

# Transdermal nicotine attenuates depression symptoms in nonsmokers: a double-blind, placebo-controlled trial

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## Abstract

**Rationale** Despite established links between nicotine dependence and depression, little research has examined the effects of nicotine on depression symptoms.

**Objective** This study evaluated the acute and chronic effects of transdermal nicotine in nonsmokers with baseline depression symptoms during a 4-week, double-blind, placebo-controlled trial.

**Methods** Nonsmokers with scores  $\geq 10$  on the Center for Epidemiological Studies Depression scale (CES-D) were recruited from the community. Mood and cognitive performance were measured at baseline (day 0) and at 1, 8, 21, and 28 days. Participants were randomly assigned to wear a placebo or nicotine patch for 4 weeks (3.5 mg/day during weeks 1 and 4; 7 mg/day during weeks 2 and 3). The final sample consisted of 11 nonsmokers with a mean baseline CES-D score of 27.36 (SD=10.53).

**Results** Salivary nicotine levels indicated the majority of participants were compliant with treatment. Acute nicotine did not alter mood. After adjusting for baseline values, chronic nicotine resulted in a significant decline in CES-D scores at day 8 (3.5 mg/day), but returned to placebo levels by the last visit. This return to baseline levels was coincident with a decrease in nicotine administration from 7 to 3.5 mg/day. A similar trend for improved response inhibition as measured by the Conners Continuous Perfor-

mance Task was also observed. Reported side effects were infrequent and minimal.

**Conclusion** These findings suggest a role for nicotinic receptor systems in the pathophysiology of depression and that nicotinic compounds should be evaluated for treating depression symptoms.

**Keywords** Cognitive performance · Depression · Nicotine · Mood

## Introduction

Links between depression and tobacco use are well established. Individuals with current or lifetime history of major depressive disorder (MDD) are twice as likely to be smokers (Lasser et al. 2000). Furthermore, individuals with a past history of MDD or depressive traits are less likely to succeed in quitting smoking (Anda et al. 1990; Gilbert et al. 1999) and, during cessation, experience more intense depressed moods (Gilbert et al. 1998, 2002) or depressive episodes (Covey et al. 1997; Glassman et al. 2001). Twin studies (Kendler et al. 1993) suggest a common genetic basis for smoking and depression, and candidate gene studies (Audrain-McGovern et al. 2004; Lerman et al. 1998) indicate specific genes may mediate relations between these two syndromes.

Animal studies support the role of nAChR systems in the pathophysiology of depression (Dursun and Kutcher 1999) as nicotine and nAChR agonists have demonstrated antidepressant effects in genetic (Djuric et al. 1999; Tizabi et al. 1999) and behavioral (Ferguson et al. 2000) models of depression in rats. For instance, both acute nicotine and chronic nicotine improve a depressive characteristic (i.e., immobility during a forced swim task) in a line of

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selectively bred rats that has been proposed as an animal model of depression (Djuric et al. 1999; Tizabi et al. 1999).

Human studies have also evaluated the effects of nicotine administration on depression symptoms. In a series of open-label small-sample trials with nonsmoking MDD patients (Salin-Pascual 2002; Salin-Pascual and Drucker-Colin 1998; Salin-Pascual et al. 1996), transdermal nicotine reduced depression symptoms and improved rapid eye movement (REM) sleep time. One small-scale randomized placebo-controlled trial of nicotine for depression has also been conducted (Cox et al. 2003). Seven unmedicated nonsmokers with MDD received a placebo patch or the following course of transdermal nicotine: 7 mg/day (2 days), 14 mg/day (2 days), and 21 mg/day (4 days). Hamilton Rating Scale for Depression (HAM-D) scores decreased significantly among patients treated with nicotine; however, similar decreases were observed in the placebo group. Thus, although previous human studies have been conducted, the design or small-scale nature of these studies precludes making any strong conclusions regarding the effects of nicotine on depression symptoms.

