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Refining the depression-nicotine dependence link: Patterns of depressive symptoms in psychiatric outpatients with current, past, and no history of nicotine dependence

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ABSTRACT

The aim of this study was to elucidate the depression-nicotine dependence link by evaluating which specific depressive symptoms are uniquely associated with nicotine dependence in psychiatric outpatients. Participants were assessed using structured clinical interviews which yielded psychiatric diagnoses and clinical ratings on a wide variety of depressive symptoms. Depressive symptoms were compared across three groups: (1) patients with no history of nicotine dependence (NND; $n=1015$); (2) patients with past nicotine dependence in full remission for at least 2 months (PND; $n=211$); and (3) patients with current nicotine dependence (CND; $n=342$). Participants with CND evidenced elevations on certain typical-vegetative, melancholic, and dysphoric depressive symptoms as compared to patients with NND and (to a lesser extent) patients with PND. Group differences were most consistent for depressed mood, anhedonia, appetite/weight loss, psychomotor disturbance, fatigue, and insomnia. Differences were least apparent for atypical symptoms. The symptomatic profiles of PND and NND patients were virtually indistinguishable. Certain vegetative, melancholic and dysphoric depressive symptoms are closely associated with nicotine dependence and could play an important etiological role in depression-nicotine dependence comorbidity.

1. Introduction

There is a robust bi-directional relationship between depression and nicotine dependence. Depression increases the risk of nicotine dependence (Breslau, Kilbey, & Andreski, 1993a), nicotine dependence increases the risk of depression (Breslau et al., 1993a; Breslau, Kilbey, & Andreski, 1993b), and depression may interfere with the ability to successfully quit smoking (Anda et al., 1990; Ginsberg, Hall, Reus, & Muñoz, 1995; Haas, Munoz, Humfleet, Reus, & Hall, 2004; Kinnunen, Doherty, Militello, & Garvey, 1996; Leventhal, Ramsey, Brown, LaChance, & Kahler, 2008b; Niaura et al., 2001), leading to more severe and persistent manifestations of nicotine dependence. Results suggest that the link between depression and nicotine dependence is specific, and is not accounted for by other variables, such as psychiatric comorbidity, demographic characteristics, nicotine withdrawal, current daily smoking, and smoking chronicity (Breslau & Johnson, 2000; Breslau, Kilbey, & Andreski, 1994; Dierker & Donny, 2008). Furthermore, the relationship between daily smoking level and nicotine dependence is stronger among individuals with depression as compared to those without depression, suggesting that depression may increase sensitivity to nicotine dependence symptoms at substantially lower levels of smoking exposure (Breslau et al., 1994; Dierker & Donny, 2008).

Despite considerable evidence supporting a depression-nicotine dependence link, the mechanisms underlying this association remain relatively unclear. A potential obstacle to understanding this relationship may be the heterogeneity of the depressive syndrome. Most investigations of smoking and depression consider depression at the broad clinical diagnostic phenotype level (e.g., presence vs. absence of MDD, severity of overall depressive symptoms), which may not capture all of the clinically-relevant variability in depression that contributes to smoking (Hall, 2004). Recent advances in psychiatric genetics indicate that depression may be best characterized as a complex set of features involving several intermediate phenotypes rather than a unitary homogenous syndrome (Hasler, Drevets, Manji, & Charney, 2004). One method to isolate these intermediate phenotypes is to partition depression into more narrow definitions based on key symptoms (e.g., depressed mood, anhedonia, vegetative symptoms, cognitive disturbance, psychomotor change, diurnal mood variation; Gottesman & Gould, 2003; Hasler et al., 2004). This method is consistent with the conceptualization that each symptom may represent a unique phenotypic marker with a distinct underlying etiological process. In support of this approach, evidence suggests that different symptoms of depression have distinct neurobiological and psychosocial correlates (Keller, Neale, & Kendler, 2007; Milak et al.,

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2005). This is important for understanding the link between depression and nicotine dependence because some depressive symptoms and their correlates may have a closer overlap with the etiological factors underpinning nicotine dependence. Accordingly, evaluating which specific depressive symptoms are associated with nicotine dependence may elucidate the psychopathological processes underlying this common comorbidity.

