

Nicotine and Attention in Adult Attention Deficit Hyperactivity Disorder (ADHD)¹

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Abstract

Nicotine, like the psychostimulants methylphenidate and dextroamphetamine, acts as an indirect dopamine agonist and improves attention and arousal. Adults and adolescents with attention deficit hyperactivity disorder (ADHD) smoke much more frequently than normal individuals or those with other psychiatric conditions, perhaps as a form of self-medication for ADHD symptoms. Nicotine might therefore have some value as a treatment for ADHD. The present study is an acute double-blind crossover administration of nicotine and placebo with smokers ($n=6$) and nonsmokers ($n=11$) diagnosed with adult ADHD. The drug was delivered via a transdermal patch at a dosage of 7 mg/day for nonsmokers and 21 mg/day for smokers. Results indicate significant clinician-rated global improvement, self-rated vigor and concentration, and improved performance on chronometric measures of attention and timing accuracy. Side effects were minimal. These acute results indicate the need for a longer clinical trial and a comparison with other stimulants in adult ADHD treatment.

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Introduction

Nicotine has significant effects on electrocortical and cardiovascular arousal (Michel et al. 1988) and vigilance (Parrott & Winder 1989) among smokers. These effects are not limited to smokers and are therefore unlikely to represent merely the alleviation of withdrawal effects (Warburton & Arnall 1994). Prospective study of well-diagnosed children with ADHD shows that as adolescents they smoke much more than controls (Barkley et al. 1990). More than 40 percent of adults with ADHD are smokers compared with 26 percent of the general population (Pomerleau et al. 1995). The high prevalence of smoking among adolescents and adults with ADHD and the stimulant-like properties of nicotine suggest that ADHD patients may smoke as a form of self-treatment for their symptoms. No studies have previously examined the direct effect of nicotine on ADHD behavioral symptoms, performance, and subjective state.

Methods

Subjects

Subjects were recruited from physicians, psychologists, and local support groups. Those meeting entry criteria had a mean age of 34 (range = 20 to 51 years), and included 18 males and 4 females. Four patients failed to complete the trial after acceptance but prior to randomization for reasons unrelated to treatment (1 moved, 1 had car problems preventing participation, 1 had depression scores that were too high, and 1 began treatment with an antidepressant). A fifth patient, a non-smoking male, failed to complete the trial because of severe nausea and dizziness following the initial dose.

Inclusion criteria for the study were:

1. T-score greater than 60 on the Wender Utah Rating Scale (Wender 1995);
2. T-score greater than 60 on at least two of the following subscales of the Conners/Wells Adolescent/Adult Self-Report Scale (Conners & Wells 1985): concentration, restlessness, learning problems;
3. *DSM-IV* criteria of ADHD, either subtype, based on a modified version of Barkley's Adult ADHD Semi-Structured Interview (Barkley 1990);
4. Hamilton Rating Scale for Depression interview (HAM-D; Hamilton 1960) raw score less than 20.

Exclusion criteria included the following:

1. Any medical contraindications to use of a transdermal skin patch (such as skin allergy or sensitivity), hypertension, cardiac disease, cerebrovascular disease, seizures, alcohol or other substance abuse, or a current diagnosis of any other Axis I condition;
2. Failure to obtain physician consent for stopping concurrent stimulant or other psychotropic drug treatment;
3. Pregnancy as determined from a BHCG (beta-human chorionic gonadotropin) serum test;
4. Concurrent use of antibiotics, sulfonamides, anti-hypertensive agents, or psychotropic medications. If patients were receiving psychostimulants to treat ADHD, they had to have a 3-day washout period approved by their physician.

Smoking status was verified by history (Ikard et al. 1969) and by end-tidal CO readings (> 15 ppm for smokers, < 15 ppm for nonsmokers).

Baseline Assessments

After completing a consent form, subjects received assessments in the following order in a single session lasting approximately 2 hours:

1. End-tidal CO.
2. Wender Scale (Wender 1995), a 61-item retrospective scale of childhood symptoms as recalled by the patient. Norms are based on 81 adult ADHD subjects, 100 normal individuals, and 70 depressed patients.
3. Tripartite Personality Questionnaire (Cloninger et al. 1991), a 110-item true/false questionnaire designed to measure three personality dimensions (novelty-seeking, harm avoidance, reward dependency) hypothesized to be related to underlying neurotransmitter functions of dopamine, norepinephrine, and serotonin.
4. Profile of Mood States (POMS; McNair et al. 1981), a measure of current mood state as rated for the past week.
5. Symptom Checklist 90 (SCL-90; Derogatis 1983), a 90-item measure of general psychopathology.
6. Hamilton Depression Scale (HAM-D; Hamilton 1960; Williams 1988).
7. Continuous Performance Test (Conners 1994a), a 14-minute computerized test that requires the subject to respond to frequently occurring letters (probability = 75%) from a set of 10, and to refrain from responding to one of the letters ("X") (probability = 25%). Blocks of 20 trials are presented at three different signal rates (1, 2, and 4 seconds), counterbalanced across trials. Each of the six possible sequences defines a supra-block. The

