Acute Effects of Nicotine on Physiological and Subjective Sexual Arousal in Nonsmoking Men: A Randomized, Double-Blind, Placebo-Controlled Trial

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ABSTRACT

Introduction. Chronic nicotine treatment has deleterious effects on vascular functioning and catecholamine modulation, which may compromise erectile functioning. Evidence that long-term cigarette smoking is an independent risk factor for introducing impotence is robust. However, limited studies have focused on the acute effects of smoking on physiological sexual response, and none have investigated the deleterious effects of isolated nicotine on human sexual arousal. Consequently, pathophysiological underpinnings of tobacco-induced—and particularly, nicotine-induced—erectile dysfunction are not well understood.

Aim. To provide the first empirical examination of the acute effects of isolated nicotine on sexual arousal in nonsmoking men.

Methods. Twenty-eight sexually functional heterosexual men (mean age 21 years), each with less than 100 direct exposures to nicotine, participated in a double-blind, randomized, placebo-controlled, crossover trial. Participants received either Nicorette polacrilex gum (SmithKline Beecham Consumer Healthcare, Pittsburgh, PA, USA) (6 mg; approximately equivalent to smoking one high-yield cigarette) or placebo gum, matched for appearance, taste, and consistency, approximately 40 minutes prior to viewing an erotic film.

Main Outcome Measures. Physiological (circumferential change via penile plethysmography) and subjective (continuous self-report) sexual responses to erotic stimuli were examined, as well as changes in mood.

Results. Nicotine significantly reduced erectile responses to the erotic films ($P = 0.02$), corresponding to a 23% reduction in physiological sexual arousal. This occurred in 16 of 20 men with valid physiological recordings. Nicotine had no significant effect on continuous subjective ratings of sexual arousal ($P = 0.70$) or on mood (all Ps > 0.05).

Conclusions. Isolated nicotine can significantly attenuate physiological sexual arousal in healthy nonsmoking men. These findings have implications for elucidating physiological mechanisms responsible for the effects of nicotine on sexual dysfunction, and for assisting public health policy in considering the deleterious effects of nicotine on sexual health. **Harte CB, and Meston CM. Acute effects of nicotine on physiological and subjective sexual arousal in nonsmoking men: A randomized, double-blind, placebo-controlled trial. J Sex Med 2008;5:110–121.**

Key Words. Nicotine; Male Sexual Arousal; Penile Plethysmography

Introduction

The link between long-term cigarette smoking and erectile dysfunction (ED) is robust and indicates that cigarette smoking is an independent risk factor for introducing vasculogenic impotence [1–3]. Large cross-sectional [4–8] and longitudinal [9] epidemiological studies suggest that smokers are about 1.5–2 times as likely as nonsmokers to report ED, even after controlling for confounding cardiovascular risk factors. In fact, a meta-analysis of 19 studies over two decades revealed that 40% of men with ED were current smokers compared with 28% of men in the general population [10].

Pathophysiological underpinnings of chronic tobacco-induced ED have not been clearly delin-

eated; however, these mechanisms are ultimately expressed as vascular phenomena [11]. Cigarette smoking decreases penile arterial inflow [12] and disrupts veno-occlusive mechanisms [13], resulting in a deficiency of genital vasoengorgement. These disruptions are mediated by a deregulation in endothelium smooth muscle relaxation [14]. Biochemical processes underlying erection physiology may also be affected by chronic smoking. Nitric oxide (NO) produced within penile endothelial cells has been identified as the principal neurotransmitter mediating erection [15,16]. Free radicals and other compounds within cigarettes may decrease the synthesis of NO directly, or indirectly by targeting precursors, resulting in decreased penile blood inflow [17]. This may have significant long-term effects on erectile functioning.

Few studies have focused on the acute effects of smoking on physiological sexual response. One animal study [2] reported impaired genital arterial inflow and impaired venous restriction in dogs after 7–12 minutes of acute smoke exposure. To date, there has only been one experimental study involving the acute effects of smoking on human sexual arousal. Gilbert and colleagues [18] tested 42 male smokers who were randomly assigned to nicotine, placebo, or wait-list conditions. Participants who smoked three 0.9-mg nicotine cigarettes within one half hour—relative to men who smoked three placebo cigarettes, and to men who had not smoked—experienced significantly attenuated physiological sexual arousal. In the first evaluation of the short-term effects of smoking cessation on physiological sexual arousal, Sighinolfi and associates [19] demonstrated a significant improvement in penile blood flow within 24–36 hours of smoking discontinuation. How this improvement in penile hemodynamics compares to that of nonsmokers was not investigated.

Experimental studies examining acute and reversible effects of tobacco inhalation on physiological sexual arousal help to elucidate underlying physiological mechanisms that may be responsible for introducing ED. However, there are several additional factors that, if addressed, would enhance our understanding of the phenomenon. First, because cigarettes contain over 4,000 active pharmacological constituents, the primary element or group of interacting compounds responsible for the deleterious effects of smoking on sexual response remains unclear. Experimental evidence indicates that chronic nicotine treatment has deleterious effects on modulating the release of epinephrine and norepinephrine [5], which may compromise erectile functioning. A study examining the direct link between acute nicotine intake and sexual arousal in bovines revealed a significant reduction in erectile response [20]. Investigating how nicotine affects human sexual response remains unknown. Second, because of underlying vascular degeneration caused by cigarette smoking [21], it is unknown whether the acute effects of tobacco smoke differentially affect long-term smokers compared to nonsmokers. Additionally, no studies have investigated the acute effects of nicotine with respect to subjective sexual arousal.

