Transdermal Nicotine and Haloperidol in Tourette's Disorder: A Double-Blind Placebo-Controlled Study

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Background: Preclinical animal and open-trial clinical trials using nicotine gum and the transdermal nicotine patch found that treatment with nicotine potentiates the effects of neuroleptics in reducing the dyskinetic symptoms of Tourette's disorder. We sought to verify and expand these findings in a prospective double-blind placebo-controlled trial.

Method: Seventy patients with DSM-IV Tourette's disorder were treated with either transdermal nicotine (7 mg/24 hours) or placebo patches in a 33-day, randomized, double-blind study. Each patient received an individually based optimal dose of haloperidol for at least 2 weeks prior to random assignment to nicotine or placebo treatment. A new patch was worn each day for the first 5 days. On the sixth day, the dose of haloperidol was reduced by 50%. Daily patch applications were then continued for an additional 2 weeks (through day 19), at which time the patch was discontinued, but the 50% dose of haloperidol was continued for an additional 2 weeks (through day 33). Clinical and safety assessments were made at each visit.

Results: Patients who completed all 19 days of nicotine (N = 27) or placebo (N = 29) patch treatment were used in efficacy analyses. As documented by the Clinician- and Parent-rated Global Improvement scales, transdermal nicotine was superior to placebo in reducing the symptoms of Tourette's disorder. The Yale Global Tic Severity Scale was less sensitive in detecting a placebo/drug difference than were the global improvement scores, suggesting that some of the improvement may not have been related to treatment-related changes in tic severity, but to the emotional and behavioral symptoms. The side effects of nausea and vomiting were significantly more common in the nicotine group (71% [N = 25] and 40% [N = 14]) than in the placebo group (17% [N = 6] and 9% [N = 3]) (nausea, p = .0001; vomiting, p = .004).

Conclusion: Transdermal nicotine was superior to placebo in reducing behavioral symptoms when patients were receiving an optimal dose of haloperidol, when the dose of haloperidol was reduced by 50%, and when the patch had been discontinued for 2 weeks. These findings confirm earlier open-label findings and suggest that combining nicotinic receptor modulation and neuroleptics could be a therapeutic option for the treatment of Tourette's disorder. While side effects limit chronic use of nicotine, it may be useful on a p.r.n. basis. Further clinical research is warranted to investigate the use of novel nicotinic receptor modulating agents with improved safety profiles over nicotine.

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Tourette's disorder is a childhood-onset hyperkinetic disorder thought to be caused by pathophysiology of cortical-striato-thalamo-cortical circuits in the brain.[1] The neuroleptics haloperidol and pimozide are the only 2 medications currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of Tourette's disorder. Although neuroleptics are effective in reducing frequency and severity of the motor and phonic tics of Tourette's disorder in about 70% of cases,[2] they often produce adverse side effects including cognitive dulling, sedation, weight gain, acute dystonic reactions, akathisia, parkinsonism, and with long-term treatment, tardive dyskinesia.[3]

Following evidence that systemic administration or intracaudate infusions of nicotine augment fluphenazine-induced catalepsy in rats,[4,5] it was determined that nicotine could, in rats, also potentiate haloperidol-induced catalepsy as well as haloperidol-reduced locomotor activity.[6,7] An intact striatum was required for this effect.[8] The findings from these preclinical studies suggested that nicotine might have potential benefit in potentiating the effect of neuroleptics used to treat striatal disorders such as Tourette's disorder.

Initial clinical investigations consisted of open-label studies of nicotine gum in Tourette's disorder patients

concurrently on treatment with haloperidol. With nicotine gum, a decrease in tic frequency and severity as well as a subjective improvement in concentration and attention was noted.[9–11] A subsequent controlled trial also yielded similar results, with nicotine gum plus haloperidol reducing both tic severity and frequency. Nicotine gum alone reduced only tic frequency, while placebo gum alone had no effect on tic symptoms.[12] A therapeutic response to nicotine gum alone was also found in 2 case reports.[13,14] The effect with nicotine gum, however, was short-lived, lasting 45 minutes to 1 hour after gum chewing. Further, because of gastrointestinal side effects and the bitter taste of the gum, noncompliance was frequent.

