations weigh in on the side of a significant number of prior studies suggesting that the link between opioid dependence and smoking may be diminished by sustained opioid antagonist treatment. An immediate clinical implication is that smoking should be taken into consideration when selecting pharmacotherapy for an OUD patient and monitored during treatment. Our findings are observational and preliminary. They address smoking reduction rather than cessation, which could be addressed in future research. However, since the harm of smoking is dose-dependent, even if the effect of XR-NTX on smoking does not extend to cessation, it would still have a significant public health impact. Lastly, in individuals without co-morbid substance use disorders, oral naltrexone has only been effective in certain subpopulations of women (24,31). However, even if the effect of XR-NTX on smoking is limited to individuals with OUD, the very large number of people currently exposed to therapeutic and illicit opioids suggests that our findings may have important public health implications. This potential public health importance justifies confirming our findings in a prospective controlled

study of XR-NTX in OUD patients with comorbid tobacco use disorder.

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