

RESEARCH REPORT

Nicotine withdrawal in women

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Abstract

Associations between self-report symptom profiles for nicotine withdrawal, personality (TPQ, EPQ-R), life-time history of psychopathology and smoking history were examined in data obtained from 553 female adult Australian twins (246 regular smokers), aged 32–48 years, who had participated in a telephone interview survey that included life-time assessments of smoking history, nicotine dependence and symptoms of withdrawal. Two hundred and two respondents were from high-risk pairs where either the respondent or the respondent's co-twin had reported a life-time history of alcohol dependence; 351 were from control pairs. Latent class analysis was used to identify subtypes ('classes') of smokers reporting similar withdrawal symptom profiles. Three major classes were identified which appeared to represent a continuum from mild to severe nicotine withdrawal. Smokers from the severe withdrawal class were best characterized by hands shaking and by the prominence of depressive features. There were marked increases in life-time alcohol dependence rates as a function of severity class. In contrast, significantly elevated rates of major depression, conduct disorder and anxiety disorder were observed only among smokers from the most severe withdrawal class. Neuroticism was the only personality factor strongly associated with the development of withdrawal symptoms.

Introduction

Persuasive evidence for the validity of the nicotine withdrawal syndrome in humans has been provided by a large number of experimental and epidemiological studies; i.e. the laboratory study of psychomotor and physiological (e.g. EEG, heart rate, diastolic blood pressure and weight gain) changes following abstinence from tobacco (reviewed in DHHS Publication No. (CDC) 88-8406, 1988); the study of relief from symptoms of withdrawal following nicotine replacement

(Jarvis *et al.*, 1982; Hughes *et al.*, 1984; Snyder & Henningfield, 1989); and through self and observer ratings on changes in mood and behavior following cessation of smoking elicited prospectively (Hughes & Hatsukami, 1986; Gritz, Carr, & Marcus, 1991; Hughes *et al.*, 1991; Hughes, 1992) as well as retrospectively from interviews with subjects recruited from the general community (Breslau, Kilbey & Andreski, 1992).

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Along with a craving for cigarettes and an increase in appetite, symptoms reflective of mood and anxiety disorders, such as irritability, low mood, restlessness and difficulty with concentration have been reported frequently by adult smokers after quitting cigarettes (Shiffman, 1979; American Psychiatric Association, 1987, 1994; Breslau *et al.*, 1992); and similar problems of nicotine withdrawal have been found in female adolescents early in their smoking careers (McNeill, *et al.*, 1986).

Preliminary work conducted by Hughes (1992) on the characterization of nicotine withdrawal symptoms using factor analysis provides evidence for at least three different factors in daily smokers after 7 days of nicotine abstinence; a mood (anxiety, restlessness, difficulty concentrating and irritability), an appetite (hunger and weight gain) and an insomnia (waking during the night) factor, with the mood factor accounting for most of the shared variance of nicotine withdrawal symptoms (39%), with equal contributions (12% each) from the other two factors. Tate, Pomerleau & Pomerleau (1993) found two types of smoker with respect to nicotine withdrawal using cluster analysis on data obtained from moderately nicotine-dependent men and women following a 48-hour period of abstinence. Consistent with the earlier findings by Hughes (1992), mood-like symptoms (i.e. irritability, impatience, difficulty concentrating, and anxiety) distinguished one group from the other.

Important relationships between life-time depression and a history of regular smoking have been supported by epidemiological data (Glassman *et al.*, 1990), including a positive association of depressive mood (Kandel & Davies, 1986) and anxiety (Patton *et al.*, 1996) with regular smoking in adolescents, and of life-time history of mood and anxiety disorders with severity of DSM-III-R nicotine withdrawal (Breslau *et al.*, 1992) and DSM-III-R nicotine dependence in adults (Breslau, Kilbey, & Andreski, 1991, 1994). Smokers with both current (West, Hajek & Belcher, 1989; Anda *et al.*, 1990; Hughes, 1992) and life-time histories (Covey, Glassman & Stetner, 1990) of mood disturbance have been reported to be less likely to quit the use of cigarettes. In a prospective study, Breslau, Kilbey & Andreski (1993) found evidence to suggest that the association between nicotine dependence and major depression may be due to factors that predispose to both disorders. Recent

work by Kendler *et al.* (1993) finds a strong genetic correlation between average life-time cigarette consumption and 1-year prevalence of major depression in a follow-up of female twins.

Despite overwhelming evidence for a link between cigarette use and mental health, it remains uncertain whether certain profiles of withdrawal symptoms (e.g. with predominant affective complaints) are especially likely to occur in smokers with a vulnerability to psychiatric disorder; and if so, whether this contributes to the progression and maintenance of the smoking habit.

Commonly observed associations between personality, risk of becoming a smoker and persistence in cigarette use (reviewed in Gilbert & Gilbert, 1995) raise the additional question of the extent to which differences in the reporting of nicotine withdrawal symptoms are a manifestation of differences in personality. Breslau *et al.* (1993) found a strong relationship between neuroticism and DSM-III-R nicotine dependence but otherwise little work has been done to clarify the association of personality and nicotine withdrawal.

In the present study we used self-report data from a volunteer sample of female adult twins to address the following aims: (i) to identify syndromes of nicotine withdrawal among regular smokers; (ii) to test whether these withdrawal symptom profiles are differentially associated with history of DSM-III-R life-time major depression, panic disorder, social phobia, alcohol dependence and adolescent conduct disorder; (iii) to test whether these withdrawal symptom profiles are associated with differences in personality as assessed by Cloninger's Tridimensional Personality Questionnaire (Cloninger, Przybeck & Svrakic, 1991) and Eysenck's Personality Questionnaire (Revised) (Eysenck, Eysenck & Barrett, 1985); and (iv) to examine the relationship between withdrawal symptom profiles and other smoking behaviors such as heavy smoking, difficulty with smoking cessation and nicotine dependence.

