Are Tobacco Dependence and Withdrawal Related Amongst Heavy Smokers? Relevance to Conceptualizations of Dependence

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Measured tobacco dependence is typically only modestly related to tobacco withdrawal severity among regular smokers making a quit attempt. The weak association between dependence and withdrawal is notable because it conflicts with core theories of dependence and because both measures predict cessation outcomes, suggesting they both index a common dependence construct. This study used data from a smoking cessation comparative effectiveness trial ($N = 1504$) to characterize relations of tobacco dependence with craving and negative affect withdrawal symptoms using multiple dependence measures and analytic methods to detect both additive and interactive effects and to determine whether withdrawal meaningfully mediates the influence of dependence on smoking cessation. We conclude: (a) Although univariate analyses suggest dependence and withdrawal measures are only modestly interrelated, more powerful analytic techniques show they are, in fact, meaningfully related and their shared variance is associated with cessation likelihood; (b) there are clear differences between craving and negative affective withdrawal symptoms, with the former more related to smoking heaviness and the latter related to trait measures of negative affect; moreover, craving more strongly mediates dependence effects on cessation; and (c) both craving and negative affect withdrawal symptoms are strongly related to a pattern of regular smoking that is sensitive to the passage of time and powerfully affected by smoking cues. These findings support models that accord an important role for associative processes and withdrawal symptoms, especially craving, in drug dependence. The findings also support the use of withdrawal variables as criteria for the evaluation of dependence measures.

Keywords: tobacco dependence, withdrawal, smoking cessation, craving, negative affect

Regular, daily smokers differ from one another markedly in measured nicotine dependence, and in its correlates. For instance, only about half of regular smokers earn diagnoses of dependence

using *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.) *DSM–IV,* American Psychiatric Association, 1994 criteria (Breslau, Johnson, Hiripi, & Kessler, 2001). In addition, regular smokers clearly vary in their ability to stop smoking, which, in turn, appears to reflect the influence of dependence (e.g., Baker et al., 2007). The link between dependence and smoking outcomes leads to the plausible assertion that highly dependent smokers are at risk for relapse because they are prone to experiencing severe postquit withdrawal symptoms. Yet, in most research, measures of regular smokers' tobacco dependence is only modestly related to the severity of their tobacco withdrawal syndrome (e.g., r's $\leq$ .30; Payne, Smith, McCracken, McSherry, & Antony, 1994; Piper, McCarthy, & Baker, 2006; Ríos-Bedoya, Snedecor, Pomerleau, & Pomerleau, 2008; Shiffman, Waters, & Hickcox, 2004). For instance, a recent study using multiple measures of dependence found no significant relations between dependence on the one hand and craving and negative-affect withdrawal symptoms on the other hand (Robinson et al., 2011). The examination of the dependence–withdrawal relation in regular smokers may restrict the range of withdrawal and dependence variables versus what would be observed in broader populations of smokers (e.g., Donny, Griffin, Shiffman, & Sayette, 2008), and this may limit levels of association. However, there is reason to believe that measures of these two constructs (dependence and withdrawal) *should* be substantially related even among regular smokers: for example, there is considerable range in both sorts of measures among regular smokers (Tobacco Use . . . Panel, 2000; Piasecki et al., 2000; Shiffman

et al., 2006), and both dependence and withdrawal measures significantly predict smoking cessation outcomes (Baker et al., 2007; Piasecki, Jorenby, Smith, Fiore, & Baker, 2003), suggesting that both index a common dependence construct. Moreover, some core theories of addiction assert that dependence influences both withdrawal and relapse, with withdrawal being a sine qua non of dependence and a driving force behind relapse (Edwards & Gross, 1976; Siegel, 1983; Solomon & Corbit, 1974; Wikler, 1980).

Relations between tobacco dependence and withdrawal severity among regular smokers may be modest for multiple reasons. First, dependence appears to be multifactorial (Piasecki et al., 2000; Piper et al., 2004; Shiffman et al., 2004), and it may be that stronger relations would be observed with some dependence subfactors than with others. Withdrawal also seems to be multifactorial. Recent animal research points to both affective and nonaffective, or somatic, types of withdrawal symptoms, which differ from one another in both mechanism and motivational significance (Hiroi & Scott, 2009; Jackson, Martin, Changeux, & Damaj, 2008). Research with humans also shows evidence of distinct withdrawal subtypes. There is evidence that affective withdrawal symptoms tend to be more highly associated with one another than they are with craving, and that these two symptom types (affective symptoms and craving) have different prevalences and time courses or profiles following abstinence (e.g., Dawkins, Powell, Pickering, Powell, & West, 2009; Hughes, 2007; Sayette, Martin, Hull, Wertz, & Perrott, 2003; also, Smith et al., 2008). Other research shows that affective symptoms and craving differ in variability and account for orthogonal proportions of variance in cessation outcomes (Piper, Cook, Schlam, Jorenby, & Baker, 2011; also see Berkman, Dickenson, Falk, & Lieberman, 2011). Finally, factor analyses reveal distinct craving and negative affect factors (Piasecki et al., 2000). So, although negative-affect and craving withdrawal symptoms are related to one another (e.g., Baker, Piper, McCarthy, Majeskie, & Fiore, 2004; Hendricks, Ditre, Drobes, & Brandon, 2006), there is evidence that they confer different information about withdrawal severity, and have different relations with other measures.[1] Their meaningful association reflects the fact that they share some causal influences in common (e.g., tobacco deprivation; Hughes, 2007), and that negative affect per se is causally determinant of craving (Baker et al., 2004). However, it also seems clear that each can reflect different causal influences (e.g., immediate availability of tobacco may elicit craving, but not necessarily negative affect; Carter & Tiffany, 2001; Gloria et al., 2009). Given the multifactorial natures of dependence and withdrawal, it may be that overarching composite measures may obscure or underestimate their potential for association. The reported research addressed this potential limitation by using multidimensional measures of both dependence and withdrawal and by using real-time assessment of withdrawal symptoms (e.g., Stone et al., 1998).

The current study uses data from a smoking cessation randomized clinical trial (RCT) to characterize the relations between tobacco dependence and tobacco withdrawal symptoms. We selected measures and analytic methods to favor the detection of meaningful relations between these constructs. The analytic strategies used were based on hypotheses about why dependence and withdrawal measures had not been more strongly interrelated in past research. Analyses addressed: (a) How strongly multiple dependence and withdrawal measures were related to one another,

and whether the magnitudes of these relations differed meaningfully across the different types of measures. These analyses, therefore, addressed the hypothesis that prior research showed modest interrelations because it did not adequately canvass measures within the dependence and withdrawal domains; (b) Whether conjoint use of multiple dependence measures would significantly improve the prediction of withdrawal symptoms, that is, did the various types of dependence measures exert additive, orthogonal effects in their relations with withdrawal symptoms? (c) Whether statistically controlling for nondependence factors (e.g., psychopathology, environmental factors) would improve the prediction of withdrawal scores by dependence measures. These analyses tested the notion that withdrawal is influenced by diverse factors, and that statistically isolating the variance that reflects nondependence influences, would more sensitively reflect dependence–withdrawal relations; (d) Whether smokers differ substantially from one another in terms of *which* dependence measures show the strongest relations with withdrawal. These analyses tested the notion that there are subpopulations of smokers and that the magnitude of dependence–withdrawal relations can be most sensitively determined if analyses reflect these subpopulations. Lastly, (e) whether the relations observed between dependence and withdrawal are *clinically* meaningful; that is, whether withdrawal mediates the influence of dependence on cessation outcome.