Investigations have revealed that some depressive symptoms are more strongly linked with nicotine dependence than others. Studies have shown that depressed individuals who meet symptomatic criteria for the melancholic subtype have higher rates of lifetime nicotine dependence (Kendler, 1997; Leventhal, Francione Witt, & Zimmerman, 2008a), whereas atypical depression is not associated with nicotine dependence (Leventhal et al., 2008a). Pomerleau, Zucker, and Stewart (2003) found that smokers scored higher than non-smokers on the anhedonia, depressed mood, and somatic/vegetative features subscales of the Center for Epidemiologic Studies Depression Scale (Radloff, 1977). Groups did not differ on the interpersonal problems subscale, which measures symptoms relevant to the interpersonal sensitivity common in atypical depression. Similarly, Leventhal et al. (2008b) found that elevations on these three subscales predicted reduced likelihood of abstinence following smoking cessation treatment, whereas interpersonal problems did not predict outcome, suggesting that some depressive symptoms are linked to more persistent nicotine dependence than others. Additional evidence suggests that smokers with greater anhedonia, depressed mood, internalization, and psychomotor disturbance may be especially prone to relapse (Acton, Kunz, Wilson, & Hall, 2005; Carton, Le Houezec, Lagrue, & Jouvent, 2002; Cinciripini et al., 2003; Doran et al., 2006; Ginsberg et al., 1995; Japuntich et al., 2007; Kassel, Yates, & Brown, 2007; Niaura et al., 2001).

It is of note that many of the aforementioned studies used non-clinical samples, relied on self-reports of depressive symptoms, did not account for the effects of comorbid disorders, assessed only a subset of the symptoms of depression, and distinguished various symptomatic expressions of depression using subtype/subscale methods. In order to better characterize patterns of depressive symptomatology in nicotine dependence, it is important to extend these findings by: (a) assessing a broader range of symptoms; (b) evaluating effects at the individual symptom level (rather than the subscale/subtype level); (c) utilizing clinician-administered measures; (d) adjusting for the influence of comorbid psychiatric conditions; and (e) investigating effects in clinical populations. Investigating these relations in psychiatric patients is particularly significant because rates of nicotine dependence are especially high in this population and quit rates are remarkably low (Hughes, Hatsukami, Mitchell, & Dahlgren, 1986; Lasser et al., 2000). Thus, data on factors that might influence nicotine dependence in this population could inform the development of interventions that reach a large number of smokers who may have especially persistent forms of nicotine dependence.

The aim of the current study was to clarify the depression-nicotine dependence link by investigating which specific depressive symptoms are most strongly associated with nicotine dependence among psychiatric outpatients. To this end, we compared the prevalence and severity of a wide range of clinician-rated depressive symptoms across three groups: (1) patients with no history of nicotine dependence (NND; $n=1015$); (2) patients with past nicotine dependence in full remission for at least 2 months (PND; $n=211$); and (3) patients with current nicotine dependence (CND; $n=342$). Participants both with and without current MDD were included in this sample because previous investigations have demonstrated that even very low levels of depressive symptoms can be associated with difficulty quitting and more persistent nicotine dependence among smokers without current MDD (Leventhal et al., 2008b; Niaura et al., 2001). Differences between NND and PND groups were of interest because of their potential for elucidating affective features that: (a) may be stable traits that increase risk of developing nicotine dependence; or (b) may be protracted effects of nicotine dependence that persist following extended periods of remission. Differences between individuals with CND and PND were of interest in order to identify aspects of depression that: (a) may contribute to difficulty quitting smoking and persistence of nicotine dependence symptoms; or (b) may be transitory effects of nicotine dependence that abate following extended periods of remission.

Based on previous findings, we hypothesized that the groups would differ most on typical-vegetative/melancholic symptoms (psychomotor disturbance, amotivation, fatigue, insomnia, cognitive disturbance, guilt, appetite/weight loss, lack of mood reactivity, anhedonia, distinct quality of mood, mood worse in morning) and dysphoric symptoms (depressed mood, crying, hopelessness, helplessness, worthlessness, suicidal features). We predicted that there would be no group differences on atypical features (interpersonal rejection sensitivity, leaden paralysis, mood reactivity, hyperphagia, hypersomnia). We expected that differences between CND and the other two groups would be the largest because these symptoms have been shown to predict poor cessation outcomes and persistent forms of nicotine dependence (Carton et al., 2002; Doran et al., 2006; Ginsberg et al., 1995; Japuntich et al., 2007; Kassel et al., 2007; Leventhal et al., 2008b; Niaura et al., 2001), suggesting that they may be more pronounced among individuals whose nicotine dependence symptoms have not yet remitted. Because each of these symptoms potentially represents a unique intermediate depressive phenotype (Hasler et al., 2004), our hypotheses were tempered by the possibility that not all of them would associate with nicotine dependence status.