The goal of the present study was to evaluate the effects of nicotine on depression symptoms, mood, and cognitive performance in a randomized, double-blind, placebo-controlled trial. We chose as our sample nonsmokers with minimal depression symptoms, but not currently being treated for MDD. Patients were administered either placebo patches or the following regimen of transdermal nicotine: 3.5 mg/day (week 1), 7 mg/day (weeks 2 and 3), and 3.5 mg/day (week 4). This dosing regimen is similar to other human trials that have observed improvements in mood and cognition in a broad range of patient groups including attention deficit hyperactivity disorder (ADHD) (Levin et al. 2001), Alzheimer disease (White and Levin 1999), and age-associated memory impairment (White and Levin 2004).

## Method

### Participants

Participants were 16 adult nonsmokers with depression symptoms recruited from the general community. Participants who reported more than three depression symptoms over the previous 2 weeks and smoking less than 100 cigarettes during their lifetime during a phone screening were invited to participate in a laboratory screening visit. The laboratory screening visit included a physical by the study physician, an electrocardiogram (EKG), and blood and urine tests. Participants were included in the study if they had a score  $\geq 10$  on the Center for Epidemiologic Studies Depression Scale (CES-D). Participants were

excluded if they were diagnosed with a psychiatric disorder or were receiving treatment (medication or psychosocial) for any psychiatric condition including MDD. All participants did not have any conditions contraindicated for transdermal nicotine treatment (e.g., skin condition, hypertension). Three participants were excluded for having CES-D scores that were too low at screening ( $< 10$ ). An additional participant whose nicotine level during the trial did not reflect compliance was also excluded from the final sample. One participant experienced an adverse effect of the patch (i.e., dizziness) and did not complete the trial. The remaining participants were randomly assigned to the placebo ( $n=6$ ) or nicotine patch ( $n=5$ ) groups. All participants read and signed an IRB-approved informed consent form.

### Procedure

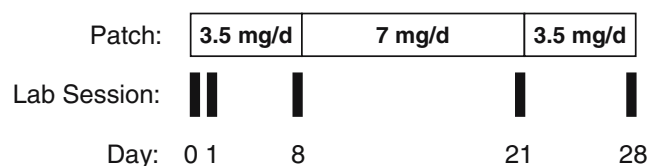
Following screening, enrolled participants completed laboratory sessions at baseline (day 0) and at 1, 8, 21, and 28 days after the baseline session (see Fig. 1). Although start times varied, all sessions started at approximately the same time of day for each participant.

At the beginning of the 4-h baseline session, vitals were measured, and participants provided a saliva sample and completed measures of mood, cognition, and side effects. A nicotine or placebo patch was then applied (see “Nicotine patches” below), and for the next 2.5 h, participants read, filled out questionnaires, and relaxed. Vitals and side effects were monitored during this time. Following this period, mood and cognitive measures were administered a second time.

The remaining laboratory sessions were similar to the baseline session, except that measures were only administered once and a patch was not applied.

### Nicotine patches

Transdermal nicotine patches were 3.5- and 7-mg/day Nicoderm CQ patches; 3.5-mg/day patches were made by cutting 7-mg/day patches in half. During pilot work, these patch doses were found to minimize nausea and other side effects in nonsmokers. Placebo patches were obtained from 1-800-PATCHES. All patches were repackaged in order to provide uniform appearance. Participants were instructed to



**Fig. 1** Nicotine patch dose and laboratory sessions by day in the trial

remove the patch before going to bed at night and apply a new patch every morning.

A 3.5-mg/day nicotine patch or placebo patch was applied during the baseline session. Participants were given 3.5-mg/day or placebo patches to wear during the first week, 7-mg/day or placebo patches for the following 2 weeks, and 3.5-mg/day or placebo patches for the last week of participation. All participants were informed of this dosing strategy throughout the study.

#### Biochemical verification

Nonsmoker status and compliance with instructions to wear the nicotine patch were verified via salivary nicotine levels. Saliva samples were collected from all participants at each laboratory session. All samples from participants in the nicotine patch group were analyzed, but we only analyzed samples from participants in the placebo group that were acquired at baseline and at the day-1 and day-28 sessions.

Salivary nicotine was assessed by gas chromatography following the method of Jacob et al. (1981), modified for use of a capillary column. Salivary nicotine levels after transdermal administration are proportional to blood levels and are approximately eight times higher (depending on the pH of saliva) (Rose et al. 1993).