Although numerous dependence measures were used in this research, substantive considerations and empiric evidence suggest a general classification strategy for grouping such instruments. Dependence instruments can generally be considered as omnibus instruments that reflect diverse dependence facets or motives, e.g., the Fagerstrom Test of Nicotine Dependence (FTND), the Tobacco Dependence Screener (TDS), the Nicotine Dependence Syndrome Scale (NDSS), and the Wisconsin Inventory of Smoking Dependence Motives (WISDM), or as more specific subscales that reflect relatively discrete dependence components. The more discrete scales can be interpreted both with regard to their specific content domains (e.g., relatively pure measures of smoking heaviness, tolerance, specific dependence motives) and with regard to two general, overarching factors (Piasecki, Piper, & Baker, 2010a, 2010b; Piasecki, Piper, Baker, & Hunt-Carter, 2011; Piper, Bolt, et al., 2008). The first of these general factors describes a pattern of smoking that is heavy, automatic, and characterized by a sense of loss of control. The second factor captures smoking motives that involve the instrumental use of smoking: For example, smoking to reduce distress, enhance pleasure, and improve cognition. This latter type of dependence motive might be conceived of as *strategic* rather than automatic. The WISDM subscales tapping the first factor have been labeled the primary dependence motives (PDM), and include the automaticity, tolerance, craving, and loss of control subscales. The subscales tapping the second factor have been labeled the secondary dependence motives (SDM) and include all other WISDM subscales, for example, smoking for negative reinforcement, positive reinforcement, cognitive enhance-

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[1] We did not consider other withdrawal symptoms for inclusion because such symptoms as hunger tend to be less important motivationally (e.g., they are not as strongly predictive of cessation outcomes or nicotine self-administration) and tend to cohere with one another less meaningfully (e.g., Piasecki et al., 2000).

ment, and so on. Research and content analysis suggest that some of the subscales from the NDSS (another multidimensional dependence instrument) also assess heavy smoking that is invariant across time and place. In particular, the NDSS drive and continuity subscales are associated with high cotinine levels (reflecting heavy self-administration) and with difficulty abstaining from smoking (Shiffman et al., 2004). The NDSS drive subscale focuses on the need to smoke fairly continuously over time, and the NDSS continuity scale focuses on highly regular, invariant smoking over time and place. The characterizations of dependence afforded by these different measures (i.e., heavy, automatic smoking vs. instrumental smoking) will be used in this research to identify dependence features that are, and are not, associated with withdrawal severity.

Together, the analyses conducted for this research test core assumptions of dependence models: That dependence and withdrawal are meaningfully related to one another and account for clinically important outcomes such as cessation ability. As noted, most models of dependence hold that withdrawal is a central manifestation of dependence (e.g., Ahmed & Koob, 2005). If, under highly favorable conditions, relations are modest or negligible in regular smokers, this finding would encourage new thinking about why indices of these theoretically linked constructs do not cohere more strongly (e.g., because withdrawal develops early over the course of nicotine use, and does not reflect accurately higher levels of dependence or tobacco use: e.g., Dierker & Mermelstein, 2010). Further, such results could support dependence models that do not accord an important role for withdrawal distress in drug motivation (e.g., incentive models; Robinson & Berridge, 1993).

Method

Procedure

Participants were recruited via TV, radio, and newspaper advertisements, community flyers, and earned media (e.g., radio and TV interviews, press releases) in the greater Madison and Milwaukee, WI areas. Primary inclusion criteria included: smoking at least 10 cigarettes per day for the past 6 months, and being motivated to quit smoking. Exclusion criteria included: certain medications (including monoamine oxidase inhibitors, bupropion, lithium, anticonvulsants, and antipsychotics); any history of psychosis, bipolar disorder, or an eating disorder; consuming six or more alcoholic beverages daily 6 or 7 days a week; pregnancy or breast-feeding; and a serious health condition that would preclude use of study medications or adversely affect study participation. Characteristics of the sample ($N = 1504$) in prevalence (%) and means (SD) were: female $n = 876$ (58%), married $n = 667$ (44.5%), employed for wages $n = 1,020$ (68%), completed only a high school education $n = 353$ (24%), White $n = 1,258$ (83%), Black $n = 204$ (14%), age $= 44.7$ (11) years, number of previous quit attempts $= 5.7$ (9.7), FTND total $= 5.4$ (2.1), cigarettes smoked/day $= 21.4$ (8.9), and baseline carbon monoxide (CO) $= 25.8$ ppm (12.5). This study was approved by the University of Wisconsin-Madison Health Sciences Institutional Review Board.

Eligible participants provided written informed consent and then completed several baseline assessments including a medical history screening, vital signs measurements, a carbon monoxide

breath test and demographic, smoking history and tobacco dependence questionnaires. Participants were randomized to one of six treatment conditions: Bupropion SR ($n = 264$); Nicotine lozenge ($n = 260$); Nicotine patch ($n = 262$); Nicotine patch + Nicotine lozenge ($n = 267$); Bupropion SR + Nicotine lozenge ($n = 262$) or Placebo (consisting of five placebo conditions that matched the five active conditions; $n = 189$). All medications were provided for 8 weeks postquit except the nicotine lozenge, which was provided for 12 weeks postquit (consistent with prescribing instructions). Randomization was conducted in a double-blind fashion using a randomization scheme, with blocking on gender and race (White vs. non-White). All participants received six individual, evidence-based counseling sessions (3 and 1 week before the quit day, on the quit day, and 1, 2, and 4 weeks after the quit day, each lasting 10–20 minutes) designed to provide social support and training in problem-solving and coping skills (Fiore et al., 2008). Bachelor-level case managers provided manualized counseling and were supervised by a licensed clinical psychologist.