2. Method

2.1. Participants and procedures

Participants were recruited as part of the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project (Zimmerman, 2003; Zimmerman & Mattia, 1999). The MIDAS Project is a large psychiatric assessment study in which patients from the Rhode Island Hospital Department of Psychiatry's outpatient practice are invited to participate in an in-depth face-to-face diagnostic evaluation prior to meeting with their treating clinician (psychiatrist, psychologist, or social worker). Patients are typically referred by primary care physicians and psychotherapists, though data on referral source were not systematically recorded. Not all patients who presented for treatment took part in the study. Rates of agreement for participation were not systematically recorded. Because one of the goals of the MIDAS project is to develop and study the reliability and validity of self-administered questionnaires, patients with significant cognitive limitations were not included; thus, we disproportionately excluded elderly patients. Nonetheless, as previously reported (Zimmerman & Mattia, 1999), patients who did and did not participate in the study were similar in scores on self-administered symptom questionnaires.

Results from 1800 participants who completed this pretreatment evaluation provided the data in the present report. Those who met *DSM-IV* criteria for a current substance use disorder (other than nicotine dependence) were excluded from the sample ($n=211$; 11.8%) because the psychoactive effects of substance misuse influence depressive symptoms (Schuckit et al., 2007), associate with smoking (Grant, Hasin, Chou, Stinson, & Dawson, 2004; Lasser et al., 2000), and may therefore confound associations between nicotine dependence and depressive symptoms. Participants with past substance use and current/past psychiatric disorders were included in order to increase generalizability to psychiatric settings and were analyzed as covariates (see Analysis section). We included patients with and without current MDD because previous studies have shown that depressive symptoms, even at very low levels, predict features linked with more persistent nicotine dependence among individuals without MDD (Leventhal et al., 2008b; Niaura et al., 2001).

Table 1
Demographic characteristics by nicotine dependence status

Demographic characteristics	NND (n=1015)	PND (n=211)	CND (n=352)	F/χ^2	p
Female, %	66.9[a]	54.0[b]	63.9[a]	12.7	.002
Age, M (SD)	37.7 (13.4)[a]	43.5 (11.6)[b]	36.7 (10.8)[a]	21.8	<.0001
Race: white, %	86.5	90.5	86.9	2.5	.28
Marital status, %	–[a]	–[b]	–[c]	28.1	<.0001
Single	31.0	17.1	29.3		
Married/living together	48.2	58.8	43.5		
Divorced/separated	18.5	22.8	26.1		
Widowed	2.3	1.4	1.1		
Level of education, %	–[a]	–[a]	–[b]	45.0	<.0001
Less than high school diploma	9.6	10.0	15.1		
High school graduate	20.1	23.7	32.1		
At least some college	30.1	31.3	29.6		
College degree or higher	40.3	35.1	23.3		

Note. N=1578; NND = no history of nicotine dependence; PND = past nicotine dependence; CND = current nicotine dependence; groups without common superscripts were significantly different (p<.05) in two-group follow up contrasts of that outcome variable.

We categorized the remaining patients based on nicotine dependence status into three groups: NND (n=1015); PND (n=211); and CND (n=352). NND patients did not meet *DSM-IV* criteria for nicotine dependence at any point in their lifetime. CND patients met full *DSM-IV* criteria for current nicotine dependence. PND patients had a history of nicotine dependence but they denied experiencing any nicotine dependence symptoms for at least two months prior to the evaluation, indicating that they were in full remission according *DSM-IV* guidelines. Nicotine withdrawal symptoms typically resolve after 2–4 weeks of abstinence (Hughes, 2007), which suggests that a 2-month remission period was adequate to avoid the potential confound of withdrawal effects among PND patients. No other information on the extent of tobacco use beyond information about *DSM-IV* diagnoses was collected. We excluded patients with nicotine dependence in partial remission from this sample (n=11; 0.6%) because there were too few of them to warrant placing them in their own group and placing them into either the CND or PND categories would increase heterogeneity of those groups. It is possible that differences between CND and PND groups other than remission status might account for differences in depressive symptoms. Therefore, we assessed the number of *DSM-IV* nicotine dependence symptoms met and age of onset of nicotine dependence in the two groups. Neither symptom count (PND: M=3.93, SD=.91; CND: M=3.85, SD=.90) nor age of onset (PND: M=19.54, SD=7.26; CND: M=20.08, SD=8.07) differed significantly between the CND and PND groups, suggesting that these variables did not confound the analyses presented herein. The Rhode Island Hospital institutional review board approved the research protocol, and all participants provided written informed consent following a complete description of the study.