Latent class analysis was used to address the aims of this study, a technique which permits an empirical exploration of the correlations between a set of categorical observations (McCutcheon, 1987). In this procedure, classes of withdrawal syndrome are defined by groups of respondents who endorsed similar combinations of symptoms. Estimates of prevalence for different classes of withdrawal are obtained along with

expected frequencies of endorsement for each symptom of withdrawal by type. Latent class analysis has been previously used to examine symptom profiles for several psychiatric disorders (e.g., Young, 1982–83, Eaton *et al.*, 1989; Heath *et al.*, 1994a; Faraone & Tsuang, 1994; Kendler *et al.*, 1996).

Methods

Sample

The sample consisted of 571 female adult twins (including 258 life-time smokers) born from 1947 to 1963 (32–48 years; mean age: 39 years) who were members of a volunteer twin register maintained by the Australian National Health and Medical Research Council (Jardine, Martin & Henderson, 1984; Martin *et al.*, 1985). The study was limited to women because major depression, a psychiatric disorder previously found to have a strong association with nicotine withdrawal (Breslau *et al.*, 1992), is more common in women than in men.

These twins had previously participated in a telephone interview survey, adapted from the SSAGA (Bucholz *et al.*, 1994) that was administered in 1992–93 (the 'phase I survey': Heath, Cloninger & Martin, 1994b). The phase I interview, which included assessments of DSM-III-R alcohol dependence and other major axis I disorders, was given to 5995 Australian twins (including 2340 women born from 1947 to 1963). Participants in the phase I survey were twins from pairs who had previously either (i) volunteered for an alcohol challenge study in 1979–80 (Martin *et al.*, 1985), or who had (ii) responded to a mailed questionnaire survey in 1980–82 ('1981 survey': Jardine *et al.*, 1984) and in the case of at least one twin from the pair, had responded to a follow-up survey in 1988–89 ('1989 survey': Heath *et al.*, 1994b). The origins of the phase I interview sample are described in more detail elsewhere (Heath *et al.*, 1994a; Heath *et al.*, 1995).

Data for the present study were obtained in 1994–95 from the follow-up telephone interview survey of a subsample of twins where at least one twin had met life-time criteria for DSM-III-R alcohol dependence at the time of their phase I interview, and from controls (twins from pairs where neither twin had a life-time history of DSM-III-R alcohol dependence at phase I). The follow-up interview obtained detailed histories of

the life-time use of nicotine and alcohol and related problems, including life-time symptoms of Fagerstrom (Fagerstrom, 1978) and DSM-III-R nicotine dependence.

Since sampling biases may lead to inaccurate estimates of prevalence and to spurious associations, information about the population under study must be represented in the sample data. Ninety-five per cent of the follow-up women whose data were used for this project ($n = 542$) had previously completed a health-related questionnaire mailed in 1988–89 (Heath *et al.*, 1994b). Therefore, to identify departures from representation, we used information on smoking history obtained through this questionnaire survey to perform a limited number of comparisons between these follow-up subjects and a subsample of women of the same ages who had participated only in the phase I telephone survey ($n = 1669$). No significant differences in smoking history were found between these groups of twins, supporting the generalizability of findings obtained from the follow-up high-risk and control follow-up subjects. The follow-up women were no more likely to be life-time smokers than the phase I only participants (prevalence of life-time smoking was 48% and 45%, respectively, $p = 0.30$). Across samples, the average duration of smoking was 12 years, with 64% of the phase I only vs. 69% of the follow-up subjects reporting to have smoked cigarettes for 10 years or longer ($p = 0.10$). Twenty per cent of the life-time smokers from both groups of women reported smoking heavily, or using more than 20 cigarettes per day ($p = 0.94$). Furthermore, similar means for age-of-smoking-onset were observed in the follow-up and the phase I only subjects, (mean \pm SD: 16.58 \pm 3.04 and 16.80 \pm 2.98 respectively; $p = 0.31$).

Well-educated individuals are over-represented in the sample used in this project; 47% achieved more than 12 years of education, but a broad range of educational (27% have less than 11 years of education, and 17% have at least one university degree) and socio-economic levels were represented. Deletion of cases with missing data reduced the final sample to 553, including 246 regular smokers.

Measures

The 1994–95 follow-up telephone interviews included an assessment of life-time DSM-III-R

