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Assessment of nicotine dependence among adolescent and young adult smokers: A comparison of measures

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ABSTRACT

Introduction: Tobacco use often starts in adolescence, yet assessment of dependence among adolescent smokers remains a challenge, particularly given the potential discord between self-reports of smoking behavior and actual use. We could find no prior study, among adolescents, that directly compares the association between objective biomarkers of tobacco exposure (e.g., cotinine) and multiple measures of dependence. This study examined the concurrent validity of two common dependence measures: the Fagerström Test for Nicotine Dependence (FTND) and the Hooked on Nicotine Checklist (HONC). We further examined the FTND by removing the one item on cigarettes smoked per day.
Methods: Based within a parent clinical trial for adolescent smoking cessation, eligible participants were 12–21 years old, smoking ≥5 cigarettes per day on average, and with urine cotinine >100 ng/ml at baseline. Results are based on participants who completed each measure and who provided a urine cotinine sample at baseline (N = 73).
Results: Results showed that the FTND was associated with cotinine ($p<0.001$; $R^2=0.25$), and that this relationship held true for the revised FTND as well ($p<0.001$; $R^2=0.18$). However, the HONC was only marginally associated with cotinine ($p=0.06$; $R^2=0.09$).
Discussion: Our results suggest that the FTND may be better associated with actual smoking behavior in adolescents as compared to the HONC. Pending replication, our data provide caution with regard to assessment of nicotine dependence at least among established adolescent smokers who have more entrenched smoking behavior.

1. Introduction

The onset of smoking typically begins in adolescence, and can follow a number of developmental trajectories into adulthood (Audrain-McGovern et al., 2004; Chassin, Presson, Rose, & Sherman, 1996; Karp, O'Loughlin, Paradis, Hanley, & Difranza, 2005). How nicotine dependence unfolds among adolescents has received considerable focus in recent years, particularly given findings that younger smoking onset is one of the strongest predictors of persistent use (Patton et al., 1998). Adolescent smokers who smoke only occasionally resemble daily smokers in several key ways (e.g., attitudes towards smoking, motivation to quit, quit history) (Carpenter et al., 2009), suggesting that onset of dependence can be steep. In fact, a number of studies have argued that initial symptoms of dependence, for some adolescents, can appear soon after smoking initiation (Difranza, 2008; DiFranza & Wellman, 2005; Kandel, Hu, Griesler, & Schaffran, 2007; O'Loughlin et al., 2003; Savageau, Mowery, & DiFranza, 2009).

Assessment of nicotine dependence among adolescent smokers is challenging (see Colby, Tiffany, Shiffman, & Niaura, 2000b for a review). The most commonly used measure of dependence, the Fagerström Test for Nicotine Dependence (FTND), was developed among adults (Heatherton, Kozlowski, Frecker, & Fagerström, 1991), and has recently been validated among adolescents as well (Nonnemaker & Homsi, 2007). An alternate version of this scale (modified Fagerström Tolerance Questionnaire; mFTQ) has been specifically adapted for adolescents (Kandel et al., 2005; Prokhorov et al., 1996). More recently, the Hooked on Nicotine Checklist (HONC) was developed as an alternative, adolescent-specific measure of dependence, one purported to have a stronger theoretical foundation than previous measures (DiFranza et al., 2002; O'Loughlin, Tarasuk, et al., 2002). One potential benefit of the HONC is that it may be more sensitive to low-level smoking (MacPherson, Strong, & Myers, 2008) and thus may be useful in predicting the development of dependence

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among adolescents (Ziedonis, Haberstroh, Hanos Zimmermann, Miceli, & Foulds, 2006). While the FTND (and mFTQ) emphasizes physiological dependence, the HONC is weighted primarily on diminished autonomy as a marker of dependence. Each of these measures has well-established psychometric profiles (Kleinjan et al., 2007; MacPherson et al., 2008). The FTND (or mFTQ) has been shown to be associated with quantity or frequency of smoking (Kandel et al., 2005; Nonnemaker & Homsi, 2007), quit behaviors (Nonnemaker & Homsi, 2007), urine cotinine (Nonnemaker & Homsi, 2007; Prokhorov et al., 2000), or other theoretically-driven domains of nicotine dependence (Cohen, Myers, & Kelly, 2002). The HONC has similarly been shown to be related to smoking frequency and/or quantity (DiFranza et al., 2002; O'Loughlin, Tarasuk, et al., 2002; Wheeler et al., 2004) and age of first use (DiFranza et al., 2002).