Silver and Sanberg,[15] examining the effects of transdermal nicotine patches designed to deliver 7 mg of nicotine in 24 hours, found a mean reduction of 47% in tic frequency and a 34% reduction in tic severity following patch application in 11 patients with Tourette's disorder who were not responding well to their neuroleptic.[16] Surprisingly, in 2 patients, the effect of a single nicotine patch persisted for a variable length of time after patch removal. Similar long-term benefits of the transdermal nicotine patch were also reported by Dursun et al.,[17–19] who found that applying 2 consecutive 10-mg transdermal nicotine patches, with each transdermal nicotine patch given for 24 hours, reduced tic symptoms significantly for 4 weeks but not 16 weeks after transdermal nicotine patch removal.

Further evidence for a long-term therapeutic response to the transdermal nicotine patch was found when Tourette's disorder patients were followed for various lengths of time after the application of transdermal nicotine patches. These retrospective case studies found that the application of a single transdermal nicotine patch titrated to deliver 7 mg of nicotine in 24 hours resulted in a significant reduction in motor and phonic tics in 17 of 20 patients, and the reduction in motor and phonic tics persisted for a mean of 10 days following the application of a single 7-mg 24-hour transdermal nicotine patch.[20,21] In these open trials, side effects included transient itching at the site of application, nausea, and occasional headache and sedation. However, there was no clinical evidence found for nicotine dependence with the transdermal nicotine patch.

When considering the addiction potential of nicotine, an important distinction between the transdermal nicotine patch and tobacco smoking is the rapid rise in blood levels of nicotine associated with inhalation of tobacco smoke. Indeed, an important characteristic of all drugs that produce dependency is the time between behavioral administration (i.e., smoking a cigarette) and the drug's entry into the brain.[22] Thus, the slower absorption of nicotine offered by the transdermal nicotine patch relative to tobacco products substantially reduces the likelihood of nicotine dependence in users of the patch.

In the present study, we reasoned that one advantage of transdermal nicotine as an adjunct to neuroleptic treatment could be a potential reduction of neuroleptic dose and the associated risks of short- and long-term adverse effects produced by neuroleptics. Because of the possibility that nicotine could be therapeutic in a number of disorders including Tourette's disorder, a controlled trial to investigate the safety and effectiveness of transdermal nicotine as an adjunct to haloperidol for the treatment of Tourette's disorder was conducted.

METHOD

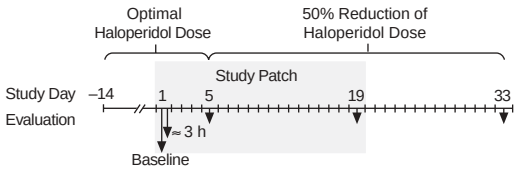
Patients

From July 1994 through July 1998, 70 patients with Tourette's disorder (59 from the University of South Florida and 11 from the University of Cincinnati) were randomly assigned to receive either transdermal nicotine (N = 35) or placebo (N = 35) patches. Inclusion depended on a primary diagnosis of Tourette's disorder by meeting DSM-IV criteria.[23] Subjects were excluded if they were less than 8 years of age, weighed less than 25 kg (55.6 lb), were pregnant, or had evidence of structural defect of the central nervous system, seizure disorder, or other illness that would render the patient at risk as determined by history, physical examination, and laboratory study including complete blood cell (CBC) count and liver function tests. Age and weight restrictions were recommended by National Institute of Neurological Disorder and Stroke review of the protocol. Because prior nicotine exposure could possibly confound the data as well as increase health risks to patients, those who smoked cigarettes, were chronically exposed to cigarette smoke, or used smokeless tobacco were excluded. Problems of attention, hyperactivity, impulsivity, obsessions and compulsions, anxiety, depression, and learning disorders were not grounds for exclusion. The ethics committees at both centers approved the study, and the parents and patients gave written informed consent.