- reaction time (RT), accuracy, and signal detection parameters of d' and beta are computed. Variability across supra-blocks as well as variability of inter-stimulus interval (ISI) blocks is calculated. The test has shown good sensitivity to stimulant drugs (Conners et al. 1994) and excellent diagnostic sensitivity (Conners 1994b).
8. Fagerström Test of Nicotine Dependency (Fagerström et al. 1989), a 6-item questionnaire for smokers to determine the degree of their cigarette dependence.
 9. Peak-Interval Timing Procedure (Church et al. 1991; Meck & Church 1987).
 10. A computerized version of the classic Stroop Task (Neurosoft 1990).
 11. Severity scale of the NIMH Clinical Global Impressions (CGI; NIMH 1985).

Procedure

Nicotine or placebo patches (Nicoderm®) were applied at the same time on each of the 2 treatment days. Smokers were abstinent for 12 hours prior to testing as was confirmed on the day of testing by an end-tidal CO reading level < 12 ppm. Subjects were randomly assigned to either a placebo-nicotine or nicotine-placebo sequence. Smokers received a 21-mg patch and nonsmokers received a 7-mg patch.

Assessment of Treatment Response

Tests were administered in a fixed order (Table 1). The CGI was re-administered after each of the two treatment sequences. A brief interview was conducted to determine subjective and objective changes during the 3 hours following placement of the nicotine or placebo patch. Between patch application and interview, subjects filled out forms and took the various response measures

TABLE 1. Schedule of Testing and Patch Administration.

Time	Procedure	Time Frame
8:30 a.m.	End-tidal CO	—
8:45 a.m.	Patch placement	—
9:00 a.m.	Peak timing procedure	—
10:15 a.m.	Modified Schiff/Jarvik	"now"
10:45 a.m.	POMS	"today"
11:00 a.m.	SCL-90-R	"today"
11:45 a.m.	CGI interview/rating	"past 3 hours"
11:55 a.m.	CPT	—
12:15 p.m.	Stroop	—
12:30 p.m.	Peak timing procedure	—

of the study. The severity, efficacy, and improvement subscales of the CGI, used as measures of overall response, included observations of the patients' behavior (body, hand, and eye movements) and subjective state.

Subjective state was estimated globally from answers to the following questions: 1. How hard was it for you to concentrate, or focus, while you filled out the forms? 2. Did you feel impatient in between forms? 3. Do you feel you gave them enough thought? 4. Did it seem to take a long time to complete them? 5. How much difficulty did you have with figuring out what you had to do for each of them? 6. Did you feel rushed? 7. Was it hard or easy to decide on your responses? 8. Did time go by quickly? 9. Did you feel restless? 10. Do you feel any different now than when you first got here? 11. Have you felt any (dizziness, headache, racing pulse, nausea, itching all over)? If yes, how much did it interfere with what you were doing? 12. Do you think you had the patch with nicotine or not? (The last question was omitted from the baseline interview.)

Results

Subject Characteristics

Given the uncertainties in diagnosing adult ADHD, documenting the behavioral and symptomatic profile of these patients is important. Table 2 presents the retrospective symptom recall on the Wender Scale. Both smokers and nonsmokers are more than two standard deviations above the mean for normal controls based on Wender's (1995) normative data. However, the smokers are significantly more symptomatic in their recall of childhood than the nonsmokers.

TABLE 2. Wender T-Scores of Study Smokers and Nonsmokers Compared to Normal Individuals, ADHD Adults, and Depressed Patients.

Smoking Status	Mean	SD
Smokers		
Normal	91.07	15.23
ADHD	47.35	9.82
Depressed	64.69	7.57
Nonsmokers		
Normal	76.21	20.76
ADHD	39.76	13.30
Depressed	56.79	15.28

TABLE 3. Tripartite Personality Questionnaire in Smokers and Nonsmokers (T-Scores).

	Novelty Seeking	Harm Avoidance	Reward Dependence
Smokers			
Mean	71.27	44.72	40.46
SD	8.69	4.80	7.47
Nonsmokers			
Mean	64.12	46.48	42.11
SD	17.66	15.44	15.95

The personality characteristics derived from the TPQ are shown in Table 3. Both smokers and nonsmokers are significantly elevated on the novelty seeking scale, and are within normal range on the harm avoidance and reward dependency scales. There is a tendency for the smokers to score higher on novelty seeking.