Most of the above studies have validated these dependence measures against self-reports of tobacco use (i.e., number of cigarettes per day, number of years of smoking, etc). Within adolescents, this may be problematic given the potential discord between self-reported smoking and other, more objective indices of tobacco exposure (Mermelstein et al., 2002; Rubinstein, 2008). For example, two recent studies found poor sensitivity and poor to moderate specificity of self-reported smoking behavior when compared to urine or saliva cotinine (a metabolite of nicotine) (Kandel et al., 2006; Malcon, Menezes, Assunção, Neutzling, & Hallal, 2008). Thus, reliance of self-report of adolescent smoking behavior can be fraught with error, which may be of concern when validating measures of dependence. While the FTND has been validated through objective criteria, we are unaware of any such studies using the HONC, and we could find no prior study, among adolescents, to directly compare the association between objective biomarkers of tobacco exposure and both the FTND (or mFTQ) and the HONC.

The purpose of this analysis was to examine the concurrent validity of both the FTND and the HONC, by examining each in relation to urine cotinine, in addition to self-reported smoking behavior. Concurrent or criterion-related validity refers to the degree to which assessment measures relate to one or more external variables that are known to measure the attribute under study (Kerlinger, 1986). While there may be no gold standard for assessment of adolescent nicotine dependence (Colby, Tiffany, Shiffman, & Niaura, 2000a), cotinine is often considered the gold standard for actual tobacco exposure (Benowitz et al., 2002; Rubinstein, 2008), and thus may serve as an additional validation tool to examine measures of dependence (Colby et al., 2000a).

Data for the present analysis come from a larger randomized clinical trial (N = 134) which examined placebo-controlled bupropion +/− contingency management (2 × 2 design) for adolescent smoking cessation (results forthcoming).

2. Methods

2.1. Participant eligibility and recruitment

Participation was based on the following criteria, many of which were imposed on the basis that the parent study was a medication trial for adolescent smoking cessation: a) age 12–21, b) regular cigarette smoker of at least 5 cigarettes per day, c) baseline urine cotinine >100 ng/ml (measured through semi-quantitative test strips; NicAlert) , d) not pregnant, and using birth control to avoid pregnancy, e) devoid of current substance abuse/dependence other than nicotine, f) without any history of affective, psychosis, or eating disorders, g) no suicide attempts in past year and no suicidal ideation in past month, h) without history of seizure disorders, or renal, hepatic, or pulmonary disease, i) without any unstable medical conditions, j) without allergy to bupropion, and k) no current pharmacological treatment for smoking cessation (including NRT and bupropion).

Adolescents were recruited primarily from local secondary schools, colleges and universities, and secondarily through local media advertisements. Potentially eligible participants who passed initial criteria via phone screening were scheduled for a baseline visit, at which time they were consented and baseline measures were collected. Parental consent was collected for all adolescents below age 18; consenting parents had full knowledge of minors' smoking status. Most baseline visits (>75%) were conducted within our research lab; the remaining were held off-site on school grounds. The final sample size eligible for analysis consisted of 73 participants (see below).

2.2. Measures

As a randomized clinical trial, many measures were collected either at baseline, during follow-up, or both. For brevity, only those measures relevant to the current analysis are presented below. All measures below were administered in person through paper/pencil format, and are based on the initial study visit only, prior to treatment initiation.

2.2.1. FTND

The Fagerström Test for Nicotine Dependence is a 6-item scale measuring nicotine dependence (possible range 0–10) and has shown adequate psychometrics (Burling & Burling, 2003; Etter, VuDuc, & Perneger, 1999). Some research has suggested that the FTND may be comprised of two factors (Radzius et al., 2003). However, we opted for analysis of both the original FTND as a whole and a revised measure, which removed the one item pertaining to number of cigarettes smoked per day (not to be confused with mFTQ; Prokhorov et al., 1996). Given our focus on the relationship between these measures and cotinine, removing this one item diminishes the circular overlap between predictor and criterion. Though the mFTQ may have been most appropriate for our adolescent sample, research available at the time of study initiation (Radzius, Epstein, Gallo, & Moolchan, 2002, March) and since (Nonnemaker & Homsi, 2007) has shown that the FTND is appropriate among adolescents.