Aim

The present investigation was designed to provide the first empirical examination of the acute effects of isolated nicotine on sexual arousal in nonsmoking men measured both subjectively and physiologically. Twenty-eight sexually functional men participated in two counterbalanced conditions in which they received either placebo or nicotine gum (6 mg), approximately 40 minutes prior to viewing an erotic film. Continuous sexual responses to the erotic film stimuli were measured subjectively using a hand-controlled device, and physiologically using penile plethysmography. The purposes of the present investigation was to examine nicotine's acute effects on sexual arousal, to help delineate physiological mechanisms responsible for the effects of nicotine on sexual dysfunction, and to assist public health policy in considering the impact of nicotine on health-related behaviors.

Methods

Participants

Sexually functional heterosexual men were recruited from an undergraduate psychology subject pool, as well as via local community and university advertisements. During an initial telephone interview, potential participants were given a detailed description of the experiment and were told that they would receive nicotine during one of the experimental sessions. The participants were screened for inclusion/exclusion criteria by a trained research assistant, reviewed by the principal investigator (C.H.). Entry criteria included people who were between the ages of 18 and 30, and reported no more than 100 direct exposures to nicotine during their lifetime (e.g., smoking

cigarettes, cigars, or a pipe; chewing smokeless tobacco). Exclusion criteria were as follows: (i) current self-reported sexual complaints within domains of sexual desire, sexual arousal, and sexual pain, and/or a history of treatment for sexual dysfunction; (ii) use of medications known or believed to affect sexual or vascular functioning; (iii) medical conditions known to affect sexual functioning, or that could make nicotine administration unsafe; (iv) jaw/chewing problems; (v) bridgework or dentures; (vi) history of high or low blood pressure; (vii) having a sexually transmitted disease; (viii) having a nonheterosexual orientation; and (ix) no current involvement in a heterosexual relationship. Heterosexuality was operationally defined as self-report of exclusive, or predominant opposite-gender sexual feelings and/or behaviors (i.e., scores of 0, 1, or 2) as assessed using the Kinsey Sexual Orientation Scale [22].

Study Design and Procedure

The study consisted of two counterbalanced experimental conditions, nicotine and placebo, to which eligible participants were randomly assigned. Participants and researchers were blind to condition allocation. The participants were scheduled at approximately the same time during both conditions (i.e., morning, afternoon, or evening), which were scheduled at approximately 1-week intervals. All participants were asked to abstain from caffeine and alcohol, and to refrain from engaging in sexual intercourse for 24 hours prior to each experimental condition. Because rapid ingestion of salivary byproducts of nicotine gum may cause stomach irritation, the participants were asked to refrain from eating and drinking (with the exception of water) for 2 hours prior to the experimental conditions.

During the experimental conditions, the participants were given either nicotine (6 mg) or placebo, both administered double-blind in gum form.[1] The nicotine dose comprised one 4-mg and one 2-mg mint-flavored Nicorette polacrilex gum piece. The placebo dose included two pieces of Dentyne Ice mint-flavored gum (Cadbury Adams, Parsippany, NJ, USA). Nicotine and placebo gum pieces were each wrapped with peppermint-flavored Wrigley's Extra sugar-free gum (Wm. Wrigley Jr Company, Chicago, IL, USA), such that all pieces were similar in appearance, taste, and consistency. The participants were asked to continually repeat a pattern of chewing for approximately 5 seconds, and placing the gum between the tooth surface and the inner part of the cheek surface for approximately 60 seconds to allow buccal absorption of nicotine.

The participants were tested individually while seated in a comfortable armchair within a dimly lit private testing room with a television monitor approximately 10 feet away. Prior to drug administration, the participants completed questionnaires assessing their demographics, mood, sexual orientation, sexual experience, and sexual functioning, and had their heart rates and systolic and diastolic blood pressures monitored twice using an automatic inflation digital blood pressure and pulse monitor. Thirty minutes after drug administration, the participants completed another mood questionnaire, and had their heart rates and systolic and diastolic blood pressures remonitored to assess placebo- or nicotine-induced mood and cardiovascular effects. The half-hour waiting period following the administration of nicotine or placebo was used to ensure that nicotine had reached its peak plasma nicotine levels. Following the half-hour waiting period, the participants were instructed on how to fit the penile plethysmograph. After privately fitting the genital gauge themselves, a 5-minute adaptation recording was taken to assess baseline arousal. Following the adaptation period, the participants were randomized to view one of two 12.5-minute audiovisual sequences that consisted of a 1-minute display of the word "relax" followed by a 3-minute neutral film (either a marine biology documentary or a documentary about Lewis and Clark), and then an 8.5-minute erotic film. In both sequences, the erotic films depicted a heterosexual couple engaging in consensual petting (1.5 minutes), oral sex (3 minutes), and vaginal intercourse (4 minutes). The participants were instructed to continuously monitor their level of subjective sexual arousal by moving a computer mouse positioned on an adjacent table. Pilot testing established that the erotic films induced equivalent genital and self-reported increases in sexual arousal. The three segments (relax, neutral, and erotic) within each film sequence were always

