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ORIGINAL INVESTIGATION

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Nicotine effects on adults with attention-deficit/hyperactivity disorder

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Abstract Several lines of evidence suggest that nicotine may be useful in treating the symptoms of Attention-Deficit/Hyperactivity Disorder (ADHD). The current study was an acute, placebo-controlled double-blind experiment to determine whether nicotine might be useful as an alternative treatment of adults with ADHD symptomatology. Six smokers and 11 nonsmokers who were outpatient referrals for ADHD were diagnosed by DSM-IV criteria. Measures of treatment effect included the Clinical Global Impressions (CGI) scale, Hopkins' symptom check list (SCL-90-R), the Profile of Mood States (POMS), Conners' computerized Continuous Performance Test (CPT), the Stroop test, and an interval-timing task. The smokers underwent overnight deprivation from smoking and were given a 21 mg/day nicotine skin patch for 4.5 h during a morning session. The nonsmokers were given a 7 mg/day nicotine skin patch for 4.5 h during a morning session. Active and placebo patches were given in a counterbalanced order approximately 1 week apart. Nicotine caused a significant overall nicotine-induced improvement on the CGI. This effect was significant when only the nonsmokers were considered, which indicated that it was not due merely to withdrawal relief. Nicotine caused significantly increased vigor as measured by the POMS test. Nicotine caused an overall significant reduction in reaction time (RT) on the CPT, as well as, with the smokers, a significant reduction in another index of inattention, variability in reaction time over trial blocks. Nicotine improved accuracy of time estimation and lowered variability of time-estimation response curves. Because improvements occurred among nonsmokers, the nicotine effect appears not to be merely a relief of withdrawal symptoms. It is concluded that nicotine deserves further clinical trials with ADHD.

Key words Nicotine · Attention Deficit/Hyperactivity Disorder · Attention · Treatment · Nicotine skin patches

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Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is characterized by impaired attentiveness, increased impulsivity, and hyperactivity (DSM-IV 1994). This disorder was once thought to be primarily a childhood problem. However, approximately 60% of adolescents with ADHD maintain this status into adulthood (Wender 1995). ADHD may be less noticeable in adulthood because people learn to accommodate to its symptoms by their choice of work, work habits, or self-medication. It is interesting in this last regard that approximately 40% of adults with ADHD smoke cigarettes as compared with 26% of the general population (Pomerleau et al. 1995b). Cigarette smoking and nicotine administration have been found to improve attentiveness (see Levin 1992 for review). Nicotine promotes the release of dopamine (Wonnacott et al. 1989), as do methylphenidate, dextroamphetamine and pemoline, presently the most effective drug treatments of ADHD. Nicotinic agonists or nicotine administered in a less hazardous form than cigarettes, such as a skin patch, may be potential treatments for ADHD.

Nicotine administration by cigarette smoking has been found to improve attentiveness (Peeke and Peeke 1984; Warburton et al. 1992; Wesnes and Warburton 1983, 1984a, b). This effect is seen clearly in smokers after smoking deprivation. However, since nicotine withdrawal does produce a discernible decrease in attentiveness, it has been argued that benefits may only represent relief of withdrawal symptoms (Hatsukami

et al. 1989). However, there is recent evidence that nicotine improves attentivenes in smokers who do not show withdrawal effects and in non-deprived smokers (Warburton and Arnall 1994), suggesting that nicotine improves attention apart from alleviation of withdrawal.

How might nicotine have this attention-enhancing effect? Nicotine has a variety of actions. It directly stimulates nicotinic acetylcholine (ACh) receptors, and it also promotes the release of dopamine (DA) and other neurotransmitters such as acetylcholine, serotonin and norepinephrine (Wonnacott et al. 1989). Nicotinic interactions with DA may be responsible for its effect on attentiveness. Currently used effective treatments for ADHD include methylphenidate, dextroamphetamine, and pemoline; all three are indirect DA agonists. Anatomic localization of nicotinic receptors and their physiological effects also support the potential importance of nicotinic-DA interactions. High concentrations of nicotinic receptors have been found in rats on DA cell bodies in the substantia nigra and ventral tegmental area and on DA terminals in the striatum (Clarke et al. 1984; Clarke and Pert 1985; Schwartz 1986). Nicotinic stimulation has excitatory influences on the activity of the DA cells in the substantia nigra and ventral tegmental area and increases striatal DA release (Clarke et al. 1985; Grenhoff et al. 1986; Imperato et al. 1986; Meru et al. 1987), while nicotinic antagonist administration has been found to inhibit DA release from both striatal and mesolimbic structures (Ahtee and Kaakkola 1978; Haikala and Ahtee 1988).