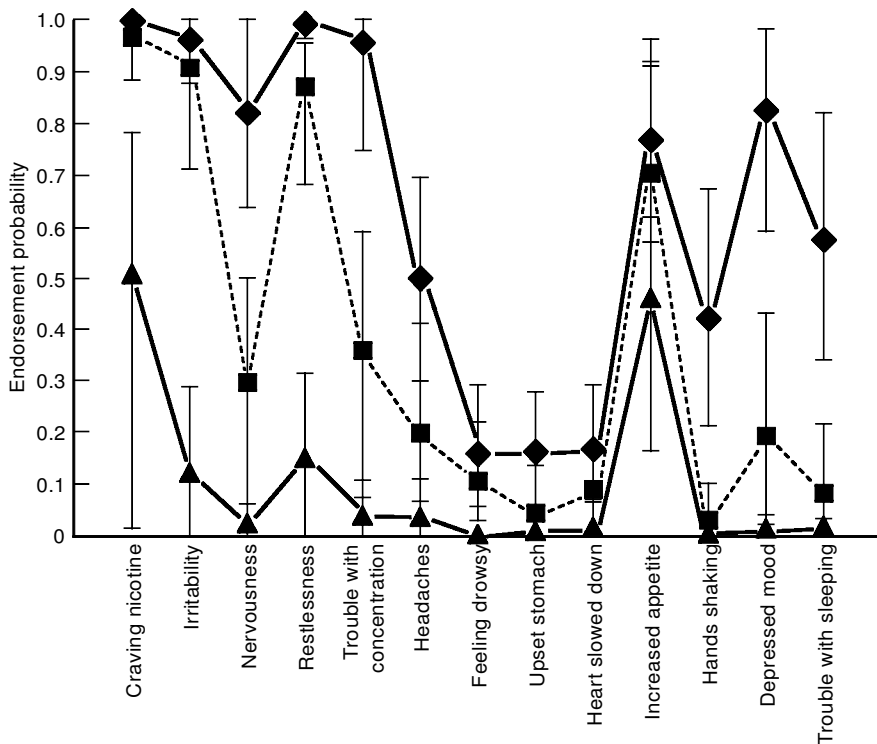


Figure 1. Symptom endorsement probabilities and bootstrapped 95% confidence intervals for mild (▲), moderate (■) and severe (◆) classes of nicotine withdrawal.

nicotine dependence, DSM-III-R nicotine withdrawal, and other problems related to nicotine dependence and deprivation (i.e. headaches, upset stomach, hands shaking and feeling drowsy) based on items adapted from the Composite International Diagnostic Interview (CIDI) (Cottler *et al.*, 1991), the Hopkins ECA follow-up (Eaton, 1992), and the Fagerstrom Test for Nicotine Dependence (FTND: Heatherton *et al.*, 1991), an abridgement of the Fagerstrom Tolerance Questionnaire (Fagerstrom, 1978). Subjects were asked to recall a period of heaviest smoking when answering items associated with the Fagerstrom scale.

Life-time measures of nicotine dependence and withdrawal were obtained from all regular smokers. A broad definition of regular smoking was employed for the purposes of this project; that is, smoking as often as once or twice weekly for a minimum of 6 months. In this sample, 92% of the regular smokers reported smoking daily at some time during their lives.

The nicotine withdrawal assessment was

modelled after the CIDI (Cottler *et al.*, 1991). Individuals who reported to have had previously deprived themselves of cigarettes, after a period of regular smoking, were asked to indicate from a list of problems associated with nicotine withdrawal (see Figs 1 and 2) those they experienced in the first few days or so after stopping or cutting down on cigarettes.

Life-time assessments of DSM-III-R alcohol dependence, major depression, conduct disorder, panic, agoraphobia and social phobia were obtained during the phase I telephone interview using an adaptation of the SSAGA, with cultural adjustments in wording (Bucholz *et al.*, 1994). Two measures of personality—the Tridimensional Personality Questionnaire (Cloninger *et al.*, 1991) which assesses the traits Novelty-Seeking, Reward Dependence and Harm Avoidance; and the short form of the Eysenck Personality Questionnaire (Revised) (Eysenck *et al.*, 1985) which evaluates for Extraversion, Neuroticism, Psychoticism and Social Non-Conformity—were assessed in the 1989 survey.

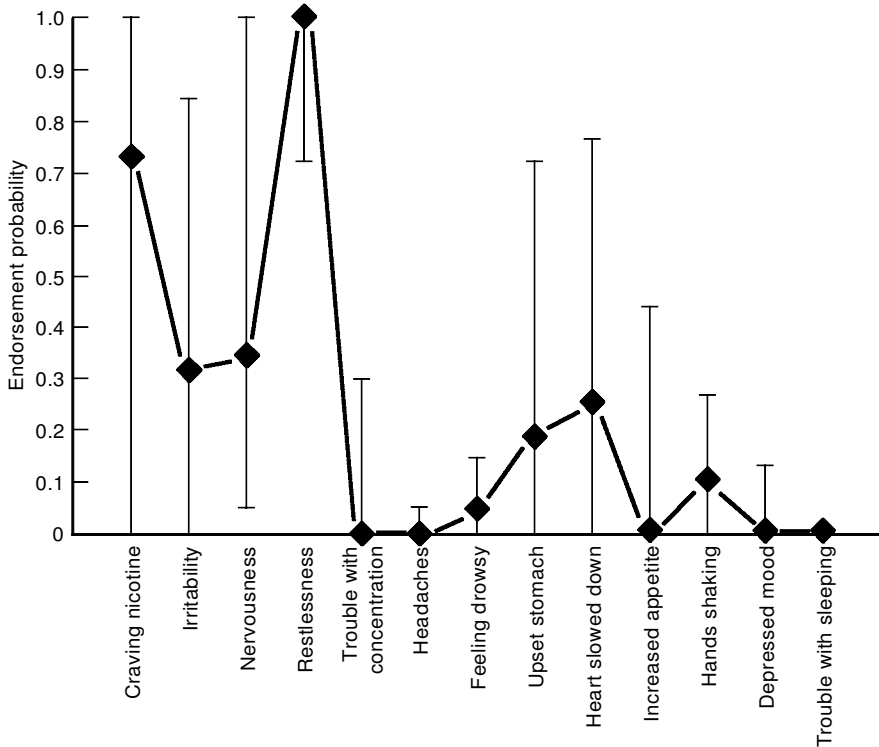


Figure 2. Symptom endorsement probabilities and bootstrapped 95% confidence intervals for the fourth nicotine withdrawal class.

Data analysis

Our approach to data analysis was guided by our interest in whether it might be possible to identify distinct subtypes of the nicotine withdrawal syndrome which might be differentially associated with predisposing personality traits or psychopathology (for example, individuals with a history of major depression might be expected to show a greater predominance of affective symptoms, whereas individuals without such a history might show a predominance of non-affective symptoms). Therefore, we fitted latent class models (McCutcheon, 1987; Eaves *et al.*, 1993; Heath *et al.*, 1994a) to the withdrawal symptom data obtained from 246 regularly smoking women. Since the numbers of complete twin pairs were too small to permit meaningful tests of genetic hypotheses, all analyses ignored the twin structure of our data.