[1]Studies that have used similar nicotine and placebo preparations have reported that, compared with a placebo condition, one 4-mg nicotine gum piece increases plasma nicotine levels by approximately 8–10 ng/mL within 30 minutes, and has a half life of approximately 120 minutes [23–26]. Comparatively, a high-yield (0.7–1.2 mg) nicotine cigarette increases plasma nicotine levels by approximately 14 ng/mL within 10 minutes [27]. Six milligrams of nicotine gum was administered to ensure that a participant's plasma nicotine level would be comparable to smoking one cigarette.

presented in the same order, and the two sequences were counterbalanced across participants. After assessment of sexual arousal, the participants removed the gum and completed questionnaires assessing any adverse effects, and were asked which drug they believed they were administered. The time from ingestion of nicotine or placebo to the onset of the erotic film was approximately 40 minutes (30-minute waiting period, 1-minute plethysmograph fitting, 5-minute baseline, 1-minute display of the word relax, and 3-minute neutral film). All participants provided written informed consent, and either received credit toward their psychology research requirement or were financially compensated (US $30). The protocol was approved by the University of Texas at Austin Institutional Review Board.

Main Self-Report Outcome Measures

Subjective Sexual Arousal

Continuous subjective arousal (CSA) was measured using a hand-controlled device developed previously for use in our laboratory [28]. This device consisted of a computer optical mouse mounted on a wooden track divided into seven equally spaced intervals, where 0 indicated *neutral*, and 1–7 reflected increasingly higher levels of feeling *sexually aroused*. The participants were instructed to continuously rate their subjective sexual arousal throughout the duration of the film presentation. A software program written in MatLab (The MathWorks, Inc, Natick, MA, USA) detected the position of the pointer with respect to the *y*-axis of the computer's monitor, and the signal was low-pass filtered (to 0.5 Hz), digitized (40 Hz), and transformed into percentage of maximum possible arousal.

Sexual Functioning

The International Index of Erectile Function (IIEF) [29] was administered to ensure that men were within the normal range of sexual functioning. The IIEF is a 15-item measure assessing five-factor analytically derived areas of male sexual functioning: erectile function (six items), orgasmic function (two items), sexual desire (two items), intercourse satisfaction (three items), and overall satisfaction (two items). The IIEF has been shown to have acceptable internal reliability (Cronbach's alpha values of 0.73 and higher), test–retest reliability ($r = 0.64$ to $r = 0.84$), and validity [29]. Participants were excluded from analysis if they reported an erectile function score of less than 25. This cutoff value has been demonstrated to have a sensitivity of 0.97 and a specificity of 0.88 to detect individuals with and without erectile dysfunction [30].

Mood

Changes in mood were evaluated with a short version of the Profile of Mood States (POMS-SF) [31], which is a 37-item self-report questionnaire assessing areas of tension (six items), depression (eight items), anger (seven items), fatigue (five items), confusion (five items), and vigor (six items). The participants rated each of the items—prior to and 30 minutes after gum administration—on a 5-point Likert scale ranging from 0 ("not at all") to 4 ("extremely"). Internal reliability of the POMS-SF subscales has been shown to be acceptable (Cronbach's alpha values of 0.80 and higher) [31]. Scores were summed within all six factors, and a total mood disturbance score was obtained by summing the scores (with vigor weighed negatively) on the six primary mood factors and adding 24 (range 0–148). Higher scores reflect greater mood disturbance.

Adverse Effects

The participants were administered a 10-item questionnaire developed in our laboratory that assessed any adverse effects attributed to either placebo or nicotine administration. Both bogus (blurred vision, dry eyes, fatigue, runny nose, and hiccups) and rationally driven (throat irritation, headache, nausea, light headedness, and dizziness) items were included, and the participants rated each of the items on a 5-point Likert scale according to the degree to which they experienced each sensation, ranging from 0 ("not at all") to 4 ("extremely"). Scores were summed within the two factors.

Main Physiological Outcome Measures

Sexual Arousal

Male genital arousal was assessed via penile circumferential change using a mercury-in-rubber strain gauge (D.E. Hokanson, Inc, Bellevue, WA, USA) positioned mid-shaft on the penis. Penile tumescence is considered the most sensitive index of sexual arousal and the most reliable measure of physiological response [32]. The signal was sampled at a rate of 80 samples/second throughout the entire 180 seconds of neutral film and 510 seconds of erotic film, low-pass filtered (to 0.5 Hz),

digitized (40 Hz), and recorded using the software package AcqKnowledge III, Version 3.73 (BIOPAC Systems, Inc., Santa Barbara, CA) and a Model MP100WS data acquisition unit (BIOPAC Systems, Inc.). Gauges were calibrated over six 5-mm steps between sessions to check for reliability [33].

Cardiovascular Measures

Heart rates, and systolic and diastolic blood pressures were assessed using an Omron HEM-712C (Omron Healthcare, Inc, Bannockburn, IL, USA) automatic inflation digital blood pressure and pulse monitor with the cuff placed on each participant's nondominant upper arm. In order to control for a participant's initial anxiety that may elevate cardiovascular measures, heart rate and blood pressure were assessed twice prior to gum administration, with only the second assessment included in analyses, as well as another assessment 30 minutes following administration of nicotine or placebo. Heart rates during the film sequence presentations were extracted from the penile plethysmography signal.

