Project Title
UW Withdraw from Tobacco Study: Enhancing and Evaluating Tobacco Withdrawal Assessment Psychometrics and Validity

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Study Purpose & Aims
The objectives of this project are to examine the assessment and nature of cigarette smoking withdrawal among adults who attempt to quit smoking without using medication initially. The objectives are to: 1) evaluate the validity and psychometric properties of the Wisconsin Smoking Withdrawal Scale-2 (Long Form: WSWS2-L; Brief Form: WSWS2-B); and, 2) understand the characteristics of smoking withdrawal and factors that relate to withdrawal severity in unmedicated individuals.

Objective 1: WSWS2 Assessment Validation
Specific Aim 1: To enhance and evaluate the validity of a self-report assessment of tobacco withdrawal, the revised Wisconsin Smoking Withdrawal Scales-2 (long: WSWS2-L; brief: WSWS2-B), in terms of sensitivity to smoking abstinence in initially unmedicated individuals making a quit smoking attempt.

Specific Aim 2: To compare the validity of the WSWS2-L and the WSWS2-B with an alternative withdrawal scale, the Minnesota Tobacco Withdrawal Scale – Revised (MTWS-R), on the bases of psychometric criteria.

Objective 2: Characterize the Dynamics and Predictors of Withdrawal Severity
Specific Aim 3: To characterize the dynamic features of withdrawal symptoms and determine factors that most accurately predict withdrawal severity (peak, trajectory, average, variability, and duration), including contextual factors, personality factors, lifestyle factors, pharmacologic factors, other substance use, pain, pre-cessation symptomatology, reward sensitivity/response, and affective processing dimensions.

Study Registration
We completed this registration of our data analysis plan on December 8, 2022. Enrollment in this study occurred between July 14, 2021, and May 26, 2022. Follow up data collection for this study was completed by September 21, 2022. This study was registered at clinicaltrials.gov (NCT04969198). We completed this complementary pre-registration to provide a greater level of detail regarding our data analysis plans. At the time of this registration, we have only reviewed data for the purposes of routine monitoring of study management and oversight (e.g., appointment attendance, adverse events). We have not yet examined any data that would inform our analysis plans. We describe the primary aims of this study and analyses in this registration. Given the scope of this study, this information will likely appear in multiple complementary manuscripts and/or presentations.

Significance

The Wisconsin Smoking Withdrawal Scale (WSWS) was developed over two decades ago to provide researchers and clinicians with a psychometrically sound, validated self-report assessment of nicotine withdrawal (Welsch et al., 1999). This 28-item scale includes a total symptom scale and 7 subscales addressing components of the tobacco withdrawal syndrome (e.g., anxiety, anger, sadness, craving, concentration difficulties, hunger, and sleep problems). The original scale has good psychometric properties, is sensitive to smoking abstinence, related to tobacco dependence measures, and has moderate predictive validity regarding smoking cessation outcomes. The WSWS has been a valuable assessment instrument that has been used by numerous researchers worldwide for investigating the nature and correlates of tobacco withdrawal. However, the field's understanding of tobacco withdrawal has advanced in recent years and the population of people who smoke has changed substantially (e.g., reduced smoking heaviness; Jamal et al., 2018; increased psychiatric comorbidity, Weinberger, Funk, Goodwin, 2016; Prochaska, Das, Young-Wolff, 2017). In addition, new components of withdrawal have been proposed (e.g., anhedonia; Cook et al., 2015; Hughes, Klemperer, Peasley-Miklus, 2020). Moreover, we believed that it was important to validate a short-form of this instrument in a contemporary sample of adults who smoke, one that would be suitable for situations where a long form would be impractical (e.g., population based studies, clinical use). These considerations motivated this effort to update and improve the assessment of withdrawal and validate a short-form scale.