Transdermal Nicotine Patch

The source of both the placebo and nicotine patches was Marion Merrill Dow Pharmaceuticals. The pharmacokinetic data from Marion Merrill Dow indicate that the initial absorption of nicotine from the transdermal patch is slower than that from tobacco products, resulting in a lower blood nicotine level than that achieved by tobacco products.[24] Following application of the 7-mg nicotine patch in adults, blood levels of nicotine reach an average peak of about 6 ng/mL in 3 hours. By contrast, smoking 1 average tobacco cigarette produces blood nicotine levels that peak at around 40 ng/mL in only 10 minutes.[24] Application of the patch for 24 hours does not increase the peak blood nicotine levels, but in the 24 hours following removal of the patch, blood levels of nicotine gradually decline. As part of our informed consent process, we emphasized to patients and their parents the importance of keeping these patches out of the reach of children.[25] The

Figure 1. Timeline for Haloperidol and Study Patch (nicotine or placebo) Administration and Testing



placebo patch was indistinguishable from the nicotine patch, having the same size, shape, and appearance. The 7-mg nicotine patch actually contains 35 mg of nicotine, but allows for the absorption of only 7 mg over a 24-hour period. A smaller quantity of nicotine (7 mg) was present in the placebo patch to produce the same smell; however, a barrier was inside the patch, designed to prevent leakage of nicotine onto the skin.

Study Design

Subjects were randomly assigned to 1 of 2 groups, each receiving either a transdermal nicotine patch titrated to release 7 mg of nicotine in 24 hours (N = 35) or the control patch (N = 35). Patients and investigators were blind to group membership, and a predetermined randomization code (using a random number generator[26]) was kept by a colleague who was not involved with the study, but who was available in the event of an emergency. On the initial visit, patients received a screening evaluation assessing inclusion and exclusion criteria. Patients who met the inclusion criteria and were willing to participate in the study signed the informed consent and were then treated with only haloperidol until they had reached a plateau in therapeutic effectiveness for at least 2 weeks prior to baseline. This "optimal" dose is that which was most effective in reducing Tourette's symptoms without inducing side effects. Patients were then scheduled for their baseline clinical evaluation, including a physical examination; vital signs; body weight; neurologic and psychiatric assessment; documentation of location, frequency, and severity of tic symptoms; and presence and severity of comorbid behavioral and/or emotional disorders. Laboratory tests including CBC count, liver function, and blood levels of nicotine, haloperidol, and prolactin were performed at each visit. Since haloperidol can increase prolactin levels due to its central D_2 dopamine receptor blocking properties,[27] prolactin levels provide an indirect measure of haloperidol's neuropharmacologic effects by treatment group. Female subjects were required to use adequate contraceptive methods if sexually active, since nicotine has been found to be harmful to the developing fetus.[28]

As outlined in Figure 1, immediately following the baseline evaluation, the initial patch was applied to the patient. In view of preliminary data obtained in open trials suggesting a rapid response to transdermal nicotine, an assessment of symptoms was obtained 3 hours after the initial patch was applied. For the next 5 days, patients applied 1 new patch each day. At the conclusion of the fifth day, the dose of haloperidol was reduced by 50% and the daily application of patches continued for an additional 2 weeks. Thus, from day 6 through day 19, patients received 50% of their original haloperidol dose and 1 transdermal patch each day. Because of the long half-life of haloperidol, 2 weeks were needed to ensure that blood levels of haloperidol were indeed reduced by 50%. Follow-up evaluation at the end of the 2 weeks (day 19) repeated the clinical and laboratory evaluations conducted at baseline and day 5. From day 20 through day 33, patients continued to receive 50% of their original haloperidol dose, but no patches. Patients and their parents monitored side effects and tic frequency and severity as well as nicotine withdrawal symptoms daily (on days 20–25) using a patient diary. A final clinical evaluation was repeated again at the conclusion of day 33.

Outcome Measures

The efficacy of transdermal nicotine patches, as an adjunctive therapy with haloperidol, in reducing the frequency and severity of Tourette symptoms was assessed using the following primary outcome measures: Clinician- and Parent-rated Global Improvement scales (CGI and PGI)[29] and the Yale Global Tic Severity Scale (YGTSS).[1] The global improvement scales were 21-point scales with positive values of 1 to 10 for improvement, 0 for no change, and negative values of 1 to 10 for worsening of symptoms. From baseline, global improvement scores reflect change in Tourette's spectrum symptoms, which include motor and vocal tics and behavior symptoms such as inattention, restlessness, irritability, obsessions and compulsions, temper outbursts, and aggression. The YGTSS provides an evaluation of the number, frequency, intensity, complexity, and interference of motor and phonic symptoms. The instrument is reliable and has appropriate construct, convergent, and discriminant validity for measurement of tic symptoms.[1] Data from 4 subscales of the YGTSS (total motor tic score, total phonic tic score, overall impairment rating, and global severity score) were analyzed.

