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DEVELOPING THREE NEW PATHOPHYSIOLOGICALLY  
BASED MEASURES OF NICOTINE DEPENDENCE

A Dissertation Presented

By

Wannakuwatte Waduge Sanouri Anaska Ursprung

Submitted to the Faculty of the  
University of Massachusetts Graduate School of Biomedical Sciences,  
Worcester

in partial fulfillment of the requirements for the degree of  
DOCTOR OF PHILOSOPHY

January 29, 2014

Clinical & Population Health Research Program

**DEVELOPING THREE NEW PATHOPHYSIOLOGICALLY BASED  
MEASURES OF NICOTINE DEPENDENCE**

**A Dissertation Presented**

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**Wannakuwatte Waduge Sanouri Anaska Ursprung**

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Dean of the Graduate School of Biomedical Sciences  
Clinical & Population Health Research Program  
January 29, 2014

## DEDICATION

This dissertation is dedicated to all the friends and family who supported me through this process. To my parents, whose dedication and perseverance through whatever life gave them taught me that hard work and faith are the mainstays of a successful life. To my brothers, who have been my tireless champions and comic relief when I most needed it. Most of all, to my loving husband Eric, who has been an anchor in every storm, my confidence when I had none, and the best friend and companion anyone could ask for. I could not have done this without all of you.

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## ABSTRACT

**BACKGROUND:** Of the 22 known measures of nicotine dependence (ND), none capture the overall disease severity of physical dependence alone. Instead, they capture constructs related to dependence, such as perceived risk, psychological addiction, smoker motivations, or smoking related behaviors, but none of the measures include only *physical withdrawal symptoms* to capture physical dependence on nicotine.

**AIM:** To develop a range of nicotine dependence measures that capture physical dependence on nicotine.

**METHODS:** The final measures were developed in a cross-sectional study conducted in three phases: 1) candidate item development through literature review and cognitive interviews, 2) developing and pre-testing the survey, and 3) survey administration and psychometric evaluation to validate three distinct measures. The final survey was conducted at four health clinics and three high schools. Psychometric tests used to select the final measure items included inter-item correlations, sensitivity analyses done by subgroup, item-total correlations, convergent validity tests, and confirmatory factor analysis. The final measures were evaluated using confirmatory factor analysis (CFA), internal reliability, total score distributions, and convergent validity correlations. Relative validity analyses were also conducted using a ratio of F-Statistics to compare the ability of each new measure to differentiate dependent smokers as compared previous measures.

**RESULTS:** The final sample included 275 smokers ranging from 14 to 76 years old (mean=30.9, SD=16.2), who smoked an average of 11.5 cigarettes per day (range=0-50, SD=9.4). The sample was 86.5% white and 57.5% male. The three new measures developed included: 1) the 4-item Withdrawal-Induced Craving Scale (WICS) used to capture severity of craving, the most common physical withdrawal symptom; 2) the 12-item Nicotine Withdrawal Symptom Checklist (NWSC), which measures both overall disease severity and the severity of a comprehensive list of individual physical withdrawal symptoms including withdrawal-induced craving, anger, anxiety, depression, headache, insomnia, loss of focus, restlessness, and stress; and 3) the 6-item brief NWSC (NWSC-b), a short measure which only captures overall disease severity. All of the new measures exhibited a unidimensional factor structure loading highly on a single factor (thought to be physical dependence). They also correlated highly (over 0.6) and significantly ( $p < 0.001$ ) to a battery of convergent validity indices including four widely used nicotine dependence measures: Hooked on Nicotine Checklist (HONC), the Autonomy Over Tobacco Scale (AUTOS), the Fagerström Test for Nicotine Dependence (FTND), and self-rated addiction.

**CONCLUSION:** The WICS, NWSC, and NWSC-b provide three distinct validated tools that can be used by researchers, clinicians, and educators to track the progression of physical dependence on nicotine across a range of smoking behaviors and histories.

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## PREFACE

Publications and presentations related to this study but not presented in detail in this dissertation are listed below:

### Publications:

Huang, W., DiFranza, J.R., Kennedy, D.N., Zhang, N., Ziedonis, D., Ursprung, W.W., & King, J.A. Progressive Levels of Physical Dependence to Tobacco Coincide with Changes in the Anterior Cingulum Bundle Microstructure. *PLoS One*. 2013 Jul 4;8(7):e67837.

DiFranza J.R., Wellman R. J., Savageau, J. A., Beccia A., Ursprung, W. W., & McMillen R. (2013) What Aspect of Dependence Does the Fagerstrom Test for Nicotine Dependence Measure?, *ISRN Addiction*, vol. 2013, Article ID 906276, 8 pages.

DiFranza, J. R., Ursprung, W. W. & Biller, L. (2012) The developmental sequence of tobacco withdrawal symptoms of wanting, craving and needing, *Pharmacol Biochem Behav*, 100, 494-7.

Ursprung, W. W., Morello, P., Gershenson, B. & DiFranza, J. R. (2011) Development of a measure of the latency to needing a cigarette, *J Adolesc Health*, 48, 338-43.

DiFranza, J. R., Sweet, M., Savageau, J. & Ursprung, W. W. (2011) An evaluation of a clinical approach to staging tobacco addiction, *J Pediatr*, 159, 999-1003 e1.

DiFranza, J. R., Ursprung, W. W. & Carson, A. (2010) New insights into the compulsion to use tobacco from an adolescent case-series, *J Adolesc*, 33, 209-14.

DiFranza, J., Ursprung, W. W., Lauzon, B. et al. (2010) A systematic review of the Diagnostic and Statistical Manual diagnostic criteria for nicotine dependence, *Addict Behav*, 35, 373-82.

DiFranza, J. & Ursprung, W. W. (2010) A systematic review of the International Classification of Diseases criteria for the diagnosis of tobacco dependence, *Addict Behav*, 35, 805-10.

### Presentations:

King, J., Ursprung W.W., DiFranza, J. R., Huang, W., Zhang, N., Kennedy, K., Ziedonis, D. Three Measures of Tobacco Dependence Independently Predict Changes in Neural Structure. Poster presented at the University of Massachusetts Medical School Center for Clinical and Translational Science 4th Annual Research Retreat. (May, 2013). Worcester, MA.

DiFranza, J. R., Ursprung W.W., Huang, W., King, J., Zhang, N., Kennedy, K., Ziedonis, D. fMRI Studies: Is Nicotine Addiction Hardwired? Paper Presented at the Annual American Academy of Pediatrics Julius B. Richmond Center of Excellence Tobacco Consortium Meeting. (April, 2013). Boston, MA.



Huang, W., Ursprung W.W., King, J., DiFranza, J. R., Zhang, N., Kennedy, K., Ziedonis, D. Increasing Severity of Physical Dependence Corresponds to Progressive Changes in Neural Structure. Paper presented at the Society of Nicotine and Tobacco Research Annual Meeting. (March, 2013). Boston, MA.

King, J., Ursprung W.W., DiFranza, J. R., Huang, W., Zhang, N., Kennedy, K., Ziedonis, D. Three Measures of Tobacco Dependence Independently Predict Changes in Neural Structure. Poster presented at the Society of Nicotine and Tobacco Research Annual Meeting. (March, 2013). Boston, MA.

Zhang, N., DiFranza, J. R., King, J., Huang, W., Kennedy, K., Ursprung W.W., Ziedonis, D. A Test of the Sensitization-Homeostasis Model of Neuroplasticity in Addiction. Poster presented at the Society of Nicotine and Tobacco Research Annual Meeting. (March, 2013). Boston, MA.

DiFranza, J. R., Ursprung W.W. Four New Measures of Tobacco Dependence Optimized for Biological Research. Poster presented at the Society of Nicotine and Tobacco Research Annual Meeting. (March, 2013). Boston, MA.

DiFranza J, Huang W, Zhang N, Ursprung W.W., Kennedy D, and King J. Exploring Biomarkers of Nicotine Addiction: Resting State and DTI Measures Linked To Physical Dependence; presented at the 18th annual meeting of the Organization for Human Brain Mapping (HBM). (June 2012). Beijing, China.

DiFranza, J. R., Wellman, R. J., Savageau, J. A., Beccia, A., & Ursprung, W. W. What aspect of dependence does the Fagerström Test for Nicotine Dependence measure? Poster (POS 3-74) presented at the 18th Annual Meeting of the Society for Research on Nicotine & Tobacco. (March 2012). Houston, TX.

Ursprung, W.W., DiFranza, J.R., Sweet, M., and Savageau, J., “A Preliminary Evaluation of Nicotine Addiction Staging Based on Nicotine Withdrawal Symptoms.” presented at the Society for Research on Nicotine and Tobacco (SRNT) 17th Annual Meeting. (February 2011). Toronto, Ontario, Canada.

Ursprung, W.W., DiFranza, J. R., Sweet, M., and Savageau, J. “A preliminary evaluation of nicotine addiction staging.” presented at Annual Conference of the International Society for the Prevention of Tobacco Induced Diseases (ISPTID). (September/October 2010) Boston, MA.

## CHAPTER I

**Introduction: *The Need for New Pathophysiologically Based Measures of Nicotine Dependence***

### **1.1 Why is physical dependence on nicotine important?**

Despite decades of nicotine dependence (ND) research and public awareness campaigns, tobacco use remains the world's number one preventable cause of death.<sup>1</sup> Of the 1 billion smokers in the world today, it is predicted that 500 million of them will die from tobacco related disease.<sup>1</sup> While there are many drivers of tobacco use, physical dependence on nicotine remains the most prevalent by far, but the clinical tools available to diagnose and monitor the progression of this disease are limited.<sup>1-7</sup> Physical dependence is evident when nicotine is no longer acting on the brain, thus triggering a withdrawal response.<sup>8-10</sup> Physical dependence is different from other forms of dependence such as psychological dependence, and cue-induced craving which are not directly related to the physical action of nicotine on the brain and therefore cannot be alleviated with nicotine administration.<sup>4,8,11-13</sup> Having a clinical diagnostic tool to establish *physical* dependence is imperative for several reasons: 1) for pathophysiological research exploring which addiction-related physical processes can be targeted to create better pharmaceutical interventions, 2) for clinicians to diagnose and track the progression of the condition, 3) for accurate epidemiological surveys to estimate the prevalence of the condition in any given population and 4) for researchers in related fields to accurately screen for or exclude subjects with nicotine dependence in other clinical trials.

### **1.2 How are current measures of physical nicotine dependence inadequate?**

Of the 22 current measures of nicotine dependence (ND) identified, none of them provide a non-acute estimate of overall physical dependence level through the inclusion

of a comprehensive list of physical withdrawal symptoms.<sup>11,14-33</sup> Four measures include some items capturing physical dependence amongst other items covering non-physical aspects of dependence.<sup>4,8,11,15,28</sup> The other 18 measures fall into one of the following categories: 1) they are intended for acute, momentary evaluation of withdrawal symptom intensity not a diagnosis of overall physical dependence level, 2) they precede current neurobiological research and are therefore reliant on outdated theoretical frameworks, 3) they were developed in niche populations to capture either onset or late stage dependence and do not differentiate well on the entire addiction spectrum, 4) they were developed or validated only for cigarettes and cannot be used to capture dependence to other forms of nicotine, or 5) they capture constructs related to physical dependence but not actual symptoms of physical dependence. Such constructs related to dependence include perceived risk, motivations for smoking, and smoking-related behaviors (such as where or when people smoke). For example, measures like the Nicotine Dependence Syndrome Scale (NDSS) ask whether smokers avoid non-smoking restaurants or airplane travel.<sup>27</sup> It is true that some highly dependent smokers may avoid flying because they suffer from symptoms of physical withdrawal. However, measuring an individual's avoidance of flying is simply a *behavioral* proxy for their succumbing to unremitting, symptoms of *physical* dependence. Furthermore this kind of proxy item is irrelevant to any smoker who cannot afford air travel, or who has no occasion to fly.

Of the remaining four measures that are said to capture some aspect of physical dependence, three contain six or more items, which may make them too long for inclusion in larger surveys. These include the Hooked on Nicotine Checklist (HONC),

Fagerström Test for Nicotine Dependence (FTND), and the Autonomy over Tobacco Scale (AUTOS).<sup>11,15,28,34,35</sup> Furthermore, none of these three instruments measure of physical dependence alone. The AUTOS captures three aspects of dependence: physical dependence, psychological dependence, and cue-induced withdrawal symptoms. The HONC was developed to detect the onset of dependence, not its progression through advanced stages. Finally, as the oldest measure, the FTND has several drawbacks. First, there is little consensus as to what the FTND actually measures, though it has been used in the field to measure physical dependence.<sup>15,36</sup> Second, it performs poorly in psychometric reliability and validity tests, and does not correlate highly to dependence as defined by the International Classification of Diseases (ICD10) criteria or the Diagnostic and Statistical Manual of Diseases (DSM-IV) criteria.<sup>35</sup> Most of its predictive power seems to come from two items: time to first cigarette of the morning (TTFC) and smoking volume (cigarettes per day or CPD).<sup>35,37-41</sup> Finally, the FTND only captures nicotine dependence in *cigarette* users, not users of other forms of nicotine, and does not include any actual symptoms of physical withdrawal.<sup>42</sup> The fourth measure, the Levels of Physical Dependence (PD), is a short measure of that captures only the most common symptom of physical dependence: withdrawal-induced craving.<sup>3,4,8,33,43</sup>

### **1.3 The Levels of Physical Dependence Measure**

The Levels of PD measure was developed using tobacco users' own words after a series of case histories and cognitive interviews in which over 200 adults and adolescents described the progression of their addiction.<sup>4,33,43</sup> After development of the items, the measure was validated in a range of populations including adults, adolescents, smokeless

tobacco users, and Spanish speaking populations.<sup>3,4,8,33,44</sup> Each symptom in the Levels of PD measure occurs in a sequential progression reflecting an escalation in the severity of withdrawal symptoms.<sup>3,4,8,10,33,43</sup> The items and scoring algorithm for this measure can be found in Figure 1.1. At first, physically dependent tobacco users experience a mild form of craving that is defined as “a mild desire that can easily be ignored.”<sup>3,4,8,33,44</sup> As dependence escalates, tobacco users experience a more intense and intrusive desire to smoke that interrupts their thoughts. This second symptom is defined as a stronger desire that it is more persistent and harder to ignore.<sup>4,8,33,45</sup> The most advanced stage defined by the Levels of PD measure is an intrusive need to smoke that prevents an individual from functioning normally and requires that they smoke to “feel normal again” (see Figure 1.1). This is distinguished from the other symptoms by its unremitting urgency and the fact that it cannot be ignored.<sup>4,8,33</sup>

The three symptoms in the Levels of PD measure occurred in a sequential progression in 99.4% of tested cases.<sup>4,33</sup> This progression is significantly correlated to an increase in dependence as measured by the HONC, FTND, and AUTOS.<sup>8,33</sup> It was also significantly correlated to higher levels of psychological addiction, years of smoking, frequency of tobacco use, daily cigarette consumption, and a battery of other indicators of nicotine dependence.<sup>8</sup> In addition to its psychometric validation, the Levels of PD has also been tested in neurobiological studies where it has correlated highly to physical changes in the addiction-related areas of the brain including the left anterior cingulate bundle, superior-frontal cortex, precuneus, insula, caudate, putamen, middle cingulate gyrus, and precentral gyrus.<sup>10</sup>

Despite its high correlation to a range of nicotine dependence and biological indices, the Levels of PD measure only differentiates dependent tobacco users into three groups. For some forms of research it could be beneficial to be able to differentiate subjects with more precision. Furthermore, the Levels of PD measure only captures one construct related to physical dependence: craving.<sup>4,8,33,43</sup> It is possible that capturing more aspects of physical dependence could create more powerful, versatile, or precise measures. The resulting instruments could provide a set of tools for use in a wide range of research and surveillance environments. For example, in some environments researchers require a comprehensive measure covering all possible withdrawal symptoms, whereas in other settings researchers may require a shorter measure for inclusion in larger surveys where space is limited. The purpose of this study is to explore an expansion of the Levels of PD measure to include additional symptoms to create a versatile set of instruments.

**Figure 1.1 The Levels of Physical Dependence Measure**

1. If I go too long without smoking or using dip, the first thing I notice is a *mild desire* to smoke or use dip that I can ignore.
  - No. This statement does not describe me.
  - Yes.
  
2. If I go too long without smoking or using dip, the desire for a cigarette or dip becomes so strong that it is hard to ignore and it interrupts my thinking.
  - No. This statement does not describe me.
  - Yes.
  
3. If I go too long without smoking or using dip, I just can't function right, and I know I will have to smoke or use dip just to feel normal again.
  - No. This statement does not describe me.
  - Yes.