Measures

At baseline, which typically occurred within 2–3 weeks of the quit attempt, participants completed a tobacco history questionnaire that assessed gender, ethnicity, age, marital status, education level, employment, and smoking history features such as number of cigarettes smoked per day, age at smoking initiation, residing with other smokers, and number of prior quit attempts. Participants also completed multiple tobacco dependence questionnaires including the FTND (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991), the NDSS (Shiffman et al., 2004), the WISDM (Piper et al., 2004), and the Tobacco Dependence Screener (TDS; Kawakami, Takatsuka, Inaba, & Shimizu, 1999). Nondependence measures included the Minnesota Personality Questionnaire (MPQ; Patrick, Curtin, & Tellegen, 2002), the Positive and Negative Affect Scale (negative affect items: NPANAS; (Watson, Clark, & Tellegen, 1988), and the Social Readjustment Rating Scale (Holmes & Rahe, 1967).

The FTND. This 7-item scale is the most frequently used measure of tobacco dependence. It has only modest internal consistency (α's $= .56–.70$; Piper et al., 2006), but is a good predictor of biomarkers of smoking heaviness and the likelihood of returning to smoking following a quit attempt (Bolt et al., 2009; Heatherton et al., 1991). Two FTND items (1 and 4, which assess time to initiate smoking the first cigarette of the day and number of cigarettes smoked/day) have been shown to be particularly predictive of smoking heaviness and cessation success (Baker et al., 2007; Bolt et al., 2009; Heatherton, Kozlowski, Frecker, Rickert, & Robinson, 1989).

The NDSS. The NDSS (Shiffman et al., 2004) is a 23-item self-report measure with five subscales: tolerance, drive, stereotypy, continuity, and priority. The internal consistencies of the subscales range from fair to good (.55–.84; Piper et al., 2006; Shiffman et al., 2004). The NDSS correlates well with other measures of tobacco dependence and with measures of smoking heaviness and relapse vulnerability (e.g., Piper, McCarthy et al., 2008; Shiffman & Sayette, 2005; Shiffman et al., 2004).

The WISDM-68. The WISDM (Piper et al., 2004) is a 68-item measure that assesses 13 theoretically derived motivational domains thought to contribute to tobacco dependence: af-

filiative attachment, automaticity, behavioral choice/ melioration, cognitive enhancement, craving, cue exposure/associative processes, loss of control, negative reinforcement, positive reinforcement, social and environmental goads, taste and sensory properties, tolerance, and weight control. Subscales have good-to-high internal consistence (α's = .80−.96). Most subscales correlate significantly with other measures of tobacco dependence and with measures of smoking heaviness, but show variability in such relations given their multidimensionality. Variance in the overall WISDM score reflects the influence of two major factors labeled as PDM and SDM (see Piasecki, Piper, Baker, & Hunter–Carter, 2011). The PDM comprises the automaticity, craving, loss of control, and tolerance subscales, while the SDM comprises the remaining subscales. The former are especially highly related to core dependence features (smoking heaviness, other valid dependence scales, laboratory self-administration of nicotine, genetic risk, and relapse likelihood). The SDM appear to be more related to severity of tobacco withdrawal symptoms (Piasecki et al., 2010a). Associations with other variables are often clarified when these two scales have their shared variance statistically controlled (Piasecki et al., 2010a; Piper, Bolt, et al., 2008).

The TDS. This 10-item self-report measure of tobacco dependence was designed to assess International Classification of Diseases (10th revision; ICD-10, World Health Organization, 2010), *DSM–III–R* (3rd ed., revised; APA, 1987), and *DSM–IV* (APA, 1994) symptoms of dependence (Kawakami et al., 1999). It has shown good internal consistency (αs ranged from .76 to .81 across three studies) and is significantly correlated with the number of cigarettes smoked per day, years smoking, and carbon monoxide levels.

Multidimensional Personality Questionnaire—Brief Form (MPQ-BF). The MPQ-BF assesses three personality dimensions: positive emotionality, negative emotionality, and constraint (i.e., lower impulsiveness, risk taking, and rebelliousness). The MPQ-BF has demonstrated excellent internal consistency, stability, factorial validity, convergent and discriminant validity, and correspondence with the extended version of the MPQ (Patrick et al., 2002; Tellegen, 1982). Based on substantive factors, only the negative emotionality and the constraint scales were used in analyses.

Positive and Negative Affect Scale (PANAS). The negative affect items from the PANAS were used to assess past 24-hr negative affect.

Social Readjustment Rating Scale. Participants rated whether or not 43 different stressors had occurred over the past year (Holmes & Rahe, 1967).

Withdrawal symptom reports. Participants completed real-time (ecological momentary assessment: EMA) reports four times a day (just after waking, prior to going to bed and at two other random times; all prompts were separated by at least an hour) for up to 2 weeks prequit and 2 weeks postquit. Data analyzed in this research used reports over the 10 days immediately postquit. EMA reports asked participants to rate how they felt within the last 15 minutes in terms of withdrawal symptoms (negative affect, craving, hunger, and difficulty concentrating) using items from the Wisconsin Smoking Withdrawal Scale (WSWS; Welsch et al., 1999), scored on a 10-point scale. Participants were trained on how to interpret and respond appropriately to EMA items. The craving items were: "Bothered by desire to smoke a cigarette," and "Urge

to smoke." The negative affect withdrawal items were: "Tense or anxious," "Impatient," "Bothered by negative moods such as anger, frustration, and irritability," "Irritable or easily angered," "Sad or depressed " and " Hopeless or discouraged." For the craving measure, $M = 4.14$ ($SD = 2.67$) with a range of 10. For the negative affect measure, $M = 1.55$ ($SD = 1.48$) with a range of 9.17, and the two measures were intercorrelated at .51.

Data Analysis

Zero-order correlations among the diverse dependence scales were computed. A broad range of correlation magnitudes would allow the various measures to yield additive effects with regard to the prediction of withdrawal. The dependence scales were then correlated with the two types of withdrawal symptoms (craving and negative affect). Mean postquit withdrawal craving and mean negative affect scores derived from the EMA reports were selected as the withdrawal symptom variables because of evidence that they reflect different withdrawal factors and share distinct relations with dependence measures (e.g., Piasecki et al., 2000; Piper, Loh, Smith, Japuntich, & Baker, 2011). Symptom *means,* rather than some other symptom profile dimension such as trajectory (Piasecki et al., 2003), were used since it seemed conceptually appropriate to use a dimension that reflects the overall severity of symptoms across relevant time periods.[2] As in other analyses in this work, treatment condition (with categorical coding for placebo, monotherapy, and combination therapy) was used as a covariate since treatment could have affected withdrawal severity, independent of dependence level.

Because of evidence that the WISDM-68 PDM and SDM measures capture two distinct tobacco dependence factors, the two withdrawal indices (craving and negative affect) were regressed on both PDM and SDM (Piasecki et al., 2010a; Piper, Bolt, et al., 2008). In addition, multiple regression analyses were conducted in which the craving and negative affect means were regressed on PDM and SDM scores residualized for one another, with treatment condition used as a covariate. As noted, such residualizing clarifies the relations of PDM and SDM with other variables (Piasecki et al., 2010a, 2010b; Piper, Bolt, et al., 2008). Finally, because the relations of PDM have been attributed to their ability to index smoking heaviness, we assessed the relation between withdrawal (craving and negative affect) and reported cigarettes smoked per day to determine if the relation of PDM with withdrawal could be accounted for by smoking heaviness per se.