2.2. Assessment

Patients were interviewed using the Structured Clinical Interview for *DSM-IV* (SCID; First, Spitzer, Williams, & Gibbon, 1997) to diagnose current and past psychiatric disorders (including nicotine dependence) based on *DSM-IV* definitions. Regardless of ratings on the depressed mood or anhedonia criterion, all participants were administered the entire SCID current depressive episode module, which rated the presence (vs. absence) of all individual current depressive symptoms that make up MDD diagnoses as well as *DSM-IV* atypical and melancholic features specifiers. Additional depressive symptoms not included in the standard SCID module (amotivation, crying, helplessness, hopelessness, inability to cry) were incorporated into the protocol and rated according to the same framework used for MDD criteria in the SCID (see McGlinchey, Zimmerman, Young, & Chelminski, 2006 for further explanation on the assessment of these symptoms). SCID symptoms were rated as present if they occurred nearly every day for the past two weeks. The SCID depression module was supplemented with questions from the Schedule for Affective Disorders and Schizophrenia (SADS; Endicott & Spitzer, 1978) to assess the severity of symptoms during the week prior to the evaluation (0–5 rating scale). SADS items were embedded within and rated concurrently with the SCID depressive episode module. The SADS contains both symptoms included in the MDD criteria as well as other depressive features (e.g., helplessness, hopelessness, poor insight into depressive illness, objectively appears depressed). For all symptoms, interviewers probed to ensure that the symptoms were not due to substance use, medication, or physical illness. Interrater reliability estimates for each of the SCID- and SADS-rated symptoms were obtained for 48 subjects by multiple diagnostic raters. Kappa estimates for SCID-rated symptoms and polychoric correlation coefficients for SADS-rated symptoms indicated adequate interrater reliability for all symptoms (SCID: average K=.81, range .54–.95; SADS: average r=.90, range .56–1.00). Personality disorders were assessed using the Structured Interview for *DSM-IV* Personality (Pfohl, Blum, & Zimmerman, 1997) for a portion of the sample (n=1000, 63%) as this assessment was incorporated midway into the study. The reliability of psychiatric diagnoses was adequate and has been reported previously (Zimmerman & Mattia, 1999), including interrater Kappa estimates of 1.0 for current MDD and nicotine dependence (Zimmerman, Chelminski, & McDermut, 2002). Diagnostic interviewers were PhD-level psychologists or college graduate research assistants who had undergone extensive training, as described elsewhere (Zimmerman & Mattia, 1999).

2.3. Statistical analyses

The analytic approach involved comparing the NND, PND, and CND groups. Preliminary analyses compared the groups on demographic characteristics and presence vs. absence of lifetime psychiatric diagnoses. The primary analyses compared the groups on current depressive symptoms. For descriptive purposes, groups were also compared on prevalence of current major depressive episodes. A univariate (rather than a multivariate) approach was chosen because this study aimed to evaluate associations between nicotine

Table 2
Diagnostic characteristics by nicotine dependence status

Diagnostic characteristics, %	NND (n=1015)	PND (n=211)	CND (n=352)	F/χ^2	p
Lifetime history					
Major depressive disorder	65.1	64.0	70.5	3.8	.15
Bipolar disorder (I and II)	5.3[a]	8.5[ab]	11.7[b]	16.4	.0003
Dysthymic disorder	9.6[a]	9.5[a]	4.0[b]	11.1	.004
Anxiety disorder	59.1[a]	68.3[b]	74.4[b]	28.7	<.0001
Psychotic disorder	3.5	2.8	2.8	0.4	.80
Eating disorder	12.5	15.2	10.8	2.3	.32
Somatoform disorder	7.1	9.0	8.5	1.37	.50
Impulse control disorder	12.4[a]	16.6[ab]	18.2[b]	8.2	.02
Attention-deficit/disruptive behavior disorder	7.2[a]	15.2[b]	10.8[b]	15.1	.0005
Personality disorder[‡]	25.8[a]	25.1[a]	36.0[b]	9.2	.01
Past alcohol use disorder	27.2[a]	48.8[b]	44.3[b]	58.4	<.0001
Past drug use disorder	12.4[a]	25.9[b]	31.5[c]	80.7	<.0001

Note. N=1578; NND = no history of nicotine dependence; PND = past nicotine dependence; CND = current nicotine dependence; groups without common superscripts were significantly different (p<.05) in two-group follow up contrasts of that outcome variable; [‡]rates based on portion of sample that were evaluated for personality disorders (n=1000).