**Scoring Algorithm:**

- 3 = the highest endorsed item is 3
- 2 = the highest endorsed item is 2
- 1 = the highest endorsed item is 1
- 0 = did not endorse any items 1-3



## CHAPTER II

### *The Development and Validation of the Withdrawal-Induced Craving Scale (WICS)*

## 2.1 Introduction

While addiction is often viewed as a purely psychological condition, it arises in part from a *physical* process in the brain.<sup>10,12,13</sup> Physical dependence on nicotine encompasses those symptoms of withdrawal that arise and escalate the longer a tobacco user waits between administrations of nicotine.<sup>8,44,46,47</sup> These symptoms of physical dependence are alleviated by an administration of nicotine. Physical dependence is distinguishable from other aspects of dependence such as psychological dependence and cue-induced craving.<sup>11,44,46</sup> Physical dependence develops through a set progression of levels characterized by an escalation in the severity of withdrawal symptoms experienced during abstinence.<sup>3,4,8,10,33,43</sup> This progression was discovered during a series of over 200 case histories in which smokers of all ages and smoking histories were interviewed about their dependence.<sup>4,33,43</sup> Interviewees described the same escalation of symptoms when recounting how their addiction progressed. In order to capture this observed phenomenon, the Levels of Physical Dependence (PD) measure was developed using these tobacco users' own words.<sup>4,8</sup>

The Levels of PD measure captures the most common symptom of dependence: withdrawal induced craving.<sup>3,4,8,33,43</sup> The items and scoring algorithm for this measure can be found in Table 2.1. At the beginning, physically dependent tobacco users experience a mild form of craving defined in the measure as “a mild desire that can easily be ignored.”<sup>3,4,8,33,44</sup> As dependence escalates, tobacco users develop a more intense and intrusive desire to smoke that interrupts their thoughts. This differs quantitatively from the first symptom in that it is a stronger, more persistent desire that is harder to

ignore.<sup>4,8,33,45</sup> The most advanced stage of the Levels of PD measure is defined as an intrusive need to smoke that prevents an individual from functioning normally and requires that they smoke to “feel normal again” (see Table 2.1). This is distinguished from the other symptoms by its unremitting urgency and the fact that it cannot be ignored.<sup>4,8,33</sup>

After development of the items, the measure was validated in a range of populations including adults, adolescents, smokeless tobacco users, and Spanish speaking populations.<sup>3,4,8,33,44</sup> Each symptom in the Levels of PD measure occurs in a sequential progression in 99.4% of tested cases.<sup>4,33</sup> As expected for a symptom arising from abstinence from nicotine, each symptom is alleviated by the administration of nicotine.<sup>4,33</sup> This progression is significantly correlated with an increase in dependence as measured by the Hooked on Nicotine Checklist (HONC), the Fagerström Test for Nicotine Dependence (FTND), the Autonomy Over Tobacco Scale (AUTOS), and self-rated addiction (“how addicted do you think you are on a scale of 0-4”).<sup>8,15,33,35</sup> It was also significantly correlated to higher levels of psychological addiction, years of smoking, frequency of tobacco use, daily cigarette consumption, and a battery of other correlates to nicotine dependence.<sup>8</sup> This battery of nicotine dependence indices consists of correlates used widely in other nicotine dependence validation studies such as: other withdrawal symptoms, self-reported addiction, lifetime cigarette consumption, desire to quit, enjoyment obtained from smoking, relief obtained from smoking, pleasure obtained from smoking, and cigarettes smoked per day. While these are not nicotine dependence

measures themselves, they are expected to trend with dependence, thus establishing convergent validity.

In addition to its psychometric validation, the Levels of PD has also been validated in neurobiological studies where it correlates highly to physical changes in known addiction regions of the brain including the left anterior cingulate bundle, superior-frontal cortex, precuneus, insula, caudate, putamen, middle cingulate gyrus, and precentral gyrus.<sup>10</sup> These studies examined the correlation of dependence score, as captured by the Levels of PD measure, to changes in brain activity and structure when in a withdrawal state versus a satiated state. Subjects were both male and female smokers with a wide range of smoking volumes and smoking histories, with non-smokers used as a control. The levels of PD score correlated significantly to both structural changes, such as increased white matter tract density, and functional changes, such as increased connectivity between key addiction regions.

While it performs well in biological studies, and correlates highly to a range of nicotine dependence indices, the Levels of PD measure is limited in its precision as it only differentiates dependent tobacco users into three levels. For some forms of research, it could be beneficial to differentiate subjects on a more gradated scale. Furthermore, the Levels of PD measure only captures one aspect of physical dependence: severity of withdrawal-induced craving.<sup>4,8,33,43</sup> However, while it establishes whether or not an individual experiences withdrawal-induced craving, it does not quantify an individual's latency to withdrawal. Latency to withdrawal-induced craving is defined as the time elapsed between using tobacco and the onset of a given withdrawal symptom.<sup>3-5,10</sup> Any

tobacco user who experiences withdrawal must have a latency to withdrawal. Based on findings from past case studies, it has been observed that the latency to withdrawal varies widely between smokers, from minutes to weeks.<sup>3,4,43</sup> These case studies demonstrate that latency shortens in a consistent, sequential manner as dependence escalates. Latency itself has been correlated to a range of nicotine dependence indices.<sup>8,43,47</sup> It has also been validated as an independent measure of nicotine dependence.<sup>3</sup> However, it has never been incorporated into a nicotine dependence instrument despite its theoretical relevance.<sup>3-5,47</sup> While the Levels of PD measure establishes whether an individual has a latency to withdrawal (by measuring whether they eventually experience a withdrawal symptom), it does not in any way quantify this the length of this latency, and thus does not distinguish between an individual who can wait five minutes between cigarettes and a person who can wait 24 hours. It is possible that quantifying the length of latency and adding it to the Levels of PD measure would allow comparison of the relative dependence level of different smokers, and could also help to track how the period between smoking and withdrawal onset shortens as dependence progresses. To this end this study explored two aims, 1) whether the Levels of PD instrument could be expanded by incorporating latency to withdrawal and 2) how best to capture the construct of latency.

The latency to withdrawal can be quantified directly by asking an individual how long after smoking they can wait before experiencing a withdrawal symptom.<sup>3,4,8</sup> It can also be captured indirectly through proxy measures. For example, the most predictive item in the FTND asks subjects how soon after waking they smoke a cigarette.<sup>35,37-41</sup>

Smokers who can wait several hours after waking before smoking would presumably have a longer latency to withdrawal than those who must smoke immediately after waking. However, because the time to first cigarette (TTFC) is measuring a behavior (actively smoking a cigarette), not a withdrawal symptom, it may not accurately capture latency in individuals who do not have an opportunity to smoke upon arising. For this reason, we hypothesized that *wanting to smoke* upon waking might be a better proxy for length of latency to withdrawal than the TTFC.

Length of latency to withdrawal is a clear, quantifiable construct directly caused by a measurable physiological process.<sup>3,4,8</sup> It has more face validity as an indicator of dependence than more traditional biological metrics like expired carbon monoxide and saliva cotinine levels, which reflect smoke intake and rate of metabolism. Because the latency is related to PD, we hypothesize that combining a measure of latency with the Levels of PD measure could create a more powerful and precise instrument.

## **2.2 Materials and Methods**

### *2.2.1 Subjects & Recruitment*

The goal for this validation study was to recruit a broad range of subjects that were diverse in age, smoking level, ethnicity, and socioeconomic status. To this end, the sample was drawn from high schools and health clinics in Massachusetts. All procedures were approved by the Human Subjects Institutional Review Board.

### *2.2.1.1 High School Subjects*

Students from three high schools were enrolled in the study. This included one rural regional school, one urban/suburban school and one vocational school. In advance of survey administration, a letter was sent to the parents allowing them to withhold their child from participation. Surveys were administered to all participating students, including nonsmokers, in order to avoid singling out smokers, and to capture novice smokers, experimenters, and other occasional tobacco users who may not yet perceive themselves as smokers. Surveys were administered in classes common to all students such as homeroom or health. Teachers read directions that informed students that their participation was voluntary and anonymous. Students handed in their surveys by placing them in an envelope or slotted box.

### *2.2.1.2 Clinic Subjects*

A convenience sample of adult smokers was recruited from two primary care and two behavioral health clinics that served a racially and socioeconomically diverse population. Patients were invited to complete an anonymous survey by study personnel in the waiting room, front desk staff, or their physicians.

### *2.2.2 Survey Items and Development*

Survey items included the previously validated Levels of PD instrument, demographic information, a battery of indices of nicotine dependence, and four validated measures of nicotine dependence to assess convergent validity. These four measures included the HONC, the AUTOS, the FTND, and self-rated addiction.<sup>11,15,28,35</sup> The battery of nicotine dependence indices included: other withdrawal symptoms, self-

reported addiction, lifetime cigarette consumption, desire to quit, enjoyment obtained from smoking, relief obtained from smoking, pleasure obtained from smoking, and cigarettes smoked per day. It is of note that the original metric of ‘pleasure’ was included because of its use in past validation studies, however two additional items ‘enjoyment’ and ‘relief’ were added after pre-testing because participants interpreted the word “pleasure” as both “relief” (like scratching an itch) and “pleasure” (like enjoying a piece of candy). To capture other withdrawal symptoms, subjects were asked whether after abstinence from nicotine they experienced symptoms including anger/irritability, increased appetite, depression, difficulty concentrating, insomnia, restlessness, stress, headache, or anxiety.

#### *2.2.2.1 Latency Items*

Three items measuring length of latency to withdrawal were also included in the survey. First, latency was captured as a continuous measure with the intent of creating categorical cutoffs during the analysis. Respondents were asked how long after smoking a cigarette they could wait (in minutes, hours, or days) before experiencing each of the PD symptoms (items 1-3 in Table 2.1). This combined construct was abbreviated as PD+Time. Second, latency was captured using the TTFC item in the FTND.<sup>35,41</sup> Answer categories for this item were taken directly from the FTND and include: within 5 min, 6-30 min, 31-60 min, or longer than 60 min. In analyses, the combined score from this construct and the original Latency to PD instrument was abbreviated as PD+TTFC. Third, we included a modified version of the TTFC item focusing on the *urge* to use tobacco and not the *act* of smoking. This new item read “I usually want to smoke right



after I wake up.” And was scored on the same 0-4 scale used in several of the standard measures: not at all, a little, pretty well, very well. This version of latency combined with the original Levels of PD instrument was abbreviated as PD+Wake.

### *2.2.3 Pretesting and Cognitive Interviews*

Items were pretested and edited through a series of cognitive interviews. Sixteen cognitive interviews were conducted with subjects covering a broad range of ages, smoking levels, and backgrounds. Over one third of the interviewees were minorities, with three African American and four Hispanic subjects. Interviewees were asked about the wording, content, format, clarity and answer choices for each item in order to edit and finalize the survey items.

### *2.2.4 Analytic Methods*

#### *2.2.4.1 General Analytic Methods*

Analyses were done in STATA version 11, and R Project 3.0.1. Surveys with incomplete data on the Levels of PD or latency items were culled (Adolescents=46, Adults=176). Continuous items were converted to categorical variables. For this reason, polychoric correlations were used. For the item level evaluations and subgroup analyses, differences in means were assessed using paired t-tests and one-way analysis of variance. The statistical significance of differences between correlation coefficients was assessed using a Fisher's r to z transformation.<sup>48</sup> Significance was established at  $p < 0.05$  for differences in means or coefficients significantly different from zero, and at  $p < 0.001$  level for correlations due to multiple comparisons.

Scores for the PD+TTFC and PD+Wake measures were calculated as described above. Several scoring algorithms were explored for the conversion of the continuous latency item into a categorical variable of 2, 3 or 4 categories. The latency item is reverse-scored such that a shorter latency is associated with a higher score. For the final version, we combined a 4-quartile categorical latency variable with the Levels of PD instrument to create the PD+Time measure as described in Figure 2.1. Each level of PD was differentiated into four possible sub-levels based on latency quartiles, resulting in a range of 0-12.

Item-level distributions were examined to compare PD+Time, PD+TTFC, and PD+Wake. Convergent validity was evaluated by comparing polychoric correlation coefficients to determine which measure correlated best to the HONC, AUTOS, FTND, and self-rated addiction.<sup>48</sup> In calculating the correlation between the FTND and PD+TTFC, the TTFC item was dropped from the FTND to avoid inflated correlation. Convergent validity was further evaluated by comparing the three new measures to a battery of correlates of dependence, i.e., indices that are not validated measures of dependence, but should theoretically correlate with dependence: other withdrawal symptoms, self-reported addiction, lifetime cigarette consumption, desire to quit, enjoyment obtained from smoking, and cigarettes smoked per day.

#### *2.2.4.2 Sensitivity Analyses*

As a sensitivity analysis, all tests were also conducted by age group and smoking history to establish whether scale development would differ by subgroup. Age based analyses were conducted in the adult (over 18 years) and adolescent (under 18 years)

samples separately. For smoking history based analyses, results were compared in smokers who had smoked less than 2 years and in those who had smoked for 2 years or more. This cut-off was selected in accordance with past evidence suggesting nicotine dependence symptoms mostly plateau after 2 years of constant use.<sup>49</sup>

#### *2.2.4.3 Relative Validity*

To select the final latency item, we also calculated the relative validity of each candidate scoring method in comparison to the original Levels of PD criteria. Relative validity (RV), also known as relative efficiency or relative precision,<sup>50</sup> is a method of estimating how well several measures or several scoring algorithms differentiate subjects in a set sequence when compared to a reference measure. An RV greater than 1 indicates that a given measure has greater precision or responsiveness than the reference measure. The selected grouping variable is generally the closest metric to a gold standard available for the test in question. Given the lack of a gold standard for nicotine dependence, we selected length of smoking history as the binning variable for this analysis, assuming that individuals who had smoked for fewer years would have lower dependence scores than those who had smoked for many years. For the reference variable, we selected the original levels of PD measure, since our goal is to improve on its precision. RV is calculated as a ratio of two measures' ANOVA F-statistics, with the comparator in the numerator and the reference group in the denominator. F-Statistics are in turn a ratio of ANOVA variances. A bias-corrected and accelerated (BCa) bootstrapping technique was used to calculate RVs from random, repeated resampling of the original sample in order

to create a larger empirical sample. The resulting sampling distribution of RVs, and the associated SD, provides a range of the estimate 95% CI of the true RV point estimate.

## **2.3 Results**

### *2.3.1 Sample Characteristics*

A total of 2243 surveys were collected. This included non-smokers (among adolescents only), ex-smokers, and smokers. Subjects who had not smoked in 30 days, had not smoked more than one cigarette in their life, and that had missing data on key variables were excluded resulting in a final sample of 273 subjects. In the adolescent sample, there was an 88% response rate across all students. The adult sample was a convenience sample, therefore response rates could not be calculated. Subjects ranged in age from 14 to 76 (mean=30.94 years, SD=16.19). They had smoked for an average of 14.74 years (range=0.5-63, SD=15.83) and smoked an average of 11.45 cigarettes per day (range=0-50, SD=9.39). The sample was 86.5% white and 57.5% male. Further sample characteristics, demographic information, and mean dependence scores on validated measures of dependence can be found in Table 2.2.

### *2.3.2 Pretesting & Cognitive Interviewing*

During the 15 cognitive interviews where items were pretested, interviewees only suggested minor changes to formatting and wording. No content changes were suggested for the original Levels of PD measure, the continuous latency items, or the new wake item.

### 2.3.3 Convergent Validity

To assess convergent validity, the strength of the correlation of each of the new measures with four standard dependence measures was assessed (Table 2.3). Of the three new measures, PD+Wake correlated best to each standard measure, and was the only measure that correlated better with all of the standard measures than the original Levels of PD instrument did ( $p < 0.05$ ). Of the three new measures, PD+Wake correlated best with the battery of correlates of dependence (Table 2.3). However, it only correlated significantly higher than the original Levels of PD instrument to: lifetime cigarette consumption, cigarettes per day, anger, and stress. Conversely, the PD+TTFC measure correlated significantly *lower* than the original Levels of PD instrument to: thinking one is addicted, desire to quit, increased appetite, anger, focus, restlessness, stress, headache and anxiety.

### 2.3.4 Sensitivity Analyses

As a sensitivity analysis to assess scale invariance, all of the above analyses were repeated, stratifying by age and years smoked. There were no differences in the items selected and scoring methods chosen (data not shown) when the same analyses were conducted among only adolescent versus adult smokers or when conducted among only novice (<2 years) or advanced smokers (>2 years).

### 2.3.5 Relative Validity

The relative validity analyses, (Table 2.6) suggest that compared to the original Levels of PD Criteria, PD+Wake has the highest relative validity (2.53). Given our

parameters, this indicates that of the three scoring versions and original measure PD+Wake sorted subjects by “years smoked” better than any other version.

### *2.3.6 Final Measure*

The final measure, abbreviated as “PD+Wake” in the exploratory analyses, was re-named the Withdrawal-Induced Craving Scale (WICS). The WICS consisted of the original Levels of PD measure combined with a proxy for latency to withdrawal that asked subjects if they had an urge to smoke a cigarette upon waking up (See Table 2.4). The WICS had a minimum possible score of 0 and a maximum possible score of 6. In our population, the WICS measure had a mean score of 3.13 (SD of 2.08). The total score distribution can be seen in Figure 2.2. There were no differences by gender (male mean = 3.07, SD = 2.09, and female mean = 3.21, SD = 2.08). There was a significant difference ( $p < 0.001$ ) between those who had smoked for 2 years or less (mean score = 2.47, SD = 2.10) and those who smoked for longer than 2 years (mean score = 3.54, SD = 1.96). The WICS also correlates better with several of the standard nicotine dependence measures than they do with each other (See Table 2.5).

