Early Course of Nicotine Dependence in Adolescent Smokers

WHAT’S KNOWN ON THIS SUBJECT: There is strong correlation between the occurrence of nicotine dependence symptoms and lifetime tobacco exposure. Symptoms of nicotine dependence occur soon after smoking initiation. Early symptoms of dependence typically precede the onset of daily smoking.

WHAT THIS STUDY ADDS: Smoking initiation triggers development of early symptoms of dependence, which in turn promotes smoking escalation. The sequence of evolution of dependence symptoms varies among individual youths. Early dependence symptoms often are not recognized as harbingers of addiction.

OBJECTIVE: The goal was to characterize the early course of nicotine dependence.

METHODS: Data were collected from 1246 sixth-graders in a 4-year (2002–2006) prospective study using 11 individual interviews. Subjects were monitored for 10 symptoms of dependence by using the Hooked on Nicotine Checklist. The bidirectional prospective relationship between the intensity of dependence (number of symptoms) and smoking frequency was examined by using cross-lagged analyses.

RESULTS: Of the 370 subjects who had inhaled from a cigarette, 62% smoked at least once per month, 53% experienced dependence symptoms, and 40% experienced escalation to daily smoking. Smoking frequency predicted the number of dependence symptoms at the next interview, and the number of symptoms predicted reciprocally the observed escalation in smoking frequency. Monthly smoking was a strong risk factor for the development of symptoms (adjusted hazard ratio: 9.9 [95% confidence interval: 6.6–14.8]). A strong desire to smoke was the most common presenting symptom, typically followed by the appearance of symptoms of nicotine withdrawal, escalation to daily smoking, and then reports of feeling addicted or difficulty controlling smoking. The appearance of any dependence symptom increased the risk for daily smoking (hazard ratio: 6.81 [95% confidence interval: 4.4–10.5]).

CONCLUSIONS: Nondaily tobacco use triggers the emergence of nicotine dependence. Early dependence symptoms promote escalation in smoking frequency and, reciprocally, more-frequent smoking accelerates the appearance of additional symptoms of dependence. As this positive feedback progresses, the symptoms of nicotine dependence present in a typical sequence, with some individual variation. Pediatrics 2010;125:1127–1133
Individuals who begin smoking during adolescence are more likely to become addicted, to progress to daily smoking, to continue smoking into adulthood, and to become heavier tobacco users as adults.1–4 Nicotine dependence symptoms often develop soon after smoking initiation, generally before the onset of daily smoking.5–7 The appearance of such symptoms was found to be a strong predictor of future smoking behavior in long-term longitudinal studies.5,8 One study found that the tobacco use trajectory of youths who went on to become heavy adult smokers diverged from that of youths who did not become heavy smokers at the point when they began smoking at a frequency of 2 cigarettes per week.9

The first Development and Assessment of Nicotine Dependence in Youth study, and subsequent published studies from other groups, described the order of presentation of nicotine dependence symptoms.5–8 Those studies presented a consistent picture of symptoms emerging with minimal nondaily tobacco use, with craving for tobacco being the most common presenting symptom.7 However, no previous studies examined the course of symptom development for individual smokers, to determine whether the typical sequence of symptom development applies to all individuals. Furthermore, the strong correlation between the occurrence of dependence symptoms and lifetime tobacco use10 suggests that the emergence of dependence symptoms and escalation in smoking during the early phase of tobacco use proceed as parallel but reciprocal events. However, no previous studies have assessed whether, among novice smokers, nicotine dependence drives the escalation of smoking and vice versa. In this prospective observational study, we examined the sequence in which symptoms of dependence present, and we assessed reciprocal relationships between smoking frequency and dependence over time.

**METHODS**

**Study Design**

The data for this report were obtained from the Development and Assessment of Nicotine Dependence in Youth 2 study, a 4-year prospective study of 1246 English-speaking students (age: median: 12 years [range: 11–13 years]) from 6 central Massachusetts communities that began when the students were in sixth grade. The details of the study, including methods for standardization of the interviews and the data collected, were fully described previously.5 In brief, participants underwent up to 11 cycles of standardized, confidential, in-person interviews, which were conducted in school at a frequency of 3 interviews per school year. The dates of the first puff on a cigarette, the appearance of each symptom of dependence, and the transitions in the frequency of tobacco use were recorded. To facilitate accurate recall of dates and events, interviews were conducted with the aid of personal landmarks, bounded recall, decomposition, and a personalized calendar.11,12 The study was approved by the institutional review board of the University of Massachusetts Medical School.