Side effects were assessed at each visit with the use of a modified version of the Side Effects Form for Children and Adolescents.[30] Each day for 5 days following patch discontinuation, parents answered 10 questions on this scale based on the following DSM-IV symptoms for nicotine withdrawal: unpleasant or depressed mood, difficulty sleeping, irritability, frustration or anger, anxiety, difficulty concentrating, restlessness, increased appetite, and a strong desire for another patch. The questions also assessed whether these symptoms caused distress or impair-

Table 1. Baseline Characteristics of Evaluable Patients for Whom Data Were Available, According to Treatment Assignment

Variable	Nicotine	Placebo	p Value[a]
Demographic characteristic			
N	27	29	
Age, y, mean (SD)	10.5 (1.8)	11.7 (2.6)	.04
% Male	93	86	.43
% White	96	93	1.0
Yale Global Tic Severity Scale			
N	27	29	
Motor tic score (0–25), mean (SD)	12.2 (3.8)	11.7 (4.8)	.62
Phonic tic score (0–25), mean (SD)	7.7 (5.5)	8.5 (4.6)	.6
Overall impairment (0–50), mean (SD)	27.8 (9.3)	25.5 (9.5)	.37
Global severity total (0–100), mean (SD)	47.8 (14.7)	45.7 (15.9)	.6
Haloperidol			
N	22	25	
Plasma level of drug, ng/mL, mean (SD)	1.63 (2.3)	1.33 (0.9)	.58
Prolactin			
N	26	28	
Plasma level of drug, ng/mL, mean (SD)	13.6 (8.4)	12.3 (6.9)	.52

[a]p Value based on 2-tailed Fisher exact test for gender and race and 2-tailed t test for all other variables.

ment at home or school, and how related these symptoms were to discontinuing the patch. Each question was answered on a scale from 0 (none) to 5 (extreme).

Data Analysis

Univariate tests, the Fisher exact test for discrete variables, and t tests for continuous variables were used to investigate the role of demographics and clinical characteristics. Patients were considered evaluable if they completed day 19 with no protocol violations. The results of the double-blind study were analyzed using a 1-way analysis of variance performed at each visit for all evaluable patients. In addition, 1-way analysis of covariance (ANCOVA) was also conducted to control for any variable that was significantly different between groups at baseline. A repeated-measures mixed-design analysis of variance was not used because the repeated-measures factor would be confounded by treatment changes that occurred between visits, making a time-by-treatment interaction impossible to interpret. An intent-to-treat analysis with the last observation carried forward for those subjects who dropped out of the study was not conducted, because it would be confounded by the changes in treatment that occurred over the course of the study, that is, 50% reduction of haloperidol dose at day 9 and discontinuation of nicotine (or placebo) patch at day 19. The efficacy of transdermal nicotine was evaluated by testing the null hypothesis of no treatment-group effect. Since there was an a priori expectation that nicotine would improve Tourette's disorder symptoms, all tests of efficacy

Table 2. Dropout Rate by Treatment Group

Patient Group	Nicotine (N = 35) N (%)	Placebo (N = 35) N (%)	p Value[a]
Dropouts due to			
Relapse	7 (20)	5 (14)	.75
Side effects	1 (3)	2 (6)	1.0
Other[b]	0 (0)	3 (9)	.24
Completed day 19	27 (77)	29 (83)	.77
Completed day 33	27 (77)	25 (71)	.77

[a]p Values based on 2-tailed Fisher exact test.
[b]One patient failed to reduce haloperidol dose by 50% following day 5, 1 patient was lost to follow-up, and 1 patient screened positive for plasma nicotine at baseline.

hypotheses were carried out at a 1-tailed level of significance (p = .1). However, to control for type I errors, a family-wise Bonferroni correction was employed with each measure tested at 4 timepoints, yielding a total of 24 tests or an alpha level of .004 needed for statistical significance.

RESULTS

Baseline Data

Seventy patients participated in the trial, with 35 in each group; however, 27 patients in the nicotine group and 29 in the placebo group were considered evaluable (completed day 19) for data analysis. At baseline, the 2 evaluable groups were similar with respect to gender, YGTSS scores, and plasma haloperidol and prolactin levels (Table 1). However, there was a marginally significant difference in age, with the nicotine group having a lower mean age than the placebo group.