Figure 1 compares smokers and nonsmokers on general psychopathologic symptoms on the SCL-90. On three symptom factors (obsessive-compulsive, depression, and interpersonal sensitivity), both groups experience significant symptom elevation, averaging more than one standard deviation above population norms. Interestingly, however, the factor scores are consistently lower for the smokers than for the nonsmokers.

Performance Measures

The CPT reaction time results are shown in Table 4. Data were analyzed by multivariate analysis of variance, with treatments as a within-subject effect and smoking status as a between-subject effect. Baseline values were used as covariates. The multivariate effect was significant ($p=.011$), and the treatment ($p=.032$) and smoking status \times treatment effects ($p=.009$) were also significant. As may be seen from Table 4, the nonsmokers were significantly faster than smokers and showed less gain from the nicotine compared with the smokers. The smokers reduced their reaction times by an average of 55 msec., and nearly halved the variability.

Another index of attentional functioning is the ability to maintain a constant level of performance over time. In the CPT this is measured by the standard deviation of the reaction time means in the six blocks. This index of variability was significantly reduced in the smokers ($F(1,4) = 9.00, p < .05$), but not in the nonsmokers. Other CPT indices, including variability over ISI and the signal detection parameters d' and beta, showed no effects of the treatment, nor were there any other differences between smokers and nonsmokers.