dependence and individual symptoms, rather than overarching dimensions or classes. Thus, separate models were run for each outcome variable. Initial omnibus tests consisted of three-group ANOVA and Chi-square tests for continuous and categorical outcome variables, respectively (results of these tests are not reported for symptom level analyses due to space limitations). For each outcome variable with significant overall group differences, planned comparisons in the form of pairwise tests comparing each two-group contrast were conducted. In two-group contrasts of depressive symptoms, logistic regression (for dichotomous SCID symptom values; see Table 3) and AN(C)OVA (for continuous SADS symptom values; see Table 4) models were performed both adjusted and unadjusted. Adjusted models included demographic and lifetime psychiatric diagnoses that were significantly different between groups as covariates in order to examine whether relations with nicotine dependence were specific to particular depressive symptoms or explained by demographic factors and psychiatric comorbidity. Because personality disorder data were missing for some participants, the history of any personality disorder variable was coded as a trichotomous categorical variable (present vs. absent vs. missing) when used as a covariate in symptom analyses. Analyses were performed using SAS (SAS Institute Inc., 2003). AN(C)OVA models were conducted using the general linear model (PROC GLM) for unbalanced cell sizes. For preliminary comparisons of demographics and comorbid psychiatric disorders, statistical significance was set at $p<.05$ (2-tailed). For primary analyses of depressive symptoms, significance was set at $p<.01$(2-tailed) because of the large number of tests conducted. This is consistent with previous approaches that used a .01 criterion to decrease the probability of Type I errors associated with multiple comparisons while not severely limiting statistical power (e.g., Hammermeister, Flint, Havens, & Peterson, 2001; Schmitz et al., 2000).

3. Results

Examination of demographic and diagnostic characteristics by group indicated that gender, age, education, marital status, and lifetime history of anxiety, dysthymic, Bipolar I or II, impulse control, attention deficit/disruptive behavior, personality, alcohol use, and drug use disorder significantly differed among the three groups (see Tables 1 and 2). Accordingly, these variables were included as covariates in adjusted two-group comparisons of depressive symptoms.

The prevalence of SCID-rated current depressive episodes and symptoms by group is reported in Table 3. Contrasts of NND and PND

Table 3
Prevalence of current depressive episodes and SCID symptoms by nicotine dependence status

	NND (n=1015)	PND (n=211)	CND (n=352)	Group comparisons					
				PND vs. NND		CND vs. NND		CND vs. PND	
	%	%	%	Unadj-OR[a]	Adj-OR[b]	Unadj-OR[a]	Adj-OR[b]	Unadj-OR[a]	Adj-OR[b]
Major depressive episode	44.1	42.7	57.8	–	–	1.75***	1.98**	1.85**	2.65**
Dysphoric									
Depressed mood	53.1	56.9	66.5	–	–	1.75***	1.53*	–	–
Worthlessness	32.9	36.5	49.2	–	–	1.97***	1.66**	1.68*	–
Thoughts of death	31.6	31.3	41.8	–	–	1.55**	–	–	–
Suicidal ideation, plans, or attempt	16.9	14.2	23.9	–	–	1.55*	–	1.89*	–
Crying	23.5	21.3	32.4	–	–	1.56*	–	1.77*	–
Helplessness	34.5	36.5	48.3	–	–	1.78***	–	1.63*	–
Hopelessness	33.8	28.0	44.3	–	–	1.56**	–	2.05**	1.86*
Typical-vegetative/melancholic									
Anhedonia	44.3	47.4	59.4	–	–	1.83***	1.47*	1.62*	–
Distinct quality of mood	59.2	57.4	57.1	–	–	–	–	–	–
Weight loss	12.1	11.4	19.6	–	–	1.77**	1.69*	–	–
Decreased appetite	25.5	19.9	38.9	–	–	1.86**	1.66**	2.56***	2.38**
Initial insomnia	29.2	22.8	41.2	–	–	1.70***	–	2.38***	1.76*
Middle insomnia	33.8	33.7	43.5	–	–	–	–	–	–
Terminal insomnia	18.8	22.8	25.6	–	–	–	–	–	–
Concentration difficulty	50.8	54.5	65.1	–	–	1.80***	–	–	–
Indecision	28.9	32.2	41.5	–	–	1.75***	–	–	–
Unreactive mood	13.7	11.9	18.5	–	–	–	–	–	–
Mood worse in AM	18.0	15.2	16.2	–	–	–	–	–	–
Psychomotor agitation	19.5	20.9	34.7	–	–	2.19***	1.60**	2.01**	–
Psychomotor retardation	14.1	15.6	24.2	–	–	1.94***	1.62*	–	–
Fatigue	57.7	60.2	70.5	–	–	1.75***	1.68**	–	–
Guilt	32.5	33.7	41.8	–	–	1.49*	–	–	–
Amotivation	56.8	60.7	68.8	–	–	1.68***	–	–	–
Atypical									
Weight gain	11.6	11.9	10.8	–	–	–	–	–	–
Increased appetite	14.3	12.8	14.8	–	–	–	–	–	–
Leaden paralysis	15.7	20.9	27.6	–	–	2.05***	–	–	–
Rejection sensitivity	29.3	31.3	33.2	–	–	–	–	–	–
Hypersomnia	13.0	10.0	14.5	–	–	–	–	–	–
Other									
Mood worse in PM	20.0	20.9	21.6	–	–	–	–	–	–
Inability to cry	6.3	7.1	7.7	–	–	–	–	–	–

Note. N=1578; NND = no history of nicotine dependence; PND = past nicotine dependence; CND = current nicotine dependence; SCID = Structured Clinical Interview for *DSM-IV*; OR = Odds Ratio; nonsignificant findings ($ps \geq .01$) not displayed; 95% Confidence Intervals around the ORs for the results of group comparisons are available upon request to the first author (AML).