Latent class analysis may be viewed as a categorical variant of factor analysis. Factor analysis hypothesizes that the correlations between a set of variables (e.g. symptoms), may be explained

by the influence of a much smaller number of continuously distributed latent variables ('factors': Harman, 1976). Maximum-likelihood estimates of factor loadings are obtained under models estimating varying numbers of factors, and the goodness-of-fit of these models can be compared by likelihood-ratio χ^2 test (or other criteria) to identify how many factors are needed to explain the observed data (Bollen, 1989). Latent class analysis, in contrast, hypothesizes that the response distribution observed for n items, summarized in the form of an n -way contingency table, can be explained by the existence of a much smaller number of mutually exclusive, discrete subject 'classes' or categories (Goodman, 1974). Parameters of the latent class model are class membership probabilities (equivalent, assuming approximately random sampling, to population prevalence estimates for the discrete classes) and symptom endorsement probabilities for each class. Key assumptions of the latent class model are that within a class, item endorsement probabilities are statistically independent,

and the same for all subjects (although symptom endorsement profiles will vary because of measurement error or stochastic factors).

For the purposes of this project, models estimating different numbers of classes were fitted to the nicotine withdrawal data using a maximum-likelihood latent class analysis program developed by Eaves *et al.* (1993) and were compared by likelihood-ratio χ^2 test. Since a 1-class model would imply that all subjects have the same probability of endorsing a given withdrawal symptom, which is implausible, we began by fitting a 2-class model, and then compared the improvement in fit as classes were added. Since we wished to evaluate the associations of personality and psychopathology with class membership, if adding a class led to a significant improvement in fit, but with a low class membership probability for at least one class (implying few individuals in that class), the simpler model with fewer classes was preferred. From latent class analysis results, the most probable class membership for every symptom endorsement profile, and therefore for every subject, was computed.

When estimating class membership and symptom endorsement probabilities we ignored the twin structure of the data, i.e. ignored twin pair resemblance for class membership. Technically, this violates the assumption of independent observation used in latent class analysis, since we might expect withdrawal symptoms reported by twin pairs to be correlated. Assuming that our sample is representative of regular smokers (i.e. approximately a random sampling of regular smokers), estimates of symptom endorsement probabilities and class membership probabilities will be statistically unbiased, but the likelihood-ratio χ^2 test may overestimate or underestimate the significance of adding an extra class, as in factor analysis (Neale & Cardon, 1992). There would therefore be the danger that we might overestimate the significance of the differences in item endorsement probabilities between classes. To adjust for this problem, we adapted the latent class program to provide approximate bootstrap estimates of the 95% confidence limits for each parameter (Efron & Tibshirani, 1986) based on 1000 resamplings from the observed data.

To examine the association between classes of nicotine withdrawal and differences in psychopathology, personality and smoking history, we computed the most probable class membership

for each subject and tested for associations of these variables with most probable class membership by χ^2 tests, and by logistic and linear regression. For these analyses, we used a more stringent significance level ($p < 0.01$) to reduce our probability of reporting spurious 'significant' results.

Results

Latent class analysis

When we compared the fit of models estimating increasing numbers of latent classes, significant improvements in fit by likelihood ratio χ^2 criterion were found for models through to the 5-class model (2- vs. 3-class model: $\chi^2 = 86.43$, $df = 14$, $p < 0.001$; 3- vs. 4- class model: $\chi^2 = 25.32$, $df = 14$, $p = 0.03$; 4- vs. 5-class model: $\chi^2 = 24.21$, $df = 14$, $p = 0.04$; 5- vs. 6-class model: $\chi^2 = 8.34$, $df = 14$, $p = 0.87$). However, under the 5-class model, the smallest class included only four of the 246 regular smokers; therefore, the 4-class solution ($\chi^2 = 2477.47$, $p = 0.03$) was chosen to summarize nicotine withdrawal symptom probabilities among regular smokers in this sample.

Three of the four classes identified under the 4-class solution appeared to represent a continuum in severity of withdrawal. The relationship between the class with the smallest prevalence ($n = 11$) and the others was less easily interpreted, hence the 4th class will be discussed separately. Figure 1 summarizes symptom endorsement probabilities for three of the four classes, with bootstrap 95% confidence intervals constructed around each endorsement probability. As shown, these three groups appear to differ in severity of withdrawal, rather than having different combinations (e.g. affective vs. non-affective) of withdrawal symptoms; therefore, they have been labeled the 'mild', 'moderate' and the 'severe' groups. Class membership probabilities (and approximate 95% confidence limits) for the mildest to the most severe of these three classes were 41% (21–52%), 36% (18–47%) and 18% (10–30%), respectively.

Smokers from the least severe of the classes shown in Fig. 1 experienced few, if any, symptoms following nicotine deprivation. While 48% of the smokers from this class reported a history of increased appetite and 51% of craving nicotine, only 16% reported experiencing restlessness, 12% irritability, and fewer than 11%

reported having any of the remaining nine symptoms following a period of abstinence from cigarettes. Nineteen per cent of the smokers from the mild class did not report having experienced any symptom of nicotine withdrawal. Smokers from the severe class were best distinguished from all other classes of smoker (including the fourth class) by depressive symptoms: a significantly larger number of smokers from the most severe class experienced trouble concentrating (96%), a depressed mood (84%) and trouble with sleeping (58%). Compared with either the mild or the moderate classes of smoker, smokers from the severe class also had significantly more problems with nervousness (82%), and with hands shaking (43%) after stopping or cutting down on cigarettes. The probabilities of endorsement for symptoms of withdrawal experienced by smokers from the moderate class were intermediate between those for the most and the least severe of these 3 classes.