Given that nicotine improves attention and that nicotine effectively promotes DA release (which is thought to be the therapeutic mechanism for the current ADHD drugs methylphenidate and dextroamphetamine), we hypothesized that nicotine administration might attenuate the symptoms of ADHD. Because recent theoretical arguments propose a central role of basic timing functions in ADHD, Barkley (1995) suggests that the inability to delay response in ADHD is its primary core symptom and that this deficit reflects a disturbance of accurate timing mechanisms. An acute study was designed to assess this potential therapeutic action. The first phase assessed the effects of a high dose (21 mg/day) nicotine skin patch on cigarette smokers who had undergone overnight smoking deprivation. The second phase assessed the effects of a low dose (7 mg/day) nicotine skin patch on nonsmokers to determine if the nicotine effects were merely due to relief from withdrawal symptoms.

Materials and methods

Subjects

Subjects (mean age 35 years, range 19–51) were recruited through communications with local physicians, psychologists, and support groups for ADHD. Each potential subject was assessed for the presence of symptoms indicative of ADHD as follows: a) completion of the Wender Utah Rating Scale (a retrospective account of ADHD in childhood, completed by subject) with a resultant T-score>60, b) completion of the Conners/Wells Adolescent and Adult Self-Report with T-scores > 60 on at least two of three sub-scales (Problems with Concentration, Problems of Restlessness, and Problems Learning), and c) completion of a modified version of Barkley's Adult ADHD Semi-structured Interview (Barkley 1990) with no outstanding signs of Major Depressive Disorder (MDD) or Generalized Anxiety Disorder (GAD), and supporting criteria to meet DSM-IV criteria for a subtype of ADHD (Inattentive, Hyperactive/Impulsive, or Combined Type). In addition, the Hamilton Depression Interview (Ham-D) was administered at the practice session to confirm the absence of MDD (raw score < 20). Medical inclusion/exclusion criteria included all relevant concerns for use of nicotine in a transdermal patch form. Subjects who were undergoing stimulant therapy (three on methylphenidate and one on amphetamine) at the time of study entry were asked to obtain signed consent to stop taking such medication 2–3 days before each session. Fifteen males and two females completed the current study. The females were required to provide proof of not being pregnant, either through a BHCG serum test or medical records of surgical procedures, and were asked to use proper contraceptive techniques to avoid pregnancy for the duration of the study (3 weeks). This study was approved by the Duke University Medical Center Institutional Review Board.

The first cohort of subjects ($n = 6$) consisted of adults with symptoms of ADHD who were moderate to heavy smokers (verified by end tidal CO reading > 15 ppm) for at least 2 years. They had smoked an average of 31.4 ± 15.5 (mean ± SD) cigarettes for an average of 18.7 ± 7.3 years. The second cohort of subjects ($n = 11$) consisted of adults with ADHD symptoms who were non-smokers (verified by end tidal CO reading < 8 ppm) for at least 1 year. Both cohorts went through nearly identical protocols.

Each subject reported to the clinic for at least three sessions. All the tests were given during a preliminary practice session to familiarize the subjects with the tests and to reduce the impact of practice effects on the experimental portion of the study. Then there was one session with the placebo patch and one session with the nicotine patch in a counterbalanced order between subjects. There were at least 4 days between each session. The statistical analyses were conducted on the test scores from the placebo and nicotine treatment sessions. The first two subjects had two sessions with each treatment. After completing informed consent, subjects provided initial levels for the following tasks: End Tidal CO, Symptom Checklist-90 item-revised (SCL-90-R) (Derogatis 1983), Profile of Mood States (POMS) (McNair et al. 1981), a computerized Continuous Performance Test (CPT) (Conners 1995), a computerized Stroop task, a timing procedure (Rakitin et al. 1995, unpublished), and the Severity scale of the Clinical Global Impressions (CGI) (NIMH 1985). In addition, the Tripartite Personality Questionnaire (TPQ) (Cloninger et al. 1991) and the Hamilton Depression Interview (Ham-D) (Hamilton 1960; Williams 1988) were administered to confirm the absence of exclusion criteria. Smokers completed the Ikard Smoking Motivation Questionnaire (Ikard et al. 1969) and the Fagerström Test of Nicotine Dependency (Fagerstrom and Schneider 1989). Each of these measures was administered according to a schedule such that time-of-day would be consistent across sessions and subjects. The subjects had a brief rest between tests when they could relax.

Subjects in the smoker cohort were required to abstain from smoking for at least 12 h prior to each of the patch test sessions. This abstinence was verified with an end tidal CO reading (level < 12 ppm) at the beginning of each of patch test sessions. In addition, these smokers were cautioned not to smoke throughout the duration of each session (4½ h). They were in the clinic for this time. After patch administration the tests were administered on a time schedule as shown in Table 1.

