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TOBACCO USE AND NICOTINE WITHDRAWAL AMONG PATIENTS WITH MENTAL ILLNESS

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TOBACCO USE AND NICOTINE WITHDRAWAL AMONG PATIENTS WITH MENTAL ILLNESS

DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Nursing
at the University of Kentucky

By

Yazan Daher Al-Mrayat

Lexington, Kentucky

Co-Directors: Dr. Ellen J. Hahn, Professor of Nursing

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Lexington, Kentucky

2020

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ABSTRACT OF DISSERTATION

TOBACCO USE AND NICOTINE WITHDRAWAL AMONG
PATIENTS WITH MENTAL ILLNESS

People with mental illness (MI) are disproportionately affected by tobacco use compared to the general population. In fact, it is estimated that people with MI consume approximately 44% of cigarettes smoked in the United States. Moreover, the MI population is at greater risk for the negative social, economic, and health consequences associated with tobacco use and are reported to have 25-year shorter life expectancies than the general population. The impact of tobacco use is further noticeable among patients with MI who require psychiatric hospitalization. Quitting smoking in this population has been linked to fewer discharges against medical advice, better quality of life, and positive physical and psychological health outcomes. Thus, it is crucial to identify and address factors such as nicotine withdrawal (NW) that may hinder successful quit attempts among hospitalized patients with MIs. Given that many psychiatric facilities have tobacco-free policies, NW is an important phenomenon to consider when delivering tobacco treatment with this population.

The NW syndrome is a set of symptoms appearing after 24 hours of abrupt cessation or reduction of tobacco after prolonged duration of use. NW has been associated with impaired patient functioning, lower likelihood of quitting tobacco use, and compromising care during psychiatric hospitalization. Approximately 65% of patients hospitalized in a psychiatric facility with a tobacco-free policy experience NW syndrome. Nonetheless, NW among hospitalized patients with MI is modestly examined in the literature.

The purpose of this dissertation is to enhance our understanding of tobacco use and NW among hospitalized patients with MI. Specific aims are to: 1) scrutinize and synthesize the research literature examining NW among tobacco-using patients with MI to outline correlates pertinent to this phenomenon, identify gaps in the literature, and guide future research; 2) evaluate the psychometric properties of the Minnesota tobacco withdrawal scale (MTWS) in capturing NW severity in the MI population during psychiatric hospitalization; and 3) examine whether tobacco-using patients with certain

psychiatric diagnoses (psychotic disorders and mood or anxiety disorders) experience varying NW severity, based on self-reported class of substance use (e.g., hallucinogens, inhalants, alcohol) within the year prior to their psychiatric admission.

Aim 1 was achieved by conducting a systematic review of the literature using the PsychINFO, MEDLINE, and CINAHL databases. The following correlates of NW among people with MI in community and hospital settings were identified: psychiatric diagnosis, sex, race, psychiatric symptom severity, alcohol and drug use, level of nicotine dependence, nicotine replacement therapy and varenicline administration, confidence in quitting, and levels of depression and anxiety. Aim 2 was achieved by conducting a reliability and validity analysis of the MTWS in a sample of psychiatric inpatients. The MTWS demonstrated adequate reliable and valid psychometric properties, and the measure may be recommended for use in clinical practice to identify patients experiencing NW. Aim 3 was achieved by performing a series of moderation analyses to examine the nature of the relationships between psychiatric diagnoses and NW severity, considering the patient's substance use profile. Lower NW severity was observed among patients with psychotic disorders who reported using hallucinogens; inhalants; opiates; sedatives, hypnotics, and anxiolytics; stimulants; or poly-substances over the past year than those who did not use these substances. Higher NW severity was documented among patients with mood or anxiety disorders who reported using hallucinogens or sedatives, hypnotics, and anxiolytics over the past year compared to those patients who did not use these substances.

Considering the high prevalence of tobacco use among patients with MI compared to the general population, a tobacco-free psychiatric hospitalization poses a valuable opportunity to promote cessation. The results of this dissertation demonstrate a need for protocols to better identify NW, based on specific patients' characteristics, in order to develop tailored interventions during psychiatric hospitalizations to limit barriers to cessation and consequences of tobacco use in this population.

