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Association of withdrawal features with nicotine dependence as measured by the Fagerström Test for Nicotine Dependence (FTND)

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Abstract

The aim of this study is to advance our understanding of how nicotine dependence level, defined by the Fagerström Test of Nicotine Dependence (FTND), relates to nicotine withdrawal features. We classified nicotine dependence in two categories, 1) low dependence (LD; FTND <4) and 2) high dependence (HD; FTND ≥4). A sample of 241 smokers was recruited via newspaper ads and public notices. Using a multivariate response model with adjustments for age, sex, age at first cigarette, race, and current or past history of depression, we observed a small to modest statistically robust association between nicotine dependence level and withdrawal features such as, irritation/anger (adjusted relative risk, aRR = 1.2; 95% CI 1.00, 1.3); nervousness (aRR = 1.3; 95% CI 1.1, 1.6); restlessness (aRR = 1.2; 95% CI 1.1, 1.4); difficulty concentrating (aRR = 1.3; 95% CI 1.1, 1.7); and trouble sleeping (aRR = 1.8; 95% CI 1.2, 2.6). Our findings are consistent with the inference that the FTND measures “physiological dependence” and that multidimensional approaches are needed to capture the full range of smoking phenotypology.

Keywords

smoking; nicotine dependence; FTND; withdrawal features; DSM-IV; ICD-10

1. Introduction

The existence of a withdrawal syndrome is generally regarded as a hallmark of drug dependence, and specifically of nicotine dependence, although instruments designed to measure dependence vary in the extent to which and how symptoms are assessed and which symptoms are included (Piper, McCarthy, & Baker, 2006). The Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991), perhaps the measure employed most frequently by nicotine dependence researchers, is brief and simple to use. It does not, however, include

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or require endorsement of specific withdrawal features as part of the dependence criteria, though it implies the existence of withdrawal discomfort in its query about ability to go for periods of time without smoking. By contrast, the criterion-based diagnostic approach used in the DSM-IV (APA, 1994) and the ICD-10 (WHO, 1997) rests heavily on lists of features, a certain number of which must be present if criteria for withdrawal are to be met. The DSM-IV, for example, specifies eight, of which at least four must be endorsed to meet criteria for physiological dependence on nicotine.

An understanding of the withdrawal patterns associated with the FTND would extend our understanding of the putative nicotine dependence phenotype represented by this instrument. Since the FTND and DSM-IV approaches are quite different and have repeatedly been shown to be largely orthogonal (Moolchan et al., 2002; Marks, Pomerleau & Pomerleau, 1998), however, there is no reason to assume or expect that the pattern of features associated with the DSM-IV diagnosis will map perfectly onto the FTND. Therefore, to explore the withdrawal patterns most likely to be reflected in high versus low FTND scores, we took advantage of data generated by a study in which both instruments were administered. The pool of withdrawal features used consisted of the eight DSM-IV features, craving, and three additional features included in the ICD-10 criteria. Of interest were the following questions: 1) Do highly-dependent smokers as defined by the FTND endorse a greater number of withdrawal features than do less-dependent smokers? 2) Which specific withdrawal features differentiate high- from low-dependent smokers? We hypothesized that smokers classified as highly dependent would report not only more withdrawal features but also a different pattern of withdrawal features.

2. Methods

2.1 Participants

A sample of 241 smokers was recruited from the local community as part of a larger case-control study of nicotine genetics, in accordance with a protocol approved by the University of Michigan Medical School Institutional Review Board. The sample was designed to include approximately equal numbers of men and women and to over-include individuals with depressive symptomatology. Candidates were excluded if they were currently pregnant or nursing; had a current or lifetime diagnosis of serious psychopathology; or were heavy users of alcohol or illicit drug. See Pomerleau et al. (2005) for details on recruitment and screening.