## **2.4 Discussion**

### *2.4.1 Scale Performance*

We conclude that combining our modified TTFC proxy item for latency with the Levels of PD measure created a better performing measure as compared to the original. Of the three candidate versions tested, the WICS is the best performing because it correlated highest to all convergent validity metrics and was the only version to correlate

$r > 0.6$  to all of the standard nicotine dependence measures. The WICS also outperformed the other scoring variations and original PD measure in relative validity tests, exhibiting the highest relative validity (2.53). Supporting these results, the WICS also correlated significantly with all of the correlates of nicotine dependence, including self-reported addiction, lifetime cigarette consumption, cigarettes smoked per day, desire to quit, all other withdrawal symptoms, and several other nicotine dependence indices (see Table 2.3). The merit of adding a measure of latency to the original Levels of PD instrument is further demonstrated by the observation that the WICS measure correlated significantly higher than the original Levels of PD measure with all of the standard nicotine dependence measures, and several of the other nicotine dependence indices as well.

As seen in Table 2.3, PD+TTFC correlated below 0.7 with all of the standard nicotine dependence measures and correlated significantly lower than the original Levels of PD instrument with several of the other convergent validity metrics. Also, because PD+TTFC performed uniformly worse than the WICS, we conclude that modifying the TTFC to focus on the subjective *symptom* of craving upon waking, instead of the *act* of smoking upon waking, improves its performance.

Because they are measuring different aspects of addiction, we would not necessarily expect high correlations between any of the measures used in this study. It is of note that the WICS correlates better with several of the standard measures than they do with each other (See Table 2.5). For example, the WICS correlates more highly to the HONC than does the FTND, the original Levels of PD instrument, or self-rated addiction. It correlates more highly to the AUTOS than all measures but the HONC. It correlates as

well or higher to self-rated addiction than all measures but the HONC, and it correlates more highly to the FTND than any of the other measures.

#### *2.4.2 Scale Development*

This study is the first to include latency and withdrawal in a larger measure of dependence. Another strength of this study is the broad range of smoking histories and volumes included in the sample. This study also had more subjects per item than most validation studies of other nicotine dependence measures. In addition, the sample population was specifically selected to include a wide range of ages, smoking volumes, and smoking histories. Because the measure was validated in such a diverse, mixed population, it is one of the few measures developed with and for smokers at a broad range of dependence levels, making it suitable for use in studies that include both novice and advanced smokers. The WICS also shows promise for use in biological studies. Because the original PD measure correlated more highly to structural changes in the brain than any other nicotine dependence measure, and because the new measure now includes latency, a quantifiable construct stemming from a physical process, we anticipate that the expanded WICS measure will perform as well or better than the original in biological and neuroimaging studies. Also, because the final measure captures symptoms of withdrawal that should occur regardless of nicotine delivery method, it should be applicable to a wide range of tobacco/nicotine products. Future studies should evaluate the measure among users of alternative nicotine products such as snus, e-cigarettes, waterpipe tobacco, etc. Finally, because the new measure is very short, only four items, it has broad applications for use in surveys/screeners with space restrictions. The new measure captures constructs



universal to smokers at all levels (withdrawal-induced craving and latency to withdrawal). These items are universal enough to be widely endorsed but discriminating enough to result in a meaningful dependence score.

#### *2.4.3 Strengths & Limitations*

While these results suggest that the objective of the study was achieved (expanding the Levels of PD measure), some limitations remain. As seen in Figure 2, the total score distribution is similar to that of the original Levels of PD measure. While physiologic parameters in healthy individuals follow a normal distribution, this is not so with disease processes. Because these instruments are capturing a chronic disease process with decades between onset and death, one would expect a skewed distribution. Despite this, it is also possible that adding further withdrawal symptoms may differentiate the most extreme portion of the scale further. Because our goal was to create the shortest measure possible, such additions were not explored in this study. However, future studies could examine whether it is possible to improve discrimination further by adding more items to this measure. Future studies could extend the validation of this new measure in other racial groups and international populations. Prospective studies should also be conducted to determine how the measure captures the escalation of dependence in the same individual over time. Such studies could also establish test-retest reliability and predictive validity. In addition, biological studies should be conducted to evaluate whether the new measure correlates with the physiological changes in the brain that accompany the progression of dependence.

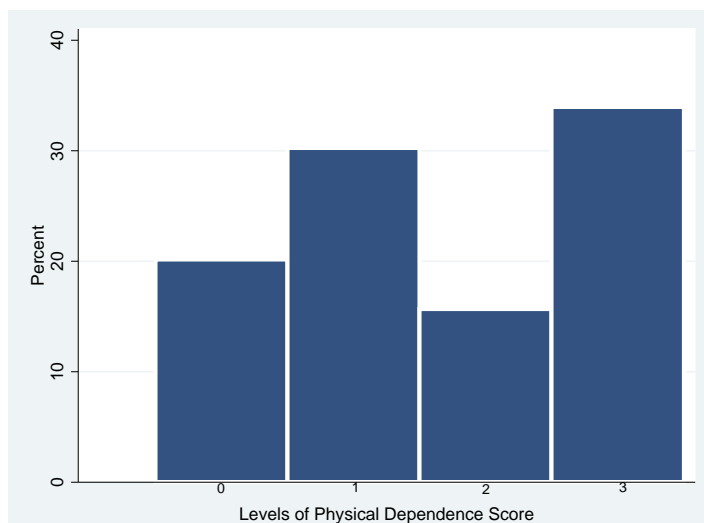
The creation of the WICS, fulfills our *a priori* goals of establishing 1) whether the Levels of PD instrument could be expanded by incorporating latency to withdrawal and 2) how best to capture latency. By expanding the original Levels of PD measure we have created a broader, more comprehensive tool that captures all aspects of the most common symptom on nicotine dependence: withdrawal-induced craving. For situations where a short measure of physical dependence is required, the WICS provides a robust tool with a wider range of dependence levels than the Levels of PD measure.

**Figure 2.1 The PD+Time Scoring Algorithm in Relation to the Original Levels of Physical Dependence (PD) Measure**

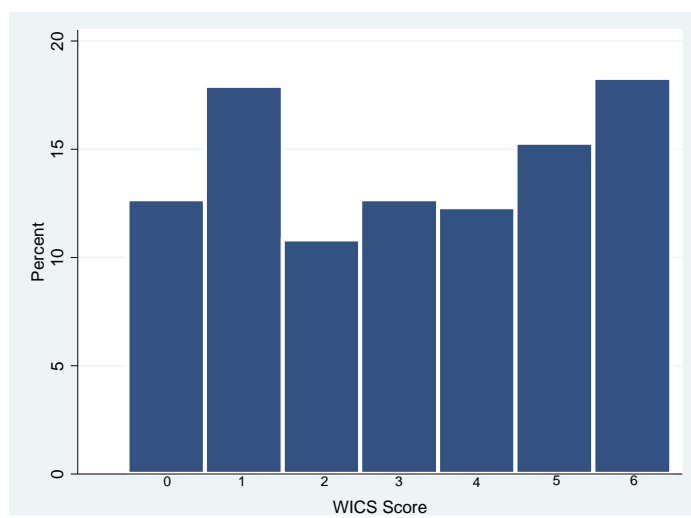
	Scoring of the PD+Time version					Original Levels of PD Measure
	Score if you experience the symptom very slowly	Score if you experience the symptom slowly	Score if you experience the symptom quickly	Score if you experience the symptom very quickly		
The highest endorsed PD symptom is Item 3	9	10	11	12	-	3
The highest endorsed PD symptom is Item 2	5	6	7	8	-	2
The highest endorsed PD symptom is Item 1	1	2	3	4	-	1
No symptoms	0	0	0	0	-	0

\*The scoring algorithm for the PD+Time expansion of the Levels of PD measure is based on four categories of latencies, (the amount of time elapsed between using tobacco and experiencing a given symptom). The four categories were assigned based on the quartiles of this duration which was measured in minutes. For example if you endorse item 3 and experience that symptom very quickly (within the 1<sup>st</sup> quartile = less than 2 hours), then you are assigned a maximum score of 12. This would correlate to a score of 3 on the original Levels of PD measure.

**Figure 2.2 Total Score Distributions of the Original Levels of Physical Dependence Measure and Withdrawal-Induced Craving Scale**



A. Original Levels of Physical Dependence Measure Score Distribution



B. Withdrawal-Induced Craving Scale Score Distribution

**Table 2.1 The Levels of Physical Dependence Measure**

4. If I go too long without smoking or using dip, the first thing I notice is a *mild desire* to smoke or use dip that I can ignore.
  - o No. This statement does not describe me.
  - o Yes.
5. If I go too long without smoking or using dip, the desire for a cigarette or dip becomes so strong that it is hard to ignore and it interrupts my thinking.
  - o No. This statement does not describe me.
  - o Yes.
6. If I go too long without smoking or using dip, I just can't function right, and I know I will have to smoke or use dip just to feel normal again.
  - o No. This statement does not describe me.
  - o Yes.

**Scoring Algorithm:**

- 3 = the highest endorsed item is 3
- 2 = the highest endorsed item is 2
- 1 = the highest endorsed item is 1
- 0 = did not endorse any items 1-3

**Table 2.2 Sample Characteristics (N=273)**

	<i>%(N)</i>	<i>Mean</i>	<i>SD</i>	<i>Range (min- max)</i>
Age		30.94	16.19	14-76
<i>Adolescents (&lt;19)</i>	44.68 (122)			
<i>Adults( 19+)</i>	55.31 (151)			
Years smoked		14.74	15.83	0.5-63
< 2 yrs	20.97 (56)			
2-5 yrs	29.96 (80)			
>5 yrs	49.06 (131)			
Cigarettes/day		11.45	9.39	0-50
HONC		6.28	3.34	0-10
AUTOS		16.60	11.40	0-36
FTND		3.87	2.630	0-10
Self-Rated Addiction		2.45	1.54	0-4
Gender				
<i>Male</i>	57.5(157)			
<i>Female</i>	42.5(116)			
Ethnicity				
<i>Prefer not to identify</i>	0.75 (2)			
<i>American Indian or Alaskan Native</i>	3.01 (8)			
<i>Asian</i>	1.13(3)			
<i>Black</i>	3.76(10)			
<i>Native Hawaiian or Pacific Islander</i>	0.38(1)			
<i>White</i>	86.47(230)			
<i>Mixed</i>	4.51(12)			
Hispanic				
<i>No</i>	88.01(235)			
<i>Yes</i>	11.99 (32)			
Smoking Frequency				
<i>Daily</i>	63.37(173)			
<i>Non-daily</i>	36.63(100)			

HONC = Hooked on Nicotine Checklist  
AUTOS = the Autonomy Over Tobacco Scale  
FTND = the Fagerström Test for Nicotine Dependence

**Table 2.3 Convergent Validity Correlation Table Comparing Three Alternative Versions With The Original Levels Of Physical Dependence (PD) Measure**

	Original Measure	The 3 Expanded Versions of the Levels of PD Measure That Were Tested		
	<i>Levels of PD</i>	<i>Levels of PD +Time</i>	<i>Levels of PD +TTFC</i>	<i>Levels of PD +Wake (WICS)</i>
<i>Other Validated Nicotine Dependence Measures</i>				
HONC	0.68	0.70	0.65	0.75 <sup>a</sup>
AUTOS	0.69	0.73	0.63	0.76 <sup>a</sup>
FTND	0.54	0.61	0.47 <sup>c</sup>	0.70 <sup>a</sup>
Self-Rated Addiction	0.52	0.55	0.48	0.66 <sup>a</sup>
<i>Indices of Nicotine Dependence</i>				
Do you think you're addicted?	0.30	0.30	NS	0.36
Lifetime Cigarette Consumption	0.23	0.27	0.23	0.38 <sup>a</sup>
Do You Want To Quit?	0.25	0.26	NS	0.34
How much enjoyment do you get from cigarettes?	0.36	0.34	0.29	0.42
How much pleasure do you get from cigarettes?	0.35	0.35	0.30	0.44
How much relief do you get from cigarettes?	0.40	0.40	0.33	0.47
Cigarettes per Day	0.28	0.33	0.39	0.46 <sup>a</sup>
<i>Other Withdrawal Symptoms</i>				
Increased Appetite	0.23	0.24	NS	0.31
Anger	0.55	0.56	0.47 <sup>b</sup>	0.67 <sup>a</sup>
Depression	0.48	0.48	0.39	0.49
Lack of Focus	0.59	0.60	0.49 <sup>b</sup>	0.62
Insomnia	0.45	0.47	0.37	0.46
Restlessness	0.57	0.60	0.43 <sup>b</sup>	0.63
Stress	0.56	0.58	0.47 <sup>b</sup>	0.65 <sup>a</sup>
Headache	0.42	0.41	0.31 <sup>b</sup>	0.44
Anxiety	0.63	0.66	0.54 <sup>b</sup>	0.64

**NOTE:** all reported correlations are significant at the  $p < 0.001$  level

HONC = Hooked on Nicotine Checklist

AUTOS = the Autonomy Over Tobacco Scale

FTND = the Fagerström Test for Nicotine Dependence

WICS = the Withdrawal-Induced Craving Scale

<sup>a</sup> correlation is significantly higher ( $p < 0.05$ ) than the original Levels of PD

<sup>b</sup> correlation is significantly lower than the original Levels of PD

<sup>c</sup> the TTFC item was dropped from the FTND score for this comparison

**Table 2.4 The Withdrawal Induced Craving Scale (WICS)\***

1. If I go too long without smoking or using dip, the first thing I notice is a mild desire to smoke or use dip that I can ignore.
  - o No. This statement does not describe me.
  - o Yes.
  
2. If I go too long without smoking or using dip, the desire for a cigarette or dip becomes so strong that it is hard to ignore and it interrupts my thinking.
  - o No. This statement does not describe me.
  - o Yes.
  
3. If I go too long without smoking or using dip, I just can't function right, and I know I will have to smoke or use dip just to feel normal again.
  - o No. This statement does not describe me.
  - o Yes.
  
4. I usually want to smoke or use dip right after I wake up.
  - o Not at all
  - o A little
  - o Pretty well
  - o Very well

**WICS Scoring Algorithm:**

Point Value for Items 1-3		Point Value for Item 4		WICS Score
<ul style="list-style-type: none"> <li>• 3 = the highest endorsed item is 3</li> <li>• 2 = the highest endorsed item is 2</li> <li>• 1 = the highest endorsed item is 1</li> <li>• 0 = did not endorse any items 1-3</li> </ul>	+	<ul style="list-style-type: none"> <li>• Not at all = 0</li> <li>• A little = 1</li> <li>• Pretty well = 2</li> <li>• Very well = 3</li> </ul>	=	Total score (range, 0-6)

\*The table includes the 4 items that comprise the WICS. The lower half shows the scoring algorithm used to compute the WICS score. The first three items are scored with one composite point value. The points assigned for the final item are added to this for the total score.



**Table 2.5 How the Withdrawal-Induced Craving Scale (WICS) Correlates to Other Validated Nicotine Dependence Measures in Comparison to How They Correlate With Each Other**

	<i>PD+Wake (WICS)</i>	<i>Levels of PD</i>	<i>HONC</i>	<i>AUTOS</i>	<i>FTND</i>	<i>Self-Rated Addiction</i>
<i>PD+Wake (WICS)</i>		0.86	0.75	0.76	0.70	0.66
<i>Levels of PD</i>	0.86		0.68	0.69	0.54	0.52
<i>HONC</i>	0.75	0.68		0.80	0.60	0.72
<i>AUTOS</i>	0.76	0.69	0.80		0.64	0.66
<i>FTND</i>	0.70	0.54	0.60	0.64		0.54
<i>Self-Rated Addiction</i>	0.66	0.52	0.72	0.66	0.54	

**NOTE:** all reported correlations are significant at the  $p < 0.001$  level

HONC = Hooked on Nicotine Checklist

AUTOS = the Autonomy Over Tobacco Scale

FTND = the Fagerström Test for Nicotine Dependence

WICS= the Withdrawal-Induced Craving Scale

**Table 2.6 The Relative Validity (RV) of Three Alternative Candidate Measures with the Original Levels Of Physical Dependence (PD) Measure**

	<i>Group 1 = Smoked less than 2 years (N=61)</i>		<i>Group 2 = Smoked between 2-5 years (N=86)</i>		<i>Group 3 = Smoked greater than 5 years (N=126)</i>		<i>F- statistic</i>	<i>P- Value</i>	<i>RV</i>	<i>95% CI of the RV</i>	
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>				<i>Lower</i>	<i>Upper</i>
<i>The Original Levels of PD</i>	1.38	1.1	1.49	1.14	1.86	1.14	4.66	0.010	1.00		
<i>Levels of PD+Time</i>	3.59	3.91	4.48	4.33	6.09	4.36	8.09	0.000	1.74	1.19	4.51
<i>Levels of PD+TTFC</i>	2.76	1.89	3.23	1.89	3.79	1.83	4.99	0.008	1.07	0.35	3.62
<i>Levels of PD+Wake (WICS)</i>	2.28	2.07	2.87	2.09	3.74	1.91	11.81	0.000	2.53	1.40	10.70

### CHAPTER III

*The Development and Validation of the  
Nicotine Withdrawal Symptom Checklist (NWSC)*

### 3.1 Introduction

Physical dependence on nicotine (PD) is distinguishable from other aspects of dependence, such as psychological dependence and cue-induced craving, by its distinctive progression through a set escalation in the severity of withdrawal-induced craving experienced during abstinence.<sup>8,10,12,14</sup> The accurate measurement of PD is imperative for pathophysiologic research where withdrawal symptoms are being compared and correlated to physiologic changes in the brain. The progression of PD is captured by the validated Withdrawal-Induced Craving Scale (WICS), which captures two constructs: 1) the severity of withdrawal-induced craving and 2) the latency to withdrawal-induced craving. Withdrawal-induced craving occurs only after abstinence from nicotine and is different from cue-induced craving, craving due to social stimuli, and other forms of craving.<sup>11,43,45</sup> Latency to withdrawal-induced craving is defined as the time elapsed between the last use of tobacco and the onset of withdrawal-induced craving symptoms.<sup>3,5</sup> In the WICS, the intensity of withdrawal-induced craving is captured by a set of 3 questions (see Table 3.1, items 1-3) and latency to withdrawal-induced craving is captured through one additional item (Table 3.1, item 4). The WICS is short and reliable, and correlates highly to other validated measures of nicotine dependence and a battery of nicotine dependence indices.