#### Measures of mood, depression, and other symptoms

*The Center for Epidemiologic Studies Depression Scale* The CES-D (Radloff 1977) is a 20-item, widely used, self-report measure of depressive symptomatology over the previous week. Items were rated on a three-point Likert scale ranging from 0 “Rarely or none of the time (less than 1 day)” to 3 “Most or all of the time (5–7 days).” Four positively worded items, such as, “I felt happy; I enjoyed life,” were reverse scored. The CES-D was used as a screening instrument and also administered at the beginning of each laboratory session. A cutoff of  $\geq 10$  for inclusion in the study was used to ensure that participants had at least minimal depression symptoms. When used as screening measure for major depression, scores between 15 and 21 are considered indicative of mild to moderate depression and scores  $>22$  indicative of probable major depression (Radloff 1977).

*The Positive and Negative Affect Schedule* The Positive and Negative Affect Schedule (PANAS) (Watson et al. 1988) is a 20-item self-report measure of positive and negative affective states. The PANAS consists of adjectives (e.g., excited, guilty, alert, jittery), and participants rate their current state on a scale from 1 “Very slightly or not at all” to 4 “Extremely.” Scale scores were calculated separately for positive and negative affect. The PANAS was used to

measure affective state at the beginning and end of the baseline laboratory session to evaluate the acute effect of nicotine and at the beginning of each subsequent session.

*The Profile of Mood States-Bipolar* The Profile of Mood States-Bipolar (POMS-Bi) (Lorr and McNair 1984) is a 72-item self-report measure of six bipolar mood states. The POMS-Bi consists of a list of adjectives and descriptive phrases (e.g., angry, dejected, nervous, bold), and participants rated how much they feel like each descriptor on a scale ranging from 0 “Much unlike this” to 3 “Much like this” over the previous 24 h. The POMS-Bi measures the following six mood states: composed–anxious, agreeable–hostile, elated–depressed, confident–unsure, energetic–tired, and clearheaded–confused. The POMS-Bi was administered at the beginning of each laboratory session.

*Side effects* A 23-item self-report questionnaire was used to measure psychological (e.g., Do you feel tense?) and physical (e.g., Do you feel nauseated?) symptoms associated with wearing a nicotine patch. Items were rated on a seven-point Likert scale from “Not at all” to “Extremely.” The side effects questionnaire was administered during the baseline laboratory session in order to monitor responses to acute nicotine and at the beginning of each subsequent laboratory session. Data from the questionnaire were tabulated, but not statistically analyzed.

#### Measures of cognition

The following measures of cognition were administered pre and post nicotine administration at baseline and once during each of the subsequent laboratory sessions. Our objective was to include a broad range of measures that had been shown to be improved by nicotine in previous studies [e.g., hit reaction variability on the Conners Continuous Performance Task (CPT); see below] or were known to be deficient among individuals with depression symptoms (e.g., verbal memory; Bearden et al. 2006). We hypothesized that nicotine would improve performance on these measures.

*The Automated Neuropsychological Assessment Metrics battery* The Automated Neuropsychological Assessment Metrics (ANAM) (Reeves et al. 1995) consisted of a battery of four computerized tasks. The simple reaction time (SRT) task required participants to press a button whenever a target “\*” appeared on the screen. The mental spatial rotation task (MSRT) required participants to determine whether a stimulus consisting of four bars of varying lengths was a rotation of a previously presented stimulus. The delayed match to sample task (DMST)

required participants to determine which of two geometric patterns matched a previously shown pattern following varying delays. Finally, participants completed a finger-tapping task in which participants were required to tap a mouse button as fast as possible. Response accuracy and reaction time were measured during the SRT, MSRT, and DMST tasks, whereas number of taps was measured during the finger-tapping task. ANAM measures have been shown to be sensitive to the effects of nicotine in schizophrenic (Smith et al. 2002) and age-associated memory impairment (White and Levin 2004) samples.