Figure 2 shows symptom endorsement probabilities for nicotine withdrawal for the fourth class. The prevalence estimate (and approximate 95% confidence limit) was 6% (2–26%). Smokers from this class reported experiencing restlessness, a craving for nicotine, nervousness, irritability or anger and their heart slowing down, and with much lower probability, upset stomach, hands shaking and trouble with drowsiness; although only the restlessness symptom replicated consistently across bootstraps. There was little evidence that class 4 smokers had problems with their ability to concentrate, with headache, increases in appetite, depressed mood or trouble sleeping when deprived of nicotine. Unlike the

three classes already discussed, there was a predominance of symptoms of anxiety (i.e. restlessness, nervousness and irritability or anger), rather than depressive symptoms, in the class 4 smokers.

Except for 'upset stomach', the symptoms evaluated in our study which were not included in the DSM-III-R or the DSM-IV lists of withdrawal symptoms (i.e. headaches, feeling drowsy, hands shaking and upset stomach) (American Psychiatric Association, 1987, 1994) were observed to have reasonable specificity (i.e. the ability to discriminate moderate from the more severe classes of withdrawal as shown by the approximate 95% CIs), but the probabilities of endorsement for two of these items 'upset stomach' and 'feeling drowsy', were quite low (0–20%), even among individuals from the severe class who were the most likely to report experiencing these withdrawal symptoms at some time in their lives. Of those symptoms listed in the DSM-III-R, the symptom 'heart slowed down' performed least well.

Nicotine withdrawal and DSM-III-R psychopathology

Table 1 summarizes rates of life-time psychiatric disorder by nicotine withdrawal severity class. Also shown are rates of psychiatric disorder among never-smokers. Compared with never-smokers, individuals from the most severe withdrawal class were observed to have significantly higher rates of life-time history of psychiatric disorder. Odds ratios (and 95% CI) for the association with membership in the severe nicotine withdrawal were 3.91 (2.02–7.56) for

Table 1. Rates of psychiatric disorder as a function of withdrawal symptom severity class (significant differences compared to never-smokers are also shown^a)

	Class 1 (Mild) (<i>n</i> = 105) (%)	Class 2 (Moderate) (<i>n</i> = 86) (%)	Class 3 (Severe) (<i>n</i> = 44) (%)	Class 4 (<i>n</i> = 11) (%)	Never Smokers (<i>n</i> = 307) (%)
Major depression	31	43	64**	55	31
Alcohol dependence	26**	31**	59**	18	8
Conduct disorder	4	5	30**	0	3
Panic disorder	5	6	11	18	2
Agoraphobia	8	6	20**	18	4
Social phobia	5	2	14*	0	3
Bulimia	2	1	9	9	4

^aComparing the four classes of nicotine withdrawal severity with those who have never smoked regularly. **p* = 0.001; ***p* = 0.0001.

major depression, 16.29 (7.88–33.71) for alcohol dependence, 21.81 (7.74–61.41) for conduct disorder, 6.28 (2.47–15.96) for agoraphobia and 6.42 (2.11–19.54) for social phobia. Rates of alcoholism were also elevated in the mild and the moderate withdrawal severity classes compared to never-smokers (OR = 3.91, 95% CI, 2.14–7.11; and OR = 5.16, 95% CI, 2.80–9.52, respectively), indicating an overall association between alcoholism and regular smoking, in addition to the association between withdrawal severity and alcoholism.

Significant linear associations were found (excluding class 4 subjects and never-smokers), by Mantel-Haenszel χ^2 test, between nicotine withdrawal severity class and life-time history of major depression, alcohol dependence, and adolescent conduct disorder (for all tests, $p < 0.001$), as well as a trend for an association with a history of agoraphobia ($p = 0.05$). Although numbers were small, there was a trend for individuals with a history of agoraphobia and panic disorder to be over-represented in the fourth withdrawal symptom class, which was characterized by predominantly anxiety-like symptoms.

Nicotine withdrawal and personality

Figure 3 (a and b) summarizes the associations between nicotine withdrawal severity class and the personality dimensions assessed by the Eysenck Personality Questionnaire-Revised and by the Tridimensional Personality Questionnaire. Using linear regression and the mild, moderate and severe classes of withdrawal as an ordinal scale (and again, excluding class 4 subjects and never-smokers from these analyses), a significant association with withdrawal severity class was found only with Neuroticism ($F(1,204) = 9.19$, $p = 0.003$, $B = 0.07$, $SE = 0.02$). There was a trend for smokers in the moderate and the severe withdrawal severity classes to have higher scores on Harm Avoidance ($F(1,190) = 4.54$, $p = 0.03$, $B = 0.05$, $SE = 0.02$), but otherwise there was no evidence of an association between reported severity of withdrawal from nicotine and the other personality variables (for all measures, $p > 0.10$).

Nicotine withdrawal and other smoking behaviors

The top half of Table 2 summarizes findings on the association between life-time severity of nicotine withdrawal and differences in other

smoking variables. Compared to smokers with mild nicotine withdrawal, we found only individuals experiencing severe withdrawal had a significantly earlier age-of-onset for regular smoking (age-of-onset of weekly smoking: $F(1,214) = 16.15$, $p < 0.001$, $B = -2.44$, $SE = 0.61$; for daily smoking: $F(1,213) = 14.65$, $p < 0.001$, $B = -2.66$, $SE = 0.69$) and a significantly longer duration of smoking ($F(1,226) = 14.49$, $p < 0.001$, $B = 4.92$, $SE = 1.29$) by multiple regression. Furthermore, a residual association between age-of-onset for daily smoking and severe nicotine withdrawal remained when Neuroticism, life-time history of psychiatric disorder (i.e. DSM-III-R major depression, adolescent conduct disorder, agoraphobia, social phobia and alcohol dependence) and DSM-III-R nicotine dependence (excluding the withdrawal criterion) were statistically controlled ($F(1,191) = 7.91$, $p = 0.005$, $B = -2.47$, $SE = 0.88$). There was no evidence for an association between severity of nicotine withdrawal and age of first cigarette.