Next, best fitting models for both craving and negative affect withdrawal symptoms were built (Hosmer & Lemeshow, 2000). These analyses were designed to determine if dependence–withdrawal relations would be strengthened when sources of variation in withdrawal scores other than dependence were statistically controlled. These models also tested the notion that multiple, different dependence measures would exert additive effects in the prediction of withdrawal, consistent with the multifactorial nature of dependence. In addition to specific dependence measures (as

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[2] Examination of profile components such as symptom trajectory or variability did not enhance relations with dependence, nor did they produce meaningful additive effects. Postquit scores were not partialled for prequit variance since such scores could remove meaningful withdrawal-related variance (Hendricks et al, 2006).

well as global measures of dependence such as the FTND, TDS, and NDSS and WISDM total scores), candidate variables in these models included environmental factors and nondependence person factors that might also predict withdrawal symptom levels, for example, recent stressors, presence of smokers and smoking cues, amount of smoking restrictions in the person's daily life, age, gender, treatment, and neuroticism. These variables were added to determine if controlling for error variance in the withdrawal scores might clarify and strengthen predictive relations with dependence measures. Model-building methods involved inspection of distributional properties of the variables, initial selection of predictors based upon substantive and empirical grounds (univariate p values < .25), systematic, stepwise-forward model building with backward deletion, examination of collinearity, and tests of all two-way interactions between treatment and dependence variables.[3]

Because relations between dependence and withdrawal could vary across subpopulations of smokers, regression-tree models were tested in which both dependence measures and theoretically relevant covariates (e.g., recent stressors, smoking restrictions, age, treatment, gender) were used in models to predict withdrawal. This was done because regression-tree models are less dependent upon model specification than are regression strategies. For example, if a linear regression model is assumed and the true model is nonlinear, each coefficient in the linear regression model represents an average slope, at best. The regression-tree model, on the other hand, quantifies the overall prediction power of the variable without any prior assumptions about the exact form of the model, because the complexity of the model automatically adapts itself to the information content and the complexity of the data (e.g., by identifying the optimal cut-off scores for continuous measures; Loh, 2002; Piper, Loh, et al., 2011).[4] These features make regression-tree modeling an appropriate strategy, given that the goal is to optimize dependence–withdrawal associations. As in the model-building analyses, individual WISDM and NDSS subscales, in addition to global dependence measures, were used to achieve a high resolution with regard to the modeling of specific dependence factors.

Finally, mediational models were tested to determine the extent to which variance in withdrawal mediated the influence of dependence on cessation ability. Two types of mediational models were estimated. Initially, multiple-mediator models were specified using both craving and negative-affect withdrawal symptoms as mediators. Models were specified using different (individual) measures of dependence (the X variable), along with two mediators (postquit craving and negative affect as the M variables), and a days-to-relapse outcome over 8 weeks postquit (the Y variable). The days-to-relapse outcome was modeled as a survival outcome, with participants who failed to relapse treated as right-censored observations, and each path to relapse thus being interpreted on a logit metric corresponding to the likelihood of a relapse, that is, positive values indicating a higher probability of relapse. Both treatment and smoking during the period of withdrawal measurement (a binary variable reflecting smoking, on average, 5 cigarettes/day or less, coded "1", vs. more than this amount, coded "0"; see Piper, McCarthy et al., 2008) were controlled by regressing variables in the mediational model onto these relevant categorical variables.

In the second type of mediational model, combinations of dependence measures were used as predictor (X) variables in the

models (i.e., WISDM tolerance, WISDM drive, and WISDM cue exposure) with the craving withdrawal measure as the sole mediator (since it proved to be the strongest mediator in the first set of mediational analyses). This was done to estimate the magnitude of the effect of dependence on withdrawal and relapse when optimal measures of dependence were jointly employed. These three dependence measures were selected, since they had the strongest relations with withdrawal across the craving and negative affect best fitting models. The mediational models were fit in Mplus 6.1 (Muthen & Muthen, 2010) using the MLR (maximum likelihood with robust standard errors) estimator and Monte Carlo integration to account for the censored observations. Indirect effects were tested using a joint significance test approach, whereby statistically detectable mediation occurs when both paths in the indirect effect—the path from dependence to mediator, and from mediator to relapse—are found statistically significant (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). To evaluate effect sizes for the mediational effects, we used a measure of the mediational pathway estimates in reference to the metrics of the relevant variables. As the outcome is a survival outcome, the effects can all be interpreted with respect to the relative likelihood of relapse.

Results

Dependence and Withdrawal Correlations

Table 1 shows that intercorrelation of the full dependence scales used in this research generated a sizable range of correlations, suggesting that some of the measures could contribute orthogonal variance to the prediction of withdrawal. The WISDM and NDSS subscales also showed considerable range in their correlations with other measures of dependence. For instance, the correlations of the WISDM subscales with the FTND total score ranged from .05–.70 (for the weight control and tolerance subscales, respectively). Table 2 displays the relations of the two withdrawal measures used in this research (craving and negative affect) with the full dependence scales and with smoking heaviness (cigarettes smoked/day). Table 2 shows some variation in prediction magnitude, but the levels of association are all modest in size, consistent with prior research (e.g., Piper et al., 2006; Shiffman et al., 2004), accounting for less than 10% of the variance in symptom magnitude. However, it is clear that most of the dependence scales predicted withdrawal symptoms better than a simple measure of smoking heaviness per se.

To achieve more discrete assays of dependence, the PDM and the SDM, derived from the WISDM, were correlated with the withdrawal indices. In addition, orthogonal variance in these two

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[3] Only two of these interactions were obtained:,They were modest (p > .03), did not change the magnitudes of the dependence–withdrawal main effects, and did not change point estimates in the models. Therefore, they were not retained in the models (Hosmer & Lemeshow, 2000).

[4] It is certainly the case that, in theory, the best fitting models could have tested all possible interaction effects versus just 2-way interactions with treatment. However, given the number of independent variables, the number of potential interactions would have been prohibitive. The regression-tree models provide an efficient method for screening possible influential moderators of outcomes that would cause dependence–withdrawal relations to be especially strong in certain smoker subpopulations.