**Conners Continuous Performance Task** The CPT (Conners 1994) is a measure of both vigilance and response inhibition. During the task, participants were required to press a button whenever a letter appears on the screen unless that letter is an “X.” Measures of attentional control (e.g., accuracy and reaction time variability) and response inhibition (e.g., errors of commission—pressing the button on “X” trials) served as the primary dependent variables. The CPT has been shown to be sensitive to nicotine effects in ADHD (Conners et al. 1996; Levin et al. 2001), Alzheimer disease (White and Levin 1999), and age-associated memory impairment (White and Levin 2004) and in individuals with suboptimal attentional functioning (Poltavski and Petros 2006).

**The Verbal Selective Reminding Task** Individuals with unipolar depression have been shown to exhibit deficits in verbal memory (Bearden et al. 2006). A six-trial version of the Verbal Selective Reminding Task (VSRT) (Hannay and Levin 1985), a measure of verbal supraspan learning, was administered. The VSRT requires participants to learn a list of 12 unrelated words over six trials. On the first trial, they are told all 12 words. On each successive trial, they are only retold those words they omitted on the previous trial. Recall and recognition are measured 30 min after the final learning trial.

## Data analysis

The acute and chronic effects of transdermal nicotine were analyzed separately. In order to evaluate the effects of acute nicotine, pre and post scores from the baseline session were entered into a 2 (patch group: placebo, nicotine)  $\times$  2 (time: pre, post) analysis of variance (ANOVA). The effects of chronic nicotine were evaluated with a 2 (patch group: placebo, nicotine)  $\times$  4 (visit: day 1, day 8, day 21, day 28) analysis of covariance (ANCOVA). Values obtained prior to patch administration during the baseline session (day 0) served as covariates in order to control for baseline individual differences. Given the nature of our design in which nicotine dose was increased and then decreased over time, we specifically evaluated quadratic effects. Greenhouse–Geisser correction was applied where appropriate. Given the a priori specificity of our hypotheses, post hoc tests were conducted at  $p < 0.05$ .

## Results

### Sample characteristics

Table 1 provides a summary of sample characteristics. No significant differences between the groups were observed for any potentially important demographic or other measures. Baseline ANAM mean finger-tapping scores were higher in the placebo (mean=54.50, SEM=1.76) than that in the nicotine (mean=43.40, SEM=3.75) group,  $t(9)=2.84$ ,  $p=0.019$ . No other baseline group differences on cognitive measures were observed.

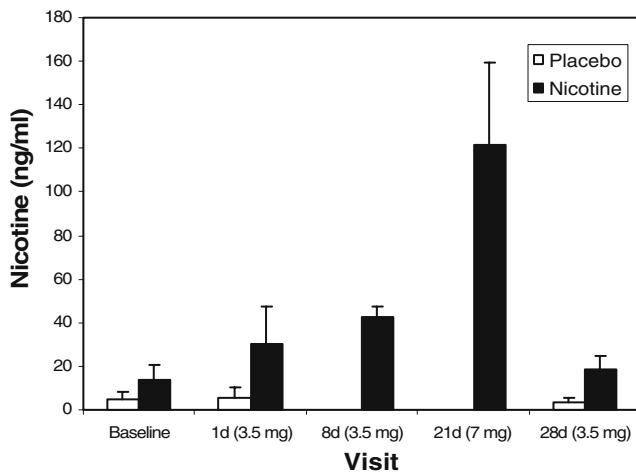
### Biochemical verification

Salivary nicotine levels were consistent with group and nicotine dose and within normal limits (see Fig. 2). For the nicotine group, levels were 4.55 ng/ml (SEM=3.09), 30.54 ng/ml (SEM=16.78), 42.82 ng/ml (SEM=4.67), 121.68 ng/ml (SEM=37.94), and 18.21 ng/ml (SEM=6.41) at screening at 1, 8, 21, and 28 days, respectively.