[a] Unadjusted.

[b] Adjusted for gender, age, education, marital status, lifetime history of anxiety disorder, dysthymia, Bipolar I or II disorder, impulse control disorder, attention deficit/disruptive behavior disorder, personality disorder, alcohol use disorder, and drug use disorder.

* $p<.01$.

** $p<.001$.

*** $p<.0001$.

groups indicated no differences in the prevalence of current MDD or other symptoms. Comparisons of NND and CND groups indicated that patients with CND endorsed higher rates of current MDD and various SCID depressive symptoms (see Table 3). Some of these differences fell below significance levels after adjusting for demographic and psychiatric characteristics. Differences on depressed mood, anhedonia, weight loss, decreased appetite, agitation, retardation, fatigue, and worthlessness were significant in both unadjusted and adjusted models. Some symptom differences between CND and PND patients were evident with CND exhibiting higher endorsement rates, but these differences were generally less consistent than the CND–NND contrasts and many comparisons fell below significance after adjusting for covariates (see Table 3). Decreased appetite, initial insomnia, and hopelessness were the only symptoms that were significantly different between CND and PND patients after adjusting for covariates.

The mean severity of SADS-rated current depressive symptoms by group is reported in Table 4. Comparisons of NND and PND groups showed no differences. Contrasts of CND and NND groups showed that patients with CND evidenced greater severity of most SADS depressive symptoms (see Table 4). Some of these differences fell below significance when adjusting for demographic and psychiatric characteristics. Differences on depressed mood, anhedonia, decreased appetite, weight loss, insomnia, agitation, retardation, fatigue, and appearing depressed were significant in both unadjusted and adjusted models. There were differences between CND and PND patients on several SADS symptoms with CND patients exhibiting greater severity, but these findings were generally less consistent than the CND–NND contrasts and sometimes fell below significance after adjusting for covariates (see Table 4). In the adjusted models, CND patients evidenced more severe decreased appetite, weight loss, insomnia, and agitation, as compared to PND patients.

Given that patients with CND had a higher prevalence of current MDD, it is possible that this relationship might explain some of the associations between nicotine dependence and depressive symptoms. Therefore, additional analyses were conducted that evaluated whether current MDD status moderated the relationship between nicotine dependence and depressive symptoms. No significant moderation effects were found for any SCID or SADS symptom, which suggests that the associations were not dependent on current MDD status.

4. Discussion

The present study found that specific depressive symptoms were uniquely associated with nicotine dependence in psychiatric outpatients and that these associations varied as a function of remission status. CND patients demonstrated a qualitatively unique pattern of depressive symptomatology characterized by elevations on particular symptoms but not others. The symptomatic profiles of PND and NND patients were virtually indistinguishable.

Concordant with hypotheses, participants with CND exhibited greater prevalence and severity of several dysphoric and typical-vegetative/melancholic symptoms as compared to participants with NND (and PND to a lesser extent). These findings are generally consistent with previous data demonstrating that individuals who are current smokers and have difficulty quitting exhibit higher levels of these symptoms (Carton et al., 2002; Cinciripini et al., 2003; Doran et al., 2006; Ginsberg et al., 1995; Japuntich et al., 2007; Kassel et al., 2007; Leventhal et al., 2008a,b; Niaura et al., 2001). However, this study extends past findings by examining relations at the symptom-level and delineating whether associations are accounted for demographic factors and psychiatric comorbidity. Results from models adjusted for relevant demographic variables and comorbid conditions revealed significantly higher depressed mood, anhedonia, appetite/weight loss, psychomotor disturbance, fatigue, and insomnia in CND patients. These findings suggest a specific link between these particular depressive symptoms and CND. For other symptoms

Table 4
Severity of SADS depressive symptoms (range 0–5) by nicotine dependence status