Dropout and Completion Rates

In the nicotine group, 8 patients (23%) were prematurely withdrawn from the study, 7 (20%) because of recurrence of Tourette's symptoms and 1 (3%) because of side effects (Table 2). In the placebo group, 10 patients (28%) were prematurely withdrawn from the study; 5 (14%) because of recurrence of symptoms and 5 (14%) for other reasons, including side effects and protocol violations. There were no significant differences between groups in terms of reasons for withdrawal from treatment. Of the 10 dropouts in the placebo group, 6 dropped out before day 19 and were not evaluated and 4 dropped out between days 19 and 33 and were evaluable. Therefore, although the total number of dropouts was 10, the total number of placebo subjects evaluated was 29.

Effects of Transdermal Nicotine on Tourette's Disorder Symptoms

Table 3 shows the results for both the CGI and PGI. Using the conservative Bonferroni correction of alpha, we found that transdermal nicotine was superior to placebo in improving the spectrum of Tourette's symptoms on days 5

Table 3. Clinician- and Parent-Rated Global Improvement for Evaluable Patients by Treatment Group

Measure	Treatment Phase	Nicotine (N = 27) Mean (SEM)	Placebo (N = 29) Mean (SEM)	F	p[a]
Clinician-rated global improvement					
1–3 h	Optimal haloperidol dose + transdermal patch	2.1 (0.34)	0.9 (0.34)	5.72	.02
Day 5	Optimal haloperidol dose + transdermal patch	3.2 (0.40)	1.4 (0.39)	9.90	.003
Day 19	50% haloperidol dose + transdermal patch	2.5 (0.56)	0.3 (0.54)	7.96	.01
Day 33	50% haloperidol dose alone	1.9 (0.53)	–0.8 (0.51)	13.98	.0004
Parent-rated global improvement					
1–3 h	Optimal haloperidol dose + transdermal patch	3.5 (0.56)	2.3 (0.54)	2.53	.10
Day 5	Optimal haloperidol dose + transdermal patch	2.8 (0.56)	1.0 (0.53)	5.04	.03
Day 19	50% haloperidol dose + transdermal patch	2.1 (0.72)	–1.1 (0.69)	10.55	.002
Day 33	50% haloperidol dose alone	0.2 (0.62)	–2.0 (0.61)	6.28	.02

[a]p Values significant if ≤ .004 according to Bonferroni correction.

Table 4. Yale Global Tic Severity Scale Point Change From Baseline for Evaluable Patients by Treatment Group

Visit	Treatment Phase	Subscale	Nicotine (N = 27)	Placebo (N = 29)	F	p[a]
1–3 h	Optimal haloperidol dose + transdermal patch	Motor tic score (0–25)	–3.3 (0.7)	–1.8 (0.7)	2.37	.13
		Phonic tic score (0–25)	–3.8 (0.9)	–2.3 (0.9)	1.52	.22
		Overall impairment (0–50)	–6.0 (1.5)	–1.7 (1.4)	4.35	.04
		Global severity total (0–100)	–13.0 (2.6)	–5.8 (2.5)	4.06	.04
Day 5	Optimal haloperidol dose + transdermal patch	Motor tic score (0–25)	–4.3 (0.6)	–1.3 (0.6)	11.58	.001
		Phonic tic score (0–25)	–3.4 (0.9)	–1.3 (0.8)	2.99	.09
		Overall impairment (0–50)	–9.6 (1.7)	–5.5 (1.6)	3.18	.08
		Global severity total (0–100)	–17.4 (2.5)	–8.2 (2.4)	6.91	.01
Day 19	50% haloperidol dose + transdermal patch	Motor tic score (0–25)	–2.6 (0.8)	–1.4 (0.8)	1.21	.28
		Phonic tic score (0–25)	–1.9 (0.9)	–1.8 (0.8)	0.02	.89
		Overall impairment (0–50)	–8.1 (2.0)	–2.4 (1.9)	4.18	.04
		Global severity total (0–100)	–12.7 (3.1)	–5.6 (3.0)	2.72	.10
Day 33	50% haloperidol dose alone	Motor tic score (0–25)	–1.7 (0.9)	0.5 (0.8)	3.45	.07
		Phonic tic score (0–25)	–0.4 (1.0)	–1.4 (0.9)	0.58	.45
		Overall impairment (0–50)	–5.4 (1.6)	1.4 (1.6)	8.85	.004
		Global severity total (0–100)	–7.5 (2.7)	0.4 (2.6)	4.51	.04

[a]p Values significant if ≤ .004 according to Bonferroni correction.

and 33 for the CGI and on day 19 for the PGI. ANCOVAs indicated that the age difference at baseline did not account for the differences found between treatment groups for either the CGI or PGI (data not shown).