We have recently developed a psychometrically robust, revised version of the WSWS (Smith et al., 2021), based on several recent smoking cessation trials conducted by UW-CTRI (Baker et al., 2016, Piper et al., 2018, Baker et al., 2021). This revised self-report assessment includes a long and brief version (Long: WSWS2-L; Brief: WSWS2-B) and comprises a revised stem, item wording, and response scale. The WSWS2-L is a 19-item scale that includes a total symptom scale and 6 revised subscales (i.e., negative affect, craving, concentration difficulties, hunger, restlessness, and sleep problems). The WSWS2-B is a 6-item scale that includes one item per symptom domain and may be useful in clinical or research contexts in which time or assessment burden is of high importance.

Most previous research, including our own (e.g., initial development and validation of the WSWS2), occurred in individuals who were using smoking cessation medication, which can significantly affect tobacco withdrawal symptoms. Cessation medication can reduce withdrawal severity and affect some symptoms (e.g., cigarette cravings) more than others. It is important, therefore, to examine individuals attempting to quit smoking during unmedicated withdrawal. For instance, the sensitivity of assessment items might be obscured amongst medicated individuals. While withdrawal scales will often be used in clinical contexts with individuals who are using medication, it is vital to determine for substantive reasons, the severity of different symptoms and their trajectories in unmedicated individuals. Assessment of unmedicated withdrawal is rarely done even though the majority of people who try to quit smoking still do so without any medication. It is of considerable scientific and clinical importance to assess tobacco withdrawal accurately since withdrawal severity is hypothesized to be a key motivator of smoking lapses and relapses (Baker et al., 2004; Bolt et al., 2012; McCarthy et al., 2008; Piasecki et al., 2000; Piper, 2015). In addition, smoking cessation pharmacotherapy may produce its effects on smoking abstinence by suppressing such withdrawal symptoms (Bolt et al., 2012).

Study Overview

Adults who smoked cigarettes daily and desired to quit smoking enrolled in this study (N=232). This treatment-delay, one-group clinical trial was intended to validate and/or enhance the assessment of tobacco withdrawal amongst participants who try to quit smoking without using

medication early in the course of their quit attempt. Participants attempted to quit smoking and were instructed not to use any smoking cessation pharmacotherapy during the first week of their quit attempt. They initiated pharmacotherapy 1 week past the target quit day (TQD) and continued pharmacotherapy through 9 weeks past the TQD. This will allow for the examination of withdrawal symptoms for 1-week post-TQD in participants who are not using pharmacotherapy. Participants received 8 weeks of combination nicotine replacement therapy (C-NRT: nicotine patch + nicotine mini-lozenge) starting 1 week past the TQD. Participants received 4 counseling sessions (1 pre-TQD, 3 post-TQD) that conform to the US PHS Clinical Practice Guideline recommendations (Fiore et al., 2008). Participants completed 4 weeks of ecological momentary assessment (EMA) including a 2-week baseline (starting TQD -14d) and 2-week post-TQD (1-week un-medicated, 1-week using C-NRT). Enrolled participants completed an Orientation Phase, Pre-cessation Phase, Cessation Phase, and Follow-up Phase (Visit 4 only if self-reported 7d point prevalence abstinence). See Tables 1-3 below for timing of assessment and study activities.

Table 1. Study Visit Schedule and Procedures: Orientation and Pre-cessation Phases

Study Phase	**Orientation**	**Pre-cessation**		
	Visit 1	**Call 1**	**Call 2**	**Call 3**
Days +/- Target Quit Day: TQD	**> -14**	**-12**	**-7**	**-3 to -1**
Consent, HIPAA, Eligibility Screening	X			
CO Breath, Urine, & Blood Pressure	X			
Smoking Status & Timeline Follow Back (TLFB)	X	X	X	X
Wisconsin Smoking Withdrawal Scale - Long (WSWS2-L)	X	X	X	X
Minnesota Tobacco Withdrawal Scale – Revised (MTWS-R)	X	X	X	X
Questionnaire of Smoking Urges (QSU)	X			
Snaith-Hamilton Pleasure Scale (SHAPS)	X		X	
Pain Numeric Rating Scale (PNRS)	X		X	
Depression, Anxiety, Stress Scale (DASS21)	X			
Smoking History	X			
Fagerström Test of Cigarette Dependence (FTCD)	X			
Brief Wisconsin Inventory of Smoking Dependence Motives (WISDM)	X			
Wisconsin Predicting Patients' Relapse (WI-PREPARE)	X			
NIAAA Recommended Alcohol Use	X			
Graded Chronic Pain Scale (GCPS 2.0)	X			
Distress Tolerance Scale (DTS)	X			
Demographics	X			
Interventions				
Counseling (in minutes)			15-25	