Table 1 Time line for nicotine patch administration and testing

8:45 a.m.	Patch administration
9:00	Preliminary Interval timing test
10:15	Modified Shiffman–Jarvik scale
10:45	Profile of Mood States (POMS)
11:00	Symptom Checklist-90 item-revised (SCL-90-R)
11:45	Clinicial Global Impressions (CGI) rating
11:55	Conners' Continuous Performance test (CPT)
12:15 p.m.	Stroop test
12:30	Interval Timing test
1:15	Patch removal

Nicotine treatment

The smokers were given a 21 mg/day nicotine patch (Nicoderm) after overnight abstinence, verified by end tidal CO measurements. The 21 mg/day patch is the dose recommended for average cigarette smokers attempting to quit smoking. The non-smokers were given a 7 mg/day nicotine patch (Nicoderm). The 7 mg/day patch is the lowest dose of Nicoderm available. This dose was chosen to minimize the side effects of nausea and dizziness in the nonsmokers who were not tolerant to these effects of nicotine. These treatments were given in a counterbalanced order with a placebo patch in a double blind fashion, whereby neither the subject nor the experimenter was informed as to the treatment condition. One nonsmoker who had nausea and vomited while on the nicotine patch volunteered to be retested and showed this effect again. Both times the patch was removed as soon as this occurred and the nausea passed quickly. Normally the patch was removed after the final test at 1:15 p.m. The therapeutic outcome measures starting with the POMS and ending with the interval timing test were conducted between 1.5 and 4.5 h after patch administration (see Table 1). The Nicoderm patch was selected for the current study because it provides a rapid onset of nicotine delivery after initial administration. A pharmacokinetic study has shown that with the 21 mg/day Nicoderm patch that plasma nicotine levels rise to about 12 ng/ml 2 h after application and to about 14 ng/ml 4 h after application (Benowitz 1993). This is near the range of eventual steady state nicotine levels delivered throughout the day with this patch.

Clinical assessment of treatment response

The subjects' ADHD symptoms were rated with a modified Clinical Global Impression (CGI) scale which consisted of three scales: severity, efficacy and improvement. This is a standardized scale which has been widely used in clinical studies (NIMH 1985). The CGI was completed following a brief interview regarding ADHD symptoms and drug side effects during that morning's session. The rater was blind to nicotine treatment.

Computerized assessment

Computerized tests consisted of the Conners' Continuous Performance Test (CPT), a Stroop task and an interval timing task. These were given at practice and the two treatment sessions.

The Conners CPT has been validated as an assessment tool for diagnosing ADHD (Conners 1994, 1995). It is a 14-min test in which the subject is instructed to respond as quickly as possible to a target stimulus but to refrain from responding to a more rarely occurring non-target stimulus. The reaction time and the variability in reaction time were measured over trial blocks during the course of the session and over different inter-stimulus intervals (ISI). Errors of omission and commission were also assessed.

The Stroop test measured the Stroop effect, the impairment in response speed resulting from incongruent color and color names, via a computerized adaptation of the original task (Stroop 1935). In this version, a color name (red, yellow, blue, or green) was projected on the computer screen for 0.2 s. This color name was written in a color (red, yellow, blue, or green). The subject was instructed to press the right mouse button if the word and color were congruent (e.g. the word "red" was written in the color red), and to press the left mouse button if the word and color were incongruent (e.g. the word "green" was written in the color blue). The response window duration was 2 s. Most subjects were able to respond within this time window for the majority of their responses.

The peak-interval timing procedure was implemented using the feedback method (Meck and Church 1987; Wearden and McShane 1988; Rakitin et al., unpublished). This procedure measures the accuracy of the subject in estimating a time interval. The subject was asked to estimate time periods of 7 or 17 s by pressing the space bar of a computer keyboard. All subjects were tested early and late in each testing session to assess the effect of nicotine. Graphical visual feedback indicating accuracy and precision was presented during the intertrial interval either after each trial or after a random one-quarter of trials. Responses were summed into 0.5-s bins for each subject to produce a response distribution as a function of time. A moving average was calculated across five adjacent points. The first and last bins just below a threshold of 50% of the maximum number of responses per bin defined the width of the response function at half the maximum height (spread: see Meck and Church 1987; Church et al. 1991; Rakitin et al., unpublished). The midpoint of start and stop (peak time) indexed the accuracy with which subjects timed their responding. The maximum number of responses in a single bin (peak response rate) was used as a measure of general arousal.

Subjective assessment

The subject rated his/her mood and physical well-being on several measures throughout the session. These included the SCL-90-R, the POMS, and the modified Shiffman-Jarvik Smoking Withdrawal Scale.