While it assesses two important features of physical dependence (withdrawal-induced craving's severity and latency), the WICS does not assess other features of nicotine withdrawal. In some research applications it could be useful to have a more comprehensive measure of physical dependence that includes a wider range of

withdrawal symptoms and provides more levels of discrimination. The WICS has a score range of 0-6. Although disease processes are not expected to demonstrate a normal distribution, it could be useful to explore whether adding more withdrawal symptoms might add additional discrimination to the upper end of the WICS, and provide a more precise measure with a wider range of possible scores. The purpose of this study was to explore whether adding a comprehensive list of additional physical withdrawal symptoms to the WICS might lead to a more discriminating and precise instrument.

### **3.2 Materials and Methods**

The study was executed in three phases. First, a literature review was undertaken to compile a comprehensive list of recognized nicotine withdrawal symptoms. Phase 2 involved developing and pre-testing potential survey items using cognitive interviews (CIs) to establish clarity and comprehension, and to finalize the wording and format of the survey instrument. The final phase involved survey administration and psychometric evaluation to winnow the pool of candidate items into a final comprehensive symptom checklist. All procedures were approved by the Human Subjects Institutional Review Board.

#### *3.2.1 Phase 1 – Literature Review and Item Development*

A systematic search of the published, peer-reviewed literature was performed to identify all studies pertaining to measures that included symptoms of physical dependence. The search was conducted using the Medline and CINAHL databases, using all combinations of the search terms: ‘nicotine’, ‘tobacco’, ‘smoking’, ‘cigar’,

‘cigarette(s)’, ‘cigarillo(s)’, ‘addiction’, ‘dependence’, ‘withdrawal’, ‘symptom,’ ‘checklist,’ ‘substance abuse’, ‘survey’, ‘instrument’, ‘measure’, ‘scale’, and ‘diagnostic test’. Manual searches of reference lists were also conducted. The search included all published validation studies as of June 2012. We considered only measures that fit the following inclusion criteria: 1) available in English, 2) represented to capture nicotine dependence, and 3) validated.

The identified studies were analyzed to identify survey items concerning symptoms of physical withdrawal, whether or not they were described as such by the study’s authors. Physical withdrawal symptoms were defined as those that occur after abstinence from tobacco. Items that captured constructs other than withdrawal symptoms, such as perceived risk, motivations for smoking, smoking routines, symptoms of psychological dependence, and cue-induced symptoms, were excluded from our list of candidate items.

After the survey items were identified that related to withdrawal symptoms, these were sorted into groups of items that dealt with similar domains of symptoms (Table 3.2). For example, items relating to anger or irritability were assigned to a single domain despite different wordings across different measures. For each symptom domain, a candidate item was drafted using a standardized wording that was based on that used by the validated Autonomy Over Tobacco Scale (AUTOS). For example, for the Anger domain, the item is worded “If I go too long without a cigarette or dip, I begin to feel angry or irritable.” This wording provides a stem “If I go too long...” that is neutral to

the amount of time passed since last smoking, and thus relevant to tobacco users with differing latencies to withdrawal-induced symptoms.

### *3.2.2 Phase 2 – Cognitive Interviewing and Pretesting*

The candidate items were finalized through a series of CIs with 16 subjects recruited from a primary care clinic waiting room. This site was selected because it would be used to recruit some of the subjects for the final study. Interviews were conducted with subjects covering a broad range of ages, smoking levels, and backgrounds. Over one third of the interviewees were minorities, with three African American and four Hispanic subjects. In order to edit and finalize the survey items, interviewees were asked about the wording, content, format, clarity and answer choices for each item, one at a time. Interviewees were also asked how they interpreted each phrase in the symptom descriptions to ensure that questions were not interpreted in multiple ways. For questions including two descriptive words in the stem (ie. “angry or irritable”) subjects were asked whether they interpreted the words differently and if they preferred having just one or both words for maximum clarity. Although some symptoms may not seem to be physical (e.g., irritability), if interviewees reported that they occurred reliably after abstinence and were relieved by the administration of nicotine, they were included because they presumably result from a physical process: neurological conditions triggered by the absence of nicotine.

The final survey items (Table 3.3) were pretested on a convenience sample of 20 subjects. Subjects were given the survey instrument in its entirety and asked afterwards

if they experienced any problems answering or understanding the questions. The surveys were then examined for any patterns in missing data or skipped items.

### *3.2.3 Phase 3 – Survey Administration & Psychometric Testing*

Final survey items included the previously validated WICS, and the final candidate items for the withdrawal symptom checklist (Table 3.4). Also included were questions on demographic information, a battery of indices of nicotine dependence for comparison purposes, and 4 validated measures of nicotine dependence to assess convergent validity. These 4 measures included the Hooked on Nicotine Checklist (HONC), the AUTOS, the Fagerström Test for Nicotine Dependence (FTND), and self-rated addiction (How addicted do you think you are on a scale of 0-4).<sup>11,15,28,35</sup> The battery of nicotine dependence indices consisted of correlates used widely in other nicotine dependence validation studies: self-reported addiction (yes or no), lifetime cigarette consumption, desire to quit, enjoyment obtained from smoking, relief obtained from smoking, pleasure obtained from smoking, and cigarettes smoked per day. While these are not nicotine dependence measures themselves, they are expected to trend with dependence. It is of note that the original metric of ‘pleasure’ was included because of its use in past validation studies, however two additional items ‘enjoyment’ and ‘relief’ were added after the CIs because participants interpreted the word “pleasure” as both “relief” (like scratching an itch) and “pleasure” (like enjoying a piece of candy).

### *3.2.4 Subjects & Recruitment*

The goal of this study was to recruit a broad range of subjects that were diverse in age and smoking histories so that the final instrument could be used with all smokers. To



this end, subjects were recruited from a convenience sample of three high schools and four health clinics in Massachusetts.

#### *3.2.4.1 High School Subjects*

Surveys were administered to entire grades at one rural regional school, one urban/suburban school and one vocational school. In advance of survey administration, a letter was sent to the parents allowing them to withhold their child from participation. Surveys were administered to all participating students, including nonsmokers, in order to avoid singling out smokers, and to capture novice smokers and other occasional tobacco users who may not perceive themselves as smokers. Surveys were administered in classes common to all students such as homeroom or health. Teachers read directions that informed students that their participation was voluntary and anonymous. To preserve anonymity, students handed in their surveys by placing them in an envelope or slotted box.

#### *3.2.4.2 Clinic Subjects*

A convenience sample of adult smokers was recruited from two primary care and two behavioral health clinics that served racially and socioeconomically diverse populations. Patients were invited by study personnel, front desk staff, or their doctors to complete an anonymous survey. Subjects were allowed to complete the survey alone and return it to study personnel in the clinic.

#### *3.2.5 Analytic Methods*

Analyses were done in STATA version 11, and R Project 3.0.1. Surveys with incomplete data on the WICS or candidate withdrawal symptoms were culled. To

maintain uniformity in analysis of continuous and categorical variables during analysis, all continuous items were converted to categorical variables. To this end, polychoric correlations were used for all relevant analyses. Differences in means were assessed using paired t-tests and one-way analysis of variance. The statistical significance of differences between correlation coefficients was assessed using a Fisher's  $r$  to  $z$  transformation. Significance was established at  $p < 0.05$  for differences in means or coefficients, and at  $p < 0.001$  level for correlations (to compensate for multiple comparisons).

The following statistical evaluations were used in an iterative fashion to produce a final measure: item-level distributions, item-level characteristics, inter-item correlations, item-total score correlations, internal reliability (Cronbach's alpha), item-level convergent validity correlations, and exploratory factor analysis (EFA). As a sensitivity analysis, some of these analyses, were examined both in the entire sample and in novice and advanced smokers separately in order to select the best performing items for the final measure. For these analyses smokers were separated into two groups: those smoking for less than 2 years and those smoking for 2 years or longer. The final measure was assessed using confirmatory factor analysis (CFA), total score distribution, scale-level convergent validity correlations, and convergent validity correlations,. Model fit for the CFA was determined using several metrics including the Chi Squared Test ( $\chi$ ) which quantifies differences between observed and expected covariance matrices, the Goodness of Fit Index (GFI) which quantifies the fit of the model and the observed covariance matrix, the Root Mean Square Error of Approximation (RMSEA) to estimate model fit using

external parameters while adjusting for sample size, and the Comparative Fit Index (CFI) which also adjusts for sample size when exploring discrepancies between the tested model and the data set.

Relative validity (RV), also known as relative efficiency,<sup>50</sup> was also calculated. RV is a method of comparing how well several measures differentiate subjects into groups defined by a theory based binning variable. Based on theory or empirical evidence, the binning variable is selected to create groups across which the measure should have distinct levels. Relative validity is calculated to quantify how well the measure in question differentiates between these predicted levels as compared to a reference measure. Relative validity is calculated as a ratio of F-Statistics, which in turn are calculated as a ratio of variances. An RV greater than 1 indicates that a given measure differentiates subjects into the predicted levels better than the reference measure does. The selected binning variable, is generally the closest metric to a gold standard available for the test in question. Because there is no physiological gold standard test for physical dependence, we conducted RV analyses using the only other physical dependence measure as a binning variable: the Levels of Physical Dependence measure. For the reference variable, we selected the most widely used nicotine dependence measure: the FTND.

### **3.3 Results**

#### *3.3.1 Phase 1 – Literature Review and Item Development*

The literature search identified 22 measures of nicotine dependence that addressed 8 domains of nicotine withdrawal symptoms as seen in Table 3.2.<sup>3,4,11,15-20,22-33</sup>

### *3.3.2 Phase 2 - Cognitive Interviewing and Pretesting*

CI participants had very few suggestions for improvements on formatting and clarity. Nobody interpreted the two active phrases in double-barreled items differently. For example, in the item “If I go too long without a cigarette or dip, I find it hard to concentrate or focus,” interviewees interpreted concentrate and focus as the same concept and preferred including both terms to dropping one. Similarly, they found the answer options appropriate and did not request more or fewer categories. When asked to describe and define how they interpreted each item, there were no inconsistencies in the interviewees’ understanding of the meaning of any item. The only change made to the wording involved the appetite item. Many CI participants did not feel that appetite was a relevant symptom, but those that did support its inclusion were clear that they did not have a latency to increased appetite, that is, they did not become acutely hungry a given time period after their last cigarette. Instead they described an overall increase in appetite after they quit smoking. Because appetite is included in the DSM criteria, it was included in the final list of candidate items for further testing even though its lack of a latency indicated that it might not be a withdrawal symptom. With the CI participants’ input, the wording of the appetite question was altered to reflect the lack of a latency.

When asked if there were any additional symptoms of withdrawal that were not included in the list of candidate symptoms, one respondent suggested nausea and another suggested headaches. Although both nausea and headache had been included on other nicotine dependence measures, they were not included on the original list of candidate items because they seemed to target symptoms of first-time use, rather than withdrawal.

Both symptoms were added to the list of candidate items for pre-testing (Table 3.3). No problems with the final items were uncovered in pretesting. Respondents did not show any systematic patterns in skipping items, or any difficulty in answering or understanding the final items.

### *3.3.3 Phase 3 – Survey Administration*

A total of 2243 surveys were collected across all sites. This included non-smokers among high school students. Subjects who had not smoked in the past 30 days, had not smoked more than 1 cigarette in their life, and those with missing data on key variables were excluded resulting in a final sample of 273 subjects.

#### *3.3.3.1 Sample Characteristics*

Subjects ranged in age from 14 to 76 (mean=30.94 years, SD=16.19). They had smoked for an average of 14.74 years (range=0.5-63, SD=15.83) and smoked an average of 11.45 cigarettes per day (range=0-50, SD=9.39). The sample was 86.5% white and 57.5% male. Additional sample characteristics, demographic information, and mean scores on validated measures of dependence can be found in Table 3.5.

### *3.3.4 Exploratory Psychometric Testing*

#### *3.3.4.1 Item Level Distributions*

In the exploratory phase of psychometric testing, item level distributions for all candidate items were examined both in the sample as a whole and in novice (<2 yrs) vs. advanced (2+ yrs) smokers separately. Based on these distributions, nausea was dropped

from consideration because it was rarely endorsed by either novice or advanced smokers. All other items were retained for further analysis.

#### *3.3.4.2 Inter-Item Correlations*

As seen in Table 3.6, the highest inter-item correlation was moderate (0.72) suggesting that none of the candidate items were redundant. Therefore, all items were retained for further analysis. However, appetite was correlated poorly with all other items.

#### *3.3.4.3 Items Internal Reliability and Item-Total Correlations*

The scale containing the remaining items (omitting nausea) showed excellent internal reliability ( $\alpha=0.91$ ). Of the candidate items, appetite had the lowest correlation to the total scale (0.45) suggesting that it may be measuring something different (Table 3.7). The internal reliability of the scale was examined with each item dropped from the scale, and appetite was the only item that improved internal reliability ( $\alpha=0.92$ ) when dropped.

#### *3.3.4.4 Exploratory Factor Analysis*

Upon conducting exploratory factor analysis (EFA) of the remaining candidate items, a one-factor solution was found suggesting a uni-dimensional structure (Figure 3.1 and Table 3.8). Appetite was the only item with a low factor loading (0.47) on this single factor (Table 3.9). All other items showed loadings above our *a priori* cut-off of 0.6.

#### *3.3.4.5 Final Item Selection*

Based on the item level distributions, nausea was dropped from the final scale. In addition, appetite was dropped based on the EFA loadings, inter-item correlations, item-total correlations, and internal reliability evaluations. The resulting measure, named the Nicotine Withdrawal Symptom Checklist (NWSC) included the WICS and the following items: anger, anxiety, depression, headache, insomnia, loss of focus, restlessness, and stress.

#### *3.3.5 Confirmatory Psychometric Testing of the NWSC*

##### *3.3.5.1 Confirmatory Factor Analysis*

The confirmatory factor analysis performed on the NWSC confirmed a single factor solution. Results suggest a well-fitting model with a GFI=0.96, RMSEA=0.06,  $\chi=192$  (df=35,  $p<0.001$ ), and CFI=0.92. All items showed standardized factor loadings over 0.6 (Table 3.10)

##### *3.3.5.2 Internal Reliability & Item-Total Correlations*

The NWSC exhibited excellent reliability with a Cronbach's alpha of 0.92. Internal reliability did not improve upon dropping any items from the scale (Table 3.11), and all of the items correlated above 0.6 with the total score.

##### *3.3.5.3 Total Score Distribution*

The final score distribution for the NWSC can be found in Figure 3.2. It is of note that the large number of subjects with a score of 0 is consistent with the number scoring 0 on other measures of nicotine dependence. This was expected given that our

sample intentionally included a large number of novice smokers to ensure that the final measure was sensitive enough to capture early stages of dependence.

#### *3.3.5.4 Convergent Validity*

As shown in Table 3.12, the NWSC correlates significantly ( $p < 0.001$ ) to each of our convergent validity metrics.

#### *3.3.5.5 Relative Validity*

The RV analysis, (Table 3.13) suggest that compared to the most widely used nicotine dependence measure (the FTND), the NWSC has the highest relative validity (3.53). Given our parameters, this indicates that compared to the older nicotine dependence measures the NWSC sorted subjects by level of physical dependence better than any other version.

#### *3.3.5.6 Subgroup Analyses*

As a sensitivity analysis, all of the above analyses were then stratified by age and years smoked. There were no significant differences in the results (data not shown).

### **3.4 Discussion**

#### *3.4.1 Scale Performance*

The NWSC is the first scale developed to capture the severity of physical dependence by including all symptoms of nicotine withdrawal along with the construct of latency. Its unidimensional structure, suggested by factor analyses (Figure 3.1, and Table 3.8), supports our *a priori* hypothesis that all symptoms would load on a single factor: physical



dependence. The NWSC exhibits excellent internal reliability ( $\alpha=0.92$ ) and correlates higher than most other nicotine dependence measures to a wide range of nicotine dependence indices. As seen in Table 3.12 it also correlates well with self-rated addiction and FTND scores and correlates highly with the HONC and AUTOS.

The NWSC also out performs all of the older nicotine dependence measures in RV analyses using the only other known physical dependence measure (the Levels of Physical Dependence Measure) as the binning variable (See Table 3.13). Binning variables are generally the closest metric to a gold standard available for the construct in question, but given the lack of a gold standard biological test for physical dependence, this was the only available method of differentiating subjects by physical dependence for a RV analysis. Results should be interpreted cautiously however, because the PD measure was used in the development of the NWSC. However, because the PD related questions make up only one item in the 12 item scale, the markedly high RV of the NWSC as compared to the FTND and Self-rated Addiction suggest that at the very least the NWSC may out perform these two measures in differentiating subjects by physical dependence. The RVs of the AUTOS and HONC are slightly closer to that of the NWSC, so future studies with larger sample sizes should further explore these connections to determine whether this difference in RV is indeed significantly different.