Table 2. Study Visit Schedule and Procedures: Cessation Phase

Study Phase	**Cessation**				
	Call 4	**Visit 2**	**Visit 3**	**Call 5**	**Visit 4**
Days +/- Target Quit Day: TQD	**+1-2**	**+7**	**+14**	**+63 (9w)**	**>64 (9w)**
CO Breath, Urine, & Blood Pressure		X	X		X
Smoking Status & Timeline Follow Back (TLFB)	X	X	X	X	X
Revised Wisconsin Smoking Withdrawal Scale - Long (WSWS2-L)	X	X	X	X	X
Minnesota Tobacco Withdrawal Scale – Revised (MTWS-R)	X	X	X	X	X
Questionnaire of Smoking Urges (QSU)	X	X	X	X	X
Snaith-Hamilton Pleasure Scale (SHAPS)	X	X	X	X	X
Pain Numeric Rating Scale (PNRS)	X	X	X	X	X
Depression, Anxiety, Stress Scale (DASS21)		X			
Interventions					
Counseling (in minutes)	15	15	15		
Medication Education/Dispensing		X			
Medication Adherence/AEs			X	X	

Ecological Momentary Assessment (EMA)

Participants provided daily ecological momentary assessment data (meaning data that has been collected “in the moment”) for 4 weeks total during the study. Participants were sent a text message that contained a link to an online survey that they could complete on their mobile smartphone. For most of the EMA portion of the study, participants were sent 3 assessments per day (morning, midday, and evening). Daytime EMA assessments were brief (<5 min) to include the brief WSWS2-B (and exploratory items: anhedonia, pain) and additional items focused on understanding the motivationally relevant affective/cognitive subjective states associated withdrawal and craving (e.g., wanting to reduce stress, to feel a high or buzz), smoking (# cigarettes), and smoking triggers since the last EMA survey. The evening assessment included a larger battery of questionnaires to include the WSWS2-B and additional targeted assessments regarding smoking, person-related, and contextual factors in the last 24 hours. These evening assessments (1x/day) included smoking (# cigarettes), e-cigarette use (yes/no), alcohol use (yes/no, quantity), cannabis use (yes/no, mode of use, tobacco co-administration), pain (worst), cessation confidence and self-efficacy, smoking triggers (e.g., stressful events, cigarette access, others smoking) and coping strategies, future smoking likelihood/prediction, and NRT medication use (e.g., yes/no, mini lozenge quantity, subjective effects). The frequency of EMA increased to 6 reports/day for 5 days from 1-day pre-TQD to 3-days post-TQD in order to provide intensive monitoring of withdrawal symptoms on a more fine-grained time course during the early period of abstinence. Participants completed the full WSWS2-L (rather than the WSWS2-B) during the evening EMA during these 5 days (1x/day). Participants were compensated $100 for completing >80% of the EMA assessments. Payments were linked to assessment completion, but not to smoking status so as not to induce participants to incorrectly report their smoking status.

Table 3. Ecological Momentary Assessment (EMA) & Combination Nicotine Replacement Therapy (C-NRT) Schedule

	Pre-cessation	TQD	Cessation	
EMA Assessments (29 days)	3/d (13 days) TQD -14 to -2	6/d (5 days) TQD -1 to +3	3/d (11 days) TQD +4 to +14	No EMA TQD ≥15
Medication Status	No Medication		C-NRT TQD ~+8 to 63 (Start Day After Visit 2)	

Data Analysis Plan

WSWS2 & MTWS-R Scoring:
The WSWS2-L (Smith et al., 2021) is a 19-item scale scored via one total score (mean) and 6 subscale scores (means). The WSWS2-B is a 6-item scale scored as one total score (mean). The WSWS2-L was assessed at all study phone calls and in-person visits (see Table 1-2 for assessment timeline). The brief version (WSWS2-B) was assessed at all EMA reports (3-6x/day), with the exception of TQD -1d through TQD +3d, while the long version (WSWS2-L) was assessed at the evening report (the WSW2-L comprises the WSWS-B items). Also see *Exploratory Withdrawal Symptoms* section below.