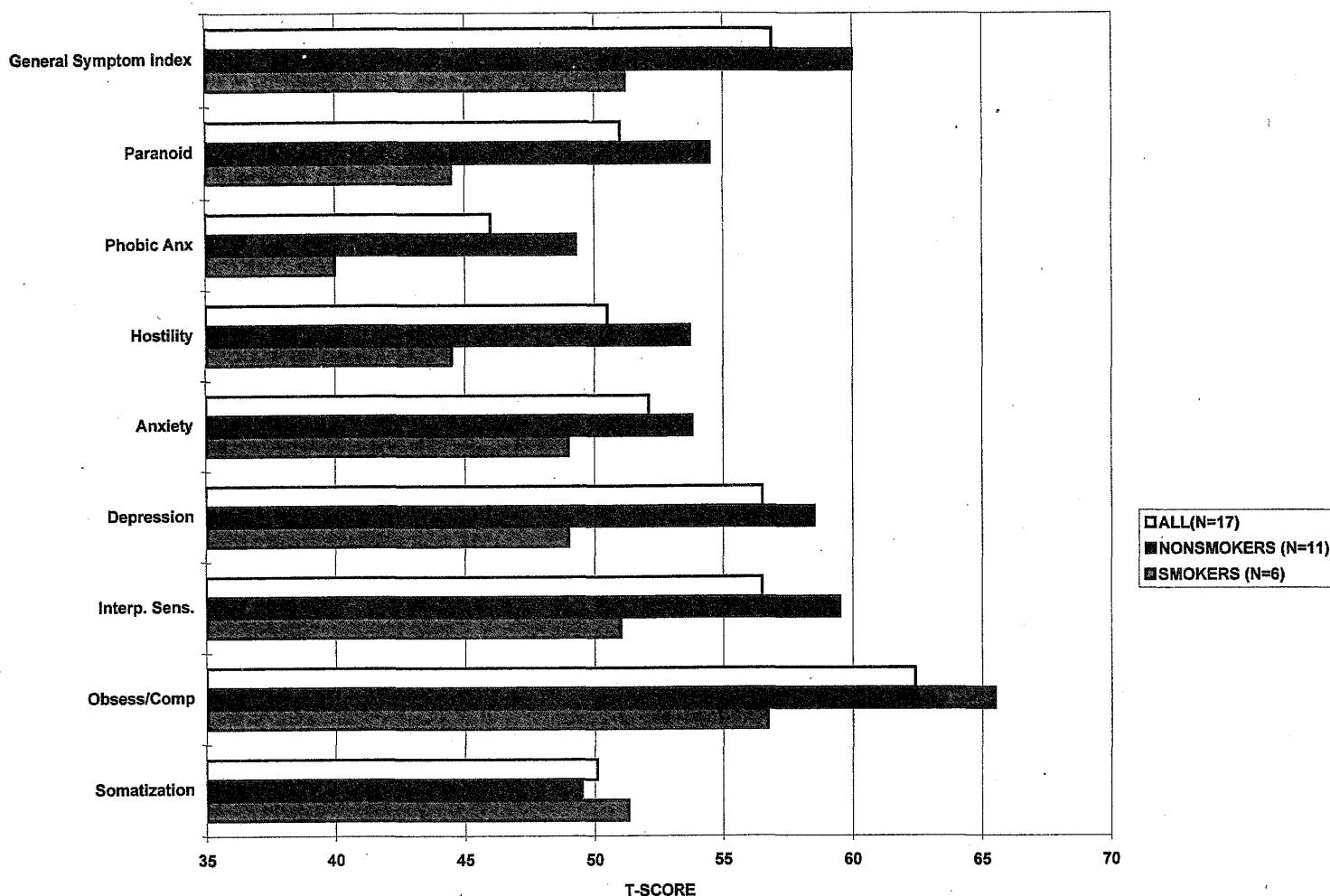


FIGURE 1. Self-reported symptoms in smokers and nonsmokers.

TABLE 4. Effect of Nicotine and Placebo on Reaction Time During Continuous Performance in Smokers and Nonsmokers.

	Mean		Standard Deviation	
	Placebo	Nicotine	Placebo	Nicotine
Nonsmoker (n=12)	342.55	344.31	44.47	38.92
Smoker (n=5)	462.72	407.10	107.10	69.68

Time Estimation

Data from the timing procedure were available for 10 of the nonsmoking subjects. The width of the timing function, used as a measure of the precision of interval timing, was 9.55 ± 0.73 seconds for placebo and 8.15 ± 0.59 seconds for nicotine (Wilcoxon signed-rank test, $p < .05$). The accuracy of time estimation was measured by the peak of the timing function, which in the 17-second condition with 25 percent feedback was 18.7 ± 0.66 seconds for placebo and 17.21 ± 0.57 seconds for

nicotine (Wilcoxon signed-rank test, $p < .05$). There were no significant effects on the Stroop Test.

Self-Report Measures

On the POMS, smokers showed improvement in concentration, but nonsmokers did not, giving a significant interaction effect ($F(1,15)=6.78$, $p < .025$) and a marginal overall effect ($p < .08$). There was a significant overall increase in vigor with nicotine ($F(1,15)=6.02$, $p < .05$). On the SCL-90-R there was an increase in somatization because of a nicotine effect in the smokers. Other scales were unaffected.

Clinical Global Impressions

The within-subjects treatment effect was significant for the severity scale of the CGI ($p < .025$), the improvement subscale ($p < .005$), and the efficacy subscale ($p < .01$). Table 5 shows the CGI severity, improvement,

TABLE 5. Clinical Global Improvement Ratings (Number/Percent).

	Placebo			Nicotine		
	Much Improved	No Change	Unchanged/Worse	Much Improved	No Change	Unchanged/ Worse
Improvement Scale	0(0)	14(88)	2(12)	9(56)	5(31)	2(12)
Therapeutic Efficacy	0(0)	4(25)	12(75)	6(38)	6(38)	4(25)
	Normal	Mild/Moderate	Severe	Normal	Mild/Moderate	Severe
Severity Scale	1(6)	11(69)	4(25)	8(50)	6(38)	2(12)

and efficacy data. On the adverse effect scale, there was a nearly significant nicotine \times smoking status interaction ($p < .09$) reflecting a slight reduction in adverse effects by the smokers and a near-significant increase among the nonsmokers ($p < .07$). The adverse side effects increased from $1.091 \pm .09$ to 1.73 ± 0.30 , which is less than the "slight" category. Four subjects experienced mild nausea, one with nausea severe enough to prompt withdrawal. There were also some brief dizziness ($n=5$), itching ($n=8$), and mild headache ($n=5$).

Discussion

Adult ADHD poses difficulties in both diagnosis and treatment. The presence of multiple comorbidities is to be expected because the subjects have passed into the age of risk for other psychiatric conditions and because many symptoms are secondary to the cumulative life stresses and educational deficits that result directly from the primary symptoms of ADHD. In the present study, our patients were elevated on three of the SCL-90-R scales: obsessive-compulsive (OC), depression (D), and interpersonal sensitivity (IS). The elevation on OC is quite common in our experience and derives from an artifact of factor naming. Since the factor includes such items as trouble concentrating, forgetfulness, worries about sloppiness and carelessness, having to go slow in getting things done, getting blocked in doing things, and several other items that are readily endorsed by adult ADHD, there is no basis for supposing that subjects truly have OC symptoms. These symptoms take on an entirely different meaning in the context of people with chronic restlessness, impulsiveness, inattention, and life-long learning problems. We excluded patients with HAM-D scores greater than 20, and no patients met criteria for major depressive disorder (MDD). Most adults with ADHD feel demoralized, have low self-esteem, and are interpersonally sensitive to the point that

they often qualify for a diagnosis of social phobia. Our patients, however, showed relatively low levels of harm avoidance and reward dependency (as we would expect with ADHD) and did not meet criteria for anxiety disorders. Their elevated D and IS factors probably reflect the insults suffered to self-esteem as a result of past behavior.