2.2.2. HONC

The Hooked on Nicotine Checklist is a 10-item measure that emphasizes loss of autonomy as a proxy for dependence. Each item is given a yes/no response option, yielding a total possible score of 0–10. Prior studies have shown a single factor structure with adequate reliability (DiFranza et al., 2007; Kozlowski et al., 2007; Wellman, DiFranza, et al., 2006; Wellman, Savageau, et al., 2006).

2.2.3. Smoking level

We considered the possibility that the relationship between each dependence measure and marker of exposure would be moderated by smoking level. Thus, we first averaged the number of cigarettes smoked per day for the week preceding the baseline visit (assessed via Timeline Follow-Back procedures (Sobell & Sobell, 1996)), and then conducted a median split (10.3) to create groups of low and high level smokers, an approach consistent with prior studies in this area (Nonnemaker & Homsi, 2007; O'Loughlin, Tarasuk, et al., 2002).

2.2.4. Cotinine

Nicotine is metabolized into cotinine by the liver; cotinine has a longer half life (about 20 h) than does nicotine (Zevin, Jacob, Geppetti, & Benowitz, 2000). Urine cotinine was analyzed via gas chromatography at the University of California, San Francisco.

2.3. Data analysis

Due to missing data and the fact that not all measures were collected from study onset, a number of participants failed to provide responses to either the HONC, FTND, or both. Analyses are restricted

to only those participants who completed *both* the FTND and the HONC at the baseline visit and who provided a urine cotinine sample. There were no significant differences between those who were included in the final sample (n = 73) and those who were not (n = 61) with regard to smoking history and baseline demographics, with the exception that sample participants were slightly younger than those who were not included (mean age 17.9 vs. 19.0; p = 0.001). Descriptive characteristics were compared across gender and smoking level. Continuous data were assessed using a two-sided Wilcoxon two-sample test statistic, and categorical data were compared using the two-sided Fisher exact test. The relationship between each measure of dependence (FTND, revised FTND and HONC) with cotinine was assessed via linear regression. Our primary interest was percentage of variance in cotinine accounted for (dependent variable) by each dependence measure (independent variable) and thus squared partial correlations were used for cross-measure comparisons. Because of the strong correlation between HONC and FTND (r = 0.35; p = 0.001), each was entered into a separate regression. These same measures were secondarily compared across gender and smoking level (high/low). A multinomial logit regression model was used to associate cotinine levels with nicotine dependence as defined by the HONC, FTND, and revised FTND. All analyses controlled for age, with the rationale that smoking behavior likely fluctuates across the developmental period within our study sample. Analyses were performed using SAS v.9.1.3 Software System and were considered significant if $\alpha < 0.05$.

3. Results

Sample characteristics are shown in Table 1. Participants were primarily male, Caucasian, and with an average age of approximately 18 years. Participants smoked 14 cigarettes per day on average, had been smoking for almost four years, and had on average at least two prior quit attempts. The HONC rated participants as having somewhat numerically higher scores (mean 7.9; SD = 1.9) than did the FTND (mean 4.6; SD = 2.2; both measures have possible ranges of scores 0–10). There were generally no significant differences in baseline variables between males and females. As expected, the smoking groups (high vs. low) significantly differed on a number of smoking variables, but generally did not differ on demographics. The HONC did not distinguish between high (mean 8.1; SD = 1.7) vs. low smokers (mean 7.6; SD = 2.0). Heavier smokers were significantly less likely to be in school (49% in either high school or college) than were smokers who smoked fewer cigarettes (89%). On the basis that school status could influence smoking behavior (smokers unable to smoke due to smoking restrictions), all subsequent analyses controlled for school status and age at study onset (uncontrolled analyses yielded nearly identical results; results not shown).