The MTWS-R is a 17-item scale with one item per symptom domain and no subscales. We will score one total score (mean) of the first 8-items that are DSM-5 symptoms as our primary MTWS-R score. We will score an exploratory MTWS-R including all 17-items (mean) that includes 'other possible symptoms' of smoking withdrawal. The MTWS-R and related information was derived from John Hughes UVM website describing the scale: http://www.med.uvm.edu/behaviorandhealth/research/minnesota-tobacco-withdrawal-scale

Sensitivity to Abstinence:
The WSWS2 (-L and -B) should demonstrate a sensitivity to abstinence from smoking. We will examine whether WSWS2 total and subscale scores display significant increases from pre-quit to post-quit using a series of linear models. First, using EMA data (evening report) we will use piecewise models that allow for discontinuity (pre- vs post-quit day) to examine within-person changes in WSWS2 (-L and/or -B) from pre- to post-quit. We will examine differences in mean withdrawal severity during the week before vs after the quit-day, modeling the TQD jump (e.g., from 1w pre-quit mean to TQD) and post-TQD trajectory (e.g., slope, quadradic) over the first 3 days (WSWS2-L and WSWS2-B) and first week (WSWS2-B). Using study call/visit data we will examine within-person changes in WSWS2-L from an averaged baseline (averaged across pre-TQD calls/visits) to TQD +1-2d (Call 4) and TQD +1w (Visit 2). For EMA and Call data, we will examine the stability of baseline scores with and without approximately 1-3 days pre-quit to determine if there are anticipatory increases in withdrawal shortly before the TQD (and therefore exclude that rise from mean baseline calculations). We will examine sensitivity of WSWS2 to detect effects of smoking abstinence on withdrawal severity among the entire study sample as well as only among participants who self-report smoking no more than 2 cigarettes in the past 24 hours during the post-TQD timepoints as these individuals should still be experiencing significant withdrawal. We will examine several cigarettes/day cutoffs in sensitivity analyses to determine the robustness of results as function of this exclusion criterion (see below for *Sensitivity Analyses*). We hypothesize that both the WSWS2-L and the WSWS2-B will increase

significantly during the first 3 days and first week post-quit relative to pre-quit baseline values. Further, we expect increases to vary across the WSWS2-L subscales; we expect to see especially large increases in WSWS2-L subscales assessing craving, hunger, and concentration difficulties.

In order to understand how short periods of abstinence might affect baseline (pre-cessation) scores and the pre-to-post jump in withdrawal, additional analyses will be undertaken to select pre-withdrawal scores that have occurred within 15 or within 30 minutes of smoking a cigarette during the baseline period. These will be used to generate pre-withdrawal or baseline estimates and then used in piecewise models to determine the pre-to-post cessation changes in withdrawal scale and subscale scores. This may constitute a more sensitive test of abstinence related withdrawal than will use of unselected baseline scores (e.g., all evening reports). Also, the relations of time-since-smoking data collected in the baseline period will be used as time varying covariates to study the relations of this with withdrawal severity in the same baseline reporting episode.

Internal Consistency, Temporal Stability, Item Analysis, & Factor Structure:
WSWS2-L total scale and subscale internal consistency will be assessed with Omega (McDonald, 1999) with bootstrap-corrected 95% confidence intervals (CIs). For comparison, we will also compute Cronbach's alpha coefficient (Cronbach, 1951). Ideally, both omega and alpha will be > 0.7 for total scale and subscale at all timepoints. Further, we will examine response distributions and item-to-total correlations and subscale to total correlations. We will conduct parallel analyses for the WSWS2-B total scale (but with no subscale analyses).