**Study Parameters**

The main outcome measure for this study was the development of diminished autonomy over tobacco use. The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, provides nomenclature for substance (including tobacco) use disorders.13 Unlike for other substances, there is no category for patients who have symptoms but fall short of the number required for a diagnosis of nicotine dependence. Therefore, investigators interested in the events leading up to a diagnosis of dependence have commonly assessed diminished autonomy over tobacco, that is, the presence of any symptom that would be expected to make it more challenging to quit smoking.14 The Hooked on Nicotine Checklist (HONC) (Table 1), which uses this approach for identifying nicotine dependence, has been extensively validated.5,8,10 Diminished autonomy is defined by the appearance of any of the 10 symptoms on the HONC, and the symptom score (range: 0–10) is the cumulative number of items endorsed.14 The HONC differs from most other measures of dependence in that it does not include any direct or indirect measure of smoking frequency. This makes the HONC a particularly suitable measure for analysis of the interaction between dependence and smoking frequency.

We defined smoking frequency as the number of cigarettes smoked per 28 days, monthly smoking as smoking at least once during each of 2 consecutive 30-day periods, and daily smoking as smoking at least once daily for 30 days. Demographic data included date of birth, gender, and race/ethnicity, which was categorized as Hispanic, non-Hispanic white, or other.

**Data Analyses**

Event-time (or survival) analyses performed with Stata 11 (Stata, College Station, TX) were conducted from the date of the first puff on a cigarette. The time to the event of interest (ie, diminished autonomy or smoking milestone of monthly or daily use) was tracked until the event occurred, the subject quit smoking, or the subject completed his or her last interview. Previous similar analyses assessed the time to the point at which 25% of those who experienced a particular event had done so.6,7 To maintain consistency with the 2 previously published reports, our Kaplan-Meier product-limit estimates...
focused on the time to 25% cumulative probability. Cox regression analyses adjusted for age, gender, and race/ethnicity were used to determine whether monthly smoking increased the risk of symptom development and whether diminished autonomy predicted progression to daily tobacco use.

To simplify the presentation of results, the 10 HONC symptoms were combined into 4 groups, as shown in Table 1. Three of these groups reflect diagnostic criteria for nicotine dependence (strong desire to smoke, withdrawal symptoms, and difficulty controlling tobacco use), leaving the item regarding feeling addicted as a separate category. These groupings do not represent factors, because the HONC measures a single construct. The date of onset for each symptom group was determined on the basis of the date of the earliest symptom within that group. To assess the sequence of symptom development, we determined the rank order of appearance for each subject. When an individual reported ≥2 symptoms at the same time, we ranked the tied symptoms for that individual in the order of their appearance for the total cohort, as shown in Table 1.

We explored autoregressive latent trajectory models by using Mplus 5.2 (Muthén & Muthén, Los Angeles, CA), as described by Bollen and Curran,16,17 to assess whether HONC symptom scores predicted future smoking frequency (number of cigarettes per month) and, reciprocally, whether smoking frequency predicted future HONC scores. Autoregressive latent trajectory analyses simultaneously control for the rate of change or growth over time in both symptom scores and smoking frequency. However, we used autoregressive (cross-lagged) model analyses alone for our analyses because autoregressive latent trajectory models did fit the data well. Poisson models were used for HONC scores, and smoking frequency was logarithmically transformed and modeled as a continuous variable. Both processes were modeled from the date of the first puff on a cigarette. We used Bayesian information criteria to select a parsimonious model that included age at smoking initiation as a covariate. We restricted these analyses to the first 7 rounds after smoking initiation and to subjects (n = 229) who had been monitored for ≥6 interviews after the first puff.