Table 1
Interrcorrelations of Major Dependence Measures

Measures	TDS	WISDM	PDM	SDM	NDSS
FTND	.21	.39	.56	.25	.45
TDS		.37	.32	.35	.37
WISDM			.80	.96	.61
PDM				.59	.63
SDM					.51

Note. N's = 1442–1500. TDS = Tobacco Dependence Screener; WISDM = Wisconsin Inventory of Smoking Dependence Motives; PDM = Primary Dependence Motives; SDM = Secondary Dependence Motives; NDSS = Nicotine Dependence Syndrome Scale. All correlations significant at $p < .01$.

dependence factors was identified (via partialing their shared variance), and the withdrawal indices were then regressed on these partialed factors. Table 2 reveals that using the relatively discrete WISDM dependence PDM and SDM subscales did not result in meaningfully larger associations with withdrawal scores. The zero-order correlations show that the partialed SDM residual was significantly more highly related to negative affect than was the residualized PDM score (r's = .210 vs. .044), whereas the residualized PDM score was significantly more highly related to craving than was the residualized SDM score (r's = .234 vs. .127; see Table 2 for confidence intervals).

Best Fitting Models

Best fitting models were then built for the prediction of each of the two withdrawal measures (Hosmer & Lemeshow, 2000). These models captured the optimal set of main effect predictors for each type of withdrawal symptom, statistically controlling for the influence of exogenous factors that could affect the withdrawal variables (to reduce error). Candidate predictors included multiple, specific dependence measures because such measures might summate to enhance predictive validity. To accomplish this, every

subscale of the two multifactorial dependence measures (the WISDM and the NDSS) was evaluated along with the omnibus tobacco-dependence measures—the TDS, and the FTND (total score plus separate inclusion of the two items that constitute the Heaviness of Smoking Index [Items 1 & 4]). The nondependence predictors included: treatment condition, age, gender, educational attainment, relevant personality dimensions (MPQ negative emotionality, constraint), stressors (Social Readjustment Rating Scale), social network factors (number of smokers in the social network, number of supportive others in the social network, presence of a spouse/partner who smokes), presence of smoke-free environments (home and work smoking restrictions), mood (baseline NPANAS), and history of panic attacks (a common anxiety diagnosis associated with relapse vulnerability; Piper, Cook, et al., 2011). Of these measures, age, gender, and treatment condition were retained in models on substantive bases (Hosmer & Lemeshow, 2000). Tables 3a and 3b depict the negative affect and craving analyses, respectively.

To reveal the extent to which the most predictive dependence measures can increment predictive accuracy when major sources of nondependence variance are statistically controlled, the nondependence measures were first forced into the models as a set, and then the dependence measures with significant associations were entered as a set. Results showed that the set of dependence measures resulted in a modest, but significant, increment in prediction for the negative affect model (the R^2 increased from .202 to .236), and a somewhat larger, and significant, increment in prediction for the craving model (an increase in Model R^2 from .06 to .178). Both models comprised both omnibus (e.g., FTND) and specific (individual NDSS and WISDM subscales) dependence measures.

Regression-Tree Models

Piecewise-constant regression-tree models were then generated with GUIDE software (Loh, 2002) using the same variables tested in the regression model fitting analyses, for example, gender, treatment, and presence of home or work smoking restriction rules.

Table 2
Relations Among Dependence Measures and Craving and Negative-Affect Withdrawal Symptoms

Measures	Post-quit craving		Post-quit negative affect	
	r	95% CI	r	95% CI
FTND	.258** (N=1283)	.207–.308	.138** (N=1283)	.084–.191
TDS	.216** (N=1281)	.164–.267	.227** (N=1281)	.175–.278
NDSS	.305** (N=1234)	.254–.354	.208** (N=1234)	.154–.260
WISDM-68	.308** (N=1282)	.258–.356	.236** (N=1282)	.184–.287
SDM	.264** (N=1281)	.213–.314	.235** (N=1282)	.183–.286
SDM controlling for PDM	.127** (N=1281)	.073–.180	.210** (N=1281)	.158–.261
PDM	.306** (N=1282)	.256–.354	.166** (N=1282)	.113–.218
PDM controlling for SDM	.234** (N=1281)	.182–.285	.044 (N=1281)	.000–.098
Cigarettes per day	.120** (N=1279)	.066–.173	.048 (N=1279)	.000–.102

Note. The correlations shown above were not adjusted for treatment conditions. The same pattern of association was obtained when treatment condition was statistically controlled. FTND = Fagerstrom Test of Nicotine Dependence; TDS = Tobacco Dependence Screener; NDSS = Nicotine Dependence Syndrome Scale; WISDM-68 = Wisconsin Inventory of Smoking Dependence Motives; SDM = Secondary Dependence Motives; PDM = Primary Dependence Motives.
** Significant at $p < .01$.

Table 3a

A Best Fitting Model for Predicting Negative Affect Withdrawal Symptoms

Variables (constant)	B	SE	Beta	t	Sig.
	−.990	.274		−3.619	.000
FTND	.045	.019	.065	2.422	.016
TDS	.060	.022	.074	2.690	.007
NDSS continuity	.146	.038	.104	3.871	.000
WISDM cue exposure	.133	.033	.108	3.984	.000
Baseline PANAS—negative affect	.056	.006	.263	9.090	.000
MPQ negative emotionality	.018	.003	.165	5.476	.000
SRRS Total	.001	.000	.086	3.218	.001
Age	−.008	.004	−.060	−2.282	.023
Gender	.171	.077	.057	2.214	.027
Treatment	−.207	.058	−.091	−3.583	.000

Note. $R^2 = .24$.

Separate models were run for the craving and negative affect withdrawal symptoms. Each tree model was obtained by first growing a large tree, using chi-squared significance tests to choose a variable to split the data at each node of the tree. Then the tree was pruned back to produce a nested sequence of smaller tree models. The tree model with the smallest mean-squared error estimated by 10-fold cross-validation was selected. The splitting algorithm is detailed in Loh (2002) and the pruning algorithm in Breiman, Friedman, Olshen, and Stone (1984).

The Negative Affect regression-tree model had only one predictor: the WISDM behavioral choice/melioration scale (see Figure 1a). This finding shows only a modest association between this SDM subscale and negative affect, such that those with a behavioral choice score of less than 3.8 had a negative affect score of only 1.3, on average (on a 10-point scale), whereas those with a higher behavioral choice score had a negative affect score of 1.9, on average, a statistically significant difference ($p = 2.1 \times 10^{-12}$).

The craving withdrawal score was predicted jointly by three different predictors: the WISDM tolerance score, the WISDM cue exposure score, and the NDSS drive score (see Figure 1b). The lowest levels of craving postquit were produced by those who were low on both the WISDM tolerance scale (≤5.50) and the NDSS drive score (≤−1.14). the highest scores were produced by those who were high on both the WISDM tolerance scale (>5.50) and the WISDM cue exposure scale (>6.09). Figure 1b shows that the 172 smokers with low scores (below the cut score) on the WISDM tolerance and the NDSS drive measures had a mean craving score postquit of 2.28, and the 122 smokers with high scores on the WISDM tolerance and WISDM cue exposure measures (above the cut scores) had a mean craving score postquit of 6.30 (differences across the four mean symptom levels are significant with an ANOVA *F* test: $p = 2.2 \times 10^{-16}$).