Data Reduction

With respect to physiological sexual arousal, movement artifacts—defined as clear spikes >5 mm within an otherwise smooth curve [34]—were deleted, and the remaining raw data were digitally transformed into millimeters of circumference change. Because differences in individual penis size cause differential circumferential changes during sexual arousal, physiological sexual responses were standardized within participants by converting all data points to percentage of full erection (PFE) [35].[2] Final PFE and CSA scores were then computed by averaging all data points within 5-second epochs, and then averaging all epochs within the neutral (36 epochs) and erotic films (102 epochs). Because not all participants demonstrate discernable genital arousal patterns to sexual stimuli, their physiological data were removed from analyses if the minimum response to sexual stimuli did not exceed their response to the neutral stimulus by at least 3 mm within the placebo condition. The physiological exclusion criterion is similar to that used by other researchers [36,37] and yielded the exclusion of eight participants, which is typical of circumferential measurement of erectile response [38]. Similarly, a participant's subjective arousal data were excluded if he did not attain a value of 15% of maximum possible arousal, which yielded the exclusion of seven participants. The exclusion of nonresponders was particularly important in order to distinguish nicotine-induced physiological attenuation from idiosyncratic nonresponding otherwise not due to nicotine administration.

Heart rates during the film presentation were averaged across the neutral and erotic films, yielding a total of four heart rate measures (one prior to drug administration, one 30 minutes after drug administration, and two during the film sequence) for each participant per experimental condition. Difference scores in mood for all six factor scores, as well as the total mood score, were computed by subtracting the baseline (before nicotine or placebo administration) from the measure taken 30 minutes after administration of nicotine or placebo.

Statistical Analysis

All dependent variables were checked for normality using Shapiro–Wilk tests with an α of $P < 0.05$ denoting a normality violation. PFE was the only variable that violated the normality assumption, and therefore was square root transformed. Because bodyweight is inversely proportional to plasma nicotine concentration level, initial Pearson product moment correlation coefficients were calculated to investigate potential confounding effects of each participant's body nicotine concentration (in μg/kg) level on physiological and subjective sexual arousal. None of the analyses were statistically significant (all Ps > 0.05), and therefore, no variables were entered as covariates in subsequent analyses.

A 2 (condition: nicotine, placebo) $\times$ 2 (film: neutral, erotic) repeated measures analysis of variance (ANOVA) was used to examine the effects of nicotine in comparison with placebo on PFE and CSA. The effects of nicotine in comparison with placebo on heart rate, and systolic and diastolic blood pressure scores were examined using separate condition $\times$ time repeated measures ANOVAs. Paired sample t-tests were used on PFE, CSA, and heart rate scores between and within the nicotine and placebo conditions during the neutral and erotic film presentations, on heart rate, and systolic and diastolic blood pressure scores prior to and 30 minutes after either nicotine or placebo administration, and on subjective ratings of mood

[2]Percentage of full erection was calculated by the equation $1 - ([\max - \chi]/[\max - \min])$, where max denotes the largest circumferential value (full erection), and min denotes the smallest circumferential value (flaccid state) observed during either the nicotine or placebo conditions. The value of χ corresponds to a particular circumferential data point.

(tension, depression, anger, fatigue, confusion, vigor, total mood disturbance score), and on both potential and bogus nicotine adverse effects, between the placebo and nicotine conditions.

All analyses were performed using SPSS statistical software version 14.0 (SPSS Inc., Chicago, IL, USA). A two-tailed α of $P < 0.05$ was considered statistically significant for all analyses with the exception of analyses of self-reported mood, and adverse side effects in which more conservative α levels of 0.007 ($P < 0.05/7$) and 0.025 ($P < 0.05/2$) were used, respectively, by employing Bonferroni corrections.

Results

Sample Characteristics

Of the 61 men who completed the initial telephone screening, 11 reported being uninterested in participating, 10 were ineligible, and 10 did not show for their appointments. Thirty men met the initial entry criteria and later completed the two experimental sessions. Of these participants, data on two men were excluded from analyses because they did not meet the IIEF cutoff score criterion. The final sample (N = 28) had a mean age of 21.3 years (standard deviation [SD], 2.70 years; range 18–27 years), and had a mean of 14.2 years of education (SD, 1.88; range 12–18). The participants reported a mean of 7.1 (SD, 9.52; range 0–30) direct exposures to nicotine during their lifetime, and 85.7% reported no passive exposure to tobacco smoke for more than 30 minutes per day at least once per week. Forty-six percent reported being in a steady relationship, of which two reported being married. Because of reported ethnic differences in sexual activity [39], ethnic demographics were collected by having participants self-report on racial background categories defined by the investigators. The sample comprised 57% European American, 11% African American, 25% Latino, 4% Asian, and 4% multiracial. No participants reported medical conditions of any kind, three reported currently taking medications (antihistamines, acne medications), and one participant reported a psychiatric condition (attention-deficit hyperactivity disorder). Characteristics of the participant sample are presented in Table 1.