As expected, both forms of the FTND were strongly linked to self-reported cigarettes per day, with correlations (Spearman's rho) of 0.53 (p < 0.001) and 0.28 (p = 0.03) for the original and revised versions, respectively. Both measures were significantly associated with cotinine (Table 2). For every one unit increase in dependence as measured by the FTND, urine cotinine increased by 202 ng/ml (p < 0.001; 95% confidence interval [CI]: 120–284), accounting for 25% of the total variance. Removing the cigarettes/day item of the FTND, each unit increase in dependence resulted in 189 ng/ml increase in cotinine (p < 0.001; 95% CI: 94–284), accounting for 18% of the total variance. The original was significantly associated with urine cotinine among sub-groups of gender and smoking level, while the revised FTND was only significant among males (marginally associated among females), significant among low rate smokers, but not high (Table 2). The HONC did not correlate with self-reported cigarettes per day (rho = 0.08; p = 0.6), and was only marginally associated with cotinine. For every one unit increase in dependence as measured by the HONC, urine cotinine increased 97 ng/ml (p = 0.06; 95% CI for slope: −1–195), accounting for 9% of the total variance. The HONC was associated with cotinine only among males.

We sought to directly compare the relationship between dependence measures and urine cotinine. We first established four groups that were either: 1) high on FTND and high on HONC, 2) high FTND/low HONC, 3) low FTND/high HONC, and 4) low FTND/low HONC (see top half of Table 3). Classification of low (0–4) vs. high (5–10) FTND scores was based on prior literature (Kandel et al., 2005; Prokhorov et al., 2001). We could find no precedent for dichotomous categorization of HONC scores; thus, classification of low vs. high HONC scores was based on median split (0–7 vs. 8–10); alternate dichotomizations yielded similar results (data not shown). As expected, the majority of adolescents (54%) who had high levels of urine cotinine were in the group that was high FTND/high HONC (group 1 above); 22% were high

Table 1
Sample characteristics.

		Gender			Smoking level		
	Overall (N = 73)	Male (n = 47)	Female (n = 26)	p	Low (n = 38)	High (n = 35)	p
Age (SD)	17.9 (1.8)	18.0 (1.9)	17.9 (1.8)	0.9	17.8 (1.8)	18.1 (1.9)	0.4
% female	36%	–	–	–	34%	37%	0.8
% Caucasian	90%	91%	88%	0.4	86%	94%	0.2
% in school	70%	72%	65%	0.6	89%	49%	**<0.001**
FTND	4.6 (2.2)	4.5 (2.1)	4.6 (2.4)	0.9	3.4 (1.8)	5.8 (1.9)	**<0.001**
HONC	7.9 (1.9)	7.4 (2.0)	8.7 (1.4)	**0.003**	7.6 (2.0)	8.1 (1.7)	0.3
Cigs/day	14.1 (7.3)	14.7 (7.7)	13.0 (6.6)	0.4	8.9 (3.4)	19.6 (6.2)	**<0.001**
% tried to quit	81%	82%	79%	0.8	74%	88%	0.2
# prior quit attempts	2.4 (2.0)	2.6 (2.3)	2.3 (1.6)	0.8	2.3 (1.9)	2.7 (2.2)	0.5
Age became regular smoker	14.4 (2.3)	14.4 (2.4)	14.3 (2.2)	0.8	15.3 (2.0)	13.4 (2.2)	**0.002**
Years of smoking	3.9 (2.3)	3.8 (2.4)	3.9 (2.2)	0.7	2.8 (1.7)	5.0 (2.3)	**<0.001**
% other forms of tobacco	16%	20%	8%	0.3	14%	18%	0.7
% illicit drug use	85%	81%	92%	0.3	82%	88%	0.7
Cotinine (ng/ml)	1163.7 (835.1)	1159.8 (869.7)	1170.7 (785.1)	0.8	852.9 (687.4)	1501.1 (858.8)	**<0.001**
CO (ppm)	7.7 (6.7)	7.9 (7.0)	7.3 (6.1)	0.7	5.4 (4.4)	10.2 (7.8)	**0.005**

Table 2
Relationship of dependence measures to urine cotinine.[a]

	Overall	By gender		By smoking level	
		Male	Female	Low	High
FTND					
Parameter estimate	201.9	226.5	156.4	172.8	164.0
Std. beta	0.53	0.55	0.48	0.46	0.36
St. error	41.8	54.4	69.6	54.1	75.9
p	**<0.001**	**<0.001**	**0.03**	**0.003**	**0.04**
Partial R^2	0.25	0.29	0.19	0.23	0.13
Revised FTND[b]					
Parameter estimate	189.3	209.6	150.9	170.0	131.0
Std. beta	0.43	0.45	0.38	0.43	0.28
St. error	48.7	62.6	83.5	55.2	82.5
p	**<0.001**	**0.002**	0.08	**0.004**	0.12
Partial R^2	0.18	0.21	0.13	0.22	0.08
HONC					
Parameter estimate	96.7	168.3	−121.9	61.7	109.3
Std. beta	0.22	0.38	−0.21	0.18	0.22
St. error	49.9	59.9	116.6	53.0	84.7
p	0.06	**0.007**	0.3	0.25	0.21
Partial R^2	0.09	0.16	0.05	0.04	0.05

[a] Controlling for school attendance and age.
[b] FTND without cigarettes/day item.