Mediational Models

The initial set of multiple-mediator models comprising both craving and negative affect withdrawal symptoms as mediators, revealed that, across different dependence measures, only the craving withdrawal measure supported a significant mediational path. (Analyses revealed that negative affect could support a

significant mediational path, but this path became nonsignificant once craving was added to the model.) Therefore, the second set of mediational models, those comprising multiple dependence measures, used only craving as the withdrawal mediator.

Therefore, to determine the extent to which variance shared by dependence and withdrawal measures was motivationally and clinically meaningful, joint mediation analyses were conducted using two dependence subscales (the WISDM tolerance and the NDSS drive subscales) as the X variables, with the craving withdrawal measure as the M variable, and relapse latency over the first 8 weeks postquit as the Y variable (see Figure 2). The model controlled for the relations between smoking during the 2-week postquit withdrawal assessment period with craving and relapse, controlled for the relations of treatment with craving and relapse (as well as with the dependence measures), estimated the direct-effects dependence on relapse, and estimated the indirect path reflecting the mediation of dependence effects on relapse via craving. The dependence measures (i.e., WISDM tolerance and NDSS drive) were selected because they were highly associated with craving in both the best fitting and regression-tree models, and because they together produced the largest reductions in craving residual variance. Figure 2a shows that both WISDM tolerance and NDSS drive significantly predict craving, and craving significantly predicts relapse. Figure 2b shows the mediation of both WISDM tolerance and WISDM cue exposure by craving. Neither NDSS drive nor WISDM cue exposure has significant direct effects on relapse once the craving mediator is entered in the models, but WISDM tolerance does continue to predict relapse.

The mediation ratios (MR) for each of the mediational models revealed considerable range in magnitude. The MR's in the WISDM tolerance and NDSS drive model with respect to craving were .17 for WISDM tolerance and .52 for NDSS drive, whereas in the WISDM tolerance and WISDM cue exposure model, the MR's were .18 for WISDM tolerance and .69 for WISDM cue exposure. Thus, with both types of dependence variables, the ratio of indirect effects to total effects was less for WISDM tolerance than for either NDSS drive or WISDM cue exposure, consistent with the weaker residual direct effects to relapse observed for NDSS drive and WISDM cue exposure.

The mediational path estimates were also evaluated with reference to the metrics of the relevant variables. As the outcome is a

Table 3b

Best Fitting Model for Predicting Craving Withdrawal Symptoms

| Variables (constant)	B	SE	Beta	t	Sig.
	−.129	.508		−.253	.800
FTND	.135	.047	.108	2.904	.004
NDSS continuity	.152	.068	.060	2.222	.026
NDSS drive	.311	.078	.122	4.009	.000
WISDM automaticity	−.115	.051	−.072	−2.240	.025
WISDM cue eExposure	.299	.070	.135	4.295	.000
WISDM tolerance	.301	.079	.156	3.810	.000
Baseline PANAS—negative affect	.051	.010	.132	4.874	.000
Age	.012	.007	.048	1.747	.081
Gender	.481	.143	.089	3.351	.001
Treatment	−.431	.108	−.105	−4.000	.000

Note. $R^2 = .18$.
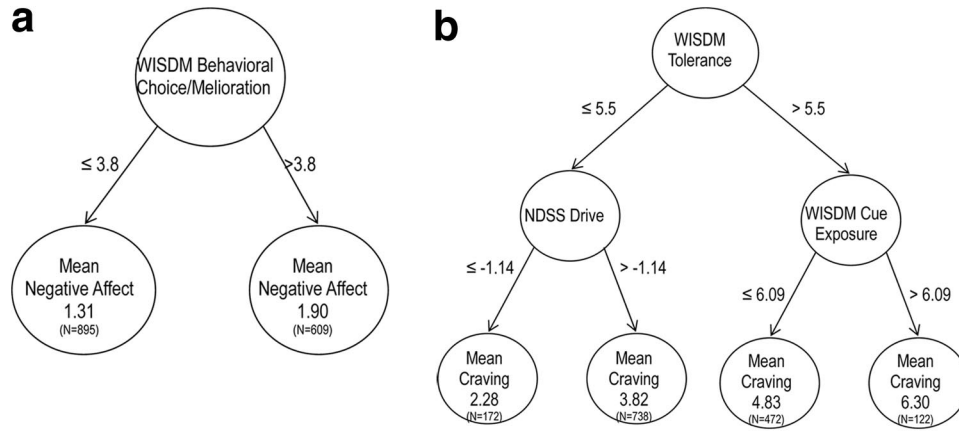
Figure 1. a. Regression tree predicting mean postquit negative affect. b. Regression tree predicting mean postquit craving.

survival outcome, the effects can all be interpreted with respect to the relative likelihood of relapse. More specifically, given a regression coefficient b (or equivalently a product of regression coefficients) related to a predictor X, exp (X × b) indicates the proportional increase (or decrease) in the likelihood of relapse. For example, comparing extreme scores on both the WISDM tolerance (1 vs. 7) and NDSS Drive (−3.63 vs. 2.47 factor scores), yields indirect effect estimates of .386 × .046 = .018 for WISDM tolerance and .472 × .046 = .022, for NDSS drive (see Figure 2a). This implies that a high scorer on both scales would have about a 30% greater chance of relapse than would a low scorer on both scales because of dependence effects that are mediated by craving: exp (.018 × 6 + .022 × 6.1) = 1.27.

Discussion

Consistent with considerable previous research, measures of dependence and withdrawal were modestly related to one another when analyzed with typical univariate regression techniques. Modest relations were obtained whether omnibus dependence scales or more specific subscales were used in univariate analyses. However, these analyses did reveal additional evidence about how withdrawal and dependence are related to one another. First, consistent with other research (Hughes, 2007), there was evidence that withdrawal symptoms are heterogeneous and that, at the very least, craving and affective composites need to be separately analyzed (see Piasecki et al., 2000; Piper, Schlam, et al., 2011). For
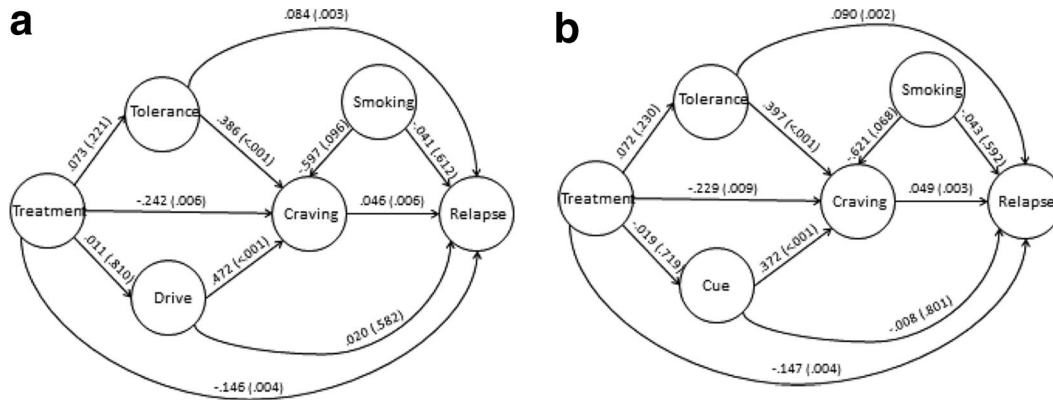