	NND (n=1015)	PND (n=211)	CND (n=352)	Group comparisons					
				PND vs. NND		CND vs. NND		CND vs. PND	
	M (SD)	M (SD)	M (SD)	Unadj-β[b]	Adj-β[c]	Unadj-β[b]	Adj-β[c]	Unadj-β[b]	Adj-β[c]
Dysphoric									
Depressed mood	2.6 (1.4)	2.6 (1.3)	3.0 (1.4)	–	–	.33***	.19**	.32**	–
Worthlessness	1.7 (1.6)	1.9 (1.5)	2.2 (1.6)	–	–	.29***	–	–	–
Hopelessness	1.7 (1.4)	1.7 (1.3)	2.0 (1.4)	–	–	.21**	–	.25*	–
Suicidal features	0.9 (1.3)	0.8 (1.2)	1.2 (1.4)	–	–	.24**	–	.32**	–
Typical-vegetative/melancholic									
Anhedonia	2.4 (2.0)	2.6 (1.9)	3.1 (1.9)	–	–	.33***	.21**	.25*	–
Decreased appetite	1.1 (1.5)	0.9 (1.4)	1.5 (1.7)	–	–	.32***	.25***	.44***	.37***
Weight loss	0.6 (1.2)	0.6 (1.2)	0.9 (1.4)	–	–	.22**	.18*	.28*	.24*
Psychomotor agitation	0.9 (1.2)	1.0 (1.2)	1.5 (1.4)	–	–	.40***	.24**	.35***	.28*
Psychomotor retardation	0.7 (1.1)	0.8 (1.2)	1.0 (1.3)	–	–	.24***	.16*	–	–
Fatigue	2.4 (1.5)	2.5 (1.5)	2.9 (1.5)	–	–	.29***	.21**	.28*	–
Guilt	1.5 (1.4)	1.6 (1.3)	1.8 (1.4)	–	–	.21**	–	–	–
Concentration problems	2.2 (1.6)	2.4 (1.5)	2.7 (1.5)	–	–	.28***	–	–	–
Indecision	1.2 (1.5)	1.4 (1.5)	1.6 (1.6)	–	–	.27***	–	–	–
Insomnia	1.9 (1.6)	1.9 (1.6)	2.3 (1.6)	–	–	.29***	.20*	.30**	.25*
Atypical									
Hypersomnia	0.7 (1.3)	0.6 (1.3)	0.7 (1.4)	–	–	–	–	–	–
Increased appetite	0.6 (1.3)	0.5 (1.3)	0.6 (1.3)	–	–	–	–	–	–
Weight gain	0.6 (1.3)	0.7 (1.4)	0.6 (1.4)	–	–	–	–	–	–
Other									
Poor insight[a]	0.3 (0.6)	0.3 (0.6)	0.4 (0.6)	–	–	–	–	–	–
Appears depressed[a]	1.6 (1.3)	1.6 (1.2)	1.9 (1.4)	–	–	.26***	.19*	.27*	–

Note. N=1578; NND = no history of nicotine dependence; PND = past nicotine dependence; CND = current nicotine dependence; SADS = Schedule for Affective Disorders and Schizophrenia; β = standardized parameter estimate; nonsignificant findings not displayed ($ps \geq .01$).

[a]N=1576 to 1577 due to missing data for these symptoms; [b]Unadjusted; [c]Adjusted for gender, age, education, marital status, lifetime history of anxiety disorder, dysthymia, Bipolar I or II disorder, impulse control disorder, attention deficit/disruptive behavior disorder, personality disorder, alcohol use disorder, and drug use disorder.

* $p<.01$.
** $p<.001$.
*** $p<.0001$.

(suicidality, crying, helplessness, amotivation, cognitive disturbance, guilt), unadjusted analyses showed significant associations with CND, whereas adjusted analyses fell below significance. This indicates that for these particular symptoms, the predictive value of nicotine dependence status over and above demographic characteristics and comorbid conditions was not statistically significant. Other melancholic symptoms (distinct quality of mood, guilt, mood worse in the morning) were not associated with nicotine dependence. Thus, the overall pattern of findings indicates that some, but not all, typical/melancholic and dysphoric symptoms were uniquely associated with nicotine dependence.

It was also hypothesized that atypical symptoms would not be associated with nicotine dependence. Unexpectedly, there was evidence that CND patients had higher rates of leaden paralysis than NND patients. The phenomenological overlap between this symptom and psychomotor retardation could account for this finding. Indeed, secondary analyses indicated a strong association between these two symptoms in this dataset ($p<.0001$). The other atypical symptoms were not associated with nicotine dependence status. In light of these findings and those of past research (Leventhal et al., 2008a,b; Pomerleau et al., 2003), it appears that symptoms which are exclusive to the atypical spectrum are not associated with nicotine dependence.