We will examine internal consistency pre-TQD and at multiple timepoints post-TQD. We will examine internal consistency at Visit 1, which provides the largest sample size of participants pre-quit. We will examine internal consistency on the TQD (i.e., EMA evening report), TQD +1 to 2d (i.e., Call 4), and TQD +1w (i.e., Visit 2). This will provide estimates and comparison of the internal consistency at critical time points and assessment modalities (e.g., EMA mobile phone self-report, phone call with study staff, in-person tablet self-report) within the first week of the quit attempt.

We will examine the idiographic variability or lability of scales and subscales across the pre-TQD period. This will be compared with such variability in the post-quit period. Regression analyses will also be used to determine associations and shared variance during the pre-cessation period between Visit 1 (TQD >-2w) and Call 1 (TQD -12d) and between Call 1 to Call 2 (TQD -7d).

We will conduct Confirmatory Factor Analyses (CFA) following the approach we took during the initial development and validation of the WSWS2 (Smith et al., 2021). We will conduct CFAs with a maximum likelihood (ML) estimator and allow factors to correlate. We will use the following model goodness of fit statistics to evaluate CFA models (Hu & Bentler, 1999): a) root mean square error of approximation (RMSEA) with values <.06 indicative of good fit, b) comparative fit index (CFI) with values >.95 indicative of good fit, c) Tucker-Lewis index (TLI) with values >.95 indicative of good fit, and d) standardized root mean residual (SRMR) with values <.08 indicative of good fit. Ideally the WSWS2-L will display a simple structure (e.g., relatively low cross-loading of items on subscales). We will examine a 6-factor model and a single higher-order factor model for the WSWS2-L and a 1-factor model for the WSWS2-B. We will examine factor structure both on the TQD (via EMA evening report) and 1-week post-TQD in-person assessment (Visit 2).

We will conduct similar internal consistency and item analyses on the MTWS scales excepting the subscale analyses.

Network Analysis (Exploratory):
As a complementary perspective on measurement, we will apply Gaussian graphical network models to examine possible interactions between individual symptoms of withdrawal, both for the WSWS2-B, WSWS2-L, and MTWS-R. We will approach such analyses with the intent of evaluating (1) similarities of network structure among WSWS2-B, WSWS2-L, and MTWS-R and (2) evaluating possible change in network structure and/or the relations between individual symptom pairs (edges) in the presence of abstinence. These analyses will be based on the estimated inter-item polychoric correlation matrices of the respective scales and apply LASSO regularization in the evaluation of edge weights within the networks.

Convergent and Concurrent Validity:
We will examine convergent validity using Pearson correlations between two assessment instruments, the WSWS2 and MTWS-R, which are both designed to measure the same construct: tobacco withdrawal severity. We will examine correlations between these two assessments on the same days during the pre-cessation phase (Visit 1, TQD >-2w) and cessation phase at TQD +1d to 2d (Call 4) and TQD +1w (Visit 2) when both are delivered at the same times and via the same delivery route. We will examine how both the WSWS2-L and WSWS2-B relate to the MTWS-R (8 and 17 item versions). Strong positive correlations will be supportive of convergent validity.

We will also examine convergent validity using Pearson correlations between the WSWS2 assessed at study Visits/Calls (Long form) and WSWS2 assessed via EMA (Brief form) for the corresponding time window. We will examine correlations between these two assessments on the same days during the pre-cessation phase (Call 1 and Call 2) and cessation phase (Call 4 and Visit 2). Strong positive correlations will be supportive of convergent validity across measurement modalities.

We will also examine whether specific WSWS2-L subscales (e.g., craving, negative affect) and exploratory subscales (e.g., anhedonia) positively correlate with other assessments that are administered at similar times: e.g., QSU total score, QSU factor 1, SHAPS anhedonia, WISDM craving subscale, that are designed to measure related constructs. We will examine Pearson correlations between WSWS2 subscales (e.g., craving, negative affect) and these other measures designed to assess the same/similar constructs at baseline (Visit 1), TQD +1 to 2d (i.e., Call 4), and TQD +1w (i.e., Visit 2). Likewise, we will examine whether these assessments that are designed to measure related constructs positively correlate with WSWS2 (WSWS2-L subscales or WSWS2-B items) assessed via EMA for the same corresponding time period. Positive correlations will be supportive of convergent validity for select subscale.