**Table 1** Participant characteristics for the total sample and each group

	Full sample ( $n=11$ )	Placebo group ( $n=6$ )	Patch group ( $n=5$ )	$\chi^2$ or $t$	$p$
Gender ( $n$ , % female)	9 (82%)	5 (83%)	4 (80%)	0.02	0.89
Education level ( $n$ , % with some college or higher)	9 (82%)	5 (83%)	4 (80%)	2.07	0.56
Race ( $n$ , % nonwhite)	6 (55%)	3 (50%)	3 (60%)	0.11	0.74
Age (mean, SEM)	33.91 (3.25)	34.33 (4.29)	33.4 (5.52)	0.14	0.89
Baseline CES-D (mean, SEM)	27.18 (3.22)	30.83 (4.32)	22.8 (4.49)	1.28	0.23
Baseline salivary nicotine (mean, SEM)	8.47 (10.66)	4.97 (3.01)	13.73 (6.87)	1.33	0.22

Chi-square (gender, race) and  $t$  tests (age, baseline CES-D, baseline salivary nicotine) did not reveal any group differences (all  $ps > 0.05$ ).



**Fig. 2** Salivary nicotine levels (nanograms per milliliter) in the nicotine and placebo groups. Samples were acquired from the placebo group at each session but only analyzed at baseline (day 0), day 1, and day 28. Nicotine patch dose is indicated for each visit

#### Effects of acute nicotine

The acute effects of nicotine administration during the baseline session were evaluated using 2 (patch group: placebo, nicotine)  $\times$  2 (time: pre, post) ANOVAs.

We observed no effects of patch group on mood. However, mood improved over the course of the session across groups as evidenced by main effects of time for the following POMS scales: composed–anxious [pre mean=19.55, SEM=2.78; post mean=24.73, SEM=2.39;  $F(1,9)=7.86$ ,  $p=0.021$ ], confident–unsure [pre mean=16.73, SEM=2.30; post mean=20.55, SEM=2.10;  $F(1, 9)=14.94$ ,  $p=.004$ ], clearheaded–confused [pre mean=19.82, SEM=2.08; post mean=23.18, SEM=1.88;  $F(1, 9)=8.72$ ,  $p=0.016$ ]. No effects were observed for the PANAS.

With regard to measures of cognition, main effects of time were observed for Conners CPT RT [pre mean=379.06, SEM=17.88; post mean=358.97, SEM=56.24;  $F(1,9)=12.79$ ,  $p=.006$ ] and ANAM match to sample RT [pre mean=1,798.83, SEM=224.97; post mean=1227.99, SEM=151.55;  $F(1,9)=15.07$ ,  $p=.004$ ]. A time  $\times$  patch group interaction was observed for match to sample accuracy [ $F(1,9)=5.347$ ,  $p=.046$ ]. In the placebo patch group, accuracy (percentage correct) decreased from pre (mean=86.66, SEM=8.07) to post (mean=81.11, SEM=11.08), whereas in the nicotine patch group, accuracy improved (pre mean=74.67, SEM=10.62; post mean=87.99, SEM=7.117). The improvement by nicotine was marginally significant ( $p=.054$ ), whereas the decrement observed in the placebo group was not. The two groups did not differ significantly at either pre or post. Participants in the placebo patch group made a significantly greater number of tapping responses (mean=53.92, SEM=1.49) than participants in the nicotine patch group (mean=43.60, SEM=3.88),  $F(1,9)=$

7.101,  $p=.026$ . However, finger-tapping performance did vary over the course of the session, and thus, these group differences likely do not reflect nicotine effects.

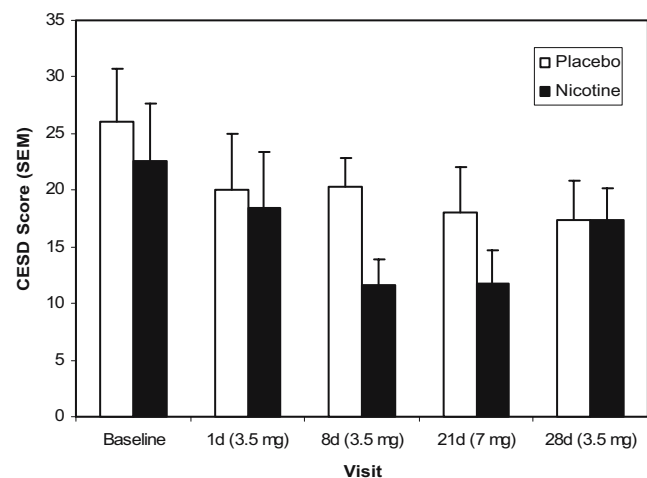
Heart rate decreased significantly over the course of the session for both groups from 78.82 bpm (SEM=4.072) to 66.55 bpm (SEM=3.571),  $F(1, 9)=10.82$ ,  $p=0.002$ . No other changes in vitals were observed.