As illustrated in Table 4, relative to placebo, transdermal nicotine resulted in statistically significant reductions in scores from baseline on the YGTSS. However, following the conservative Bonferroni correction of alpha, the most treatment-sensitive YGTSS subscale was the motor tic score, which was significantly different between groups at day 5. In addition, the overall impairment score was significantly different between groups at day 33. The phonic tic score showed no significant difference at any timepoint tested. ANCOVAs indicated that the age difference at baseline did not account for any of the differences found between treatment groups (data not shown).

Side Effects

Side effects were more frequently reported in the nicotine group than in the placebo group (Table 5). Nausea and vomiting were significantly more common in the nicotine group than in the placebo group. Dizziness when standing was also more common in the nicotine group than in the placebo group, but failed to reach statistical significance. Headaches and itching under the patch were also common, but not significantly different between groups. Patients in both groups reported various other side effects, which were transient. There were no significant differences between groups for the presence of nicotine withdrawal symptoms for the 5 days following nicotine discontinuation (data not shown).

Plasma Nicotine and Cotinine Levels

The mean plasma levels of nicotine in the nicotine-treated group were 3.5 ng/mL and 6.2 ng/mL on days 5 and 19, respectively. Plasma cotinine levels for this group averaged 61 ng/mL and 92 ng/mL on days 5 and 19, respectively. Three patients treated with the placebo patch had detectable plasma levels of cotinine, but not nicotine, on day 19, suggesting that some leakage of small amounts of nicotine onto the skin may have occurred in these patients.

DISCUSSION

Our primary finding was that transdermal nicotine is superior to placebo as an adjunct to haloperidol in the treatment of Tourette's disorder, as demonstrated by the

Table 5. Side Effects by Treatment Group

Side Effect	Nicotine (N = 35) N	Nicotine (N = 35) %	Placebo (N = 35) N	Placebo (N = 35) %	p Value[a]
Nausea	25	71	6	17	.0001
Itching	20	57	15	43	.34
Headache	17	49	14	40	.63
Vomiting	14	40	3	9	.004
Dizziness	9	26	4	11	.21
Drowsiness	8	23	5	14	.54
Dizziness when standing	8	23	2	6	.08
Abdominal pain	7	20	6	17	1.0
Lethargy	6	17	1	3	.11
Anger outbursts	6	17	10	29	.39
Sweating	4	11	0	0	.11
Akathisia	4	11	1	3	.35
Difficulty arousing from sleep	3	9	4	11	1.0
Irritability	3	9	9	26	.11
Difficulty staying asleep	2	6	7	20	.15

[a]p Values based on 2-tailed Fisher exact test.

primary outcome measures, the CGI and PGI. This was true while patients were receiving an optimal dose of haloperidol (through day 5), when the dose of haloperidol was reduced by 50% (through day 19), and when the patch had been discontinued for 2 weeks (through day 33). The effect of transdermal nicotine patches was further confirmed by reductions in the severity of tic symptoms as assessed by the YGTSS, although the effects were specific to motor tics and strongest on day 5. Since the YGTSS was less sensitive in detecting a placebo/drug difference than the global improvement scores, some of the nicotine-related improvements may have not been related to changes in tic severity, but to changes in behavioral and emotional comorbid symptoms.

Although in our open-trial studies individual patients have responded to transdermal nicotine patches with a reduction in phonic tic severity,[31] this response was not found in the present study. A greater effect of transdermal nicotine patches on motor tics was also noted recently by another group.[17] The differential sensitivity of motor tics to transdermal nicotine patches could be related to different neuropharmacologic substrates underlying motor and phonic tics. For example, Tanner et al.[32] found that motor and phonic tics responded in opposing ways to cholinergic agents administered to Tourette's patients.

Overall, the present findings are consistent with previous preclinical[6,7,9] and clinical[12,20,31] studies suggesting that nicotine potentiates the effects of neuroleptics in the treatment of Tourette's disorder. Moreover, this study substantiated the long-term therapeutic effect of transdermal nicotine patches, which lasted 2 weeks after the transdermal nicotine patches had been discontinued.