Table 3
Comparative relationships between dependence measures and urine cotinine.

Dependence groups[a]		Cotinine levels by median split		Total
FTND	HONC	Low (≤980 ng/ml)	High (≥980 ng/ml)	
High	High	5	20	**25**
		13.9%[b]	80%	**34.3%**[c]
		20%[c]	54.1%	
High	Low	2	8	**10**
		20%	80%	**13.1%**
		5.6%	21.6%	
Low	High	18	4	**22**
		81.8%	18.2%	**30.1%**
		50%	10.8%	
Low	Low	11	5	**16**
		68.8%	31.3%	**21.9%**
		30.6%	13.5%	
	Total	**36**	**37**	**73**
		49.3%[b]	**50.7%**	**100%**
Revised FTND[d]	HONC			
High	High	7	20	**27**
		25.9%[b]	74.1%	**37.0%**[c]
		19.4%[c]	54.1%	
High	Low	5	7	**12**
		41.7%	58.3%	**16.4%**
		13.9%	18.9%	
Low	High	16	4	**20**
		80%	20%	**27.4%**
		44.4%	10.8%	
Low	Low	8	6	**14**
		57.1%	42.9%	**19.2%**
		22.2%	16.2%	
	Total	**36**	**37**	**73**
		49.3%[b]	**50.7%**	**100%**

[a] See text for classification of high/low dependence groups.
[b] Row percentage.
[c] Column percentage.
[d] FTND without cigarettes/day item.

FTND/low HONC (group 2), 11% were low FTND/High HONC (group 3), and 14% were low FTND/low HONC (group 4). In contrast, half of the participants who had low levels of urine cotinine were in the group that was low FTND/high HONC. Collectively, these data suggest that FTND was the primary determinant of urine cotinine. This finding is underscored by the comparison between groups that were high in only one measure of dependence (and low in the other): adolescents in the high FTND/low HONC group were 15 times more likely to have high urine cotinine concentrations than were adolescents in the low FTND/high HONC group (adjusted OR = 15.0; 95% CI = 2.2–102.9). Parallel findings were found when comparing the revised FTND (low vs. high categorized via median split: 0–3 vs. 4–7) with HONC (see bottom half of Table 3). Again, even after removal of the one item on cigarettes per day, adolescents in the high revised FTND/low HONC group were 5 times more likely to have high urine cotinine concentrations than were adolescents in the low revised FTND/high HONC group (adjusted OR = 5.1; 95% CI = 1.0–26.3).

These data suggest that adolescents within the high HONC group smoked fewer cigarettes per day and had lower levels of urine cotinine than those with high FTND scores, a conclusion supported by Table 4. Both cigarettes per day and urine cotinine were lower among those in the high HONC group vs. those in the high FTND (revised) groups. In contrast, both cigarettes per day and urine cotinine were higher in the low HONC group vs. those in the low FTND (revised) groups.

4. Discussion

To our knowledge, this is the first study to actively compare the relationships between both the HONC and the FTND with a biologically validated measure of tobacco exposure among adolescent smokers. Our results confirm prior research which shows that the

Table 4
Smoking variables stratified by nicotine dependence measures.

FTND					
	Low (n = 38)[a]		High (n = 35)[a]		
	Mean	SD	Mean	SD	p
Cpd[b]	10.2	4.5	18.2	7.5	<**0.001**
Cotinine (ng/ml)	734.1	491.8	1630.0	885.2	<**0.001**
Revised FTND					
	Low (n = 34)		High (n = 39)		
Cpd	12.4	7.8	15.5	6.7	**0.03**
Cotinine	788.8	501.3	1490.5	931.8	<**0.001**
HONC					
	Low (n = 26)		High (n = 47)		
Cpd	14.0	8.4	14.1	6.7	0.63
Cotinine	1034.1	661.5	1235.4	915.9	0.55

[a] See text for classification of high/low dependence groups.
[b] Cigarettes per day.