Reports of side effects due to wearing the patch during the baseline session were infrequent. Participants in the nicotine patch group reported increased heart rate ( $n=2$ ), unusual sleepiness ( $n=2$ ), and dizziness ( $n=1$ ). Participants in the placebo patch group reported increased heart rate ( $n=1$ ), fluttery feelings in the chest ( $n=1$ ), unusual sleepiness ( $n=1$ ), headache ( $n=1$ ), upset stomach ( $n=1$ ), and tightness in the chest ( $n=1$ ).

#### Effects of chronic nicotine

Consistent with our hypothesis, chronic nicotine did improve scores on the CES-D. A significant quadratic patch group  $\times$  visit interaction was observed [ $F_{\text{quadratic}}(1, 8)=10.82$ ,  $p=0.011$ ] for CES-D scores (see Fig. 3). Significantly lower scores were observed in the nicotine group at day 8 ( $p<0.05$ ). A similar pattern of results was observed for the elated–depressed scale of the POMS-Bi [ $F_{\text{quadratic}}(1, 8)=10.54$ ,  $p=0.012$ ]. No other effects were observed for mood measures (i.e., PANAS, POMS).

A trend for a significant patch group  $\times$  visit quadratic interaction for number of errors of commission on the Conners CPT task was observed [ $F_{\text{quadratic}}(1, 8)=4.74$ ,  $p=0.061$ ]. Similar to depression scores, commission errors were lower in the nicotine group following 8 (nicotine mean=10.00, SEM=2.28; placebo mean=12.33, SEM=3.14) and 21 (nicotine mean=8.20, SEM=2.24; placebo mean=12.83, SEM=2.65) days of nicotine treatment,



**Fig. 3** Mean CES-D scores in the nicotine and placebo groups. CES-D scores were significantly lower in the nicotine group ( $p<0.05$ ) at day 8 compared with that in the placebo group

although post hoc tests did not indicate significant group differences. Baseline commission errors did not differ between the two groups [nicotine mean=11.2, SEM=1.98; placebo mean=14.17, SEM=4.98;  $t(9)=0.51$ ,  $p=0.62$ ]. No other effects on cognitive performance were observed.

No effects of nicotine or visit were observed for heart rate, blood pressure, or weight. Participants reported infrequent side effects associated with wearing the nicotine patch. One participant reported greater than usual sleepiness and perception of increased heart rate while wearing the 3.5-mg/day patch. Another participant reported a headache while wearing the 3.5-mg/day patch. One participant experienced significant dizziness upon starting the 7-mg/day nicotine patch and discontinued participation in the trial. No other adverse events or significant side effects were reported.

## Discussion

This double-blind, placebo-controlled trial provides additional evidence that transdermal nicotine can attenuate depression symptoms among nonsmokers. Administration of 3.5 mg/day transdermal nicotine for 8 days decreased depression symptoms as measured by the CES-D and also showed limited evidence of improving response inhibition as measured by the Conners CPT. Acute effects of nicotine were observed for one cognitive measure but not measures of mood. Nicotine was well tolerated by our sample, resulting in very few side effects or adverse events.

Our findings are consistent with the hypothesis that some individuals smoke in order to attenuate negative affect. Smokers are higher in trait negative affect than their nonsmoking counterparts (Terracciano and Costa 2004), and a disproportionately large number of individuals with lifetime depression smoke (Lasser et al. 2000). Furthermore, quitting smoking increases depression symptoms (Gilbert et al. 1998, 2002), and individuals with a history of major depression are at increased risk for a major depressive episode following quitting (Glassman et al. 2001).