Figure 2. a. Mediation model showing craving withdrawal symptoms mediating the effect of WISDM tolerance and NDSS drive subscale scores on cessation outcome. "Smoking" is a binary variable reflecting smoking during the 2-week postquit period when withdrawal symptoms were assessed. It reflects average smoking rates during this period of 5 cigarettes/day or less versus more than this amount. It is intended to control for any influence of moderate or heavy smoking during this period on withdrawal symptoms and relapse. b. Mediation model showing craving withdrawal symptoms mediating the effect of WISDM tolerance and cue exposure subscale scores on cessation outcome. The variable "smoking" is a binary variable reflecting smoking during the 2-week post-quit period when withdrawal symptoms were assessed. It reflects average smoking rates during this period of 5 cigarettes/day or less versus more than this amount. It is intended to control for any influence of moderate or heavy smoking during this period on withdrawal symptoms and relapse.

instance, we found that craving and negative affect tended to be predicted by different sorts of variables. The best fitting models showed that whereas some measures predicted both craving and negative affect withdrawal symptoms (i.e., the FTND, the NDSS continuity subscale, the WISDM cue exposure subscale, and gender), some predictors were related to only one symptom. For instance, the MPQ negative emotionality scale and the SRRS (stressor measure) predicted only the negative affect symptoms. Conversely, the WISDM tolerance and NDSS drive subscales predicted only the craving symptoms.

These patterns of predictive relations suggest certain inferences with regard to the causal influences on tobacco withdrawal symptoms. First, both craving and negative affect withdrawal symptoms are significantly related to a pattern of continuous smoking throughout the day (based on salient items for the NDSS continuity scale: e.g., "My smoking pattern is very irregular throughout the day. It is not unusual for me to smoke many cigarettes in an hour, then not have another one until hours later," reverse scored). To the extent that a person spends time not smoking, and their smoking pattern is irregular, they are likely to experience reduced affective and craving withdrawal symptoms. Notice that regularity or pattern of smoking seems to be more important than is the number of cigarettes smoked per day, which had low levels of association in zero-order tests and performed poorly in model building tests. (A caveat is that all participants in this work smoked at least 10 cigarettes per day, so this characterization might not apply to very light smokers.) This observation suggests that an important determinant of withdrawal severity is the cueing of smoking by internal or external cues over the passage of time (Baker et al., 2004; Kozlowski & Herman, 1984; see the rationale for the NDSS continuity scale in Shiffman et al., 2004).

The major discrepancy between the two withdrawal symptoms (craving and negative affect) as predicted in the best fitting models is that only craving symptoms are predicted by the WISDM tolerance and NDSS drive subscales[5], with both subscales showing relatively strong associations (see Tables 3a and 3b). Both of these subscales ask about the need to smoke as a function of the passage of time. For instance, the NDSS drive subscale (based on salient items) focuses on withdrawal-related discomfort and craving ("After not smoking for a while, I need to smoke to relieve feelings of restlessness and irritability," and "After not smoking for a while, I need to smoke in order to keep myself from experiencing any discomfort."). The WISDM tolerance subscale also focuses on the difficulty of allowing time to pass without smoking ("I can only go a couple hours between cigarettes," and "I usually want to smoke right after I wake up"). Thus, both of these subscales, to some extent, reinforce the message that the passage of time is a critical imperative for smoking. These subscales also assess smoking heaviness (WISDM tolerance) and the strength of craving per se (NDSS drive) more directly than does the NDSS continuity subscale, and this more direct assessment may contribute to their greater association with craving than with negative-affect withdrawal symptoms. Of course, another key distinction between the predictors of the craving and negative affect models is that measures of neuroticism or negative affect relate more strongly to the latter.

In sum, it appears that a critical correlate of strong withdrawal symptoms measured in real-time is a pattern of highly regular, cue-elicited smoking. It remains unknown why smokers would differ from one another in these determinants of withdrawal severity. Why would one smoker versus another be more likely to form strong cue-withdrawal associations? Perhaps differences in the influence of smoking periodicity might arise from differences in nicotine clearance (Piper, Bolt, et al., 2008; Schnoll et al., 2009) and homeostatic defense of blood nicotine levels (Kozlowski & Herman, 1984). The nature of the cue is also unknown, but the importance of the passage of time suggests the detection of interoceptive signals of withdrawal or cues signaling falling nicotine levels in the body (Baker et al., 2004; Bevins et al., 2011).

Other evidence suggests that dependence is associated with a shift in influence from exteroceptive to interoceptive cues, a shift most starkly illustrated in research with chippers (aperiodic smokers). Chippers use tobacco regularly but without escalating their use markedly or apparently losing control over its use. In contrast to heavy dependent smokers, whose smoking is fairly constant throughout the day and sensitive to tobacco deprivation, chippers' smoking is more aperiodic and under greater (apparently external) stimulus control (Coggins, Murrelle, Carchman, & Heidbreder, 2009; Shiffman & Paty, 2006). (It is interesting to note, that the NDSS drive subscale, which directly assesses how the passage of time affects withdrawal, strongly discriminates chippers from heavier smokers; Shiffman & Sayette, 2005). These findings with chippers reinforce the notion that tobacco dependence that manifests in strong withdrawal (perhaps especially in withdrawal craving), is characterized by an intolerance to a disruption in smoking (also see Piasecki et al., 2010b). It may be, in fact, that there *is* a developmental progression such that severe nicotine dependence is associated with a shift to time-based, interoceptive cueing (vs. chippers; Coggins et al., 2009; Shiffman & Paty, 2006). However, the regression tree analyses suggest that internal cueing does not wholly replace the effects of environmental cueing (see Figure 1b); those individuals prone to both types of cueing are at greatest risk for severe withdrawal craving.