FTND, either in its original or revised form, is significantly associated with urine cotinine (Nonnemaker & Homsi, 2007; Prokhorov et al., 2000). This was true for males and females, and for low (≤10 cigarettes per day; cpd) and high rate smokers (>10 cpd). Thus, at least among the variables studied here, there is no reason to believe that the FTND offers more or less concurrent validity among certain demographic groups. None of these results is altogether surprising, since the FTND is heavily weighted on cigarette consumption as a marker of dependence. However, even the revised FTND, which removed the one item on smoking consumption, was significantly associated with cotinine, but only among low (and not high) rate smokers. This confirms that the FTND's relationship to tobacco exposure (cotinine) is not driven by cigarette consumption alone (Prokhorov et al., 2000), but also suggests that, among high rate smokers, consumption is the prime determinant of dependence, at least as assessed by this measure.

We believe this is the first study to examine objective indicators of tobacco exposure as they relate to the HONC, and interpretation here is more difficult. The HONC was unassociated with self-reported smoking and was poorly associated with urine cotinine. Among adolescents who were high on the HONC but low in the FTND, only 18% had cotinine concentrations in the upper 50th percentile (20% for adolescents high on the HONC but low in the revised FTND). One immediate possibility is that the adolescents in this sample were low in dependence, at least as measured by the HONC, creating a floor effect in which we did not have sufficient levels of nicotine dependence to assess for a relationship to tobacco exposure. This does not appear to be the case: average HONC scores were 7.9 (SD = 1.9; possible range 0–10) for the entire sample and 7.6 (SD = 2.0) among even low-level smokers (those smoking ≤10 cpd), scores that are somewhat higher than are reported elsewhere among treatment seeking adolescent smokers (Wellman, DiFranza, et al., 2006). In fact, the HONC could not distinguish among low vs. high level smokers within our study sample, a finding that is inconsistent with prior literature (see below). Finally, the unexpected gender difference in HONC scores could reflect a potential gender bias in need of further clarification.

The HONC is heavily weighted on loss of autonomy as a marker of nicotine dependence. It follows that loss of autonomy should manifest itself through a number of clinically relevant markers of severity of use. Prior studies have shown the HONC to be associated with smoking frequency and quantity (O'Loughlin, Tarasuk, et al., 2002; Wellman et al., 2005; Wellman, Savageau, et al., 2006; Wheeler et al., 2004), desire and attempts to quit (O'Loughlin, Kishchuk, et al., 2002), and quitting success (Wellman, DiFranza, et al., 2006). The authors of this latter study noted that the HONC's ability to prospectively predict

smoking status provides affirmation of construct validity as an index of diminished autonomy. Data from the current study stand in contrast to above and cast some questions on the HONC's concurrent validity, since it was poorly associated with both self-reported smoking and urine cotinine. However, this should not be interpreted to invalidate the measure, and the HONC may offer greater value for low rate smoking (MacPherson et al., 2008; see limitations below).

We believe our findings highlight the central issue of a broader, ongoing debate on the assessment of nicotine dependence; i.e., whether consumption is a necessary and/or sufficient indicator of dependence, particularly among early stage smokers. On one hand, loss of control is often considered a hallmark of any dependence, including tobacco (Dackis & O'Brien, 2005; Hughes & Shiffman, 2008). Thus, it logically follows that consumption is a *necessary* element of dependence. A recent longitudinal study of adolescents found that intensity and frequency of smoking were among the strongest predictors of onset of each of three hallmark criteria of dependence: craving, withdrawal, and tolerance (Wileyto et al., 2009). Thus, if the assertion that consumption is a necessary element of dependence is correct, then objective measures of tobacco exposure (such as cotinine) could be used as one validational tool (Colby et al., 2000a). Several have suggested that cotinine may be a more meaningful marker of consumption than recall of consumption (Joseph et al., 2005; Man et al., 2009), and the use of biomarkers to validate dependence measures is particularly relevant among adolescents, in whom self-reports of smoking behavior may be imprecise (Kandel et al., 2006; Malcon et al., 2008; Rubinstein, 2008). We are mindful however, that a small but not inconsequential number of adolescent smokers within our study were low in both dependence measures, yet had cotinine concentrations in the upper 50th percentile. This suggests either a) limitations in using cotinine as a biomarker of use, b) shortcomings of both measures for assessment of cigarette smoking, or likely c) both.