KEYWORDS: Nicotine Withdrawal, Tobacco Withdrawal, Mental Illness, Psychiatric Hospitalization, Substance Use

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05/08/2020

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TOBACCO USE AND NICOTINE WITHDRAWAL AMONG PATIENTS WITH MENTAL ILLNESS

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CHAPTER 1. INTRODUCTION

1.1 Tobacco use and mental illness

Compared to the general U.S. population, tobacco use among people with mental illnesses (MI) is two- to three-fold more prevalent, especially for those with psychotic, mood, anxiety, and substance use disorders.[1] In fact, the prevalence of smoking increases exponentially among those with a higher number of co-occurring MI diagnoses.[1] Accordingly, an estimated 21-59% of people with MI currently use tobacco.[2-7] This considerable tobacco use prevalence rate in this population is best exemplified by the fact that people with MI consume around 44% of all cigarettes smoked annually in the U.S.[7] Consequently, people with MI have a shorter life-expectancy and are predisposed to a higher incidence of negative smoking-related social and economic influences, diseases, and deaths every year.[1,8,9] On the other hand, quitting smoking in this population can decrease the likelihood of being discharged against medical advice, lower anxiety and depression, and enhance positive affect and quality of life.[10,11] Therefore, it is crucial to address factors that hinder tobacco cessation and promote quit attempts in this population.

1.2 Nicotine withdrawal defined

Nicotine withdrawal (NW) syndrome is a well-known factor that decreases the likelihood of quitting tobacco use. NW syndrome is a set of symptoms appearing within 24 hours of the abrupt cessation or reduction of a nicotine-containing product used on a daily basis for a prolonged period of time.[12] These symptoms typically include irritability/frustration/anger, anxiety, difficulty in concentration, increased appetite,

restlessness, depressed mood, and insomnia.[12] Previously, the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) included the decrease in heart rate as an eighth symptom of NW. However, this symptom was dropped in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-V).[12,13] The DSM-V also specified that 4 or more of the NW symptoms need to be present for a NW syndrome diagnosis.[12] In addition to NW symptoms outlined by the DSM-V, other clinical manifestations of NW include negative affect, working memory deficits, increased dreaming, constipation, dizziness, coughing, craving, anhedonia, fear, and mouth ulcers.[14-16] Moreover, changes in physiologic parameters such as electroencephalogram (EEG) power and heart rate have been observed within 12 hours of smoking abstinence.[17]

1.3 Nicotine withdrawal and MI

It is estimated that up to 65% of patients with MI experience moderate-to-severe NW symptomatology during a psychiatric tobacco-free hospitalization.[18] NW among people with MI is associated with fewer successful quit attempts, compromising psychiatric care, clinically-significant distress, mood changes, and functional impairment.[11,12,19] Also, NW among patients with MI has been associated with female gender, African American race, having greater psychiatric symptoms severity, lower confidence in quitting, and having a diagnosis of an alcohol or other substance use disorder.[18,20]

Using data from two large national surveys involving participants with and without MI, Smith, Homish, Giovino, and Kozlowski (2014)[19] found that MI accounted for approximately 44% of NW diagnoses, with a greater likelihood of being diagnosed

with NW among people with MI, compared to those without. Specifically, as compared to those without MI, the likelihood of NW was greater among people with psychotic disorders, externalizing (past year alcohol use disorders and drug use disorders, and lifetime antisocial personality disorder), internalizing disorders (past year mood and anxiety disorder), and co-occurring internalizing disorders and externalizing disorders, consecutively.[19] Among community-dwelling individuals meeting criteria for an anxiety disorder diagnosis, researchers found that these participants experienced greater difficulties with NW during their quit attempt and had poor smoking cessation outcomes, compared to their counterparts with no anxiety disorder diagnosis.[21] Moreover, having a lifetime diagnosis of major depressive disorder was associated with 2.5 times greater risk for relapse due to NW, particularly for women with a history of alcohol use or dependence.[22] Similarly, higher likelihood of NW and associated relapse was found among patients with alcohol and substance use disorder than patients with MI without these disorders.[22,23] These findings underscore the importance of addressing NW for people with MI to enhance tobacco cessation and ultimately reduce tobacco use prevalence.

Nicotine replacement therapy (NRT) (i.e., nicotine gum, patches, inhaler, and lozenges) has been offered to psychiatric inpatients as a tobacco treatment measure used to alleviate NW symptom severity during hospitalization.[20,24] In these studies, NRT was prescribed for patients with higher levels of nicotine dependence and prior use of NRT. However, older and African American patients are less likely to be offered NRT during their hospital stay.[18] Interestingly, the timing of providing NRT may influence NW

symptoms severity. The delayed receipt of NRT after admission was associated with a more intense NW experience.[20]

Because tobacco-free psychiatric hospitalizations may intensify the experience of NW among tobacco-using patients,[12] a thorough understanding of this phenomenon among psychiatric inpatients is necessary. The importance of exploring NW among hospitalized psychiatric patients has become more emergent considering the increasing trend of adopting tobacco-free policies across mental health institutions in the U.S.[25-27] In addition, as a strategy to ensure that providers address NW and tobacco treatment among hospitalized psychiatric patients, the Centers for Medicare and Medicaid Services (CMS) has implemented a reimbursement program for psychiatric facilities reporting specific institutional tobacco treatment measures.[28] Thus, psychiatric tobacco-free hospitalizations introduce a valuable opportunity for health care professionals to reduce NW and assist this population to engage in tobacco treatment.

