Evidence for an association between nicotine and the endogenous opioid system comes from several lines of research. Studies have shown that administration of nicotine and/or stimulation of nicotinic receptors activates beta-endorphin and enkephalin release and biosynthesis (Eiden et al., 1984; Gilbert et al., 1992; Houdi et al., 1991; Pomerleau et al., 1983). In addition to having higher rates of smoking than in the general population, heroin addicts have been shown to smoke more during heroin self-injection (Mello et al., 1980) and smoke less during methadone dose tapering (Bigelow et al., 1981). Furthermore, opioid antagonists block certain effects of nicotine, including antinociception, operant responding, and prolactin release (Aceto et al., 1993; Corrigall et al., 1988; Flores et al., 1989). The opioid antagonist naloxone has also been shown to induce withdrawal-like states in nicotine-dependent rats and humans (Krishnan-Sarin et al., 1999; Malin et al., 1993, 1996). Conversely, nicotine has also been shown to suppress opioid antagonist effects such as decreasing naloxone-induced jumping in morphine-dependent mice (Brase et al., 1974; Zarrindast and Farzin, 1996).

Although there seems to be evidence of an opioid–nicotine interaction from in vivo and in vitro studies, human preclinical studies have largely shown mixed results. Specifically, there are varied results from laboratory studies on the effects of the opioid antagonists naltrexone (or intravenous naloxone) on aspects of smoking response. Some studies have shown that naltrexone or naloxone significantly reduce subjects’ self-reported pleasure or satisfaction from smoking; perceived difficulty in abstaining, craving, and urge to smoke; and the number of cigarettes smoked or puffs taken (Gorelick et al., 1989; Houtsmuller et al., 1997; Nemeth-Coslett and Griffiths, 1986; Sutherland et al., 1995). Also, naltrexone or naloxone has been shown to increase smokers’ negative mood and withdrawal-like symptoms (Brauer et al., 1999; Krishnan-Sarin et al., 1999). Collectively, there seems to be a lack of consistency in findings from preclinical human laboratory studies on opioid antagonist effects on smoking behaviors. Although there are no simple explanations, several methodological issues may be contributing to this disparity, such as the use of small sample sizes, lack of statistical power, a range of naltrexone or naloxone doses or routes of administration, and fundamental differences in paradigms (timing issues, degree of naturalism, baseline abstinence, etc.).

A few studies have examined naltrexone in smoking cessation, and no studies have examined concurrent smoking and alcohol behaviors in study patients. As in laboratory studies, the results from clinical trials using adjunct treatment with naltrexone for nicotine dependence have shown mixed results, with negative findings in one study (Wong et al., 1999) and positive or mixed findings in two other studies (Covey et al., 1999; O’Malley et al., 1997). Although it is well established that alcohol may increase the risk for smoking relapse (Baer and Lichtenstein, 1988; Brandon et al., 1990; Shiffman 1982, 1986), smoking cessation trials have not systematically targeted pharmacological treatment strategies that may affect both behaviors. It is possible that naltrexone, a medication used for alcohol dependence (O’Malley et al., 1992; Volpicelli et al., 1992) and posited to block alcohol’s pleasurable effects (King et al., 1997; O’Malley et al., 1996; Swift et al., 1994; Volpicelli et al., 1995), might theoretically be an effective smoking cessation treatment agent, especially in smokers who drink. This may be due in part to direct nicotine–opioid system interactions (as stated earlier), as well as blockade of alcohol reward and concomitant drinking episodes, which bode poorly for smoking outcome. Finally, the timing of naltrexone may be an important variable. Data from our previous laboratory study (King and Meyer, 2000) indicate that naltrexone attenuated smoking urge and pleasure during and after cigarette exposure; therefore, medication randomization...
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preceeding the quit date (QD) could potentiate the desired medication effect.

The current study explored preliminary data from an ongoing double-blinded, placebo-controlled trial examining the efficacy of naltrexone in comprehensive smoking cessation treatment. All participants received individual behavioral counseling for six sessions with a master's- or doctoral-level therapist (King and Riley, 2001). At the second therapy session, participants were randomized to naltrexone or placebo and given instructions to start taking their assigned tablets daily starting 3 days before the QD (at 25 mg daily) and to continue for 8 weeks (at 50 mg daily). The subjects' QD was usually on their third session in the program (i.e., 2 weeks after starting therapy sessions), and the nicotine patch was initiated on this day and proceeded for 1 month (at 21 mg daily for 2 weeks; 14 mg daily for 1 week; 7 mg daily for 1 week). Assessments were made during weekly visits with the main outcome intervals at 1 and 2 months after the QD, as well as during a 6-month follow-up.