Table 1 Participant characteristics (N = 28)

Characteristic	Value
Age (years)	
Mean (SD)	21.3 (2.76)
Range	18–27
Education (years)	
Mean (SD)	14.2 (1.88)
Range	12–18
Weight (kg)	
Mean (SD)	74.7 (13.06)
Range	56.7–108.9
Height (m)	
Mean (SD)	1.79 (0.11)
Range	1.60–2.21
Body mass index (kg/m^2)	
Mean (SD)	23.3 (2.76)
Range	18.3–32.6
Ethnicity, N (%)*	
European American	16 (57.1)
African American	3 (10.7)
Latino	7 (25)
Asian	1 (3.6)
Multiracial	1 (3.6)
IIEF erectile function score†	
Mean (SD)	29.4 (1.10)
Range	26–30
Nicotine direct‡ exposures (lifetime)	7.1 (9.52)
Mean (SD)	0–30
Range	
Nicotine passive§ exposures (hours/week)	
Mean (SD)	0.4 (1.48)
Range	0–7
Nicotine body concentration (μg/kg)	
Mean (SD)	82.5 (12.85)
Range	55.1–105.8

*Because of rounding, percentages do not total to 100%.
†Mean IIEF erectile function score is based on a scale of 1–30, with 1 indicating the most severe erectile difficulties and 30 indicating the least severe (or no difficulty).
‡A direct exposure was defined as ingesting nicotine pulmonarily (e.g., smoking a cigarette, cigar, or pipe), or buccally (chewing smokeless tobacco).
§Passive nicotine exposure was defined as ingesting nicotine via indirect means (i.e., passive smoke exposure).
SD = standard deviation; IIEF = International Index of Erectile Function.

Analyses of Physiological Sexual Arousal

The condition (nicotine, placebo) × film (neutral, erotic) repeated measures ANOVA revealed a significant main effect of the erotic films on square root PFE scores ($F_{1,19} = 93.94$, $P < 0.001$), and a significant interaction between condition and film ($F_{1,19} = 8.77$, $P = 0.01$). More detailed examination of the data revealed that there was a significant decrease in square root PFE scores with nicotine administration during the erotic films ($t_{19} = -2.53$, $P = 0.02$), compared to placebo. This corresponded to a 23% reduction in physiological sexual arousal and occurred in 16 of 20 participants. There was no significant difference in square root PFE scores between nicotine and placebo conditions during the neutral films ($t_{19} = 0.13$, $P = 0.90$). A one-way repeated measures ANOVA with film type (neutral, erotic) and film order as within- and between-subject factors, respectively, revealed a significant main effect of film type on square root PFE scores ($F_{1,18} = 18.0$,