Because the levels of PD measure is included in a small part of the NWSC a relative validity analysis was conducted using a more general metric of overall dependence as a binning variable: length of smoking history (see Table 3.14). Length of smoking history has been used as a crude metric of overall dependence in past studies, because it can be

assumed that individuals who had smoked for fewer years would have lower dependence scores than those who had smoked for many years. However, length of smoking history would also capture other addiction related constructs that progress over time such as: smoking routines/habits, easy of accessibility, smoking volume, and psychological/learned dependence. While it is not strongly related to *physical dependence* specifically we conducted the analysis so that the NWSC's performance can be compared to previous studies in which smoking history was used as a comparator. As predicted the older nicotine dependence measures generally exhibited higher relative validity when using the more general dependence parameter as the binning variable, suggesting that the construct captured by the FTND and other older nicotine dependence measure is more closely related to general dependence than physical dependence specifically. Given that some items in the AUTOS capture psychological dependence (which is learned over time), and many items in the FTND capture smoking routines and volume (which also develop over time), it is unsurprising that these measures would better differentiate individuals by length of smoking history, a time-based continuum.

Because RV analyses are highly dependent on both the binning variable and the reference variable selected, the results from all of our RV analyses should be interpreted with caution. Until future studies better establish physiological parameters that can be used to differentiate individuals by physical dependence, we are left with only crude measures with which to establish RV. While our RV results are consistent with the results of our psychometric analyses, future studies should further explore the relative

validity of the NWSC using more concrete physiological metrics such as physical and functional changes in brain structure.

### *3.4.2 Scale Development*

The candidate symptoms for the NWSC were collected through a systematic literature search and a series of CIs to ensure that all reported symptoms were considered. Items were not selected based on face validity or theory alone. Rather, iterative psychometric testing in a sample with a wide range of smoking histories was used to select the most relevant items. Subjects included both novice and advanced smokers, and non-daily and daily smokers to ensure that the measure captured both the early and late stage symptoms of dependence. Stratified psychometric analyses by age resulted in the selection of the same items. The psychometric properties of the NWSC did not differ significantly in these subgroups.

The appetite item was dropped based on the EFA loadings, inter-item correlations, item-total correlations, and internal reliability evaluations. One factor that could have contributed to the observed differences between appetite and the other items is the slightly different wording. It was drafted and tested with this wording because cognitive interview respondents were clear that they did not feel acute hunger if they went too long without a cigarette, but rather they experienced an overall increase in appetite upon quitting. This is consistent with the fact that nicotine suppresses appetite. Without this suppression, a tobacco user's appetite would return to baseline after quitting, a phenomenon known as an offset effect. The analyses completed in this study suggest that increased appetite is not a true nicotine withdrawal symptom, but rather an offset effect.

While a fear of gaining weight could contribute to resumption of smoking, this is a different phenomenon than a relapse that is triggered by the need to obtain relief from withdrawal. None of the CI subjects reported needing to smoke to satiate unbearable hunger.

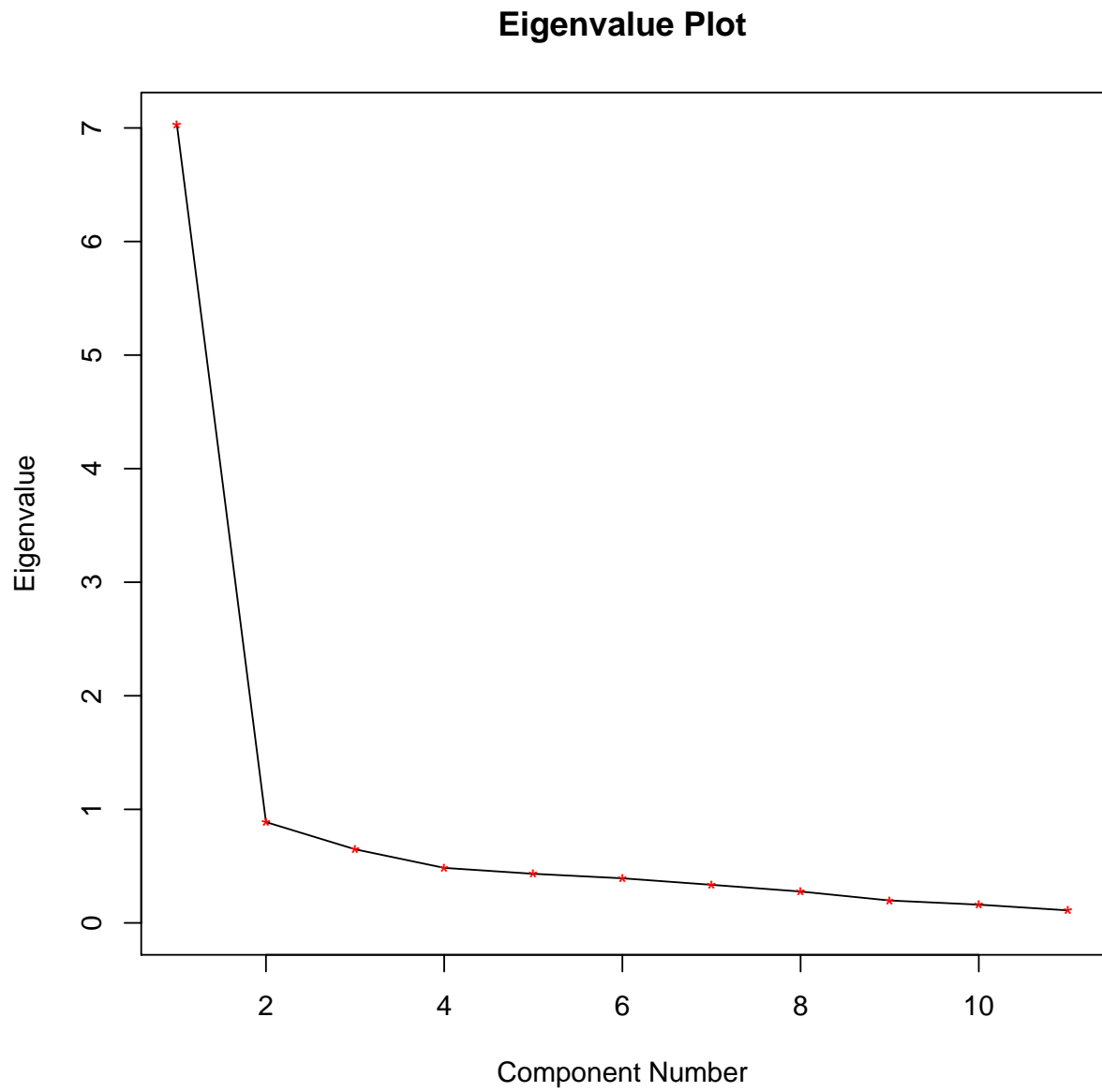
### 3.4.3 Strengths & Limitations

The NWSC is currently the only psychometrically validated, comprehensive symptom checklist that captures both overall physical dependence severity *and* changes in the severity of individual symptoms as physical dependence progresses. For researchers who wish to capture an *acute* change in symptom severity instead (for example: before and after smoking), a measure like the Wisconsin Smoking Withdrawal Scale would be a more appropriate tool.<sup>21</sup> Unlike this kind of momentary measure, the NWSC captures overall physical dependence both during abstinence and after nicotine administration. This could be particularly useful in studies examining cessation, interventions, and medications intended to target specific withdrawal symptoms.

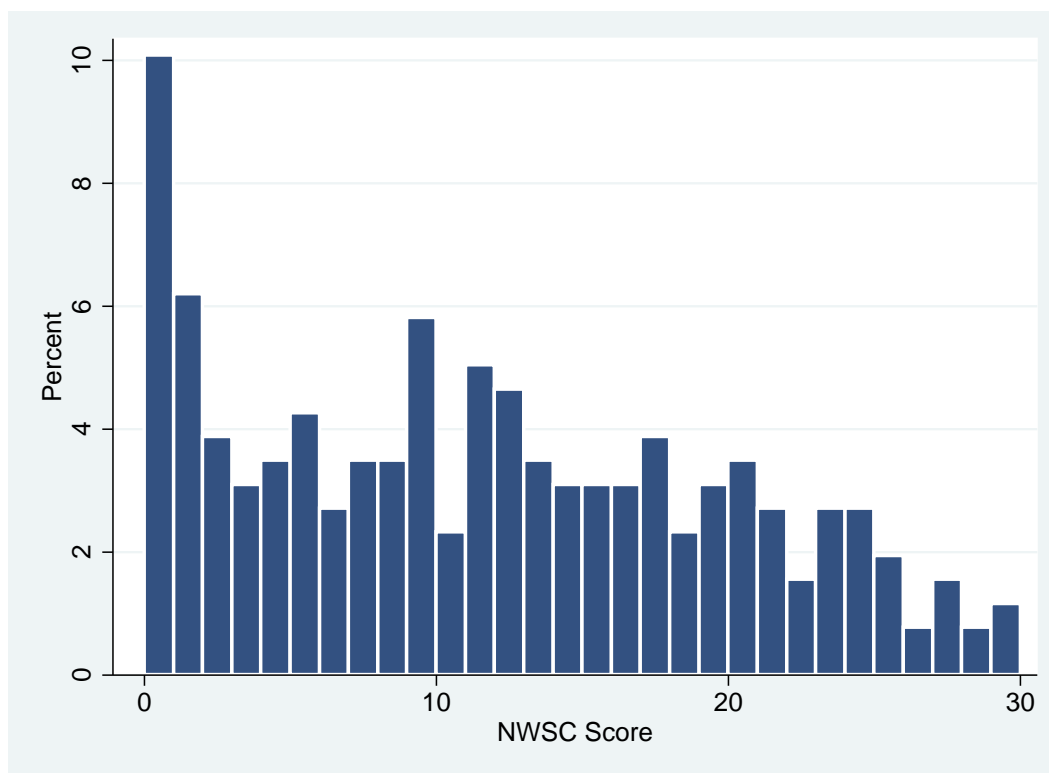
As seen in the final score distribution (Figure 3.2), the NWSC provides more levels of discrimination than the WICS. This is especially true at the upper end of the dependence spectrum. Finally, because the NWSC does not rely on smoking behaviors to capture nicotine dependence (such as when and where one smokes), there is no theoretical reason why the item stems could not be adapted for other forms of nicotine delivery such as chewing tobacco, e-cigarettes, and water pipe tobacco. Future studies should assess the performance of the NWSC among users of these products.

While useful in a range of settings, the NWSC contains 12 items, which may be too long for surveys where space is limited. Future studies should explore the creation of a brief version for use in these space or time restricted settings. Studies with larger subgroup sample sizes should also further explore convergent validity using more targeted analytic approaches such as structural equation modeling, item response theory, and known group validity tests. Prospective studies should evaluate predictive validity and test re-test reliability, and explore whether the NWSC symptoms appear in a specific order as dependence progresses. This may provide insight into which symptoms arise only at very late stages of dependence.

In conclusion, the NWSC fulfills our *a priori* goals of creating a broader, more comprehensive scale that 1) includes all known symptoms of withdrawal and 2) better differentiates the more dependent smokers as categorized by high WICS scores. In situations where a short measure of physical dependence is required, the WICS may be recommended since it performs equally well in convergent validity tests despite having 7 fewer items (Table 3.12). However in non space or time restricted capacities, or when researchers wish to track the progression of all known symptoms of physical dependence, the NWSC is a robust and versatile tool.



**Figure 3.1** Plot of Eigenvalues Resulting from the Exploratory Factor Analysis of Candidate Items



**Figure 3.2.** Nicotine Withdrawal Symptom Checklist Score Distribution

**Table 3.1 The Withdrawal Induced Craving Scale (WICS)\***

7. If I go too long without smoking or using dip, the first thing I notice is a *mild desire* to smoke or use dip that I can ignore.
- No. This statement does not describe me.
  - Yes.
8. If I go too long without smoking or using dip, the desire for a cigarette or dip becomes so strong that it is hard to ignore and it interrupts my thinking.
- No. This statement does not describe me.
  - Yes.
9. If I go too long without smoking or using dip, I just can't function right, and I know I will have to smoke or use dip just to feel normal again.
- No. This statement does not describe me.
  - Yes.
10. I usually want to smoke or use dip right after I wake up.
- Not at all
  - A little
  - Pretty well
  - Very well

**WICS Scoring Algorithm:**

Point Value for Items 1-3		Point Value for Item 4		WICS Score
<ul style="list-style-type: none"> <li>• 3 = the highest endorsed item is 3</li> <li>• 2 = the highest endorsed item is 2</li> <li>• 1 = the highest endorsed item is 1</li> <li>• 0 = did not endorse any items 1-3</li> </ul>	+	<ul style="list-style-type: none"> <li>• Not at all = 0</li> <li>• A little = 1</li> <li>• Pretty well = 2</li> <li>• Very well = 3</li> </ul>	=	Total score (range, 0-6)

\*The table includes the 4 items that comprise the WICS. The lower half shows the scoring algorithm used to compute the WICS score. The first three items are scored with one composite point value. The points assigned for the final item are added to this for the total score.



**Table 3.2 Nicotine Dependence Symptom Domains  
Identified in the Literature Search**

---

Anger/Irritability

Craving

Depressed mood/Feeling blue

Difficulty concentrating/Focusing

Increased appetite

Insomnia

Nervousness/Anxiety/Worry

Restlessness

Latency to withdrawal-induced craving/Smoking upon waking

Stress

---

**Table 3.3 Final Candidate Items Derived from the Cognitive Interviews and Literature Search**

<i>Domain</i>	<i>Item Wording</i>
<i>Anger</i>	If I go too long without a cigarette or dip, I begin to feel angry or irritable.
<i>Anxiety</i>	If I go too long without a cigarette or dip, I feel nervous or anxious.
<i>Craving</i>	<p><i>As Captured by the WICS:</i></p> <p>If I go too long without smoking or using dip, the first thing I notice is a mild desire to smoke or use dip that I can ignore.</p> <p>If I go too long without smoking or using dip, the desire for a cigarette or dip becomes so strong that it is hard to ignore and it interrupts my thinking.</p> <p>If I go too long without smoking or using dip, I just can't function right, and I know I will have to smoke or use dip just to feel normal again.</p> <p>I usually want to smoke or use dip right after I wake up.</p>
<i>Depression</i>	If I go too long without a cigarette or dip, I feel down or depressed.
<i>Headache</i>	If I go too long without a cigarette or dip, I begin to get headaches.
<i>Increased Appetite</i>	Tobacco controls my appetite and keeps me from eating more than I should.
<i>Insomnia</i>	If I go too long without a cigarette or dip, I suffer from insomnia or troubled sleep.
<i>Lack of Focus</i>	If I go too long without a cigarette or dip, I find it hard to concentrate or focus.
<i>Nausea</i>	If I go too long without a cigarette or dip, I feel nausea.
<i>Restlessness</i>	If I go too long without a cigarette or dip, I feel restless.
<i>Stress</i>	If I go too long without a cigarette or dip, I feel stressed.

**Table 3.4 Final Nicotine Withdrawal Symptom Checklist (NWSC) Items\***

	This describes me....			
	Not at all	A little	Pretty well	Very well
1. If I go too long without a cigarette or dip, I begin to feel angry or irritable.	0	0	0	0
2. If I go too long without a cigarette or dip, I feel down or depressed.	0	0	0	0
3. If I go too long without a cigarette or dip, I find it hard to concentrate or focus.	0	0	0	0
4. If I go too long without a cigarette or dip, I suffer from insomnia or troubled sleep.	0	0	0	0
5. If I go too long without a cigarette or dip, I feel restless.	0	0	0	0
6. If I go too long without a cigarette or dip, I feel stressed.	0	0	0	0
7. If I go too long without a cigarette or dip, I begin to get headaches.	0	0	0	0
8. If I go too long without a cigarette or dip, I feel nervous or anxious.	0	0	0	0
9. I usually want to smoke or use dip right after I wake up.	0	0	0	0
10. If I go too long without smoking or using dip, the first thing I notice is a <i>mild desire</i> to smoke or use dip that I can ignore.				
	<input type="radio"/> No. This statement does not describe me. <input type="radio"/> Yes.			
11. If I go too long without smoking or using dip, the desire for a cigarette or dip becomes so strong that it is hard to ignore and it interrupts my thinking.				
	<input type="radio"/> No. This statement does not describe me. <input type="radio"/> Yes.			
12. If I go too long without smoking or using dip, I just can't function right, and I know I will have to smoke or use dip just to feel normal again.				
	<input type="radio"/> No. This statement does not describe me. <input type="radio"/> Yes.			

NWSC Scoring Algorithm:

Point Value for Items 1-9		Point Value for Items 10-12		NWSC Score
3 = Very well 2 = Pretty well 1 = A little 0 = Not at all	+	3 = the highest endorsed item is 12 2 = the highest endorsed item is 11 1 = the highest endorsed item is 10 0 = did not endorse any items 10-12	=	Total score (range, 0-30)

\*The table includes the 12 items that comprise the NWSC. The lower half shows the scoring algorithm used to compute the NWSC score. All items are scored on a 0-3 point Likert Scale, except items 10-12 which are scored as one composite item.