### RESULTS

#### Study Subjects

Of the 370 subjects included in the analyses, 56% were female, 64% were non-Hispanic white, 23% Hispanic, and 13% of other racial/ethnic groups. The median age at first cigarette was 12 years (interquartile range: 4 years). The proportions of subjects reporting each HONC symptom and smoking milestone and the time to 25% cumulative probability are shown in Table 1. At least 1 HONC symptom (diminished autonomy) was reported by 33% of subjects who had ever puffed on a cigarette.

#### Course of Symptom Development

Figure 1 shows variability in the order of symptom presentation on the basis of the symptom groups. In the entire cohort, strong desire was the most common presenting symptom type (reported by 88 [24%] of 370 subjects), and withdrawal symptoms were the second most common presenting symptom (n = 17 [5%]). Generally, symptoms appeared in the following

### TABLE 1 Time to 25% Cumulative Probability of HONC Symptoms and Smoking Frequency Among Subjects Who Had Initiated Smoking

<table>
<thead>
<tr>
<th>HONC Symptoms</th>
<th>Proportion Reporting Symptom square (N = 370), %a</th>
<th>Time to 25% Cumulative Probability, Estimate (95% CI), mo b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diminished autonomy (any symptom)</td>
<td>32.7</td>
<td>27.0 (21.0–37.0)</td>
</tr>
<tr>
<td>Strong desire to smoke</td>
<td>Have you ever had strong cravings to smoke?</td>
<td>27.0 (30.6–55.5)</td>
</tr>
<tr>
<td>Have you ever felt like you really needed a cigarette?</td>
<td>27.3</td>
<td>39.0 (28.2–53.8)</td>
</tr>
<tr>
<td>Withdrawal symptoms</td>
<td>When you have tried to stop smoking or when you haven’t been able to smoke...</td>
<td>21.1 (35.0–83.9)</td>
</tr>
<tr>
<td>Did you feel a strong need or urge to smoke?</td>
<td>18.1</td>
<td>76.9 (40.8–90.1)</td>
</tr>
<tr>
<td>Did you feel more irritable because you couldn’t smoke?</td>
<td>16.8</td>
<td>73.7 (40.5–??)</td>
</tr>
<tr>
<td>Did you feel nervous, restless, or anxious because you couldn’t smoke?</td>
<td>15.4</td>
<td>86.4 (55.0–131.4)</td>
</tr>
<tr>
<td>Did you find it hard to concentrate because you couldn’t smoke?</td>
<td>18.9</td>
<td>25.1 (30.0–63.0)</td>
</tr>
<tr>
<td>Feeling addicted</td>
<td>Have you ever felt like you were addicted to tobacco?</td>
<td>19.7</td>
</tr>
<tr>
<td>Difficulty controlling use</td>
<td>Have you ever tried to quit smoking but couldn’t?</td>
<td>14.3</td>
</tr>
<tr>
<td>Do you smoke now because it is really hard to quit?</td>
<td>13.5</td>
<td>90.1 (58.0–??)</td>
</tr>
<tr>
<td>Is it hard to keep from smoking in places where you are not supposed to, like school?</td>
<td>10.0</td>
<td>?? (74.1–??)</td>
</tr>
<tr>
<td>Symptom groups</td>
<td>Strong desire to smoke</td>
<td>30.8 (24.5–42.3)</td>
</tr>
<tr>
<td>Withdrawal symptoms</td>
<td>25.1</td>
<td>65.6 (42.3–80.0)</td>
</tr>
<tr>
<td>Feeling addicted</td>
<td>19.7</td>
<td>57.2 (43.1–79.9)</td>
</tr>
<tr>
<td>Difficulty controlling use</td>
<td>18.9</td>
<td>?? (74.1–??)</td>
</tr>
<tr>
<td>Smoking frequency</td>
<td>Monthly</td>
<td>37.0 (13.0–30.9)</td>
</tr>
<tr>
<td>Daily</td>
<td>24.5</td>
<td>50.5 (32.7–64.1)</td>
</tr>
</tbody>
</table>

aProportion of the cohort reporting each symptom. Each student could report >1 symptom.

bFor some outcomes, there were not enough events to estimate the 25% cumulative probability.
order: strong desire, withdrawal symptoms, feeling addicted, and difficulty controlling smoking.