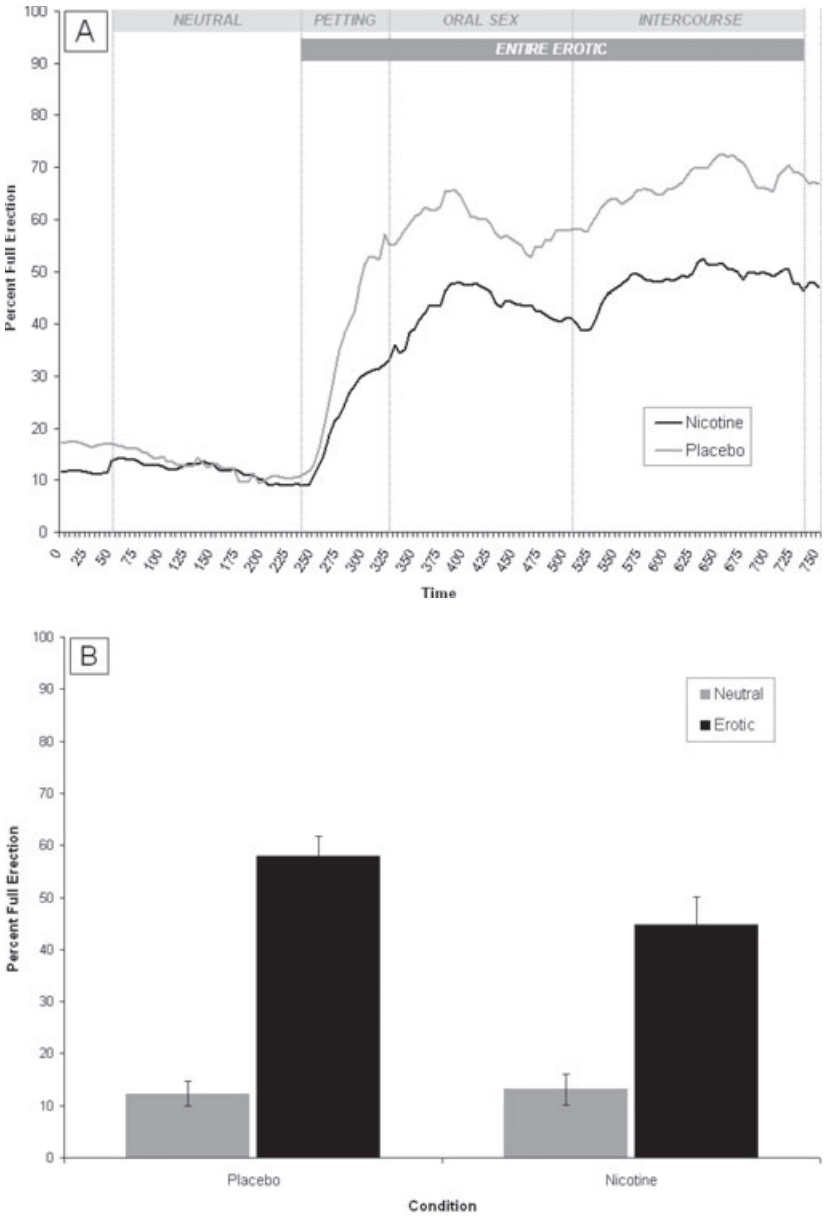

Figure 1 Physiological sexual arousal in response to drug administration. (A) Mean percent full erection (PFE) in 5-second intervals across the neutral and various erotic film stimuli during nicotine and placebo conditions. (B) Mean (±standard error of the mean [SEM]) PFE between the neutral stimulus and the entire erotic film stimulus (average of petting, oral sex, intercourse) during nicotine and placebo conditions. Untransformed PFE values are depicted in order to facilitate visual interpretation of the data; all analyses were conducted using square root transformations.

$P < 0.001$). Specifically, there were significant increases in response to the erotic films in both nicotine ($t_{19} = 6.16$, $P < 0.001$) and placebo ($t_{19} = 9.94$, $P < 0.001$) conditions, indicating that the audiovisual stimuli were effective in eliciting reliable physiological sexual responses, irrespective of which 12.5-minute video sequence (relax, neutral, and erotic) was viewed first (as noted by the absence of a film type × film order interaction; [$F_{1,18} = 0.08$, $P = 0.78$]). Mean PFE scores for the nicotine and placebo conditions during the neutral and erotic film stimuli are presented in Figure 1.

Analyses of Continuous Subjective Sexual Arousal

The condition (nicotine, placebo) × film (neutral, erotic) repeated measures ANOVA revealed a significant main effect of the erotic films on CSA scores ($F_{1,20} = 294.0$, $P < 0.001$). Significant increases in CSA scores were demonstrated in response to the erotic films in both the nicotine ($t_{20} = 14.73$, $P < 0.001$) and placebo ($t_{20} = 15.66$, $P < 0.001$) conditions, indicating that the audiovisual stimuli were effective in eliciting reliable subjective sexual responses. However, there was no significant between-condition difference in mean CSA scores