The WSWS2 should demonstrate meaningful positive relations with measure of tobacco dependence (e.g., WISDM-PDM, WISDM-SDM, FTCD, time to first cigarette) and possibly smoking heaviness (e.g., cigarettes per day, baseline exhaled CO). We will examine Pearson correlations between WSWS2 (WSWS2-L and WSWS2-B) on the TQD (via EMA) and baseline measures of tobacco dependence (Visit 1).

We will conduct similar measures of convergent validity with the MTWS-R versions.

Discriminant Validity:
The WSWS2 subscales should demonstrate weaker relations with measures of an unrelated construct relative to a related/similar construct either measured with the same method (e.g., EMA vs EMA) or different method (e.g., EMA vs. Visit 1 baseline self-report). We will examine Pearson correlations between specific WSWS2-L subscales (e.g., EMA TQD craving, negative affect) and other measures designed to assess unrelated constructs at baseline (e.g., Visit 1 WISDM weight control). Smaller correlations (vs. those observed for convergent validity) will be supportive of discriminant validity for select subscales.

We will conduct similar measures of discriminant validity with the MTWS-R versions.

Predictive Validity:
We will examine prospective predictive validity using logistic regression to evaluate if withdrawal severity in the first week post-TQD (via EMA) predicts biochemically confirmed abstinence 1-week post-TQD (Visit 2). The primary outcome is biochemically confirmed (CO $\leq$5ppm) 3d and 24hr point prevalence abstinence (PPA). We will also examine longer-term predictive validity using separate logistic regressions to evaluate if early withdrawal severity (e.g., TQD via EMA, TQD +1-2d Call 4, TQD +1w Visit 2) predicts biochemically confirmed 7-day PPA at end of treatment (>9w Visit 4). For these analyses we will examine both the linear model estimates of TQD jump and post-TQD mean and trajectory (e.g., linear slope, quadratic) as predictors of biochemically confirmed PPA. We will examine predictive validity of post-TQD withdrawal severity both controlling (primary) and not controlling (secondary) for pre-TQD scores as well as controlling for smoking status at time of withdrawal assessment. We will examine the predictive validity of both the WSWS2-L and WSWS-B.

We will also use logistic regression and linear model estimates to examine associations of individual items and subscales of the WSWS2 forms with abstinence outcomes to identify those that are significantly predictive of cessation.

We will also conduct analyses focused on the prediction of 1-week (pre-medication, Visit 2) and 9-week (end-of-treatment, Visit 4) abstinence using *pre-quit* WSWS2-L subscale and scale scores and WSWS2-B scale scores. These analyses will use dimensions of withdrawal scores as used in the piecewise models described above (e.g., capturing trajectory, average, intra-subject variability). The magnitude of the relations with abstinence outcomes will be compared with the magnitude of relations of those dimensions as reflected by pre- to post-withdrawal change scores. In addition, regression and regression tree analyses will be used to identify person factors that predict strength of withdrawal-abstinence associations using baseline withdrawal dimensions and then using withdrawal change dimensions. The intent is to determine if different factors may influence trait-like withdrawal symptom elevation versus deprivation-induced elevation.

As an exploratory outcome, we will also plan to examine predictive validity using survival analysis (e.g., Cox proportional hazards regression models) to determine how withdrawal severity (scale and subscales) influence time to first lapse (e.g., any smoking in a 24hr period) and progression from first lapse to return to regular smoking (e.g., 7 consecutive days of smoking) through end of treatment (Call 5, 9w).

Similar predictive validity analyses will be conducted with the MTWS-R forms. Logistic regression analyses will be used to determine if either the WSWS2 or the MTWS-R shows significant incremental prediction of abstinence with the alternative assessment statistically controlled.