Figure 2 compares the cumulative probability of onset of symptoms with the onset of monthly and daily smoking. Diminished autonomy was reported by 4% of subjects within 1 month after the first cigarette, and there was a progressive increase in the development of HONC symptoms over time. On the basis of the 25% cumulative probabilities (Table 1) and the cumulative probability curves (Fig 1), monthly smoking typically preceded all other measures, including the first HONC symptom of any type. Strong desire and withdrawal symptoms typically preceded the onset of daily smoking, and feeling addicted and difficulty controlling tobacco use tended to appear at approximately the same time as one another and after the onset of daily smoking. Follow-up times beyond the 4 years of the study entail increasing periods of recall for subjects who initiated smoking before the initial study interview. Sensitivity analyses excluding subjects who had initiated smoking >4 months before the first interview (the average interval between interviews) produced similar results.

Relationship of Diminished Autonomy to Smoking Frequency

Smoking at least once per month was reported by 92% of subjects who reported HONC symptoms but by only 10% (n = 22) of those who did not report symptoms (P < .001). Approximately 21% of the 121 subjects who experienced diminished autonomy did so before monthly smoking, whereas the remaining 79% experienced diminished autonomy coinciding with or following the onset of monthly smoking. Symptoms of diminished autonomy were reported by 96% of daily smokers (n = 87) and by 81% (n = 111) of those who reported smoking at least monthly (including weekly and daily smokers). Compared with subjects who had not initiated daily smoking before the development of HONC symptoms (n = 53), subjects who began smoking daily before the onset of HONC symptoms (n = 38) reported symptoms more rapidly (log-rank test, P < .001).

In Cox proportional-hazards analyses that adjusted for gender, age, and
race/ethnicity, experiencing monthly smoking increased the risk for diminished autonomy over tobacco use (adjusted hazard ratio [HR]: 9.9 [95% confidence interval [CI]: 6.6–14.8]). Experiencing any symptom of diminished autonomy increased the risk of progressing to monthly smoking (HR: 3.7 [95% CI: 2.4–5.5]) or daily smoking (HR: 6.8 [95% CI: 4.4–10.5]).

Figure 3 depicts the results of the cross-lagged regression model analyses. Smoking frequency in rounds 1 to 3 predicted the number of HONC symptoms in subsequent rounds ($P < .01$), and the number of HONC symptoms in rounds 2 to 4 predicted smoking frequency in subsequent rounds ($P < .01$). Neither factor was predictive of the other in subsequent rounds.

**DISCUSSION**

The traditional theoretical model describing the onset of nicotine dependence holds that the sensory and social rewards derived from smoking are the sole motivators of adolescent tobacco use for the first several years.\(^\text{18,19}\) According to this model, escalation in tobacco use results from tolerance to the pleasure of smoking, and smokers develop dependence when their pursuit of pleasure causes them to smoke at frequent intervals throughout the day.

The sensitization-homeostasis theory contradicts the traditional model.\(^\text{20}\) It proposes that symptoms of dependence that appear during nondaily smoking motivate continued tobacco use. According to this model, even smoking at monthly intervals entails a strong risk for developing dependence. Supporting this theory are 4 independent studies showing that symptoms of dependence develop during nondaily smoking, sometimes quite soon after the first cigarette.\(^\text{6–8,10}\) The findings of the current study, demonstrating that monthly smoking may increase the risk of developing dependence nearly 10-fold, support the sensitization-homeostasis theory.

The sensitization-homeostasis theory also posits that, once symptoms of craving and withdrawal appear, smokers experience symptoms whenever they go too long without smoking.\(^\text{20}\) At first, smoking intervals may be comfortably spaced at intervals of days or weeks; as repeated exposures promote tolerance, smokers must smoke at more-frequent intervals to keep symptoms at bay. The theory asserts that early symptoms drive an escalation in the frequency of smoking to daily use. In this study, the early appearance of dependence symptoms increased the risk of progression to daily smoking (HR: 6.8), and the number of symptoms predicted the magnitude of escalation in smoking frequency that occurred between interviews. Previous studies found that dependence severity correlated with current smoking frequency and cumulative lifetime exposure,\(^\text{21–25}\) but we think that our study is the first to demonstrate that increased frequency of smoking puts youths at risk for more-rapid development and progression of dependence. This is important, because it suggests a dose-response effect of early nicotine exposure on the development of dependence.