1.4 Substance use and NW

Substance use among psychiatric patients is common, with around one-third of patients with MI meeting criteria for at least one substance use disorder (SUD) diagnosis.[29-31] Specifically, in a Danish cohort, 46% of patients with personality disorders, 32-37% of those with bipolar, schizophrenia, and schizoaffective disorders, 25-28% of those with depression, anxiety, and other psychoses, 17% of patients with post-traumatic stress disorder, and 11% of those with obsessive-compulsive disorders were reported to have co-occurring SUDs.[32] Nonetheless, considering the relatively high prevalence of SUD and NW among patients with MI, the nature of the relationship

between the classes of substances used (e.g., opiates, cannabis, alcohol … etc.) and NW during psychiatric hospitalizations has not been studied sufficiently.

1.5 Conceptual model

The Affective Processing Model of Negative Reinforcement[33] was founded on the roles that negative affect and motivation play in substance use withdrawal. Negative affect is a manifestation of specific emotions, such as sadness, irritability, or anxiety.[34,35] Regardless of the withdrawal syndrome symptom profile produced by different substances, negative affect is a common feature in substance use withdrawal. Also, negative affect is a marker of the aversiveness of the withdrawal syndrome, prompting self-administration of the substance and relieving withdrawal symptoms rapidly after drug administration. Because of the fluctuations in drug levels in a substance user's body over time, the user acquires a proceduralized drug motivational processing routine. In particular, the user preconsciously detects interoceptive (internal) cues of negative affect taking place whenever the drug level decreases in the body; which in turn produces biased response options motivating the user to respond by using the drug to avoid the resulting negative affect (see Figure 1.1). However, this proceduralized drug motivational processing routine is only effective when negative affect levels are low.

On the other hand, experiencing a significant stressor and/or interrupting drug use, in instances when the drug is unavailable, may produce high levels of negative affect. These high levels of negative affect (which increase linearly with the withdrawal duration) operate on the conscious level and influence information processing in a way that biases the response options of the individual (i.e., using the drug to escape the negative affect becomes the primary motivational concern) (see Figure 2.1). However,

cognitive control resources are believed to not operate at either high or low levels of negative affect. The Affective Processing Model is employed in this dissertation to guide our understanding of high levels of negative affect leading to the development of NW symptoms during a psychiatric hospital stay due to the associated abrupt cessation of tobacco use upon admission and the presence of a significant stressor (i.e., hospitalization and/or exacerbation of MI condition).

1.6 Purpose of dissertation

The purposes of this dissertation are to: 1) synthesize and summarize the current literature about NW correlates among tobacco users with MI; 2) critically evaluate the validity and reliability of the Minnesota Tobacco Withdrawal Scale (MTWS) in detecting NW severity among tobacco-using patients with MI during a psychiatric tobacco-free hospital stay; and 3) examine the nature of the relationships between psychiatric diagnoses and substance use classes on NW severity among psychiatric inpatients, in the context of a tobacco-free psychiatric hospitalization. The three manuscripts presented in this dissertation achieve these purposes.

1.7 Summary of subsequent chapters

Chapter two is a systematic review of the research literature on the factors associated with NW among tobacco users with MI. Three electronic databases were searched for research articles addressing NW among tobacco users with MI between 2008 and 2019. Research articles examining NW among tobacco users with no previous substance use or MI were excluded. In addition, research articles examining NW using neurobiological approaches were excluded. MI and its associated symptom severity, sex,

race, depression and anxiety factors, substance use, and nicotine use dependence and treatment were associated with NW among tobacco users with MI. There were few studies examining the progression of the severity of NW during outpatient or acute tobacco-free psychiatric hospitalization settings. Moreover, there was a scarcity of research investigating the association between the development of NW and use of alcohol and other substances in tobacco users with MI.