2.2 Assessments

Nicotine dependence was assessed using the Fagerström Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991), using scores of ≥ 4 versus ≤ 3 to determine high-dependence (HD) versus low dependence (LD). *Depression* was assessed using the Center for Epidemiological Studies–Depression Scale (CES-D; Weissman et al., 1977) and a computerized version of the Composite International Diagnostic Interview (CIDI; World Health Organization, 1997). High depression was defined as CES-D ≥ 16 or a CIDI lifetime depression diagnosis; low depression required CES-D < 16 and no CIDI lifetime depression diagnosis. *Withdrawal features* were assessed as part of the CIDI tobacco dependence module, by asking: “The last time you tried to quit smoking or were in a situation where you could not smoke for several hours, did you experience any of the following.” Choices were: irritability/anger, nervous, restless, difficulty concentrating, decreased heart rate, increased appetite/weight gain, depressed, trouble sleeping, craving, persistent cough, sores in mouth, and tired or weak.

3. Results

3.1 Sample characteristics

Baseline and demographic characteristics are shown in Table 1.

3.2 Group differences in symptom count

HD exhibited marginally more withdrawal features (6.7 ± 0.2) than did LD (6.0 ± 0.3 ; $p=0.052$).

3.3 Relationship of dependence level to specific withdrawal symptoms

We estimated the degree of association of specific withdrawal features with dependence using a multivariate response regression approach based upon the generalized linear model and generalized estimating equations (GLM/GEE) described by Liang et al. (1992), adjusting for sex, age, age of smoking initiation, race, and current and lifetime depression. Results are shown in Table 2.

4. Discussion

Consistent with previous reports that the FTND does not tap the same dimensions of dependence as does the DSM-based approach (Moolchan et al., 2002; Marks et al., 1998), the percent diagnosed as dependent using DSM-based criteria was virtually identical for the two groups.

Somewhat surprisingly, HD reported on average less than one more withdrawal feature than LD in univariate analysis. Such a small difference casts doubt on whether symptom counts are a valid approach to differentiating smokers with varying levels of dependence based on the FTND.

In multivariate analyses that take in consideration interdependencies among withdrawal features, we observed a modest difference in the degree to which 5 of the 12 features—irritation/anger, nervousness, restlessness, trouble concentrating, and trouble sleeping—were associated with level of dependence, an association that persisted even after adjusting for sex, age at smoking initiation, and current or lifetime depression. Thus, the likelihood of experiencing the majority of the features assessed was similar for both groups. Those that did differentiate HD and LD share similar physiological responses associated with disruptions of normative patterns of behavior and emerge within the first 7 days of abstinence (Hughes, 2007). Thus, the excess risk for these specific features may signal an early neuroadaptational process to abstinence once dependence is established.

Our study also sheds light on the issue of whether restlessness should be grouped with irritability/anger (Hughes, 2007). The use of GLM/GEE allowed us to borrow information across withdrawal features simultaneously while at the same time estimate each individual feature's contribution with fewer assumptions than latent class or latent trait analyses. The fact that restlessness was robustly associated with HD even after accounting for its suspected correlation with other features, especially irritability/anger, argues that it constitutes a separate withdrawal feature.

Some limitations of our study must be noted: 1) Reliance on retrospective reports and a cross sectional design preclude testing of temporal sequence of events. 2) The checklist format used to assess withdrawal fails to capture gradations in response or to measure change from baseline. 3) Our sample is not representative of all smokers, limiting generalizability.

Further research in larger, randomly-recruited samples, using a more refined measure of withdrawal symptomatology will be needed to determine conclusively whether the observed

differences are 1) qualitative (i.e., representing separate phenotypes), 2) a function of longer exposure time (despite our controlling for age), or 3) (as seems most likely) simply part of a continuum of dependence. Meanwhile, our findings are largely consistent with the inference that what the FTND measures is “physiological dependence.” An earlier report by our group showing that withdrawal symptomatology tends to be “matched” to baseline clinical or sub-clinical psychopathology (Pomerleau, Marks, and Pomerleau, 2000) suggests that multidimensional approaches (e.g., Hudmon et al., 2003; Piper et al., 2006) will be needed to capture the full range of smoking phenotypology.