Nicotine withdrawal and indicators of nicotine dependence

The bottom half of Table 2 presents life-time rates of Fagerstrom (Revised) and DSM-III-R nicotine dependence (excluding the withdrawal criterion) and other indicators of nicotine dependence by nicotine withdrawal severity class. Significant linear associations were found (excluding class 4 subjects and never-smokers) by Mantel-Haenszel χ^2 test, between severity of nicotine withdrawal and heavy smoking (i.e. more than 20 cigarettes per day), unsuccessful efforts to quit or cut down on smoking, life-time nicotine dependence as defined by the Revised Fagerstrom scale (a score ≥ 5) and by DSM-III-R criteria (excluding withdrawal criterion) and DSM-III-R withdrawal syndrome (for all tests, $p < 0.001$), but *not* for continued smoking (i.e. whether the respondent was still smoking in the 3 months prior to interview, $p = 0.21$).

Compared to smokers with mild nicotine withdrawal, except for continued smoking, individuals having either moderate or severe withdrawal were found to have significantly elevated life-time rates for the indicators of nicotine dependence (all tests, $p < 0.001$). There were no cases of DSM-III-R nicotine withdrawal syndrome

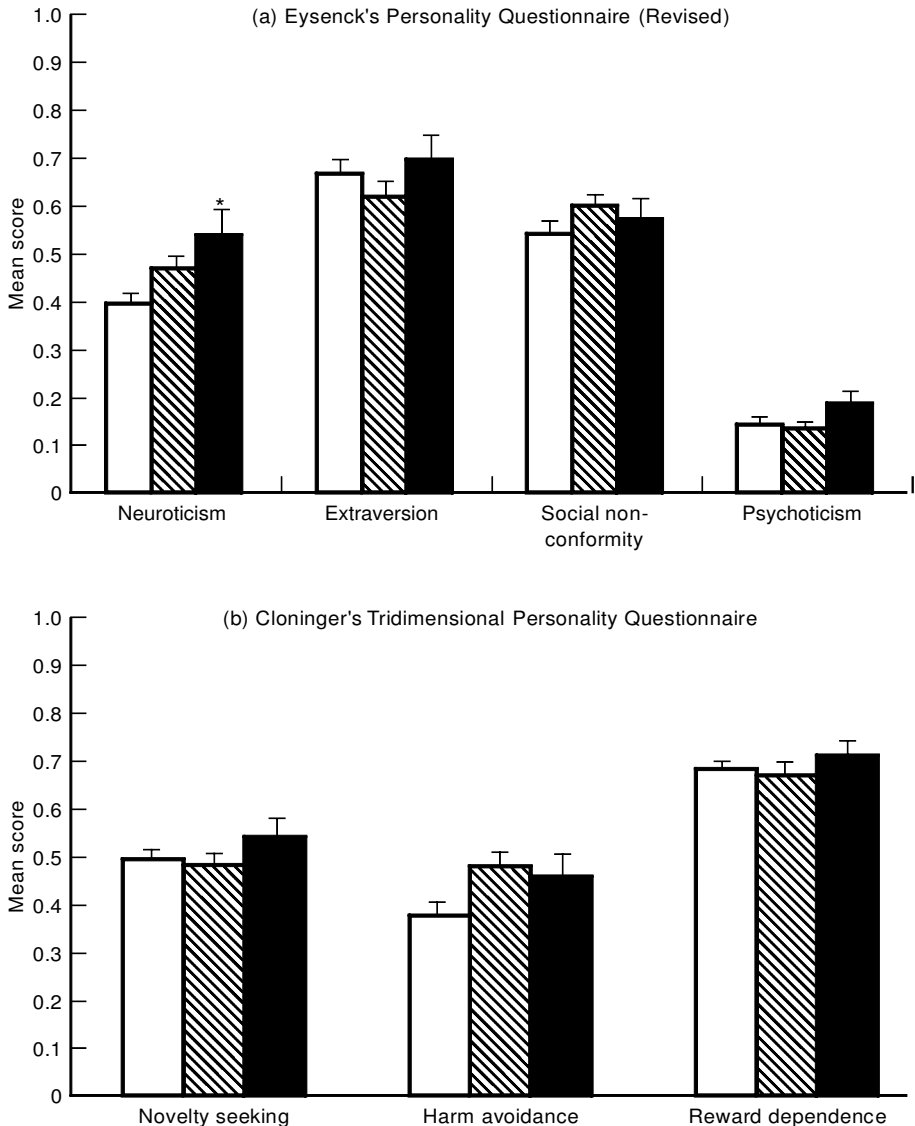


Figure 3. Scores on (a) Eysenck's Personality Questionnaire (Revised) and (b) Cloninger's Tridimensional Personality Questionnaire, and standard errors, as a function of nicotine withdrawal severity class (□ class 1—mild; ▨ class 2—moderate; ■ class 3—severe). Significant differences are indicated (* $p < 0.01$) for the comparison with those who have never smoked regularly.

among smokers from the mild nicotine withdrawal severity class, but a marked increase in lifetime DSM-III-R nicotine withdrawal syndrome was found among smokers from severe compared with moderate nicotine withdrawal severity classes ($p = 0.001$).