**Table 3.5 Sample Characteristics (N=273)**

	<i>% (N)</i>	<i>Mean</i>	<i>SD</i>	<i>Range (min- max)</i>
Age		30.94	16.19	14-76
Adolescents (<19)	44.68 (122)			
Adults( 19+)	55.31 (151)			
Years smoked		14.74	15.83	0.5-63
<2 yrs	20.97 (56)			
2-5 yrs	29.96 (80)			
>5 yrs	49.06 (131)			
Cigarettes/day		11.45	9.39	0-50
HONC		6.28	3.34	0-10
AUTOS		16.60	11.40	0-36
FTND		3.87	2.630	0-10
Self-Rated Addiction		2.45	1.54	0-4
Gender				
<i>Male</i>	57.5 (157)			
<i>Female</i>	42.5 (116)			
Ethnicity				
<i>Prefer not to identify</i>	0.75 (2)			
<i>American Indian or Alaskan     Native</i>	3.01 (8)			
<i>Asian</i>	1.13 (3)			
<i>Black</i>	3.76 (10)			
<i>Native Hawaiian or Pacific     Islander</i>	0.38 (1)			
<i>White</i>	86.47 (230)			
<i>Mixed</i>	4.51 (12)			
Hispanic				
<i>No</i>	88.01 (235)			
<i>Yes</i>	11.99 (32)			
Smoking Frequency				
<i>Daily</i>	63.37 (173)			
<i>Non-daily</i>	36.63 (100)			

HONC = Hooked on Nicotine Checklist

AUTOS = Autonomy Over Tobacco Scale

FTND = Fagerström Test for Nicotine Dependence

**Table 3.6 Inter-Item Correlation Coefficients for Candidate Items**

	<i>Anger</i>	<i>Anxiety</i>	<i>Depression</i>	<i>Headache</i>	<i>Increased Appetite</i>	<i>Insomnia</i>	<i>Lack of Focus</i>	<i>Latency to Craving</i>	<i>Restlessness</i>	<i>Severity of Withdrawal Induced Craving</i>	<i>Stress</i>
<i>Anger</i>		0.61	0.56	0.46	0.33	0.46	0.68	0.60	0.62	0.67	0.71
<i>Anxiety</i>	0.61		0.54	0.44	0.30	0.47	0.62	0.48	0.64	0.64	0.66
<i>Depression</i>	0.56	0.54		0.52	0.23	0.56	0.61	0.37	0.42	0.49	0.55
<i>Headache</i>	0.46	0.44	0.52		0.22	0.54	0.51	0.34	0.38	0.44	0.51
<i>Increased Appetite</i>	0.33	0.30	0.23	0.22		0.21	0.28	0.31	0.33	0.31	0.34
<i>Insomnia</i>	0.46	0.47	0.56	0.54	0.21		0.51	0.34	0.53	0.46	0.46
<i>Lack of Focus</i>	0.68	0.62	0.61	0.51	0.28	0.51		0.48	0.67	0.62	0.72
<i>Latency to Withdrawal Induced Craving</i>	0.60	0.48	0.37	0.34	0.31	0.34	0.48		0.51	0.51	0.57
<i>Restlessness</i>	0.62	0.64	0.42	0.38	0.33	0.53	0.67	0.51		0.63	0.72
<i>Severity of Withdrawal Induced Craving</i>	0.67	0.64	0.49	0.44	0.31	0.46	0.62	0.51	0.63		0.65
<i>Stress</i>	0.71	0.66	0.55	0.51	0.34	0.46	0.72	0.57	0.72	0.65	

All reported values are significant at the  $p < 0.001$  level

Polychoric correlation coefficients are reported because all items were categorical

**Table 3.7 Internal Reliability & Item-Total Correlations for the Candidate Items**

	<i>Item-total Correlation*</i>	<i>Cronbach's Alpha without the item</i>
<i>Anger</i>	0.78	0.90
<i>Anxiety</i>	0.75	0.90
<i>Depression</i>	0.65	0.90
<i>Headache</i>	0.57	0.91
<i>Increased Appetite</i>	0.36	0.92
<i>Insomnia</i>	0.61	0.91
<i>Lack of Focus</i>	0.78	0.90
<i>Latency to Withdrawal Induced Craving</i>	0.61	0.91
<i>Restlessness</i>	0.74	0.90
<i>Severity of Withdrawal Induced Craving</i>	0.69	0.90
<i>Stress</i>	0.80	0.90
<b>Total Scale Cronbach's Alpha = 0.91</b>		

\* Item to total correlations were corrected for overlap.

**Table 3.8 Exploratory Factor Analysis of Candidate Items**

<i>Factor</i>	<i>Eigenvalue</i>
Factor 1	7.03
Factor 2	0.89
Factor 3	0.65
Factor 4	0.48
Factor 5	0.43
Factor 6	0.39
Factor 7	0.34
Factor 8	0.28
Factor 9	0.20
Factor 10	0.16
Factor 11	0.11

**Table 3.9 Factor Loadings from the Exploratory Factor Analysis of Candidate Items**

	<i>Factor Loading</i>
<i>Anger</i>	0.87
<i>Anxiety</i>	0.84
<i>Depression</i>	0.76
<i>Headache</i>	0.69
<i>Increased Appetite</i>	0.47
<i>Insomnia</i>	0.75
<i>Lack of Focus</i>	0.88
<i>Latency to Withdrawal Induced Craving</i>	0.72
<i>Restlessness</i>	0.86
<i>Severity of Withdrawal Induced Craving</i>	0.76
<i>Stress</i>	0.91



**Table 3.10 Factor Loadings from the Confirmatory Factor Analysis of the Final Nicotine Withdrawal Symptom Checklist**

	<i>Factor 1</i>
<i>Anger</i>	0.87
<i>Anxiety</i>	0.83
<i>Depression</i>	0.76
<i>Headache</i>	0.69
<i>Insomnia</i>	0.75
<i>Lack of Focus</i>	0.89
<i>Latency to Withdrawal Induced Craving</i>	0.71
<i>Restlessness</i>	0.86
<i>Severity of Withdrawal Induced Craving</i>	0.76
<i>Stress</i>	0.91

**Table 3.11 Nicotine Withdrawal Symptom Checklist Item-Total Correlations & Internal Reliability**

	<i>Item-total Correlation*</i>	<i>Cronbach's Alpha without the item</i>
<i>Angry</i>	0.78	0.906
<i>Anxiety</i>	0.75	0.908
<i>Depression</i>	0.65	0.913
<i>Headache</i>	0.58	0.917
<i>Insomnia</i>	0.62	0.915
<i>Lack of Focus</i>	0.79	0.905
<i>Latency to Withdrawal Induced Craving</i>	0.61	0.917
<i>Restlessness</i>	0.74	0.908
<i>Severity of Withdrawal Induced Craving</i>	0.69	0.911
<i>Stress</i>	0.80	0.905
<b>Total Scale Cronbach's Alpha = 0.920</b>		

\* Item to total correlations were corrected for overlap.

**Table 3.12 Polychoric Correlation Coefficients between Selected Nicotine Dependence Indices and the NWSC and the WICS Respectively**

	<i>NWSC</i>	<i>WICS</i>
<i>HONC</i>	0.80	0.75
<i>AUTOS</i>	0.88	0.76
<i>FTND</i>	0.62	0.70
<i>Self-Rated Addiction</i>	0.66	0.66
<i>Do you think you're addicted?</i>	0.35	0.36
<i>Lifetime cigarette consumption</i>	0.33	0.38
<i>Do you want to quit?</i>	0.30	0.34
<i>Enjoyment</i>	0.41	0.41
<i>Pleasure</i>	0.38	0.43
<i>Relief</i>	0.51	0.47
<i>Cigarettes/day</i>	0.35	0.45

All reported values are significant at the  $p < 0.001$  level

NWSC = Nicotine Withdrawal Symptom Checklist

WICS = Withdrawal-Induced Craving Scale

HONC = Hooked on Nicotine Checklist

AUTOS = Autonomy Over Tobacco Scale

FTND = Fagerström Test for Nicotine Dependence

**Table 3.13 Relative Validity Analyses Using Level of Physical Dependence (PD) as the Binning Variable**

	<i>PD Level 0</i>	<i>PD Level 1</i>	<i>PD Level 2</i>	<i>PD Level 3</i>			
	<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>F-statistic</i>	<i>P-Value</i>	<i>RV</i>
<i>Self rated addiction</i>	1.22 (1.57)	2.04 (1.48)	3.05 (1.06)	3.3 (1.08)	33.76	<0.001	0.97
<i>FTND*</i>	2.29 (2.15)	2.35 (1.99)	4.34 (2.12)	5.57 (2.33)	34.75	<0.001	1.00
<i>AUTOS</i>	7.08 (8.78)	10.04 (7.73)	21.59 (8)	25.99 (8.33)	84.37	<0.001	2.43
<i>HONC</i>	3.56 (3.06)	4.17 (2.78)	7.98 (2.22)	8.86 (1.47)	85.20	<0.001	2.45
<i>NWSC</i>	3.68 (5.09)	6.46 (4.62)	14.95 (5.46)	18.72 (5.81)	122.67	<0.001	3.53

\* Reference measure: FTND

Binning Variable: Levels of Physical Dependence

**Table 3.14 Relative Validity Analyses Using Years Smoked as the Binning Variable**

	<i>Smoked &lt;2 yrs</i>	<i>Smoked 2-5 yrs</i>	<i>Smoked &gt;5 yrs</i>			
	<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>F-statistic</i>	<i>P-Value</i>	<i>RV</i>
<b><i>PD</i></b>	1.38 (1.1)	1.49 (1.14)	1.86 (1.14)	4.66	0.0103	0.41
<b><i>NWSC</i></b>	9.28 (9.33)	10.42 (8.11)	13.3 (7.49)	5.99	0.0029	0.53
<b><i>AUTOS</i></b>	12.66 (12.46)	15.39 (11.01)	19.41 (10.6)	7.95	<0.001	0.71
<b><i>FTND</i></b>	2.61 (2.61)	3.46 (2.49)	4.6 (2.47)	11.23	<0.001	1
<b><i>HONC</i></b>	4.59 (4.01)	5.9 (3.03)	7.27 (2.82)	14.72	<0.001	1.31
<b><i>Self rated addiction</i></b>	1.56 (1.48)	2.19 (1.53)	3.09 (1.29)	26.16	<0.001	2.33

\* Reference measure: FTND  
 Binning Variable: Years Smoked

## CHAPTER IV

### *The Development and Validation of the Brief Nicotine Withdrawal Symptom Checklist (NWSC-b)*

## 4.1 Introduction

Nicotine dependence is a debilitating condition that affects millions of people across the world.<sup>1,18</sup> One aspect of nicotine dependence is physical dependence (PD), which is characterized by withdrawal symptoms that appear during abstinence from nicotine.<sup>3,4,8,10,11,33,43,44,46</sup> Based on over 200 case histories we identified two primary aspects of early physical dependence: 1) intensifying withdrawal-induced craving, and 2) a shortening latency to this craving. Latency is defined as the time elapsed between the last use of tobacco and the onset of withdrawal-induced craving. As dependence progressed, smokers described the appearance of additional withdrawal symptoms including anger, anxiety, depression, headache, insomnia, lack of focus, restlessness, and stress.<sup>43,45</sup>

The Nicotine Withdrawal Symptom Checklist (NWSC) is a 12-item measure (Table 4.1) designed to include all three of these aspects of PD: 1) withdrawal-induced craving, 2) latency to withdrawal-induced craving, and 3) the subsequent appearance of more advanced withdrawal symptoms. The NWSC exhibits strong internal reliability and strong convergent validity by correlating highly to a battery of nicotine dependence indices. Another strength of the NWSC is that the included symptoms were drawn both from a review of the literature and cognitive interviews. As such, the NWSC is a comprehensive measure that includes all known nicotine dependence withdrawal symptoms. In some applications, however, a 12-item instrument may be too long. The purpose of this study was to develop a shorter version of the NWSC for use in these situations. To keep this measure as short as possible, we aimed to include only the

minimum number of items needed to 1) capture the three main aspects of PD (withdrawal-induced craving, latency, and non-craving withdrawal symptoms) and 2) retain adequate reliability and validity.

## **4.2 Materials and Methods**

### *4.2.1 Subjects and Recruitment*

The study utilized the same dataset as that used to develop the NWSC. In order to include a broad range of subjects that were diverse in age, smoking level, ethnicity, and socioeconomic status, the sample was drawn from three high schools and four health clinics in Massachusetts. All procedures were approved by the Human Subjects Institutional Review Board.

#### *4.2.1.1 High School Subjects*

Students from three high schools were enrolled in the study. This included one rural regional school, one urban/suburban school and one vocational school. In advance of survey administration, a letter was sent to the parents allowing them to withhold their child from participation. Surveys were administered to all participating students, including nonsmokers. This was done to avoid singling out smokers, and to ensure that novice smokers, experimenters, and other occasional tobacco users who may not yet perceive themselves as smokers were captured. Surveys were administered in classes common to all students such as homeroom or health. Teachers read directions that informed students that their participation was voluntary and anonymous. To maintain



anonymity, students handed in their surveys by placing them in an envelope or slotted box.

#### *4.2.1.2 Clinic Subjects*

In addition to the high school sample, a convenience sample of adult smokers was recruited from two primary care and two behavioral health clinics that served an educationally and socioeconomically diverse population. Patients were invited to participate by front desk staff, study personnel in the waiting room, or their doctors. Volunteers were instructed to complete the anonymous, self-administered survey and return the survey to study personnel in the clinic.

#### *4.2.2 Survey Development*

The only items considered for inclusion had been developed, validated, and pre-tested during the development of the NWSC so no additional pre-testing was conducted. Final survey items included the previously validated the NWSC items, demographic information, a battery of indices of nicotine dependence for comparison purposes, and four validated measures of nicotine dependence to assess convergent validity. These four measures included the Hooked on Nicotine Checklist (HONC), the Autonomy Over Tobacco Scale (AUTOS), the Fagerström Test for Nicotine Dependence (FTND), and self-rated addiction (How addicted do you think you are on a scale of 0-4).<sup>11,15,28,35</sup> The battery of nicotine dependence indices consisted of correlates used widely in other nicotine dependence validation studies: self-reported addiction (yes or no), lifetime cigarette consumption, desire to quit, enjoyment obtained from smoking, relief obtained from smoking, pleasure obtained from smoking, and cigarettes smoked per day. While

these are not nicotine dependence measures themselves, they are used as convergent validity metrics because they are expected to trend with dependence. It is of note that the original metric of ‘pleasure’ was included because of its use in past validation studies, however two additional items ‘enjoyment’ and ‘relief’ were added after the CIs because participants interpreted the word “pleasure” as both “relief” (like scratching an itch) and “pleasure” (like enjoying a piece of candy).

#### *4.2.3 Analytic Methods*

Analyses were done in STATA version 11, and R Project 3.0.1. Surveys with incomplete data on any of the candidate items were culled. All variables were captured or converted to categorical variables, so polychoric correlations were estimated for all related analyses. Differences in means were assessed using paired t-tests and one-way analysis of variance. The statistical significance of differences between correlation coefficients was assessed using a Fisher’s  $r$  to  $z$  transformation. Significance was established at  $p < 0.05$  for differences in means or coefficients, and at  $p < 0.001$  level for correlations to adjust for multiple comparisons.

The primary goals in creating the brief version of the NWSC were: 1) to include the minimum number of items necessary to retain adequate internal reliability (0.80) and validity and 2) to include the minimum number of items needed to capture the three main domains of the NWSC: withdrawal-induced craving, latency to withdrawal-induced craving, and non-craving withdrawal symptoms. Because only one question was needed to capture latency, and three questions were needed to capture withdrawal-induced craving, these four questions were included as a given at the onset. The three

withdrawal-induced craving questions were subsequently scored together as a single item as shown in Table 4.1. The strength of the remaining NWSC items that assess non-craving withdrawal symptoms was assessed by: 1) inter-item correlations to establish which candidate withdrawal symptoms related most closely with each of the non-craving withdrawal symptoms, 2) item-total correlations to establish which items correlated most closely with the dependence scale as a whole, 3) convergent validity tests to establish which items correlated most highly to the previously described battery of nicotine dependence indices, and 4) standardized factor loadings to explore which items loaded most strongly on the single factor captured by the NWSC: physical dependence. The items that performed according to these parameters were added one by one to the four given questions (capturing withdrawal-induced craving and latency to withdrawal-induced craving) until an *a priori* internal reliability cutoff of 0.80 was reached. The final measure was evaluated using confirmatory factor analysis (CFA), internal reliability, total score distribution, and convergent validity correlations. For some of these analyses, results were examined both in the entire sample and in novice and advanced smokers separately in order to select the best performing items for the final measure. Novice smokers were defined as those smoking for less than 2 years, and advanced smokers for 2 years or longer.

## **4.3 Results**

### *4.3.1 Sample Characteristics*

A total of 2243 surveys were collected across all sites. This included non-smokers (among adolescents only), ex-smokers, and smokers. Subjects who had not

smoked in 30 days, had not smoked more than 1 cigarette in their life, and those with missing data on key variables were excluded, resulting in a final sample of 273 subjects. Subjects ranged in age from 14 to 76 (mean=30.94 years, SD=16.19). They had smoked for an average of 14.74 years (range=0.5-63, SD=15.83) and smoked an average of 11.45 cigarettes per day (range=0-50, SD=9.39). The sample was 86.5% white and 57.5% male. Further sample characteristics, demographic information, and mean dependence scores on validated measures of dependence can be found in Table 4.2.