The SCL-90-R is a 90-item symptom inventory designed for patient self-report of psychological symptoms. Subjects indicated the frequency of occurrence of each item on a five-point scale (ranging 0–4). Subjects were asked to complete this measure based on their feelings that day only. This measure yields the following nine factors: Somatization, Obsessive-compulsive, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, and Psychoticism. In addition, a Global Severity Index, Positive Symptom Distress Index, and Positive Symptom Total can also be derived.

The POMS is a listing of 65 adjectives describing mood state, and is designed for patient self-report. Subjects reported severity of occurrence for each item on a five-point scale (ranging 0–4) for that day only. The POMS produces ratings for six mood states: Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, and Confusion-Bewilderment.

The modified Shiffman-Jarvik questionnaire is a series of 32 questions regarding various signs of nicotine withdrawal. This questionnaire was administered to both cohorts of subjects (smokers and nonsmokers) 1.5 h after application of the patch. These items group into the following six factors: Craving, Negative Affect, Appetite, Arousal, Somatic Symptoms, and Habit Withdrawal.

Data analysis

Analysis of variance (ANOVA) was used to assess the effect of nicotine treatment on the clinical evaluation, computerized test performance and subjective reports described above. The ANOVA used

Table 2 *F*-ratios and *P*-values for nicotine effects

	Overall	Smokers	Nonsmokers
Clinical Global Impression (CGI)			
Severity	$F = 6.95$, $P < 0.025$	NS	$F = 3.40$, $P < 0.10$
Improvement	$F = 11.22$, $P < 0.005$	NS	$F = 28.82$, $P < 0.001$
Therapeutic effect	$F = 9.08$, $P < 0.001$	NS	$F = 21.70$, $P < 0.001$
Adverse effect	NS	NS	$F = 4.22$, $P < 0.07$
Profile of Mood States (POMS)			
Difficulty Concentrating	$F = 3.60$, $P < 0.08$	NS	NS
Vigor	$F = 6.02$, $P < 0.05$	NS	$F = 5.97$, $P < 0.05$
Symptom Check List (SCL-90-R)			
Somatization	NS	NS	$F = 7.72$, $P < 0.025$
Shiffman-Jarvik			
Overall score	$F = 4.69$, $P < 0.05$	NS	NS
Continuous Performance Task (CPT)			
Reaction Time (RT) for Hits	$F = 8.97$, $P < 0.01$	$F = 9.48$, $P < 0.05$	NS
SE change of RT over blocks	NS	$F = 9.00$, $P < 0.05$	NS
SE change of RT over ISI	$F = 8.49$, $P < 0.025$	NS	$F = 4.60$, $P < 0.06$
Interval Timing 17-s 25% feedback post-condition		Only nonsmokers tested	
Mean spread of the timing functions		Wilcoxon signed-rank test, $P < 0.05$	
Accuracy of interval timing		Wilcoxon signed-rank test, $P < 0.05$	

a between subjects factor of smoking status and a within subjects factor of patch type (nicotine or placebo). In tests with repeated measures or subscales, these were included as within-subjects factors as well. Alpha was established at 0.05. For measures in which there were significant nicotine treatment effects, a supplemental analysis of the order of nicotine and placebo treatment was made. In no case was there a significant interaction of nicotine treatment × order of nicotine and placebo administration. An important question in the field of nicotine research is whether nicotine effects are due merely to the relief of withdrawal symptoms in deprived smokers or whether they could also be seen in the absence of withdrawal effects. To answer this question, analyses were also conducted with the smokers and nonsmokers separately. The *F*-ratios for the analyses are shown in Table 2.

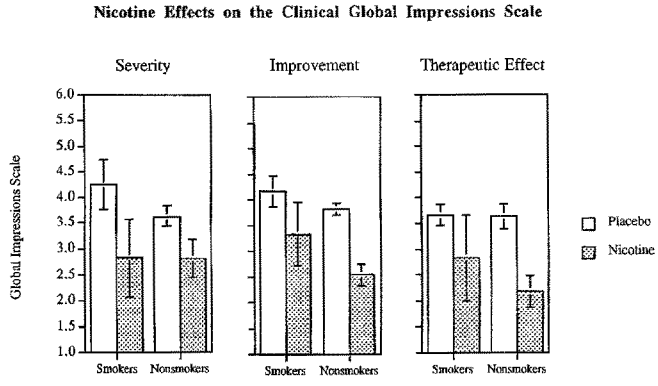

Fig. 1 Nicotine effects on the Global Clinical Impression Scale (mean ± SEM) approximately three hours after patch administration. There were six smokers and eleven nonsmokers. The nicotine effects for the Severity Subscale were $P < 0.025$ for all subjects and $P < 0.10$ for nonsmokers. The nicotine effects for the Improvement Subscale were $P < 0.005$ for All subjects and $P < 0.001$ for Nonsmokers. The nicotine effects for the Therapeutic Effect Subscale were $P < 0.01$ for all subjects and $P < 0.001$ for Nonsmokers