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Table 1

Demographic data, depression, and smoking-related variables in high-dependent and low-dependent smokers (s.e.m. stands for standard error of the mean).

	High Dependent FTND ≥ 4 (n=155)	Low Dependent FTND < 4 (n=86)	<i>p</i> -value*
FTND (mean \pm s.e.m.)	5.8 \pm 0.12	1.6 \pm 0.1	-
Age (mean \pm s.e.m.)	39.7 \pm 0.8	35.3 \pm 1.1	0.001
Sex (% female)	56.1	46.5	0.178
Race (% White)	66.5	66.3	0.222
Comorbidity (% depressed)	43.4	45.4	0.893
Amount smoked (cigarettes/day)	19.8 \pm 0.6	11.3 \pm 0.7	< 0.001
Missing cases	5	2	
Age started smoking (mean \pm s.e.m.)	15.1 \pm 0.4	15.5 \pm 0.4	0.580
Missing cases	13	3	
Current or lifetime DSM-IV nicotine dependence (% positive)	54.8	57.0	0.788
Number of withdrawal symptoms (mean \pm s.e.m.)	6.7 \pm 0.2	6.0 \pm 0.3	0.052
Missing cases	19	11	

* T-tests and Fisher's exact tests as appropriate.

Table 2

Unadjusted and adjusted^a estimates^b of the relative risk^c linking high level of nicotine dependence with experiencing specific nicotine withdrawal features.

Withdrawal Features	High Dependence FTND ≥ 4		High Dependence FTND ≥ 4	
	Unadjusted R.R. (95% C.I.)	<i>p</i> -value	Adjusted ^b R.R. (95% C.I.)	<i>p</i> -value
DSM-IV				
IRRITABILITY/ANGER	1.1; (1.00, 1.3)	0.149	1.2; (1.00, 1.3)	0.048
NERVOUS	1.2; (1.00, 1.5)	0.054	1.3; (1.1, 1.6)	0.008
RESTLESS	1.2; (1.01, 1.3)	0.032	1.2; (1.1, 1.4)	0.010
DIFFICULTY CONCENTRATING	1.6; (1.1, 2.4)	0.017	1.3; (1.1, 1.7)	0.018
DECREASED HEART RATE	0.7; (0.4, 1.0)	0.062	0.7; (0.4, 1.1)	0.091
INCREASED APPETITE/WEIGHT GAIN	1.0; (0.8, 1.2)	0.852	1.1; (0.9, 1.3)	0.669
DEPRESSED	1.1; (0.8, 1.7)	0.577	1.3; (0.9, 1.9)	0.247
TROUBLE SLEEPING	1.3; (1.0, 1.7)	0.030	1.8; (1.2, 2.6)	0.005
ICD-10 Additional Features				
CRAVING	1.0; (0.9, 1.1)	0.669	1.0; (0.9, 1.2)	0.434
PERSISTENT COUGH	0.9; (0.7, 1.3)	0.740	1.0; (0.7, 1.4)	0.863
SORES IN MOUTH	0.4; (0.5, 2.4)	0.285	0.6; (0.03, 11.3)	0.707
TIRED OR WEAK	1.4; (0.9, 2.3)	0.160	1.5; (0.9, 2.3)	0.108

^aEstimates are adjusted for age, sex, age at first cigarette, race, and current or past history of depression.

^bThese multivariate model estimates of relative risk are from the generalized linear model (logit link) with a generalized estimating equations approach to address interdependencies of the twelve binary responses (cumulative occurrence of nicotine withdrawal features).

^cThese relative risk estimates convey the magnitude of increased risk for each withdrawal feature of the HD group.