To be eligible for participation, subjects must have been between the ages of 21 and 65 years inclusive, self-reported smoking at least 15 cigarettes daily for 2 or more years with a current desire to quit (scoring at least a 6 of 10 on a contemplation ladder), have no current major medical or psychiatric disorders as deemed through medical evaluation and a modified diagnostic interview, and have ≥1 year abstinence from alcohol or drug dependence, if applicable. In addition, for study inclusion, urine toxigology screening (e.g., opiates, benzodiazepines, barbiturates, amphetamine, phencyclidine) must have been negative, and pregnancy screening must have been negative and adequate birth control must have been reported during participation for female participants.

Preliminary data on smoking and alcohol behaviors during initial smoking cessation, i.e., the first month after the QD, were examined in the first 41 participants enrolled in the trial. Five subjects (12%) were enrollment failures and dropped out before randomization, leaving a total of 36 randomized to naltrexone (n = 17) or placebo (n = 19). The subjects had a mean age of 40 years (range 23–58); education level of 14.7 years (range 12–18); and racial/ethnic composition of 67% non-Hispanic white, 22% black, and 11% Other. They smoked on average one pack of cigarettes daily (mean 20.4, range 12–40) for approximately 20 years (mean 19.8, range 2–40), with moderate/heavy levels of nicotine dependence [mean score on the Fagerström Test of Nicotine Dependence (Heatherton et al., 1991) 5.8, range 1–10]. The average weekly alcohol consumption was 6.0 drinks weekly (range 0–30 drinks). Finally, history (≥1 year of abstinence) of alcohol dependence or current or past alcohol abuse was prevalent in 33% of the participants.

Outcome was examined on a variety of domains for the present article. Because data were available only during the first month of smoking cessation, we examined several behavioral and subjective effects during this period. These measures included acute subjective effects (smoking, drinking, eating) before and after the QD, incidence of side effects, craving scores measured by the Brief Questionnaire of Smoking Urges (B-QSU) (Cox et al., 2001), smoking and alcohol behaviors measured by a timeline follow-back method (Sobell et al., 1979), and smoking quit rates (i.e., continuous abstinence) at the 1-month interval.

The preliminary data revealed that naltrexone, compared with placebo, diminished pre-QD ratings of pleasure in alcohol, the urge to smoke, pleasure in smoking, and cigarette taste. There were no differences between the groups in ratings of pleasure from food, appetite, or pre-QD drinking behaviors. Although the absolute number of side effects reported during the first few weeks of cessation was similar between the groups, naltrexone seemed to be increasing ratings of nausea and tiredness in particular by approximately 10 to 25% over placebo, but headache was 10% lower than in placebo. In most cases, the side effects endorsed were rated in the mild range. In terms of smoking urge, levels before the QD were higher than after the QD for both groups, with the naltrexone group showing reduced post-QD ratings for B-QSU factor 1 (smoking for stimulating effects) and factor 2 (smoking to relieve unpleasant affect or withdrawal) compared with placebo.

Data from the timeline follow-back indicated lower levels of alcohol drinking in the naltrexone versus placebo group, especially during the first few weeks after smoking cessation with drinking levels starting to increase by the fourth week. Participants reported dramatic declines in the average number of cigarettes smoked per week (from a baseline mean of 120.5 cigarettes/week to a mean of 6.6 cigarettes/week), with these declines relatively similar in the naltrexone and placebo groups. However, in terms of initial continuous abstinence at 1 month, the naltrexone group showed better quit rates than the placebo group (59% vs. 37%).

In conclusion, although the data are preliminary, they do warrant continued investigation of naltrexone in smoking cessation. The study also bridges laboratory and clinical methodologies, and the results showed that during the several days leading to the QD, naltrexone altered subjective response to cigarettes; after the QD, naltrexone decreased alcohol drinking and improved smoking quit rates. During the initial, acute outcome phase in the program, all participants were receiving individual behavioral counseling sessions, nicotine patch, and either naltrexone or placebo. The next month in the program, the relapse prevention phase (i.e., second month after QD), and the 6-month follow-up may provide more rigorous tests of the longer-term effects of naltrexone on outcome indices because participants will no longer be in concomitant therapy or nicotine replacement.

Finally, it is also advised that clinical trials in smoking cessation begin to systematically investigate the complex interplay between alcohol and cigarette use, both before
and after the QD. Examining concurrent use of alcohol and tobacco in smokers during a cessation trial and targeting pharmacotherapy and psychotherapy interventions may improve outcome for patients who historically have had difficulty in quitting smoking.

REFERENCES