Our findings suggest that the loss of autonomy over tobacco use proceeds in a typical sequence, with some individual variation. The order in which symptoms typically present is consistent with the mechanism described for the development of dependence under the sensitization-homeostasis theory. Among the symptoms assessed in this
study, a strong urge to smoke was typically the first to appear, followed by withdrawal symptoms. These symptoms typically develop before the onset of daily smoking. In previous studies, the early appearance of dependence symptoms was very strongly predictive of future smoking and withdrawal symptoms predicted relapse among adolescent smokers, which indicated their clinical importance. Difficulty controlling use may not be reported until later in the course of symptom development, because refraining from smoking where it is not allowed may not be a problem when dependence can be satisfied by smoking less often than once per day.

The most important observation from our study is that the early course of nicotine dependence seems to involve a vicious cycle in which exposure to nicotine through smoking promotes the early development of craving and withdrawal, these symptoms drive an escalation in smoking frequency as tolerance develops, and this escalation promotes the development of additional symptoms of dependence. The strength of the reciprocal relationship between diminished autonomy and smoking frequency decreased over time. There are several potential explanations for this. A previous study found that the correlation between smoking frequency and levels of the nicotine metabolite cotinine decreased rapidly as consumption exceeded 4 or 5 cigarettes per day. Therefore, at a certain level of cigarette consumption, the dose of nicotine received may reach a physiological steady state with nicotine requirement within individual persons. This suggests that the urge for escalating tobacco use diminishes once the dose of nicotine is sufficient to satisfy physiological needs or to saturate receptor sites. Alternatively, at higher levels of consumption, differences in smoking frequency may reflect only individual differences in levels of tolerance to nicotine that may be unrelated to dependence. In our study, some youths began smoking daily from their first cigarette, although they had no symptoms that would require them to do so. A possible explanation for frequent smoking in the absence of symptoms is easy access to tobacco. Reducing the accessibility of cigarettes might slow the progression of dependence.

Our subjects typically did not report feeling addicted at the time when they experienced craving and withdrawal. Apparently, youths do not recognize strong craving and withdrawal as symptoms of addiction. Educating youths to recognize early symptoms of dependence may be a useful goal for secondary prevention programs, because it might prompt earlier and more successful cessation efforts. Our findings are consistent with a study by Gervais et al., which found that craving typically precedes withdrawal and both symptoms typically precede daily smoking. However, our study found that feeling addicted was a late symptom, in contrast to the findings of Gervais et al., who reported that self-diagnosed mental addiction typically preceded all other symptoms. This discordance may be attributable to differences in how these terms are interpreted by smokers.

Strengths of this study include the close, long-term, follow-up monitoring of novice smokers, with prospective data collection on symptom development and detailed records of smoking frequency, including dates for each event. The smoking prevalence in our cohort was comparable to that for the state of Massachusetts. A recent study demonstrated that youths’ reports of symptoms of diminished autonomy are valid and is not merely the result of false reporting or expectations based on the observations of other smokers.

Study limitations include the limited number of subjects who had all 4 symptom types and the use of a geographically limited convenience sample. The results may not be applicable to individuals who initiate smoking after adolescence. The earliest dependence symptom that was assessed in this study was strong craving. However, a recent case series indicated that strong craving is not the initial symptom of dependence, because it may be preceded by recurrent wanting, which is milder and less intrusive than craving. In this study, youths were not asked about wanting and were not trained to recognize symptoms of dependence. If youths were taught to recognize symptoms or were given the opportunity to describe them in their own terms, they might report symptoms earlier. Between-subject variations in awareness and recognition of symptoms could contribute to variations in the order of symptom reporting.

CONCLUSIONS

Intermittent tobacco use among young adolescents promotes the early development of symptoms of dependence. These symptoms promote an escalation in the frequency of tobacco use, which in turn promotes the development of additional dependence symptoms in a mutually reinforcing vicious cycle. The early symptoms of nicotine dependence develop in a typical sequence with some individual variation. Youths generally do not appear to recognize their own craving and withdrawal as symptoms of addiction. Therefore, it is worth investigating whether educating youths to recognize early symptoms of dependence would prompt earlier and more-successful cessation efforts.
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