Significant therapeutic effects of nicotine at 1 to 3 hours following the initial application of the transdermal nicotine patch were not found in this study. This finding is in contrast to the rapid tic-reducing effects reported in previous open-trial studies.[12,20,31] The difference in results could be due to significant placebo effects operating in open-label studies or due to different patient characteristics in the present controlled study. With respect to patient characteristics in the present study, most patients had been receiving the optimal dose of haloperidol for only a short period of time before the trial with transdermal nicotine began. Thus, the therapeutic effects of haloperidol could have created a ceiling effect (or maximum therapeutic effect) at baseline, making it difficult to observe therapeutic effects of nicotine 1 to 3 hours after administration. This is in contrast to the situation in the open-label studies in which most patients had been receiving neuroleptics for months and were no longer responding adequately to the medication at the time transdermal nicotine was administered. In retrospect, a better study design would have been to stabilize patients on haloperidol treatment for 6 to 8 weeks before initiating adjunctive therapy, as recommended by others.[30]

Due to the high incidence of nicotine-related adverse experiences, blinding inevitably presents difficulties in clinical studies involving nicotine. This was particularly true in this study because the patients were children and adolescents who were, for the most part, naive to nicotine exposure before entering the trial. However, every attempt was made to minimize this potential confound. For example, the lowest dosage of transdermal nicotine available (7 mg/24 hours) was employed, and a placebo patch containing a small amount of nicotine, but with a barrier to significantly minimize absorption, was used to ensure that the patches were identical in both appearance and smell. Although the reports were not systematically documented, many of the patients treated with placebo indicated that they thought they were receiving nicotine because of the smell. In addition, many of the placebo patients reported having nicotine-like side effects, including nausea, itching under the patch, and headaches.

Consistent with the hypothesis that the temporal absorption determines the addictive nature of nicotine,[33] no evidence of withdrawal symptoms was found following the discontinuation of transdermal nicotine therapy. Despite this desirable characteristic, the high rate of nicotine-related side effects in this study indicates a limitation to the widespread use of transdermal nicotine as a daily adjunctive therapy for the treatment of Tourette's disorder, particularly for children and adolescents. However, using the transdermal nicotine on a p.r.n. basis may be all that is needed. Following termination of this controlled study, 11 subjects did receive benefit from intermittent treatment on a p.r.n. basis.[31] Occasional therapeutic success with nicotine in individual patients, however, is no substitute for carefully controlled randomized studies of large numbers of patients. Further controlled studies of the therapeutic value of transdermal nicotine are required from other clinical centers, perhaps with adult patients receiving

transdermal nicotine alone and/or in combination with neuroleptics under intermittent administration protocols.

The rapid proliferation of recent attempts to exploit the therapeutic potential of nicotinic receptor modulation for a variety of neuropsychiatric disorders has resulted in the development and identification of several nicotinic receptor ligands with greater selectivity and substantially improved side effect profiles.[34] These include novel nicotinic receptor agonists, which are now entering clinical research development for Alzheimer's[35] and Parkinson's[36] disease. In addition, because nicotine has agonist and antagonist properties, nicotinic receptor antagonists, one of which (mecamylamine) is currently on the market, may also prove beneficial, with significantly fewer side effects than occur with nicotine therapy.[37,38] Although preliminary evidence suggests that mecamylamine monotherapy is not effective for reducing tic symptoms,[39] animal studies[4,40] suggest that mecamylamine, like nicotine, may potentiate the tic-reducing actions of haloperidol. Moreover, preliminary findings from a recently completed controlled study suggest that mecamylamine may have mood-stabilizing properties in Tourette's disorder patients with comorbid mood disorders,[39] a finding that is consistent with open-label clinical experience.[41]

The present study demonstrates for the first time, under controlled conditions, that transdermal nicotine potentiates the actions of a neuroleptic in the treatment of Tourette's disorder, even when the dose of neuroleptic is reduced by 50%. Future studies should look at ways of reducing side effects, such as using novel nicotinic agonists or coadministering a nicotinic antagonist.

Drug names: haloperidol (Haldol and others), mecamylamine (Inversine), nicotine (Nicoderm CQ and others), pimozide (Orap).

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