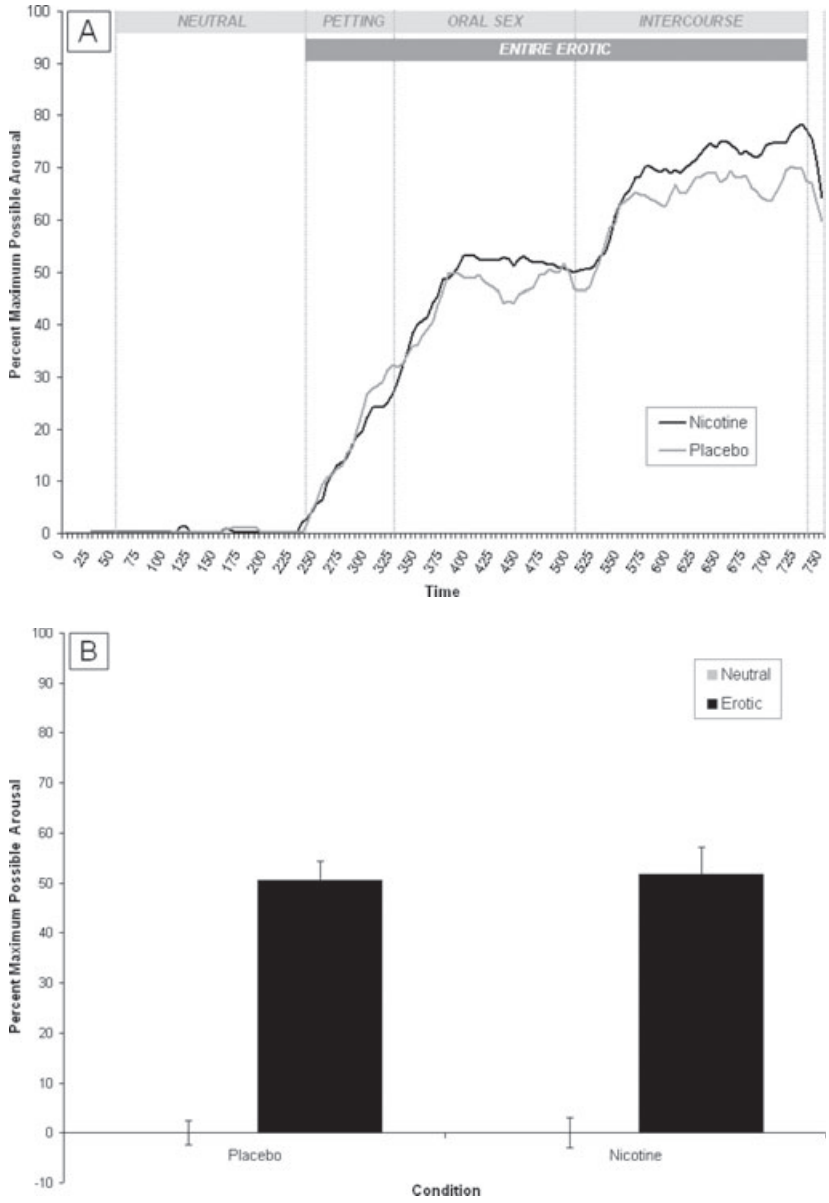

Figure 2 Subjective sexual arousal in response to drug administration. (A) Mean percent of maximum possible arousal in 5-second intervals across the neutral and various erotic film stimuli during nicotine and placebo conditions. (B) Mean (±standard error of the mean [SEM]) percent of maximum possible subjective arousal between the neutral stimulus and the entire erotic film stimulus (average of petting, oral sex, intercourse) during nicotine and placebo conditions.

during the neutral ($t_{20} = 1.0$, $P = 0.33$) or erotic ($t_{20} = 0.39$, $P = 0.70$) films. Mean CSA scores for the nicotine and placebo conditions during the neutral and erotic film stimuli are presented in Figure 2.

Analyses of Heart Rate

A repeated measures ANOVA with condition (nicotine, placebo) and time (four time measures: one prior to drug administration, one 30 minutes after drug administration, and two during the film sequence) as within-subjects factors revealed a significant main effect of both condition ($F_{1,27} = 7.56$, $P = 0.01$) and time ($F_{3,25} = 27.04$, $P < 0.001$), as well as a significant condition × time interaction ($F_{3,25} = 5.18$, $P = 0.01$). No significant differences in heart rate were demonstrated prior to drug administration ($t_{27} = 0.12$, $P = 0.91$); however, participants showed significantly higher heart rates at 30 minutes after the administration of nicotine ($t_{27} = 3.19$, $P = 0.004$) compared to placebo, and during both the neutral (approximately 37 minutes after nicotine administration) ($t_{27} = 3.0$, $P = 0.01$) and erotic (approximately 40 minutes after nicotine administration) ($t_{27} = 2.79$, $P = 0.01$) film presentations after nicotine administration. These findings suggest that the cardiovascular consequences of nicotine were in effect during assessment of sexual arousal. Within-condition analyses indicated that participants demonstrated significantly higher

heart rates during the erotic film compared to during the neutral film, during both the nicotine ($t_{27} = 3.33$, $P = 0.002$) and placebo ($t_{27} = 4.92$, $P < 0.001$) conditions.

Analyses of Blood Pressure

The condition (nicotine, placebo) × time (prior to drug administration, 30 minutes after drug administration) repeated measures ANOVA revealed a significant main effect of time on both systolic ($F_{1,27} = 8.13$, $P = 0.01$) and diastolic ($F_{1,27} = 7.28$, $P = 0.01$) blood pressure scores, and a trend for a statistically significant condition × time interaction for systolic blood pressure scores ($F_{1,27} = 3.75$, $P = 0.06$), and a significant condition × time interaction for diastolic blood pressure scores ($F_{1,27} = 16.01$, $P < .001$). Significant increases in both diastolic ($t_{27} = 4.25$, $P < 0.001$) and systolic ($t_{27} = 3.17$, $P = 0.004$) blood pressure scores were observed between baseline and 30 minutes after drug administration, during the nicotine condition but not the placebo condition. Additionally, participants demonstrated significantly higher diastolic blood pressure scores ($t_{27} = 2.37$, $P = 0.03$) during the nicotine condition. Systolic blood pressure scores were also higher within the nicotine condition, but this did not reach statistical significance ($t_{27} = 0.96$, $P = 0.34$).

Analyses of Mood

There were no significant effects of condition for tension ($t_{27} = -1.42$, $P = 0.17$), depression ($t_{26} = -0.55$, $P = 0.59$), anger ($t_{27} = -0.43$, $P = 0.67$), vigor ($t_{26} = 1.75$, $P = 0.09$), fatigue ($t_{26} = -0.13$, $P = 0.90$), and confusion scores ($t_{27} = -0.53$, $P = 0.60$), or for the overall mood disturbance score ($t_{24} = -1.32$, $P = 0.20$), indicating that changes in mood in response to drug administration did not change differentially between placebo and nicotine conditions.

Analyses of Adverse Effects

Results indicated a significant increase in self-reported ratings of both bogus ($t_{25} = 3.73$, $P = 0.001$) and potential ($t_{25} = 7.16$, $P < 0.001$) adverse effects in response to nicotine administration.

Post Hoc Analyses

Because participants reported more adverse effects during the nicotine condition compared to the placebo condition, we examined whether self-reported ratings of adverse effects were a potential confounding variable with respect to physiological sexual arousal. Within-subjects difference scores were derived separately for both untransformed PFE scores and potential adverse effects scores by subtracting these values acquired during the placebo condition from the values acquired during the nicotine condition (i.e., PFE nicotine condition–PFE placebo condition; adverse effects nicotine condition–adverse effects placebo condition) for men displaying reliable genital arousal. Both difference score variables were checked for normality using Shapiro–Wilk tests, and were entered into a regression analysis. Results indicated that the correlation was not statistically significant ($r_{18} = -0.09$, $P = 0.70$), and the magnitude of adverse effects accounted for less than 1% of the variance ($R^2 = 0.008$) in genital arousal. That is, there was no statistical relationship between attenuated genital arousal and increased drug symptomatology.