It is interesting to note that the smokers in the sample retrospectively rate their past as more severe on the Wender Scale than nonsmokers do. This perception could represent a retrospective negative halo based on current symptomatology; however, this seems unlikely in view of the fact that the smokers actually had significantly less current psychopathology than the nonsmokers. Rather, it may mean that the severity of their past symptoms encouraged them to take up smoking and that their psychopathology is lower than nonsmokers' precisely because the nicotine lessens the severity of their symptoms. The fact that smokers have higher levels of novelty seeking than the nonsmokers is consistent with this interpretation and suggests that smokers may have a more immediate need than nonsmokers to calm their excitability and restlessness. An alternative explanation is that cigarette smoking among adult ADHD subjects is a correlated phenomenon of their general pattern of stimulus-seeking rather than a means of treating their primary symptoms. In this case, cigarette smoking would be merely an epiphenomenon of lifestyle, and neither a cause nor treatment of the ADHD symptoms.

The clinician-observed changes in behavior and in judgment of symptom severity were based on a single interview after 3 hours of nicotine or placebo treatment. The patients showed unequivocal statistical improvement from the nicotine condition. However, since patients also reported side effects in this interview, it is possible that the clinician was biased by their reports. The POMS self-ratings indicated improved vigor and concentration from nicotine, but these too could be influenced by subjective awareness of purely somatic

changes. The increase in SCL-90-R somatization confirms that the patients as a group experienced more bodily symptoms. This finding was mostly apparent in the nonsmokers, however, indicating the importance of documenting the effects by other methods.

The CPT showed clear improvement in speed of response (RT) and ability to sustain attention (reduced variability across trials). However, that benefit was almost exclusively attributable to the smokers who exhibited a substantial decrease in RT resulting from nicotine that the nonsmokers did not. The combination of a slower RT and good response to nicotine in the smokers suggests the possibility that smokers tend to be cognitively impaired, compared with nonsmokers, when they are not smoking or when their nicotine levels are low.

Unfortunately, the other performance test that might have thrown some light on the objective response to nicotine, the Stroop Test, showed no effect whatsoever. Since we have no information regarding stimulant-like effects on the Stroop, it is not possible to decide between the test's drug insensitivity and other explanations of lack of effect found in this study.

Improved speed, in combination with the subjective experience of increased vigor and concentration, suggests that nicotine's ability to arouse may be important in achieving the effects seen in this study. The lack of effect on impulsive errors cannot be attributed to the ceiling effect that occurs in most CPTs, because our CPT was designed to elicit more impulsive errors specifically to prevent a ceiling effect. The mean error rate was about 33 percent, which is actually close to the norm for adults on this test, suggesting that impulsive action is less of a problem for adults with ADHD than are cognitive limitations in attention and concentration. Nicotine may affect impulsive action less than speed, precision, and ability to sustain attention. Similarly, the lack of effect (and of baseline abnormality) in beta—a function that measures the subject's subjective criterion for making a response—suggests that regulation over response may have been less important here than the effects on ability to focus and sustain attention.

The timing estimation task also showed a significant nicotine impact. Though limited to 10 nonsmokers, our data nevertheless suggest that adults with ADHD tend to overestimate the passage of time and to become more veridical and less variable in their estimates as a result of nicotine. Barkley (1995) has recently theorized that ADHD children have difficulty delaying the time between stimulus and response, a problem that could result from impairment of fundamental timing generators in

the brain. In our study, the ADHD patients had the greatest difficulty determining when to stop responding, which caused their response distribution to be broader and to shift rightward. Nicotine appears to partially correct this behavior. It is tempting to attribute this ameliorating effect to the increased availability of dopamine to brain areas involving timing generators, but in addition to being an indirect dopamine agonist, nicotine also has a wealth of actions on cholinergic, serotonergic, and noradrenergic functions.

Further trials on adult ADHD patients, comparing the effects of nicotinic agonists with those of standard stimulants like methylphenidate seem warranted based on our present results. The possible addictive effects of nicotine need to be weighed against the therapeutic benefits of symptom alleviation as well as the health benefits that would accrue to a nonsmoking form of drug delivery. The potential for preventive effects in high-risk children also need to be factored into the risk-benefit equation.

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