Results

Clinical Global Impression (CGI) Scale

Nicotine significantly improved clinical ADHD symptoms as measured by the CGI Scale. There was a significant nicotine-induced benefit on the severity ($P < 0.025$) subscale (Fig. 1, Table 2). With the nicotine patch, eight subjects (50%) were rated as normal or borderline in severity of ADHD symptoms, six subjects (38%) were rated as mildly to moderately affected, and only two subjects (12%) were rated as markedly to severely affected. With the placebo patch only one subject (6%) was rated as normal or borderline in severity of ADHD symptoms, 11 subjects (69%) were rated as mildly to moderately affected, and four subjects (25%) were rated as markedly to severely affected. When only the nonsmokers were considered, there was a nearly significant improvement on the severity CGI subscale ($P < 0.10$) with a decrease from 3.64 ± 0.20 (mean ± SEM) with the placebo to 2.82 ± 0.38 with the nicotine patch. When assessed alone, the smokers did not show a significant nicotine effect.

There was a significant nicotine-induced benefit on the improvement ($P < 0.005$) subscale (Fig. 1, Table 2). With the nicotine patch, nine subjects (56%) were rated as having much improved or very much improved ADHD symptoms, five subjects (31%) were rated having minimal or no improvement, and two subjects (12%) were rated as having minimally worsened. In contrast, with the placebo patch no subjects were rated as having much improved or very much improved ADHD symptoms, 14 subjects (88%) were rated having minimal or no improvement, and two subjects (12%) were rated as having minimally worsened. When

only the nonsmokers were considered, there was a highly significant nicotine-induced enhancement on the CGI improvement subscale ($P < 0.001$) with a decrease from 3.82 ± 0.12 (mean ± SEM) with the placebo to 2.54 ± 0.21 with the nicotine patch. When assessed alone the smokers did not show a significant nicotine effect.

The therapeutic subscale of the efficacy measure effect of nicotine was significantly ($P < 0.01$) greater than placebo (Fig. 1, Table 2). With nicotine, six subjects (38%) showed marked improvement, six (38%) showed slight to moderate improvement, and four (25%) were unchanged or worse. With placebo none of the subjects showed marked improvement, four (25%) showed slight to moderate improvement, and 12 (75%) were unchanged or worse. The nicotine effect was clearly apparent when only the nonsmokers were assessed ($P < 0.001$). With the nonsmokers the average score improved from 3.64 ± 0.24 (mean ± SEM) with placebo to 2.18 ± 0.30 with nicotine. When assessed alone, the smokers did not show a significant nicotine effect.

There was no significant nicotine main effect on the adverse effect subscale of the efficacy measure. There was, however, a nearly significant ($P < 0.09$) nicotine × smoking status interaction. No indications of adverse side effects were noted by the smokers. In contrast, with the nonsmokers there was a nearly significant ($P < 0.07$) increase in reported adverse side effects subscales [Placebo = 1.1 ± 0.1 (mean ± SEM), Nicotine = 1.7 ± 0.3]. The average report of side effect severity increased from 1.09 ± 0.09 with the placebo patch to 1.73 ± 0.30 with the nicotine patch, less than the "slight" category. The average for the nicotine patch condition was less than the slight adverse effects. Most of the subjects tolerated the nicotine patch well, but some subjects had adverse effects which included nausea ($n = 4$), brief dizziness ($n = 5$), itching ($n = 8$), and slight headache ($n = 5$). There was no hint of an association of the therapeutic effect with the adverse side effects in the nonsmokers ($P > 0.86$, $r = 0.045$, $r^2 = 0.002$).

Profile of Mood States (POMS)

For the POMS Difficulty Concentrating item, there was a significant nicotine treatment by smoking status interaction ($P < 0.025$). The smokers showed improvement [Placebo = 46.7 ± 3.3 (mean ± SEM), Nicotine = 38.2 ± 1], while the nonsmokers did not (Placebo = 40.2 ± 1.4, Nicotine = 41.5 ± 1.9). The Vigor Scale showed a significant nicotine-induced increase [$F(1,15) = 6.02$, $P < 0.05$]. No differential effects in smokers versus nonsmokers were noted (Smokers: Placebo = 49.2 ± 3.0, Nicotine = 54.6 ± 1.8; Nonsmokers: Placebo = 49.7 ± 3.0, Nicotine = 55.9 ± 2.9). When considered alone, the nonsmokers showed a significant nicotine-induced increase in vigor scores ($P < 0.05$), but the smokers did not. The other subscales on the POMS scale did not show significant nicotine-related effects.