Because of the strong associations found between severity of nicotine withdrawal and

Neuroticism and the life-time occurrence of psychiatric disorder, we used stepwise logistic regression analysis to determine whether the best variables for predicting nicotine withdrawal severity were measures of vulnerability to psychopathology rather than of smoking history or of nicotine dependence. In Table 3 are shown odds ratios (and 95% CIs) for measures for

Table 2. *Classes of nicotine withdrawal and other smoking behaviors in women^a*

	Class 1 (Mild) (<i>n</i> = 105)	Class 2 (Moderate) (<i>n</i> = 86)	Class 3 (Severe) (<i>n</i> = 44)	Class 4 (<i>n</i> = 11)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age first tried a cigarette	15.03 (2.99)	15.42 (4.21)	13.86 (3.11)	16.00 (2.50)
Age first smoked one or two times a week	17.31 (2.82)	16.97 (3.47)	14.87 (2.45)**	18.30 (5.50)
Age first smoked daily or nearly every day	19.14 (3.72)	19.06 (4.09)	16.49 (2.86)**	19.30 (5.19)
Number of years smoked	16.15 (7.01)	15.81 (7.06)	21.07 (6.64)*	15.30 (8.51)
	Percentage (Mild)	Percentage (Moderate)	Percentage (Severe)	Percentage
Heavy smoking (more than 20 cigarettes per day)	23	47**	75***	36
One or more unsuccessful efforts to quit smoking	43	74***	89***	73
Continued smoking (last cigarette > 3 months ago)	42	35	32	27
FTND life-time (score \geq 5)	9	33***	66***	18
DSM-III-R nicotine dependence ^b	30	64***	86***	64
DsM-III-R withdrawal syndrome ^c	0	34	64***	9

^aCompared to smokers with mild (if any) symptoms of nicotine withdrawal (Class 1); ^bexcludes withdrawal criterion;

^ccompared to smokers with moderate symptoms of nicotine withdrawal (Class 2).

* $p < 0.01$; ** $p < 0.001$; *** $p = 0.0001$.

personality, psychopathology, smoking history and markers of nicotine dependence having significant associations with nicotine withdrawal severity class and, therefore, selected as candidate variables for the regression models. As noted previously, no associations were observed between severity of nicotine withdrawal and age of first cigarette or continued smoking. Life-time history of social phobia was excluded from these regression models because of the low prevalence of this disorder in smokers with moderate nicotine withdrawal (see Table 1).

By stepwise logistic regression, using an entry criterion of 0.01, significant differences in nicotine dependence as defined by FTND criteria (OR: 8.35, 95% CI: 3.15, 22.14) and in having one or more unsuccessful attempts to quit smoking (OR: 4.47, 95% CI: 2.13, 9.40) were found in smokers experiencing moderate or severe, rather than mild nicotine withdrawal. Compared with smokers having moderate nicotine withdrawal, those with severe withdrawal were best

predicted by a history of adolescent conduct disorder (OR: 14.50, 95% CI: 2.93, 71.89). Only after dropping 'adolescent conduct disorder' from our models was the number of years smoked found predictive of severe vs. moderate nicotine withdrawal severity (OR: 1.11, 95% CI: 1.04, 1.20).

Discussion

The primary goal of this project was to identify distinct nicotine withdrawal profiles that might be differentially associated with a history of psychopathology or with predisposing personality traits. To address this issue we explored whether different combinations (or classes) of symptoms could be observed in data on past episodes of nicotine deprivation, and then determined whether the rates of psychopathology, different aspects of smoking history, and certain personality traits varied by class of smokers reporting similar nicotine withdrawal profiles.

Table 3. Odds ratios from univariate logistic regression models of the association between nicotine withdrawal severity and psychopathology and other smoking behaviors

	Unadjusted odds ratio (95% CI)	
	Mild vs. moderate severe	Moderate vs. severe
Age first smoked one or two times a week	1.41 (1.05, 1.90)	2.97 (1.57, 5.64)
Age first smoked daily or nearly every day	1.30 (0.98, 1.73)	3.97 (1.82, 8.66)
Number of years smoked	1.34 (0.92, 1.94)	3.09 (1.65, 5.77)
Heavy smoking (more than 20 cigarettes per day)	4.32 (2.44, 7.66)	3.45 (1.55, 7.70)
One or more unsuccessful efforts to quit smoking*	5.09 (2.87, 9.03)	2.68 (0.94, 7.66)
FTND life-time (score ≥ 5)*	8.33 (3.87, 17.92)	4.01 (1.86, 8.64)
DSM-III-R nicotine dependence	5.73 (3.26, 10.08)	3.57 (1.36, 9.39)
Major depression	2.18 (1.28, 3.73)	2.32 (1.10, 4.90)
Alcohol dependence	1.99 (1.14, 3.48)	3.16 (1.49, 6.71)
Adolescent conduct disorder**	3.80 (1.24, 11.66)	8.60(2.60, 28.38)
Agoraphobia	1.46 (0.59, 3.63)	4.17 (1.30, 13.33)
Neuroticism	1.84 (1.17, 2.88)	1.51 (0.87, 2.81)

*Predictive of nicotine withdrawal of moderate severity in stepwise logistic regression (entry criterion: 0.01); **predictive of severe nicotine withdrawal in stepwise logistic regression (entry criterion: 0.01).

The main limitation of this study was our use of self-report data obtained retrospectively, which may be affected by the subject's ability to recall past events and response style. As with all studies using cross-sectional data, we could not distinguish between symptoms caused by the occurrence of nicotine deprivation from factors that influence recall and reporting; therefore, symptoms related to some other event, such as a physical or mental illness, might have been inadvertently attributed to an episode of nicotine deprivation. However, significant positive associations of life-time nicotine withdrawal severity with other measures of nicotine-related problems (i.e. nicotine dependence and heavy smoking) were found to remain after adjusting for the life-time occurrence of psychopathology, providing some support for the validity of our data.

Another limitation of this work is that all subjects were women, and the findings may not entirely generalize to men. Some (Svikis *et al.*, 1986; Hughes, 1992; Pomerleau *et al.*, 1994), but not all studies (Shiffman, 1979), have concluded that the experience of nicotine withdrawal is similar in men and women. Interestingly, a recent study on gender differences in nicotine withdrawal found severity to be similar in men and women assessed prospectively, but different when these same symptoms

were rated for past episodes of nicotine deprivation (Pomerleau *et al.*, 1994). Men (but not women) appeared to minimize symptomatology reported retrospectively.