Despite these links between smoking and depression, it has been unclear whether smokers with depression symptoms self-administer nicotine in order to gain improvements in mood (positive reinforcement) or to avoid mood worsening brought on by nicotine abstinence (negative reinforcement). Whereas many studies have demonstrated the negative reinforcing effects of smoking abstinence and subsequent nicotine administration among smokers, the absolute, positive reinforcing effects of nicotine have been difficult to accurately evaluate among these individuals since they cannot be readily distinguished from withdrawal alleviation effects. Several studies, however, have demon-

strated beneficial effects of nicotine on mood among nonsmokers. For instance, in a study with a design similar to ours but in a sample of nonsmoking adults with ADHD, Levin et al. (2001) observed nicotine to decrease depression scores as measured by the POMS following the 15th (but not first) day of nicotine administration. In another study, nicotine was shown to reduce anger states among both smokers and nonsmokers high in trait-hostility (Jamner et al. 1999). These findings, along with our own, suggest that nicotine administration can result in reductions in negative affect, independent of any negative reinforcing effects. Furthermore, these findings suggest that mood-enhancing effects may arise only after chronic administration.

Consistent with previous research, we observed very limited acute effects of nicotine on mood and/or cognition. With regard to mood and affect, nonsmokers typically find nicotine aversive and acute administration typically results in increases in negative affect that diminish to some degree with repeated administrations (Heishman and Henningfield 2000). A great deal of research has sought to identify cognition-enhancing effects of acute nicotine in nonsmokers (Heishman 1998; Heishman et al. 1994), although these effects have typically been small and difficult to replicate (Kleykamp et al. 2005; McClernon et al. 2003). In contrast, a number of studies have found acute nicotine to improve cognition in nonsmoking clinical samples including ADHD, Alzheimer, Parkinson, and schizophrenia (for a review, see Levin et al. 2006). Thus, although our results are from a small sample that only received a single acute dose of nicotine, they are more consistent with previous studies of the effects of acute nicotine in nonclinical samples of nonsmokers.

Our findings are also largely consistent with previous research seeking to evaluate the effects of nicotine on depression symptoms (Cox et al. 2003; Salin-Pascual 2002; Salin-Pascual and Drucker-Colin 1998; Salin-Pascual et al. 1996). Salin-Pascual (2002) observed 17.5 mg/day transdermal nicotine to decrease depression symptoms as measured by the HAM-D over 4 days of treatment in a sample of medication-free nonsmokers with major depression. During a 4-day follow-up phase during which no nicotine was administered, HAM-D scores returned to pretreatment levels. Cox et al. (2003) also sought to evaluate the effects of transdermal nicotine in nonsmokers with major depression in a double-blind, placebo-controlled trial. Patients assigned to the nicotine group received the following course of nicotine: 7 mg/day for 2 days, 14 mg/day for 2 days, and 21 mg/day for 4 days. Nicotine resulted in decreased depression scores as measured by the HAM-D, but depression scores also declined significantly in the placebo group. However, the authors recognize that their small sample may have resulted in these findings. The current study differs from these by utilizing a sample with

depression symptoms but without diagnosed MDD. This approach made recruiting an unmedicated sample of non-smokers less difficult, but may limit generalizability to individuals without the disorder. At the same time, the majority of participants in our study reported baseline CES-D scores at or above the cutoff for probable major depression ( $n=7$ , 64%), and thus, our findings might extend to individuals with MDD. The current study also differed from previous studies by administering a lower dose of nicotine for a longer period of time.

The present results provide additional evidence for neurobiological links between smoking and depression. Treatments designed to increase levels of brain amines (e.g. selective serotonin reuptake inhibitors; SSRIs) are effective in the treatment of depression. Since nicotine stimulates the release of neurotransmitters including serotonin, dopamine, and norepinephrine (Watkins et al. 2000), it has been proposed that nicotine may have antidepressant effects which may account for the disproportionately greater use of tobacco products among individuals with depression and/or elevated trait negative affect (Dursun and Kutcher 1999). Although our results support this view, it should be noted that tobacco use results in the administration of other compounds that may alleviate depression symptoms. Smokers have been shown to have significantly lower brain monoamine oxidase enzyme (MAO) levels than nonsmokers (Fowler et al. 1996a,b), and research has identified compounds in tobacco smoke that inhibit MAO (Castagnoli et al. 2002). The effect of MAO inhibition by tobacco constituents is a decrease in brain amine turnover which would likely serve to potentiate any antidepressant effects of nicotine. Thus, although the present study did not manipulate MAO levels, findings regarding MAO-inhibitory effects of cigarette smoke and the use of MAO inhibitors to treat depression suggest that MAO inhibition likely plays a role in the link between smoking and depression.