Symptom Check List (SCL-90-R)

The nonsmokers showed a significant increase in the Somatization factor on this checklist ($P < 0.025$). With placebo, the subjects in this group had scores averaging 42.9 ± 4.7 (mean ± SEM); with nicotine they averaged 52.7 ± 4.7. No such increase was seen with the smokers (Placebo = 43.8 ± 5.3, Nicotine = 41.8 ± 4.3). There was not a significant overall main effect of nicotine, but there was a nearly significant interaction of smoking group × nicotine treatment ($P < 0.07$). Lightheadedness and dizziness were noted by four of the nonsmoking subjects. These symptoms passed within an hour on the patch. Two nonsmoking subjects asked for the patch to be removed. One nonsmoking subject vomited during nicotine administration and the session was halted. The subject volunteered to be retested in another session and this reactivity was seen again upon re-test. With both subjects the nausea dissipated quickly after removal of the nicotine skin patch.

Shiffman-Jarvik questionnnaire

Nicotine treatment significantly attenuated the severity of withdrawal as measured by the Shiffman-Jarvik questionnaire ($P < 0.05$). There was no significant differential effect of nicotine treatment on the clusters within this test. As expected, there was a significant smoking group × nicotine treatment interaction ($P < 0.05$). The smokers showed a decrease from 104 ± 10 with placebo to 87 ± 7 with nicotine, while the nonsmokers stayed relatively constant with placebo (56 ± 2) and nicotine (57 ± 3). No significant nicotine effects were seen with analyses of the individual groups.

Continuous Performance Task (CPT)

With the Reaction Time for Hits there was a significant nicotine × smoking status interaction ($P < 0.005$). Smokers showed a significant nicotine-induced speeding in response ($P < 0.05$; Placebo = 463 ± 48, Nicotine = 407 ± 31), while the nonsmokers did not (Placebo = 338 ± 13, Nicotine = 344 ± 11).

The change in standard error (SE) of reaction time over the trial blocks within the session (Fig. 2, Table 2) showed a significant nicotine-induced reduction in the smokers ($P < 0.05$), but not in the nonsmokers. The overall effect of nicotine on this measure was not significant. In contrast, as shown in Fig. 2, the change in SE of reaction time over different

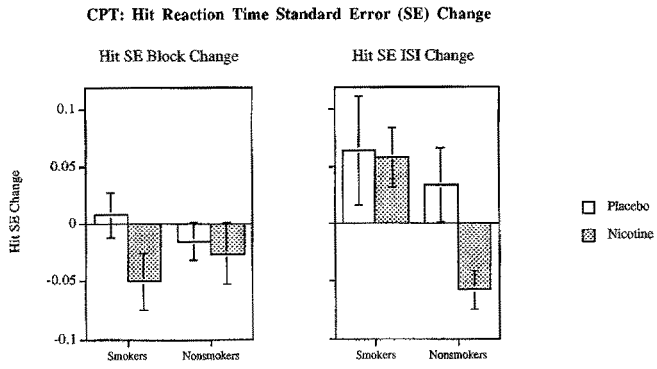

Fig. 2 Nicotine effects on the Conners' CPT reaction time standard error (SE) change over trial blocks and different inter-stimulus intervals (ISIs) approximately 3 h after patch administration. There were 5 smokers and 11 nonsmokers. For SE change over trial blocks the nicotine effect for smokers was significant ($P < 0.05$). For SE change over ISIs the nicotine effect for nonsmokers was nearly significant ($P < 0.06$)

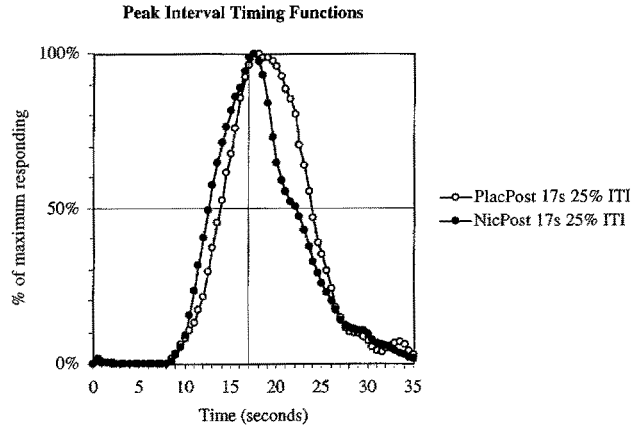

Fig. 3 Peak-interval response distribution functions under placebo and nicotine for the 17-s 25% ITI feedback conditions averaged across ten non-smoking subjects approximately four hours after patch administration. There were nonsmokers. Nicotine significantly ($P < 0.05$) reduced the mean spread of the timing function, increasing the precision of interval timing, and made the mean peak time significantly ($P < 0.05$) more accurate

inter-stimulus intervals (ISIs) was marginally significantly reduced in nonsmokers ($P < 0.06$), whereas there was no difference in the smokers. The overall effect of nicotine on this measure was significant ($P < 0.025$), with nicotine decreasing SE change over different ISIs.