Four classes of smoker reporting similar withdrawal symptom profiles were identified using latent class analysis, and differences among three of these classes were best characterized as differences in severity, defined by a monotonic increase in probabilities of symptom endorsement from mild to severe classes. A fourth class characterized by anxiety-like symptoms (e.g. restlessness, nervousness, etc.) seemed to have quite different patterns of response; however, since only a small proportion of regular smokers (6%) were represented more data are needed before we can describe this class with some confidence. Our findings provided no clear evidence for distinct profiles of nicotine withdrawal.

Symptoms that best distinguished smokers with severe nicotine withdrawal were predominantly complaints characteristic of mood disorder, especially dysphoria, difficulty with concentration and trouble with sleeping. Similar to Hughes, Gust & Pechacek (1987), we found craving for nicotine, restlessness and increased appetite to be the most frequently endorsed symptoms of nicotine deprivation. A number of symptoms not listed in the DSM (III-R or IV)

were also endorsed, particularly headache and hands shaking. However, low probabilities of endorsement were found for 'upset stomach' and 'feeling drowsy', even in the more severe classes of withdrawal, supporting the exclusion of these symptoms from the diagnostic criteria.

We examined the relationship between withdrawal symptom profiles and other smoking behaviors such as heavy smoking, difficulty with smoking cessation and nicotine dependence. A strong relationship was found between classes of withdrawal severity, history of nicotine dependence as defined by either the FTND or the DSM-III-R criteria (excluding withdrawal as a symptom) and heavy smoking (more than 20 cigarettes per day), supporting the utility of the FTND scale for predicting nicotine withdrawal after smoking cessation. Even when Neuroticism and DSM-III-R major depression, anxiety disorder, adolescent conduct disorder and alcohol dependence were controlled for, there were substantial differences in the life-time prevalence of heavy smoking and of nicotine dependence between the mild, the moderate and the most severe classes of nicotine withdrawal, with the FTND the strongest predictor of moderate/severe over mild (or an absence of) nicotine withdrawal. These findings are consistent with the work of some (Fagerstrom & Schneider, 1989), but unlike the findings of others (Hughes & Hatsukami, 1986; Hughes *et al.*, 1991; Hughes, 1992) who obtained contemporaneous measures of nicotine withdrawal soon after the onset of a specific period of smoking abstinence. The reason for this discrepancy is unclear; however, the range of variation of severity in self-reports of nicotine dependence and nicotine withdrawal among volunteers for a study of smoking cessation may be reduced compared to the variances observed in a sample that was not selected for cigarette use. A prospective study of smokers randomly chosen from the general population is needed to properly address this issue.

We did not find an association between withdrawal severity and continued smoking. However, smokers with moderate/severe rather than mild (or an absence of) nicotine withdrawal were over five times more likely to have made unsuccessful attempts at quitting or cutting down on their use of cigarettes, supporting the conclusion by Breslau and her colleagues (1992) that severity of nicotine withdrawal may have more effect

on difficulty with achieving nicotine abstinence in the short term, than with successful abstinence in the long term.

Interestingly, we found a substantial association between age-of-onset of regular smoking and severity of withdrawal. Our results suggest that, even controlling for Neuroticism, psychiatric disorder and DSM-III-R nicotine dependence (excluding the withdrawal criterion) those who begin to smoke daily at an early age are likely to experience more severe periods of nicotine withdrawal compared with those starting to smoke regularly in later adolescence or in adulthood. However, as we did not observe an association between nicotine withdrawal severity and age of first cigarette, the question is raised of whether vulnerability to nicotine withdrawal plays an important role in the transition from experimentation to the regular use of cigarettes.

Smokers with a history of major depression (Covey *et al.*, 1990; Breslau *et al.*, 1992), and to a lesser extent an anxiety disorder (Breslau *et al.*, 1992) have been found to endorse more severe periods of nicotine withdrawal. Consistent with these reports, we found significant associations of severity of withdrawal with DSM-III-R major depression, social phobia and agoraphobia. However, we observed an even stronger association with history of DSM-III-R adolescent conduct disorder. Smokers with a history of conduct disorder were more than eight times as likely to have severe rather than moderate levels of nicotine withdrawal. This finding is consistent with the observation that those with more severe nicotine withdrawal were also more likely to have an early age-of-onset of regular smoking (mean: age 15), when smoking is still a deviant behavior.

Greater numbers of smokers were observed to have histories of alcohol dependence among smokers with severe (59%), compared with moderate nicotine withdrawal (31%); and among smokers with moderate compared with mild (if any) symptoms of nicotine withdrawal (26%). The close correspondence between alcohol dependence risk and severity of nicotine withdrawal suggests that the relationship between these two substance-related disorders may be qualitatively different from the association observed between nicotine withdrawal and mood, anxiety or conduct disorders.

Similar to the findings of Breslau *et al.* (1993) for DSM-III-R nicotine dependence, we found Neuroticism to have a strong association with

nicotine withdrawal severity; but otherwise, there was little evidence of an association between nicotine withdrawal and other measures of heritable personality traits.

Our results suggest strong associations between the development of nicotine withdrawal and a wide range of psychopathology, including problems associated with depressed mood (e.g. major depression and Neuroticism) and a history of behavior problems (i.e. adolescent conduct disorder). Prospective research is needed to determine whether the close relationship between severe nicotine withdrawal and psychopathology is due to risk factors shared in common, and to evaluate the extent to which co-occurrence of smoking abstinence during an episode of some form of psychopathology intensifies or modifies the course of withdrawal from nicotine.

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