Several explanations could account for the overall pattern of findings. One is that associations were driven by group differences in reporting, such that those with CND were most likely to over-report their symptoms. If this was the case, one might expect that all symptoms would have higher rates of endorsement. However, differences were specific to particular symptoms, generally concordant across SCID and SADS ratings, evident on ratings that rely on behavioral observation (e.g., psychomotor disturbance, appears depressed), and consistently absent on certain symptoms (e.g., reversed vegetative features). It is also possible that PND and CND differences were due to nicotine dependence characteristics other than remission status. However, no group differences were found on number of dependence symptoms and age of onset. Another explanation is that differences in current MDD could account for the pattern of results and could be a more parsimonious explanation of the findings. Although current MDD was more prevalent in the CND group, it did not moderate the relationships between nicotine dependence and depressive symptoms, suggesting that regardless of current MDD status, CND patients exhibited a unique symptomatic profile. Finally, differences in depressive symptoms could be due to greater nicotine withdrawal in the CND group. While this is possible, interviewers in this study provided detailed queries of all depressive symptoms to elucidate whether they are central to the depressive syndrome or merely epiphenomena.

The pattern of differences between the three groups is informative regarding the nature of the nicotine dependence-depression relationship. Given the higher symptom endorsement in CND and the absence of differences between PND and NND groups, this pattern is fairly consistent with the notion that these particular symptoms may contribute to difficulty quitting smoking or may represent transitory effects of nicotine dependence that abate following extended periods of remission. By contrast, these findings are not consistent with the explanation that these symptoms are stable factors that precede onset and follow offset or are protracted effects of nicotine dependence.

The limitations of this study should be noted. First, the design was cross-sectional and correlational, thus any conclusions about the temporal and causal nature of these associations are speculative. Second, comparisons between CND and PND included fewer subjects as compared to the contrasts involving NND groups, which may have limited the power to detect effects in these particular comparisons. Third, although including patients with additional comorbidity enhanced the generalizablity of this sample to the psychiatric outpatient population, there were demographic and diagnostic differences between groups. PND patients were older and had a lower proportion of females and CND patients met criteria for more comorbid psychiatric disorders than the other two groups. Even though adjusted analyses statistically controlled for these influences, it is still possible that differences other than nicotine dependence status could account for some of associations that were found. Fourth, although alpha-levels were adjusted to .01, the large number of comparisons increased probability of Type-I error. Accordingly, replication studies may be warranted. Fifth, concordant with *DSM-IV*, the absence of any nicotine dependence symptoms was used to define remission. It is therefore possible that some patients in the PND group who qualified for remission might have made significant smoking reductions but were not completely abstinent from tobacco. Thus, it would have been preferable to use additional self-report and biochemical measures of tobacco use and exposure. Accordingly, future studies of the depression-nicotine dependence link should utilize biochemical and self-report measures of tobacco use. Additionally, no quantitative measure of dependence was used. It would have been informative to compare the results across multiple measures of nicotine dependence, given that different measures have been shown to assess different aspects of the dependence process (Moolchan et al., 2002). Finally, treatment history was not assessed in this sample. Thus, it is possible that there were differences in previous behavioral or pharmacological treatment among the groups that could have influenced expression of depressive symptoms.

This study also had several offsetting strengths. The assessment was comprehensive and rigorous in that: (a) a wide range of symptomatology was examined, (b) symptoms were evaluated at both taxonic (SCID-based presence vs. absence ratings) and dimensional levels (SADS severity ratings), (c) clinician ratings were used to prevent measurement biases associated with self-report methods, (d) symptoms were analyzed at the symptom-level, rather than the subtype or subscale level, and (e) the diagnostic protocol was extensive and reliable. In addition, the inclusion of patients in a psychiatric treatment setting extends previous findings to individuals with disproportionately high smoking rates and low cessation rates (Grant et al., 2004; Hughes et al., 1986; Lasser et al., 2000). Thus, the results of this study are relevant to understanding nicotine dependence in an especially high-risk group.

The present findings have several implications for future research of depression and nicotine dependence. They highlight the importance of considering narrower depressive phenotypes when examining depression-nicotine dependence comorbidity and suggest that assessment solely at the clinical diagnostic phenotype level (e.g., presence vs. absence of MDD, severity of overall depressive symptoms) may overlook important clinical heterogeneity. In addition, these findings point towards future research of the common correlates of typical-vegetative/melancholic and dysphoric depressive symptoms and nicotine dependence as potential factors that underlie depression-nicotine dependence comorbidity. For example, nicotine dependence and some of the melancholic symptoms it was associated with in this study have both been linked with dopaminergic and hypothalamic–pituitary–adrenocortical axis dysfunction (Balfour, 2002; Mendelson, Sholar, Goletiani, Siegel, & Mello, 2005; Pizzagalli et al., 2004; Rush, Giles, Schlesser, & Orsulak, 1997). Thus, these biological factors could be fruitful targets for future research on the etiological sources of depression-nicotine dependence comorbidity.

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