No significant nicotine effects were seen in either errors of omission or errors of commission.

Stroop effect

There was no significant effect of nicotine treatment on the Stroop effect in either smokers or non-smokers.

Interval timing

The data were analyzed by a nonparametric test because they were nonhomogeneous due to the frequent occurrence of multimodal response functions in the placebo condition. Consequently, a Wilcoxon signed-rank test was used to compare parameters derived from the complete response distribution functions for each condition. The nicotine effect was clearest for the longer signal duration and under the low feedback condition. Only the 17-s 25% feedback post-conditions were compared between placebo and nicotine (see Fig. 3 for response distribution functions). The mean spread of the timing functions, used as a measure of the precision of interval timing, was 9.55 ± 0.73 s for placebo and 8.15 ± 0.59 s for nicotine (Wilcoxon signed-rank test, $P < 0.05$). The mean peak time, an indication of the accuracy of interval timing, was 18.7 ± 0.66 s for placebo and 17.21 ± 0.57 s for nicotine (Wilcoxon signed-rank test, ($P < 0.05$). There was no significant difference between the two conditions in peak response rate, a measure of general arousal: in the placebo condition the subjects had a mean value of 22.5 ± 1.77 responses/bin while in the nicotine condition they had a mean of 21.0 ± 2.93 responses/bin (Wilcoxon signed-rank test, NS).

Discussion

This study demonstrated that nicotine given via a skin patch can significantly improve symptoms of ADHD. With the smokers, we found indications that nicotine may decrease ADHD clinical symptoms in smokers after withdrawal. However, this may have been due to alleviation of withdrawal symptoms by the nicotine patch. More importantly, similar effects were seen with nonsmokers for whom withdrawal was not an issue. In fact, the nictoine effects for most of the measures were more pronounced in the nonsmokers than in the smokers. The nicotine effect was most clearly seen in the blind clinical rating (CGI), but was also seen in components of the computerized Conners' Continuous Performance Test and the time estimation task. In the computerized tasks significant beneficial effects of nicotine were seen in the nonsmokers. The magnitude and consistency of the nicotine effects were sufficient to be significant even with the modest numbers of subjects in the present study. The magnitude of the nicotine effect on clinical ratings in adults with ADHD were of the same magnitude as improvements seen with methylphenidate in a similar population (Wender et al. 1991). Nicotine or other nicotinic agonists may be useful treatments for ADHD.

It was necessary to use a lower dose of nicotine in the nonsmoking group (a 7 mg/day patch) relative to the smoking group (a 21 mg/day patch), presumably because the nonsmokers had not developed tolerance to the nausea and dizziness that may be experienced on initial exposure to nicotine (Henningfield 1984).

Nonsmokers occasionally showed mild evidence of these unpleasant side effects, although they were generally transient and passed within an hour after patch administration; only two subjects out of 13 in this group asked that the patch be removed. Tolerance to the nausea and dizziness typically develops with chronic administration. These effects were not seen in the smokers despite being given triple the dose of nicotine. Interestingly, the effect of nicotine (albeit a higher dose) was undiminished relative to nonsmokers in the smokers even though they had a chronic history of nicotine use.

People with symptoms of inattention may smoke as a form of self-medication. Adults with ADHD show a greater smoking rate (40%) than the general population (26%) (Pomerleau et al. 1995a, b). They may be self-medicating with nicotine to address their ADHD symptoms, and the current results support this contention. Nicotine given via skin patches significantly reduces clinical symptoms of ADHD. Given the many health risks associated with cigarette smoking these results should not be construed as a reason to smoke. Rather, they may provide an indication why certain people do smoke. If the goal is to get these smokers to quit, one must meet the need they are addressing by self-medicating. Nicotine skin patches or other nicotinic agonists may offer relatively safer ways of doing this.

The abuse liability of nicotine may be of concern when giving nicotine treatment to nonsmokers. In the limited information thus far available, the abuse liability of nicotine given via skin patches appears to be low. Hughes (1989) surveyed a variety of nicotine delivery systems and rated the nicotine skin patch as probably having lower abuse liability than the others because of the slow rate of nicotine absorption and infrequent self-administration. Recently, Henningfield's group (Pickworth et al. 1994) specifically assessed the abuse liability of the nicotine skin patch in an experimental study and determined it to be minimal. Whatever abuse liability occurs must be weighed against the high rate of smoking among ADHD patients and the possible prophylactic value of early treatment with nicotine in a skin patch or a nicotinic agonist.