#### *4.3.2 Item Selection*

Of the non-craving withdrawal items, the four items with the highest inter-item correlations were Anger, Lack of Focus, Restlessness, and Stress (Table 4.3). As seen in Table 4.4, Anger, Anxiety, Lack of Focus, Restlessness, and Stress were the items with very high item-total correlations (above 0.80). Similarly, Anger, Anxiety, Lack of Focus, and Stress correlated best with the nicotine dependence indices (Table 4.5). In exploratory and confirmatory factor analyses of the NWSC, Anger, Anxiety, Lack of Focus, Restlessness, and Stress were also the items with the highest standardized loadings (above 0.80) on the single factor as seen in Table 4.6. Based on these results, Anger, Anxiety, Stress, Lack of Focus, and Restlessness were selected as candidates to be added to the four given items (capturing withdrawal-induced craving and latency).

The candidate items were added individually to the 4 given items and the psychometric tests described above were repeated to determine which items improved the working measure's internal reliability and correlation to a battery of nicotine dependence indices (used to establish convergent validity). Of all the candidate non-craving

withdrawal symptoms added to the four given questions, Anger improved the internal reliability most ( $\alpha=0.77$ ). Because of this the decision was made to add Anger as the fifth question to the working measure. However, the reliability was still below our *a priori* cutoff of 0.80. Therefore we proceeded to evaluate whether adding a sixth item would improve the internal reliability. Of the remaining items, Stress improved the 5-item measure most ( $\alpha=0.85$ ). This combination of Withdrawal-Induced Craving, Latency, Anger, and Stress met our *a priori* criteria for internal reliability (above 0.80) and showed good convergent validity. While the addition of other candidate items did improve internal reliability, it did not significantly improve the measure's correlation to any of the convergent validity metrics. For this reason, the final Brief NWSC (NWSC-b) measure included the four questions capturing Withdrawal-Induced Craving and Latency to withdrawal-induced craving, along with the additional non-craving withdrawal symptoms of Anger and Stress (Table 4.7).

#### 4.3.3 Confirmatory Testing of the NWSC-b

As with the full NWSC, confirmatory factor analysis of the NWSC-b confirmed the single factor structure suggested in exploratory analyses (Table 4.8 & Figure 4.1). All of the final items exhibited high factor loadings (over 0.6, Table 4.9). The final items showed high item-total correlations (Table 4.10) and an internal reliability of 0.85. Like the full NWSC (Table 4.11), the NWSC-b also correlated significantly to a battery of nicotine dependence indices ( $p<0.001$ ) including four widely used nicotine dependence measures: the HONC, AUTOS, FTND, and Self-rated Addiction. The NWSC-b total

score distribution (Figure 4.2) does not exhibit any ceiling or floor effects and is similar to that of the other nicotine dependence measures in this sample.

#### **4.4 Discussion**

The NWSC is a comprehensive measure that assesses the severity of all known symptoms of tobacco withdrawal. For situations where time or space limitations preclude the use of the NWSC, the NWSC-b provides a short, but reliable ( $\alpha=0.85$ ) measure that covers the three aspects of withdrawal symptoms: 1) withdrawal-induced craving, 2) latency to withdrawal-induced craving, and 3) non-craving withdrawal symptoms. The convergent validity of the NWSC-b was demonstrated by its high correlation (above 0.6,  $p<0.001$ ) with four widely used nicotine dependence measures: the HONC, AUTOS, FTND, and Self-Rated Addiction. It also correlates significantly ( $p<0.001$ ) with a battery of nicotine dependence indices including self-reported addiction, desire to quit, and relief obtained from smoking a cigarette.

In order to capture both the early and late stage symptoms of dependence, the NWSC-b was developed in a diverse sample of smoking histories and backgrounds including both novice and advanced smokers, as well as non-daily and daily smokers. Stratified analyses by age did not indicate a significant difference in the performance of the NWSC-b in these subgroups (data not shown). The NWSC-b is suitable for use with tobacco users of all ages and levels of experience. While subgroup analyses in this sample were limited by sample size, future studies should pursue further validity tests using structural equation modeling, item response theory, and known group validity tests.

Test-retest reliability and predictive validity could not be evaluated because data was collected cross-sectionally. Future studies should evaluate both of these longitudinal assessments of reliability and validity.

The NWSC-b's inclusion of all three aspects of withdrawal (withdrawal-induced craving, latency to craving, and non-craving withdrawal symptoms) ensures that despite being a brief measure, it still captures multiple salient aspects of withdrawal. As such, the NWSC-b could also be useful in clinical settings where clinicians may wish to assess physical dependence without necessarily tracking the progression of all physical withdrawal symptoms as captured by the full NWSC. Similarly the NWSC-b would be a useful short measure for inclusion in national health surveys or other population-wide surveys that track the incidence and prevalence of nicotine dependence. Because the NWSC-b focuses on withdrawal symptoms, it would be suited for use in physiologic research, such as neuroimaging studies, where dependence levels are being correlated to changes in the structure or function of the brain. However, like the full NWSC, the NWSC-b captures overall disease severity, not momentary withdrawal intensity (e.g., "How strong is your craving right now?").

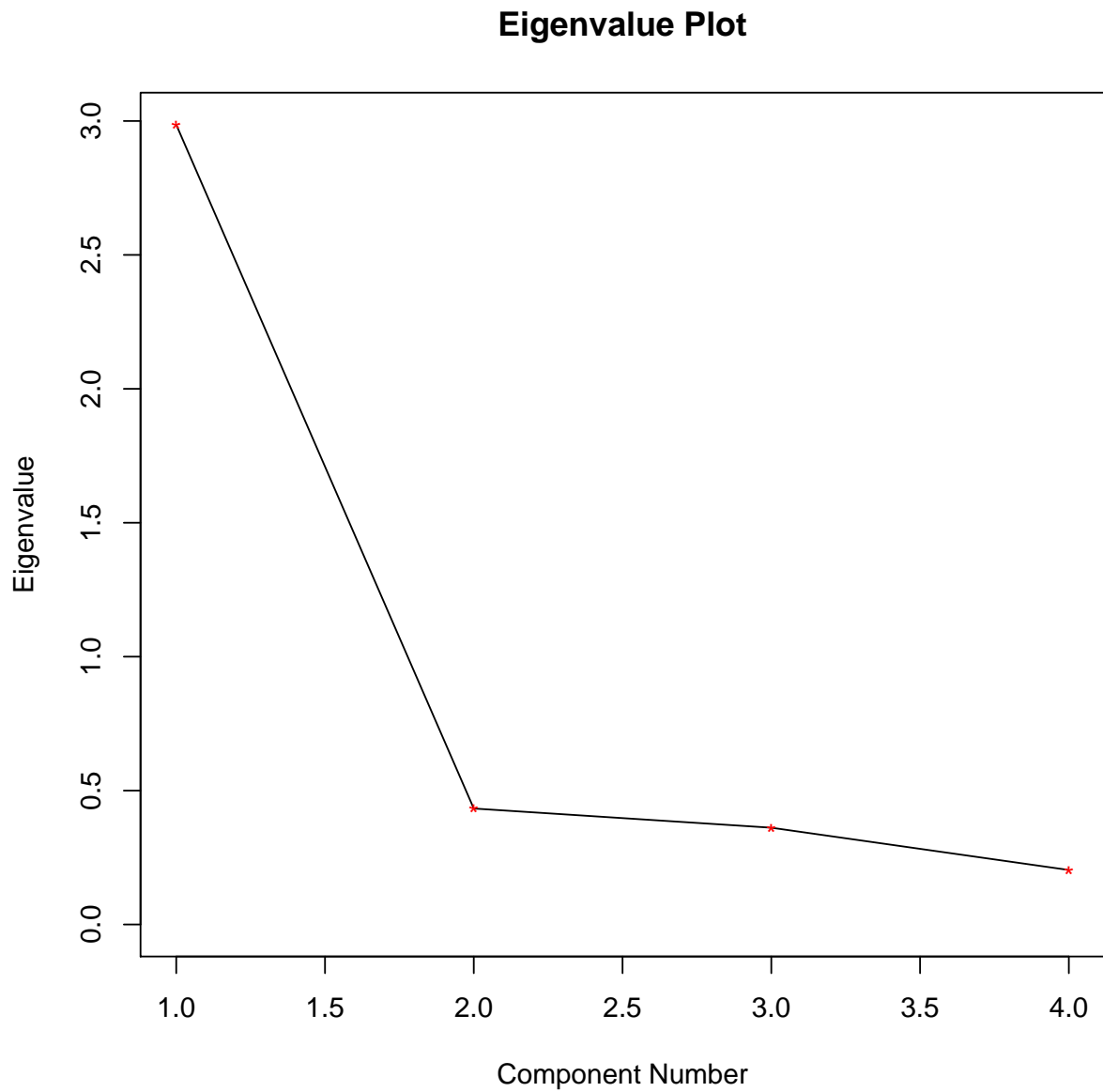
Like the NWSC, the NWSC-b does not rely on smoking behaviors (such as when and where one smokes) to assess nicotine dependence. Instead, it focuses on the symptoms that arise when an individual remains abstinent from nicotine for a period of time. Because of this, the NWSC-b could be adapted for users of chewing tobacco, e-cigarettes, water pipe tobacco, and other nicotine delivery methods with minor wording changes.

Future studies should assess the performance of the NWSC-b among users of these products.

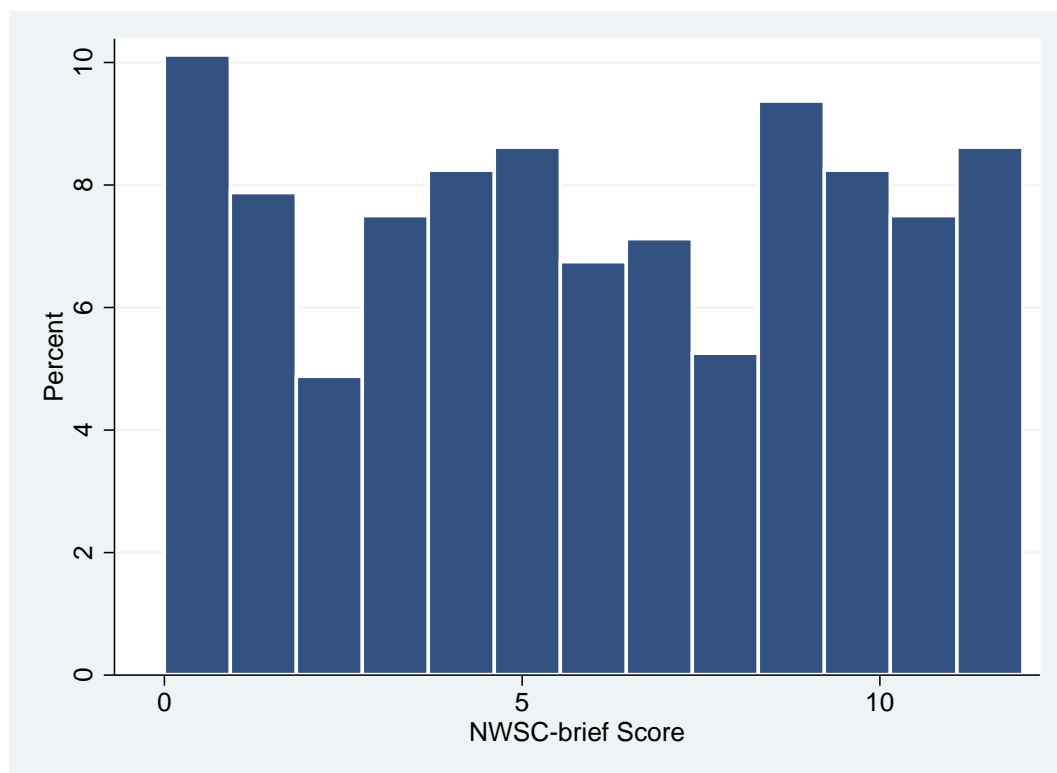
Despite being half the length, the NWSC-b compares favorably to the full NWSC in its correlation to the battery of nicotine dependence indices used to establish convergent validity (Table 4.11). Because of this, the NWSC-b may be substituted for the full version when an overall measure of physical dependence is desired. If however, one wishes to capture and track a comprehensive list of withdrawal symptoms, the full NWSC would be the more appropriate measure. Due to the cross-sectional nature of the study, we could not evaluate how the NWSC-b compares to the full NWSC in test-retest reliability, predictive validity, and known group validity. It is possible that the full version of the NWSC may perform better using these metrics. It is also possible that by including all known symptoms of physical dependence, the full NWSC may correlate more highly to structural changes in the brain. Future prospective and biologic studies should explore these issues.

In conclusion, the NWSC-b fulfills our *a priori* goal of creating a shorter version of the NWSC that retains high internal reliability and validity. Where the length of a measure is not a consideration, and in situations where a comprehensive evaluation of symptoms is desired, the full NWSC would be more appropriate. When a short measure is needed, the NWSC-b provides a versatile, valid, and reliable measure of physical dependence.





**Figure 4.1 Plot of Eigenvalues Resulting from the Exploratory Factor Analysis of the Brief Nicotine Withdrawal Symptom Checklist**



**Figure 4.2** Brief Nicotine Withdrawal Symptom Checklist Final Score Distribution

**Table 4.1 The Nicotine Withdrawal Symptom Checklist (NWSC) Items\***

	This describes me....			
	Not at all	A little	Pretty well	Very well
1. If I go too long without a cigarette or dip, I begin to feel angry or irritable.	0	0	0	0
2. If I go too long without a cigarette or dip, I feel down or depressed.	0	0	0	0
3. If I go too long without a cigarette or dip, I find it hard to concentrate or focus.	0	0	0	0
4. If I go too long without a cigarette or dip, I suffer from insomnia or troubled sleep.	0	0	0	0
5. If I go too long without a cigarette or dip, I feel restless.	0	0	0	0
6. If I go too long without a cigarette or dip, I feel stressed.	0	0	0	0
7. If I go too long without a cigarette or dip, I begin to get headaches.	0	0	0	0
8. If I go too long without a cigarette or dip, I feel nervous or anxious.	0	0	0	0
9. I usually want to smoke or use dip right after I wake up.	0	0	0	0
10. If I go too long without smoking or using dip, the first thing I notice is a <i>mild desire</i> to smoke or use dip that I can ignore.				
	<input type="radio"/> No. This statement does not describe me. <input type="radio"/> Yes.			
11. If I go too long without smoking or using dip, the desire for a cigarette or dip becomes so strong that it is hard to ignore and it interrupts my thinking.				
	<input type="radio"/> No. This statement does not describe me. <input type="radio"/> Yes.			
12. If I go too long without smoking or using dip, I just can't function right, and I know I will have to smoke or use dip just to feel normal again.				
	<input type="radio"/> No. This statement does not describe me. <input type="radio"/> Yes.			

NWSC Scoring Algorithm:

Point Value for Items 1-9		Point Value for Items 10-12		NWSC Score
3 = Very well 2 = Pretty well 1 = A little 0 = Not at all	+	3 = the highest endorsed item is 12 2 = the highest endorsed item is 11 1 = the highest endorsed item is 10 0 = did not endorse any items 10-12	=	Total score (range, 0-30)

\*The table includes the 12 items that comprise the NWSC. The lower half shows the scoring algorithm used to compute the final NWSC score. All items are scored on a 0-3 point Likert Scale, except items 10-12 which are scored as one composite item.