Exploratory Withdrawal Symptoms:
We included new items with every assessment of the WSWS2-L and WSWS2-B to assess symptom domains that have been proposed as possible symptoms of tobacco withdrawal: anhedonia (two items) and pain (one item). We will conduct the above analyses with and without these new items where possible (e.g., no subscale factor analysis due to limited number of items). These analyses may yield recommendations for a revised scale (e.g., WSWS3) or a parallel version for research purposes if these new items substantially improve the psychometric properties or construct validity of the WSWS2: e.g., improve prediction of abstinence or show sensitivity to tobacco abstinence from pre- to post-TQD.

Sensitivity to Pharmacotherapy:
We will examine sensitivity to pharmacotherapy (nicotine patch + mini lozenge), which is hypothesized to decrease withdrawal severity. We will calculate residualized change scores (adjusting for pre-quit baseline) to quantify the change in WSWS2 total scale and subscale scores after 1 week of pharmacotherapy (Visit 3 scores, TQD +2w) relative to immediately prior to initiating pharmacotherapy (Visit 2 scores, TQD +1w) and separately, relative to a stable pre-quit baseline (Mean scores: Visit 1, Call 1, Call 2). We will examine these residualized change scores using GLMs to test whether the change significantly differs from zero and the corresponding effect size. We will examine unadjusted models as well as models controlling for medication dose (e.g., patch 7mg vs 14mg) and medication adherence. A valid assessment of withdrawal severity should be sensitive to decreases in symptoms following pharmacotherapy use.

We will conduct similar analyses with regard to the MTWS-R forms.

Withdrawal Scale Comparison:
As noted above, we will conduct parallel psychometric and validation analyses for the WSWS2-L, WSWS2-B, and MTWS-R, except when not possible due to constraints placed on single item-subscales (e.g., subscale internal consistency, CFA).

Idiographic Examination of Withdrawal Waveforms & Prediction of Withdrawal Severity:
We will examine plots of individual waveforms of withdrawal scores for the WSWS2 forms and subscales and the MTWS-R in order to reveal individual variation in withdrawal profiles over the pre-TQD and post-TQD assessment periods (e.g., peak, trajectory, average, variability, duration). Related to this, changes in symptom volatility and associations with episodic events (e.g., stressor occurrence, cue exposure) will also be examined in the pre- and post-TQD periods using piecewise linear models. The intent is to determine sensitivity to such events and to determine whether such sensitivity changes from pre- to post-TQD. Additionally, we will examine baseline factors (e.g., demographics, alcohol/cannabis use, chronic pain, anhedonia, anxiety/depression/stress, distress tolerance) that are most strongly associated with withdrawal severity during the pre-TQD and post-TQD periods.

Craving Construct Exploration:
We assessed specific motives for smoking occasions that were temporally contiguous with craving assessments (e.g., via EMA). Craving is consistently the most informative withdrawal symptom with regard to abstinence prediction and the mediation of smoking treatment effects. Moreover, there are different theoretical accounts of the nature of motives that may underlie or

instigate craving. The various theories yield somewhat different predictions about the subjective states or smoking motives that should be related to craving reports. This research gathered EMA reports assessing smoking motives such as smoking to: reduce distress, to escape nagging thoughts/interrupts regarding smoking, experience the taste/feel of smoking, experience the cigarette high/buzz, enhance pleasure from other activities, and so on. The associations of these items with craving self-report will be examined in order to determine which relatively specific smoking motives are most highly associated with craving in the pre-quit and post-quit periods. This will be done using both zero-order correlations as well as using network analytic methods. Further, the associations of such individual craving items with abstinence onset and smoking status at 1-week post-TQD (Visit 2) and end of treatment (Call 5 & Visit 4) will be determined.

Sensitivity Analyses:
We will conduct all psychometric and validation analyses on the maximum available sample at each specified time point as well as on subsets of data to evaluate how the results differ. For instance, we will conduct analyses only on the subset of participants who self-report abstinence at each post-TQD time point as well as with different cut-offs of maximum number of cigarettes smoked per day during each post-TQD period (e.g., <2cpd, <5cpd). We will examine the extent to which results vary as a function of including participants who report complete abstinence versus significant reductions in smoking (and presumably still may be experiencing significant withdrawal symptoms). Likewise, we will examine smoking since the last report as a time-varying covariate in linear models to determine how results vary when controlling for smoking status in this manner.