The linkage of chronic, heavy self-administration with sensitivity to cues and abstinence-induced craving accords with considerable recent research on drug dependence. This work shows that heavy, chronic self-administration results in habit learning (mediated by the dorsal striatum; Everitt & Robbins, 2005)—a cornerstone of which is strong stimulus-response bonds that result in the automatic elicitation of drug use in the presence of highly mapped cues (Takahashi, Roesch, Stalnaker, & Schoenbaum, 2007; Vanderschuren, Di Ciano, & Everitt, 2005). Further, research shows that drug deprivation increases activity in the dorsal striatum (Vollstädt-Klein et al., 2010), and this results in strong abstinence-induced craving (Volkow et al., 2006; Vollstädt-Klein et al., 2010). Thus, the linkage of heavy self-administration, sensitivity to drug abstinence, and strong elicitation of craving by abstinence, is consistent with recent basic research on the role of habit learning in addiction.

The predictors comprised by the best fitting model of the negative-affect withdrawal symptoms are different from those comprised by the best fitting craving model. Not only does the

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[5] The WISDM automaticity subscale was negatively associated with craving symptoms in the best fitting model. However, this appears to be due to suppression effects, since it is positively associated with craving in zero-order associations.

negative-affect model comprise multiple measures of affective vulnerabilities, but its nicotine dependence measures are less focused on smoking heaviness. For instance, the *DSM* symptoms tapped by the TDS scale do not reflect smoking heaviness well (Baker, Breslau, Covey, & Shiffman, 2011), and instead seem to more sensitively reflect psychological distress (Breslau & Johnson, 2000). Therefore, although withdrawal-related negative affect may reflect dependence-related genetic influence (Edwards & Kendler, 2011), withdrawal-related negative affect is not closely related to the core elements of nicotine dependence that have been highlighted in recent research (drug use that is heavy, uniform across time and place, and automatic; see Piasecki et al., 2010a, 2010b), and that most strongly motivate relapse (see results of the mediational models). This calls into question models that posit a central role for negative affect in dependence (Baker et al., 2004).

The best fitting models underscore the importance of a multifactorial approach to the assessment of dependence. None of the omnibus dependence measures was able, by itself, to account optimally for the dependence–withdrawal covariation present in the data (see results of the best fitting models and the regression-tree analyses). Multiple scales, including relatively discrete dependence subscales, were able to account for significant increments in variance in the two types of withdrawal symptoms.

Finally, the issue that inspired this research was the question of whether measures of the dependence construct and withdrawal are meaningfully related, which would affirm the theories that posit strong causal relations between these constructs (Edwards & Gross, 1976; Koob, 2006; Siegel, 1983; Solomon & Corbit, 1974; Wikler, 1980). This issue boils down to whether dependence can account for meaningful differences in withdrawal symptom magnitude, and then, whether such differences are consequential. The regression-tree analyses showed that dependence measures were related to very large differences in withdrawal symptoms when subpopulations of smokers were considered. Individuals who scored low on both the WISDM tolerance and the NDSS Drive subscales reported very low levels of craving, whereas individuals with high scores on the WISDM tolerance and WISDM cue exposure subscales generated postquit craving scores that were almost three times larger than those reported by the former individuals (see Figure 1b). Thus, optimal combinations of dependence measures can indeed predict large differences in withdrawal scores.

The mediational models pertain to the meaningfulness of the relation of dependence and withdrawal. The mediational analyses allow us to determine if the variance shared by dependence and withdrawal predicts the clinically important outcome of relapse latency. These analyses showed that exemplar dependence measures (e.g., WISDM tolerance and NDSS drive) predicted significant variance in relapse latency via their relations with craving. Though significant mediation by craving was found, the clinical impact should be viewed as modest in size, with the highest scores on the two exemplar dependence measures increasing risk by only about 30%[6]. This level of increase is not large, but it must be remembered that relapse is a function of diverse factors and reflects such influences as educational status, self-efficacy, presence of smokers in the home, fortuitous exposure to episodic events (cues, stressors), and comorbid psychopathology (e.g., Bolt et al., 2009). Given the causally promiscuous nature of relapse, the degree to which relapse was influenced by dependence via withdrawal craving is impressive. Another potentially important finding of the mediational analyses arose from multimediator models; namely the relation between dependence and relapse could be accounted for entirely by craving. That is, dependence appears to increase relapse risk, and it does so via the withdrawal symptom of craving and not negative affect (Berkman et al., 2011).

This research leaves many questions unanswered and has limitations. One limitation is that the current results might not generalize well to other smoking populations. For instance, this sample participated in a formal cessation trial and this requirement may have selected for smokers who differ from smokers in general on multiple dimensions, for example, motivation to quit, dependence level, and so on. Another concern is that although the present results elucidate the relation between dependence and withdrawal, the majority of withdrawal variance remains unexplained. A final caveat is that the hypotheses advanced in this research are based only upon self-report of perceived dependence motives and withdrawal. This strategy may have missed important information that would have been captured by measures other than self-report (e.g., physiological or cognitive measures). Future researchers might use actual behavioral indices of smoking regularity or patterning and physiological assays of self-administered nicotine dose to ground tests of hypotheses with multimethod measures. Finally, the stepwise methods upon which best fitting model development depends, have limitation such as inflated R^2 values and sample specificity in the ordering of predictors (Harrell, 2001). However, many of the problems encountered with such models arise from multicollinearity with regard to the original set of predictors and concern the exact form of the developed model. Regression-based models, though, show good stability in terms of the replication of the particular identified model across derivation to predictor samples (Dreiseitl & Ohno-Machadob, 2002; Harper, 2005). In other words, concerns about replication of such models primarily arise from the consistency with which the same model will be derived from different data sets/samples; derived models often show good stability when the best fitting predictors are tested in new samples (e.g., Dreiseitl & Ohno-Machadob, 2002). This means that the dependence measures comprised by the models in Tables 3a and b would likely show meaningful relations with withdrawal criteria in new samples (assuming appropriate initial sampling and derivation strategies).

In closing, the results suggest the following conclusions: (a) Although univariate analyses suggest that dependence and withdrawal measures tend to be only modestly interrelated, more powerful analytic techniques show that they are, in fact, meaningfully related and their shared variance is related to the important clinical outcome of relapse; (b) There are clear differences between craving and negative-affective withdrawal symptoms, with the former more related to smoking heaviness and the latter more related to trait measures of negative affect; moreover, craving exerts stronger effects as a mediator of dependence effects on relapse than does negative affect; (c) Both craving and negative-affect withdrawal symptoms, and especially craving, appear to be

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[6] When only a single dependence measure (e.g., WISDM tolerance) was used, an extreme score on that measure increased relapse risk by about 15%, showing that the combined use of dependence measures does enhance the prediction of relapse due to craving mediation.

relatively strongly related to a pattern of regular smoking that is spurred by the passage of time, and that is powerfully affected by smoking cues. These findings support models that accord an important role for withdrawal symptoms, especially craving, and associative processes in drug dependence. These findings also support the practice of using multidimensional withdrawal measures as criteria for the evaluation of dependence measures.

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