On the other hand, measures of dependence are not synonymous with measures of use (Colby et al., 2000b), and since most would agree that dependence is not unidimensional (Kleinjan et al., 2007), we would assert that neither smoking behavior nor urine cotinine is a *sufficient* indicator of nicotine dependence. Other clinically relevant aspects of dependence include withdrawal, tolerance, continued use despite known harms, and inability to quit, all listed as symptoms of dependence within major diagnostic classification systems (American Psychiatric Association, 1994; World Health Organization, 1992). Some of these phenomena correlate strongly with consumption (tolerance and withdrawal) and others less so. It is possible that the HONC specifically taps into these or other aspects of dependence that may be relatively distinct from consumption.

Our study is not without limitations. Given that our sample was derived from a larger clinical trial of adolescent smoking cessation, which a priori selected for a restricted range of smokers, our sample is likely unrepresentative of the general population of adolescent smokers. Our findings would be enhanced had we included a full range of smokers, including those smoking less than five cigarettes per day, and experimental smokers as well. This would have allowed us to more fully examine the association between measures and biomarkers across the range of smoking behavior. Similarly, our findings are specific to treatment-seekers only, which may not generalize to the broader population of adolescent smokers. It is also possible that null findings reflect limitations in power, particularly within analysis restricted to different demographic sub-groups. However, in instances where the relationship between dependence measure and cotinine was non-significant, the percentage of variance accounted for (i.e., effect size) was small. Thus, a larger sample size would likely yield similar results. Further, our sample was primarily Caucasian, and it may be useful to consider dependence measures separately (not necessarily separate measures) for non-white smokers (Okuyemi et al., 2007).

Per above, it is also worth bearing in mind that this study is by no means an exhaustive analysis of the validity of the two selected nicotine dependence measures. We focus solely on the association between each measure and objective indicators of tobacco use (i.e., concurrent validity). As done prior (see above), other means of assessing validity exist. Given that our data was derived from a cessation trial, we would ideally examine predictive validity as well (i.e., prediction of future abstinence, quit attempts, latency to relapse, etc.), but this was not possible due to the overall low abstinence rates. Furthermore, our assessment of the FTND and the HONC was based on measures available within the parent study; other measures of dependence exist (Piper et al., 2004; Shiffman, Waters, & Hickcox, 2004) and further comparisons across measures are warranted. We do, however, believe that there is merit in the current analysis, as no prior study has compared these particular measures of dependence to biological indices of tobacco use among young smokers.

5. Conclusion

Our data provide confirmation that the FTND, either in its original or revised form (omitting the single item on cigarettes per day), is associated with objective indices of tobacco exposure among adolescent smokers. Our data also cast some doubt on the relationship between the HONC and these same biomarkers of use, at least among established adolescent smokers who have more entrenched smoking behavior. However, we caution readers not to conclude that the HONC is an inappropriate screening tool for adolescent nicotine dependence. Assessment of nicotine dependence among adolescents likely requires a multidimensional approach, one that uses an array of dependence measures. Only through such methods can research further examine the relative strengths and weaknesses of all measures.

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Contributors

The study was based on a parent clinical trial originally conceived and led by Dr. Upadhyaya (Drs. Carpenter and Gray each as co-I). Drs. Carpenter and Gray, and Mr. Baker all contributed to the conception and write-up of the current manuscript. Mr. Baker led all statistical analyses, in coordination with Dr. Carpenter. All authors contributed to the editing of the manuscript, and all have approved the final manuscript.

Conflict of interest

No conflicts are declared for Dr. Carpenter or Mr. Baker. Dr. Gray receives research support from Pfizer, Inc. Dr. Upadhyaya recently joined Eli Lilly and Company; prior to that he was a consultant and advisory board member of Eli Lilly and Company and Shire Pharmaceuticals. Dr. Upadhyaya is an ex-stockholder of New River Pharmaceutical company, was on the Speakers' Bureau of Shire Pharmaceuticals and Pfizer, Inc., and has received research support from Cephalon, Inc., Eli Lilly and Company, and Pfizer, Inc.

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