**Table 4.2 Sample Characteristics (N=273)**

	<i>%(N)</i>	<i>Mean</i>	<i>SD</i>	<i>Range (min- max)</i>
Age		30.94	16.19	14-76
<i>Adolescents (&lt;19)</i>	44.68 (122)			
<i>Adults (19+)</i>	55.31 (151)			
Years smoked		14.74	15.83	0.5-63
<2 yrs	20.97 (56)			
2-5 yrs	29.96 (80)			
>5 yrs	49.06 (131)			
Cigarettes/day		11.45	9.39	0-50
HONC		6.28	3.34	0-10
AUTOS		16.60	11.40	0-36
FTND		3.87	2.630	0-10
Self-Rated Addiction		2.45	1.54	0-4
Gender				
<i>Male</i>	57.5(157)			
<i>Female</i>	42.5(116)			
Ethnicity				
<i>Prefer not to identify</i>	0.75 (2)			
<i>American Indian or Alaskan Native</i>	3.01 (8)			
<i>Asian</i>	1.13 (3)			
<i>Black</i>	3.76 (10)			
<i>Native Hawaiian or Pacific Islander</i>	0.38 (1)			
<i>White</i>	86.47 (230)			
<i>Mixed</i>	4.51 (12)			
Hispanic				
<i>No</i>	88.01 (235)			
<i>Yes</i>	11.99 (32)			
Smoking Frequency				
<i>Daily</i>	63.37 (173)			
<i>Non-daily</i>	36.63 (100)			

HONC = Hooked on Nicotine Checklist

AUTOS = Autonomy Over Tobacco Scale

FTND = Fagerström Test for Nicotine Dependence

**Table 4.3 Inter-Item Correlation Coefficients for the Non-Craving Withdrawal Symptoms in the Nicotine Withdrawal Symptom Checklist**

	<i>Anger</i>	<i>Anxiety</i>	<i>Depression</i>	<i>Headache</i>	<i>Insomnia</i>	<i>Lack of Focus</i>	<i>Restlessness</i>	<i>Stress</i>
<i>Anger</i>		0.61	0.56	0.46	0.46	0.68	0.62	0.71
<i>Anxiety</i>	0.61		0.54	0.44	0.47	0.62	0.64	0.66
<i>Depression</i>	0.56	0.54		0.52	0.56	0.61	0.42	0.55
<i>Headache</i>	0.46	0.44	0.52		0.54	0.51	0.38	0.51
<i>Insomnia</i>	0.46	0.47	0.56	0.54		0.51	0.53	0.46
<i>Lack of Focus</i>	0.68	0.62	0.61	0.51	0.51		0.67	0.72
<i>Restlessness</i>	0.62	0.64	0.42	0.38	0.53	0.67		0.72
<i>Stress</i>	0.71	0.66	0.55	0.51	0.46	0.72	0.72	

All reported values are significant at the  $p < 0.001$  level  
 Polychoric correlation coefficients are reported because all items were categorical

**Table 4.4 Nicotine Withdrawal Symptom Checklist Item-Total Correlations**

	<i>Item-total Correlation</i>	<i>Item-rest Correlation</i>
<i>Angry</i>	0.83	0.78
<i>Anxiety</i>	0.81	0.75
<i>Depression</i>	0.72	0.65
<i>Headache</i>	0.66	0.58
<i>Insomnia</i>	0.68	0.62
<i>Lack of Focus</i>	0.84	0.79
<i>Latency to Craving</i>	0.70	0.61
<i>Restlessness</i>	0.80	0.74
<i>Severity of Withdrawal Induced Craving</i>	0.76	0.69
<i>Stress</i>	0.84	0.80

**Table 4.5 Polychoric Correlation Coefficients Between Candidate Items and Selected Nicotine Dependence Indices**

	<i>Anger</i>	<i>Anxiety</i>	<i>Depression</i>	<i>Headache</i>	<i>Restlessness</i>	<i>Insomnia</i>	<i>Lack of Focus</i>	<i>Stress</i>
<i>HONC</i>	0.68	0.69	0.49	0.44	0.65	0.47	0.63	0.68
<i>AUTOS</i>	0.73	0.84	0.59	0.49	0.68	0.49	0.69	0.80
<i>FTND</i>	0.44	0.56	0.38	0.29	0.43	0.36	0.45	0.48
<i>Self Rated Addiction</i>	0.62	0.55	0.36	0.38	0.55	0.37	0.47	0.61
<i>Do you think you're addicted?</i>	0.36	0.29	0.19	-	0.30	0.21	0.26	0.34
<i>Lifetime cigarette consumption</i>	0.33	0.26	0.17	-	0.36	-	0.18	0.36
<i>Do you want to quit?</i>	0.36	0.26	-	-	0.28	-	0.22	0.24
<i>Enjoyment</i>	0.37	0.32	0.33	0.29	0.30	0.24	0.31	0.34
<i>Pleasure</i>	0.39	0.29	0.20	0.22	0.28	0.18	0.25	0.36
<i>Relief</i>	0.52	0.37	0.30	0.32	0.44	0.30	0.42	0.51
<i>Cigarettes/day</i>	0.31	0.31	-	-	0.24	-	0.32	0.27

All reported values are significant at the  $p < 0.001$  level

Polychoric correlation coefficients are reported because all items were categorical

HONC = Hooked on Nicotine Checklist

AUTOS = Autonomy Over Tobacco Scale

FTND = Fagerström Test for Nicotine Dependence

**Table 4.6 Factor Loadings from the Confirmatory Factor Analysis of the Nicotine Withdrawal Symptom Checklist**

<i>Factor</i>	<i>Loading</i>
<i>Anger</i>	0.87
<i>Anxiety</i>	0.83
<i>Depression</i>	0.76
<i>Headache</i>	0.69
<i>Insomnia</i>	0.75
<i>Lack of Focus</i>	0.89
<i>Latency to Withdrawal Induced Craving</i>	0.71
<i>Restlessness</i>	0.86
<i>Severity of Withdrawal Induced Craving</i>	0.76
<i>Stress</i>	0.91



**Table 4.7 The brief-Nicotine Withdrawal Symptom Checklist (NWSC-b) \***

	This describes me....			
	Not at all	A little	Pretty well	Very well
1. If I go too long without a cigarette or dip, I begin to feel angry or irritable.	0	0	0	0
2. If I go too long without a cigarette or dip, I feel stressed.	0	0	0	0
3. I usually want to smoke or use dip right after I wake up.	0	0	0	0
4. If I go too long without smoking (or using dip), the first thing I notice is a <i>mild desire</i> to smoke (or use dip) that I can ignore. <input type="radio"/> No. This statement does not describe me. <input type="radio"/> Yes.				
5. If I go too long without smoking (or using dip), the desire for a cigarette (or dip) becomes so strong that it is hard to ignore and it interrupts my thinking. <input type="radio"/> No. This statement does not describe me. <input type="radio"/> Yes.				
6. If I go too long without smoking (or using dip), I just can't function right, and I know I will have to smoke (or use dip) just to feel normal again. <input type="radio"/> No. This statement does not describe me. <input type="radio"/> Yes.				

NWSC-b Scoring Algorithm:

Point Value for Items 1-3		Point Value for Items 4-6		NWSC-b Score
3 = Very well 2 = Pretty well 1 = A little 0 = Not at all	+	3 = the highest endorsed item is 6 2 = the highest endorsed item is 5 1 = the highest endorsed item is 4 0 = did not endorse any items 4-6	=	Total score (range, 0-12)

\*The table includes the 6 items that comprise the NWSC-b. The lower half shows the scoring algorithm used to compute the NWSC-b score. Items 1-3 are scored on a 0-3 point Likert Scale; items 4-6 are scored as one composite item.

**Table 4.8 Exploratory Factor Analysis  
results for the Brief Nicotine Withdrawal  
Symptom Checklist**

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	<i>Eigenvalues</i>
<i>Factor 1</i>	2.99
<i>Factor 2</i>	0.43
<i>Factor 3</i>	0.36
<i>Factor 4</i>	0.20

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**Table 4.9 Factor Loadings from the Confirmatory Factor Analysis of the brief Nicotine Withdrawal Symptom Checklist**

<i>Factor</i>	<i>Loading</i>
<i>Anger</i>	0.89
<i>Latency to Withdrawal Induced Craving</i>	0.77
<i>Severity of Withdrawal Induced Craving</i>	0.72
<i>Stress</i>	0.88

**Table 4.10 The Brief Nicotine Withdrawal Symptom Checklist Item-Total Correlations & Internal Reliability**

	<i>Item-total Correlation</i>	<i>Item-rest Correlation</i>	<i>Cronbach's Alpha without the item</i>
<i>Anger</i>	0.86	0.74	0.78
<i>Latency to Withdrawal Induced Craving</i>	0.82	0.65	0.82
<i>Severity of Withdrawal Induced Craving</i>	0.79	0.63	0.83
<i>Stress</i>	0.85	0.73	0.79
<b><i>Total Scale Cronbach's Alpha</i></b>			0.85

**Table 4.11 Polychoric Correlation Coefficients Between Selected Nicotine Dependence Indices and the Full vs. Brief Nicotine Withdrawal Symptom Checklist**

	<i>NWSC-b</i>	<i>NWSC</i>
<i>HONC</i>	0.81	0.80
<i>AUTOS</i>	0.86	0.88
<i>FTND</i>	0.66	0.62
<i>Self-Rated Addiction</i>	0.71	0.66
<i>Do you think you're addicted?</i>	0.39	0.35
<i>Lifetime cigarette consumption</i>	0.40	0.33
<i>Do you want to quit?</i>	0.36	0.30
<i>Enjoyment</i>	0.42	0.41
<i>Pleasure</i>	0.45	0.38
<i>Relief</i>	0.55	0.51
<i>Cigarettes/day</i>	0.42	0.35

All reported values are significant at the  $p < 0.001$  level  
 NWSC-b = Brief Nicotine Withdrawal Symptom Checklist  
 NWSC = Nicotine Withdrawal Symptom Checklist  
 HONC = Hooked on Nicotine Checklist  
 AUTOS = Autonomy Over Tobacco Scale  
 FTND = Fagerström Test for Nicotine Dependence

**CHAPTER VI: *Conclusion***

Over the course of this study, three distinct physical dependence measures were developed for use in a range of research settings: the Withdrawal-Induced Craving Scale (WICS), the Nicotine Withdrawal Symptom Checklist (NWSC), and the brief Nicotine Withdrawal Symptom Checklist (NWSC-b) (See Table 5.1). Each performs a distinct function in the study of nicotine dependence.

### *5.1 WICS Summary*

The WICS is a 4-question measure capturing the progression of the most common symptom of physical withdrawal: withdrawal-induced craving. The WICS is the first comprehensive measure to capture the complex construct of “craving” by teasing apart its many stages and including the construct of latency. It is also the first nicotine dependence measure to include latency as an item. The WICS is an expansion of the previously validated Levels of Physical Dependence criteria, providing six levels of discrimination for use in situations where more than three categories of comparison are required. The WICS correlates more highly than the Levels of Physical Dependence measure to a range of convergent validity metrics including several gold standard nicotine dependence measures like the Hooked on Nicotine Checklist (HONC), Fagerström Test for Nicotine Dependence (FTND), the Autonomy Over Tobacco Scale (AUTOS), and self-reported addiction. In addition, the WICS has a higher relative validity than the FTND (See Table 5.2) when examining how well it differentiates individuals by level of physical dependence (which is the only validated measure of physical dependence available to establish relative validity). Given that some items are included in both the WICS and the Levels of Physical Dependence measure, these results

should be interpreted cautiously. The WICS also outperforms the FTND in differentiating individuals by years smoked (See Table 5.3), though without a confidence interval, it is not possible to know whether such a small difference is statistically significant. Future studies with larger sample sizes should better establish whether there is a significant difference between the relative validity of the two measures. As discussed in previous chapters, years smoked is a weak indicator of physical dependence, but due to the absence of a gold standard metric it was included in the relative validity analyses. Because it is more related to smoking routines and habits than dependence itself, the marginally better performance of the WICS over the FTND should also be interpreted with caution. Future studies using more concrete markers of physical dependence (like structural changes in the brain) should be conducted to further establish the relative validity of the WICS over other gold standard measures in estimating physical dependence.

### *5.2 NWSC & NWSC-b Summary*

The NWSC is a 12-question measure that allows research to track not only the severity of overall dependence using the total score, but also the onset and severity of each symptom individually. The brief version of the NWSC (NWSC-b) captures only the former, but performs as well as the full version in validity tests despite being half the length. The NWSC and NWSC-b both exhibit a single factor structure with high standardized factor loadings on said factor, suggesting that the selection process for identifying only survey items that capture a single construct was successful. Both measures exhibit high internal reliability ( $\alpha > 0.85$ ) and correlated significantly ( $p < 0.001$ )



with a battery of nicotine dependence indices. The score distributions for both measures were consistent with those of other gold standard nicotine dependence measures within the tested population.

Like the WICS, both the NWSC and the NWSC-b display a higher relative validity than the FTND (See Table 5.2) in differentiating individuals by level of physical dependence. However they do not outperform the FTND in differentiating individuals by years smoked. As previously discussed, years smoked is a very weak indicator of dependence, as it correlates more highly to smoking routines and habits than dependence itself. The results of the relative validity tests in Table 5.3 confirm this, showing that the FTND, which focuses entirely on such habits and routines, does better at differentiating smokers by years smoked than the more pathophysiologically based measures. As with the WICS, future studies using more concrete markers of physical dependence should also be conducted to further establish the relative validity of the NWSC and NWSC-b compared to other common nicotine dependence measures.

### *5.3 Study Limitations*

In despite the strengths of the WICS, NWSC and NWSC-b, there were some limitations to this study. First, due to the cross sectional design of the study, the progression of withdrawal symptoms or overall dependence in a single individual over time cannot be assessed. Future prospective studies should further explore this. Such studies should also evaluate test-retest reliability and predictive validity, which we were also unable to estimate in a cross sectional sample. Larger studies in more diverse populations should further explore whether the measures are equally valid when tested in

minority subgroups and translated into different languages. Finally, as previously discussed, each measure should be further validated against physiologic metrics such as neural structure or regional connectivity to better establish how specific physical changes relate to physical dependence scores.

#### *5.4 Strengths and Future Directions*

The WICS, NWSC and NWSC-b were developed with a higher sample size per item than most other nicotine dependence validation studies. They were also among the first to be developed in a diverse population of smokers, making them useful for studies enrolling a broad spectrum of dependent individuals. All three measures are also among the first to be developed using smoker feedback in item selection, and as such uncovered both the presence of new non-traditional symptoms of withdrawal and the limitations of more widely accepted symptoms. Finally because they focus on symptoms that arise during abstinence from tobacco, not cigarette smoking related behaviors, there is no theoretical reason why they could not be adapted for other forms of nicotine delivery. Future studies should explore whether the measures are as valid among users of e-cigarettes, hookah, chewing tobacco, etc.

The WICS, NWSC and NWSC-b are the first measures to capture only the overall disease severity of physical dependence on nicotine, and as such provide valuable tools for researchers examining the biology of the disease. Only once we establish how pathophysiological changes in brain structure or connectivity correlate to changes in physical dependence, can we develop better medical procedures and treatments to target these regions and pathways. These three measures can also be used in related fields to

track how overall physical dependence or individual symptom severity change in relation to procedures and treatments developed in non-nicotine related clinical trials. Finally, all three measures provide useful tools for population level surveillance, to track how average physical dependence is changing over time or in relation to new tobacco policies. Through the exploration of these future directions, it is hoped that these three physical dependence measures will better equip researchers in nicotine dependence and related fields to understand, treat, and prevent this serious condition.

**Table 5.1 A Series of Physical Dependence Measures**

		<i>Aim 1</i>	<i>Aim 2</i>	<i>Aim 3</i>
<i>Measure Name</i>	<b>Original Levels of Physical Dependence Criteria (PD)</b>	<b>Withdrawal-Induced Craving Scale (WICS)</b>	<b>Nicotine Withdrawal Symptom Checklist (NWSC)</b>	<b>Brief Nicotine Withdrawal Symptom Checklist (NWSC-b)</b>
<i>What does it Capture?</i>	Withdrawal-induced craving	Withdrawal-induced craving & Latency	Overall level of physical dependence	All symptoms of physical dependence
<i>Score Range</i>	0-3	0-6	0-30	0-12
<i>Number of Questions</i>	3	4	12	6
<i>Uses</i>	To estimate physical dependence based on the intensity of withdrawal-induced craving	A stronger measure to stage physical dependence based on intensity and latency of withdrawal-induced craving	1. To estimate overall level of physical dependence 2. To track the change in severity of withdrawal symptoms as dependence progresses	To estimate overall level of physical dependence

**Table 5.2 Relative Validity Analyses Using Level of Physical Dependence (PD) as the Binning Variable**

	<i>PD Level 0</i>	<i>PD Level 1</i>	<i>PD Level 2</i>	<i>PD Level 3</i>			
	<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>F-statistic</i>	<i>P-Value</i>	<i>RV</i>
<i>Self rated addiction</i>	1.22 (1.57)	2.04 (1.48)	3.05 (1.06)	3.3 (1.08)	33.76	<0.001	0.97
<i>FTND*</i>	2.29 (2.15)	2.35 (1.99)	4.34 (2.12)	5.57 (2.33)	34.75	<0.001	1.00
<i>AUTOS</i>	7.08 (8.78)	10.04 (7.73)	21.59 (8)	25.99 (8.33)	84.37	<0.001	2.43
<i>HONC</i>	3.56 (3.06)	4.17 (2.78)	7.98 (2.22)	8.86 (1.47)	85.20	<0.001	2.45
<i>NWSC</i>	3.68 (5.09)	6.46 (4.62)	14.95 (5.46)	18.72 (5.81)	122.67	<0.001	3.53
<i>NWSC-b</i>	1.83 (2.34)	3.95 (2.4)	7.88 (2.11)	9.49 (2.42)	152.03	<0.001	4.37
<i>WICS</i>	0.65 (0.97)	2.01 (1.15)	3.98 (1.18)	5.21 (1.01)	248.68	<0.001	7.16

\* Reference measure: FTND

Binning Variable: Levels of Physical Dependence

**Table 5.3 Relative Validity Analyses Using Years Smoked as the Binning Variable**

	<i>Smoked &lt;2 yrs</i>	<i>Smoked 2-5 yrs</i>	<i>Smoked &gt;5 yrs</i>			
	<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>F-statistic</i>	<i>P-Value</i>	<i>RV</i>
<i>PD</i>	1.38 (1.1)	1.49 (1.14)	1.86 (1.14)	4.66	0.0103	0.41
<i>NWSC</i>	9.28 (9.33)	10.42 (8.11)	13.3 (7.49)	5.99	0.0029	0.53
<i>AUTOS</i>	12.66 (12.46)	15.39 (11.01)	19.41 (10.6)	7.95	<0.001	0.71
<i>NWSC-b</i>	4.62 (4.17)	5.61 (3.83)	6.99 (3.47)	8.82	0<0.001	0.79
<i>FTND</i>	2.61 (2.61)	3.46 (2.49)	4.6 (2.47)	11.23	<0.001	1
<i>WICS</i>	2.28 (2.07)	2.87 (2.09)	3.74 (1.91)	11.81	<0.001	1.05
<i>HONC</i>	4.59 (4.01)	5.9 (3.03)	7.27 (2.82)	14.72	<0.001	1.31
<i>Self rated addiction</i>	1.56 (1.48)	2.19 (1.53)	3.09 (1.29)	26.16	<0.001	2.33

\* Reference measure: FTND  
 Binning Variable: Years Smoked

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