Nicotine, like amphetamine and methylphenidate, the stimulants currently used for ADHD, has sympathomimetic actions which can have adverse cardiovascular effects (Palmer et al. 1992). Cigarette smoking and nicotine administered via a skin patch increases both blood pressure and heart rate. Tolerance to these effects seems to develop as they become attenuated with continued administration. Clearly, as with stimulant medication, cardiovascular effects of nicotine must be considered when determining its potential usefulness as a therapeutic treatment.

The mechanisms for nicotine effects in reducing the symptoms of ADHD are not known. Nicotine is known to have stimulant properties and indirectly to increase the actions of DA in a manner similar to methylphenidate and dextroamphetamine (Wonnacott et al. 1989). However, nicotine has a variety of other actions on cholinergic, serotonergic, noradrenergic and other systems which may also underlie its effects (Wonnacott et al. 1989). Studies using nicotinic agonists which have different subtype specificity should help define critical mechanisms of action .

Whether the therapeutic effect of nicotine would be maintained with chronic administration is currently unknown. However, there is some reason to think that would continue to be effective. In studies of smokers, the attention-improving effects of nicotine seem to be clearly present, even in very experienced smokers who have been exposed to nicotine for many years. (Wesnes et al. 1983). In our preclinical studies, chronic nicotine for 4 weeks is as effective as acute nicotine in improving working memory performance in rats (Levin and Rose 1995). The mechanism, however, seems to differ. The acute effect of nicotinic drugs on memory seems to be closely related to DA systems, while the chronic effect seems to be less closely related to DA system (Levin and Rose 1995).

Recent theoretical arguments propose a central role of basic timing functions in ADHD. Barkley (Barkley 1995) suggests that the inability to delay response in ADHD is its primary core symptom and that this deficit reflects a disturbance of accurate timing mechanisms. In agreement with this idea, subjects with ADHD in the current study demonstrated severely degraded temporal processing when provided with feedback on only a random quarter of the trials instead of after each trial. This phenomenon is not observed in normal subjects (Penney et al. 1993). Nicotine produces both a sharper and a more accurate timing function than placebo, particularly in the 17-s 25% feedback condition, which places the greatest cognitive demand on the subject. While the ADHD subjects are often able to initiate responding at the correct time, they have greater difficulty determining when to terminate responding, particularly under the low feedback condition. Their timing function under the placebo condition is therefore broader and shifted to the right. The deficit may reflect difficulty maintaining attention on the task and is corrected by nicotine administration.

Nicotine reduced the variability of responding over the trial blocks of the CPT in smokers indicating a more consistent attentional focus. It also reduced variability in response to changing inter-stimulus intervals (ISI) in nonsmokers. This latter effect is thought to represent a higher-order executive monitoring of attention that establishes a consistent tempo. Both of these effects are found in response to methylphenidate (Conners 1994; Conners et al. 1994). Variability of response over trials and variability increase with longer ISIs show steady developmental improvements (reductions) with increasing age in normal subjects (Conners 1995), possibly representing a normal maturation of

attentional capabilities. It could be clinically and theoretically important if nicotine agonists improve this developmental function.

The subjective effects of nicotine as measured by the POMS questionnaire showed that while both smokers and nonsmokers reported increased vigor, only the smokers reported decreased difficulty concentrating. The latter report may have been due to any of several factors. Since the smokers had more experience with the subjective effects of nicotine they may have more readily perceived improvements in concentration. Also related to their experience with nicotine, they had fewer adverse side effects and thus may have been less distracted in their self report by nausea and dizziness. The fact that the smokers were in nicotine withdrawal state during the placebo condition may have caused them to report greater difficulty in concentrating than nonsmokers, a condition which was reversed by the nicotine patch. This is supported by the generally higher scores for the difficulty concentrating measure by the smokers compared to the nonsmokers in the placebo condition.

Nicotinic agonists may be a new class of therapeutic agents (Jarvik 1991; Levin et al. 1993; Levin and Rosecrans 1994; Westman et al. 1995). Nicotine and nicotinic agonists have been shown to have potential therapeutic use in a variety of disorders. Initial clinical studies have shown nicotine-induced improvements in Alzheimer's disease (Newhouse et al. 1988; Sahakian and Jones 1991; Jones et al. 1992), Parkinson's disease (Fagerström et al. 1994), Tourette's syndrome (McConville et al. 1991) and ulcerative colitis (Pullen et al. 1994). The current study provides initial information concerning the possible use of nicotinic therapy for ADHD. Further investigation is warranted to determine the extent of nicotine effects in ADHD, whether improvements persist, and how they compare with and may complement current stimulant treatment for ADHD.

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