In addition to stimulating brain amine release, another possible mechanism by which nicotine might improve depression symptoms involves neurogenesis. Studies have demonstrated that nicotine administration can result in changes in the expression of genes linked to neurogenesis (Belluardo et al. 1998, 2005), and this mechanism has been proposed as a possible explanation for neuroprotective and neurotrophic effects of the compound (Belluardo et al. 2000). For instance, Maggio et al. (1998) found nicotine to be neuroprotective of dopamine neurons in animal models of parkinsonism and to be associated with upregulation of genes responsible for the transcription of neural protective factors in the striatum. Furthermore, recent studies suggest that alteration of neurogenesis may play a critical role in both the pathophysiology and treatment of depression (for a review, see Duman and Monteggia 2006). For instance, exposure to inescapable stress—a rat model of depression—

was shown to attenuate hippocampal neurogenesis and this effect was reversed by administration of an antidepressant SSRI (Malberg and Duman 2003). Taken together, these lines of evidence suggest that nicotine might possibly exert antidepressant effects via the upregulation of genes that regulate neural growth. Although untested to our knowledge, this hypothesis could be evaluated using animal models of depression.

Nicotine is not currently indicated in the treatment of any medical disorder outside of nicotine dependence. However, nicotine and nicotinic agonists have been tested as possible treatments for a broad range of disorders including ADHD (Wilens et al. 1999), Alzheimer (Potter et al. 1999), and Parkinson disease (Kelton et al. 2000). The results of the present study, although limited by a small sample size, suggest that these compounds could have therapeutic benefits in the treatment of depression symptoms and that additional trials testing a broad range of nicotinic agonist doses administered over weeks are warranted.

The results of the present study are limited by several factors. First, the small sample size likely limited our ability to observe all but large effects, and thus, there may have been other potentially important effects of our intervention that did not reach statistical significance. Furthermore, our small sample size did not allow us to examine whether individual differences might serve as predictors of the effects of nicotine (e.g., baseline depression level, gender, etc.). Second, although we did conduct testing on the baseline day 2.5 h following nicotine administration, the absence of blood or saliva measures at this time makes it difficult to know whether steady-state nicotine levels had been achieved at the time of testing. Third, the administration of 3.5 mg/day of nicotine by cutting 7-mg/day patches in half assumes that nicotine is distributed evenly over the surface of the patch, and participants may not have received consistent or accurate levels of nicotine during administration of the 3.5-mg/day patches. Future studies administering nicotine via methods that allow for consistent administration of smaller doses (e.g., oral nicotine) should be conducted. Furthermore, we only tested a single dosing regimen across all subjects; thus, it is unknown whether higher doses might be more effective or lower doses as effective as the employed regimen. Finally, our sample was predominantly female (82%). As research has shown that female smokers may be less sensitive to the effects of nicotine (Perkins et al. 2001), our findings may underestimate the effects of nicotine on depression symptoms. Future studies with larger numbers of male participants can allow for analysis of potentially important sex differences.

Despite the limitations noted above, this study provides additional evidence that nicotine administration can im-

prove depression symptoms in nonsmokers in the context of a randomized, placebo-controlled, double-blind trial. Participants experienced significant decreases in depression symptoms following 8 days of nicotine administration, and a trend for an improvement in response inhibition was also observed. These changes were reversed following a dose reduction. Very few side effects or adverse events were observed. Our findings help elucidate the basis of relations between depression and smoking behavior and suggest that nicotinic stimulation may be useful in the treatment of depression symptoms.

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