Discussion

The present study examined the effects of nicotine on physiological and subjective sexual arousal in healthy nonsmoking men. The results indicated that nicotine significantly reduced erectile responses to erotic film stimuli. The attenuation of physiological sexual arousal following nicotine administration is consistent with literature delineating nicotine's effects on sympathetic nervous system (SNS) activity. Specifically, nicotine instigates cardiovascular constriction by direct stimulation of epinephrine and norepinephrine release from peripheral sympathetic nerve endings [40]. It has also been widely established that the SNS is primarily responsible for maintaining erectile flaccidity [41].

Nicotine had no significant effect on subjective sexual arousal. This indicates that the decrease in physiological sexual arousal in response to nicotine administration was not a result of negative feedback from cognitive appraisal of the erotic films. That is, nicotine may have caused a variety of adverse effects (e.g., dizziness, light headedness) that would have distracted the participants from processing sexual cues. The absence of a decrement in self-reported sexual arousal in response to nicotine administration supports the notion that nicotine attenuates genital arousal directly via physiological mechanisms, rather than impacting cognitive processes. Like self-report measures of sexual arousal, subjective measures of tension, depression, anger, vigor, fatigue, and confusion did not change differentially with respect to nicotine

or placebo administration. Together, these findings suggest that the reduction in physiological sexual response resulting from nicotine intake was not likely mediated by nicotine-induced changes in cognitive states.

Participants reported experiencing more adverse effects in response to nicotine administration compared to placebo. This is consistent with studies delineating the physical effects of nicotine replacement therapies in never smokers. Heishman and colleagues [42] found that 4-mg nicotine gum vs. placebo produced both euphoria and negative effects that persisted over the 45-minute session. Similarly, intermediate doses of nicotine nasal spray introduce both positive and negative effects (e.g., increased head rush, increased tension) [43]. In consideration of these accounts, it is imperative to rule out whether self-reported ratings of adverse effects are a potential confounding variable with respect to physiological sexual arousal. We determined that there was no statistical relationship between attenuated genital arousal and increased drug symptomatology, indicating that the nicotine-induced reduction in sexual arousal is likely to be directly attributable to underlying biochemical and physiological involvement, rather than sequelae of adverse physical effects.

The current investigation had several strengths such as (i) the administration of nicotine gum (compared to nicotine nasal spray or transdermal nicotine patch) to establish a relatively fast and stable peak plasma nicotine concentration; (ii) the assessment of only young men without a history of smoking and with a low incidence of passive smoke exposure. The exclusion of smokers precluded potential long-term cardiovascular disruptions that may have deleterious effects on sexual arousal, and assessing only young men eliminated confounding age-related effects on genital functioning; (iii) the use of a randomized, double-blind, placebo-controlled crossover protocol; and (iv) the assessment of subjective and physiological responses using rigorous quantitative methods. A number of limitations warrant mention. First, given that nicotine was responsible for discernable increments in heart rate and blood pressure levels assessed by the experimenters, the integrity of the double-blind protocol was partially compromised. Additionally, all participants correctly identified the session to which they were administered nicotine. Although rigorous steps were taken to preserve the double-blind protocol, maintaining experimenter blindness in studies investigating cardiovascular effects of adrenergic agents is, for the most part, infeasible. Second, expectancies about a substance's drug content or its actions may be responsible for observed drug-like effects [44]. It is feasible that participants' expectancies about nicotine's effects on sexual arousal influenced the results of this study. However, if there were experimenter biases or participant expectancies at play, they most likely would have expressed themselves within subjective reports of mood and/or sexual arousal. Because these self-report measures did not differ between experimental conditions, it is unlikely that expectancy effects can account for the significant changes in genital arousal noted in this study. Moreover, given that nicotine administered in gum form is a relatively novel route of administration (compared to cigarettes), the expected relationship between a nicotine replacement therapy product and its effects on sexual function is likely weak. A third limitation is that, because of the method of drug delivery, nicotine dose was not titrated for participant body weight, resulting in varying plasma nicotine concentrations. Although participants' varying body nicotine concentrations were not correlated with subjective or physiological sexual responses, individual differences in nicotine metabolism may exist, irrespective of standardized nicotine dosing [45,46]. The most rigorous way to redress this issue is to collect saliva or blood samples and covary dependent variables by a participant's plasma cotinine (a byproduct of nicotine) concentration.

Conclusions

The results of the present investigation provide the first empirical evidence that an intermediate dose of isolated nicotine significantly reduces erectile response in healthy, young, nonsmoking men. That nicotine significantly reduces physiological sexual arousal provides support to the hypothesis that nicotine may be the primary pharmacological agent responsible for genital hemodynamic disruption, by acting on the nervous system centrally or peripherally. The findings of this study have important clinical implications. That nicotine intake significantly impairs erectile function acutely in never smokers could be used as a convincing public health claim to assist in the prevention of cigarette smoking in adolescents and adults.

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Conflict of Interest: The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the National Center for Complementary and Alternative Medicine.

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