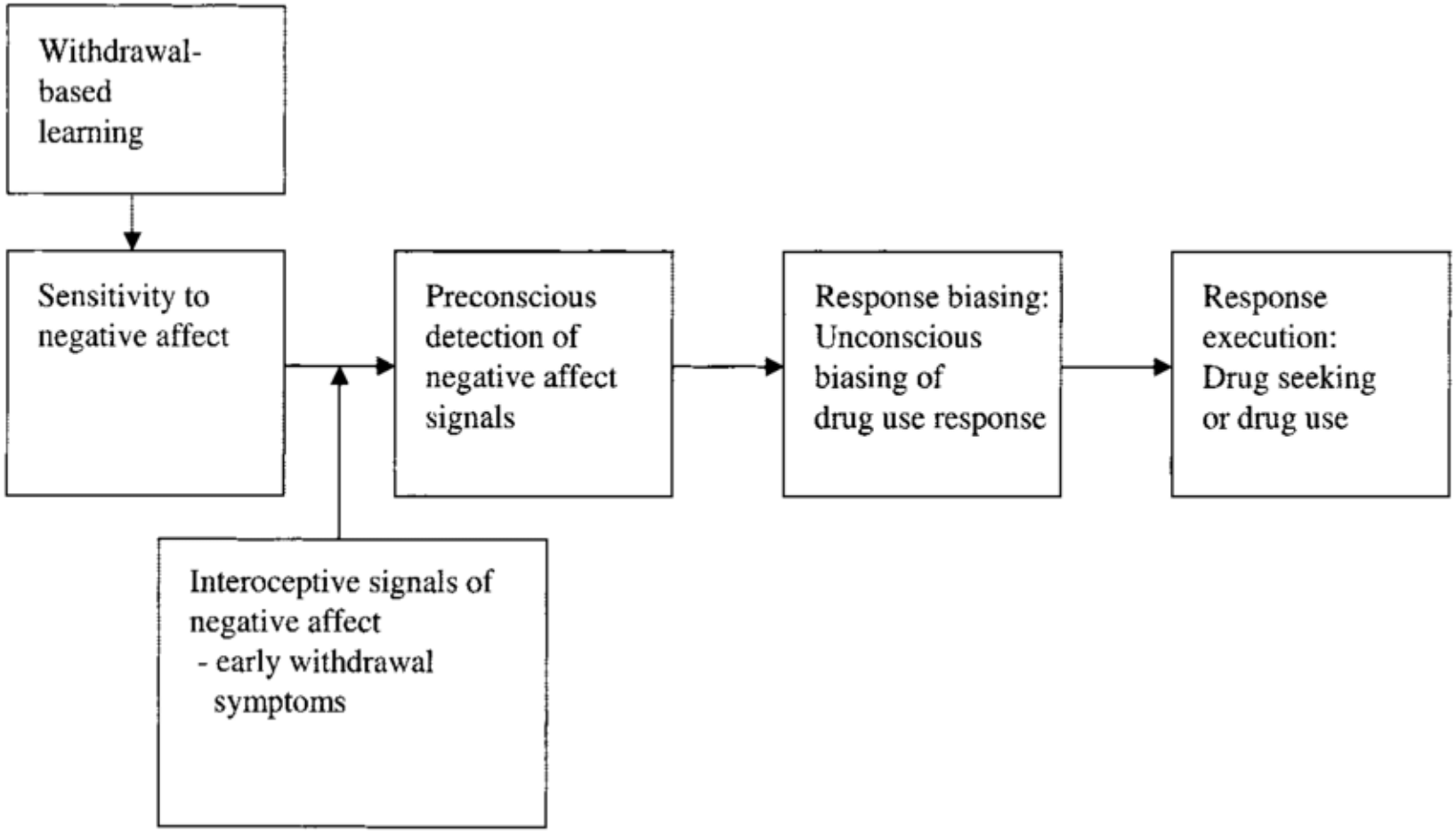
Chapter three is a psychometric evaluation of the MTWS during psychiatric hospitalization in a sample of 255 inpatients. Cronbach's alpha and item analysis were used to assess reliability, and hypothesis testing and exploratory factor analysis were used to assess the instrument's validity. The analysis revealed adequately reliable parameters in terms of Cronbach's alpha, item-item correlation coefficients, and item-total correlations. Factor analysis revealed a unidimensional scale and hypothesis testing confirmed the construct validity of the scale. However, the generalizability of findings was limited primarily by the convenience nature of participant sampling, i.e., data from participants represented only 24% of the total tobacco-using patients admitted to the psychiatric facility over a 12-month period.

Chapter four is an observational study using moderation analysis to examine the relationship between selected psychiatric diagnoses (i.e., psychotic disorder vs. not; mood or anxiety disorder vs. not) and NW severity during a psychiatric hospital stay, when certain classes of substances (e.g., sedatives, hypnotics, and anxiolytics) were used pre-admission. Lower NW severity was observed among those with psychotic disorders coupled with the reported use of inhalants; opiates; hallucinogens; sedatives, hypnotics, and anxiolytics; stimulants; or poly-substance. Higher NW severity was found among

patients with mood or anxiety disorders who reported use of hallucinogens or sedatives, hypnotics, and anxiolytics. Tobacco users with different MI diagnoses and substance use profiles may experience different NW severity during tobacco-free hospitalizations.

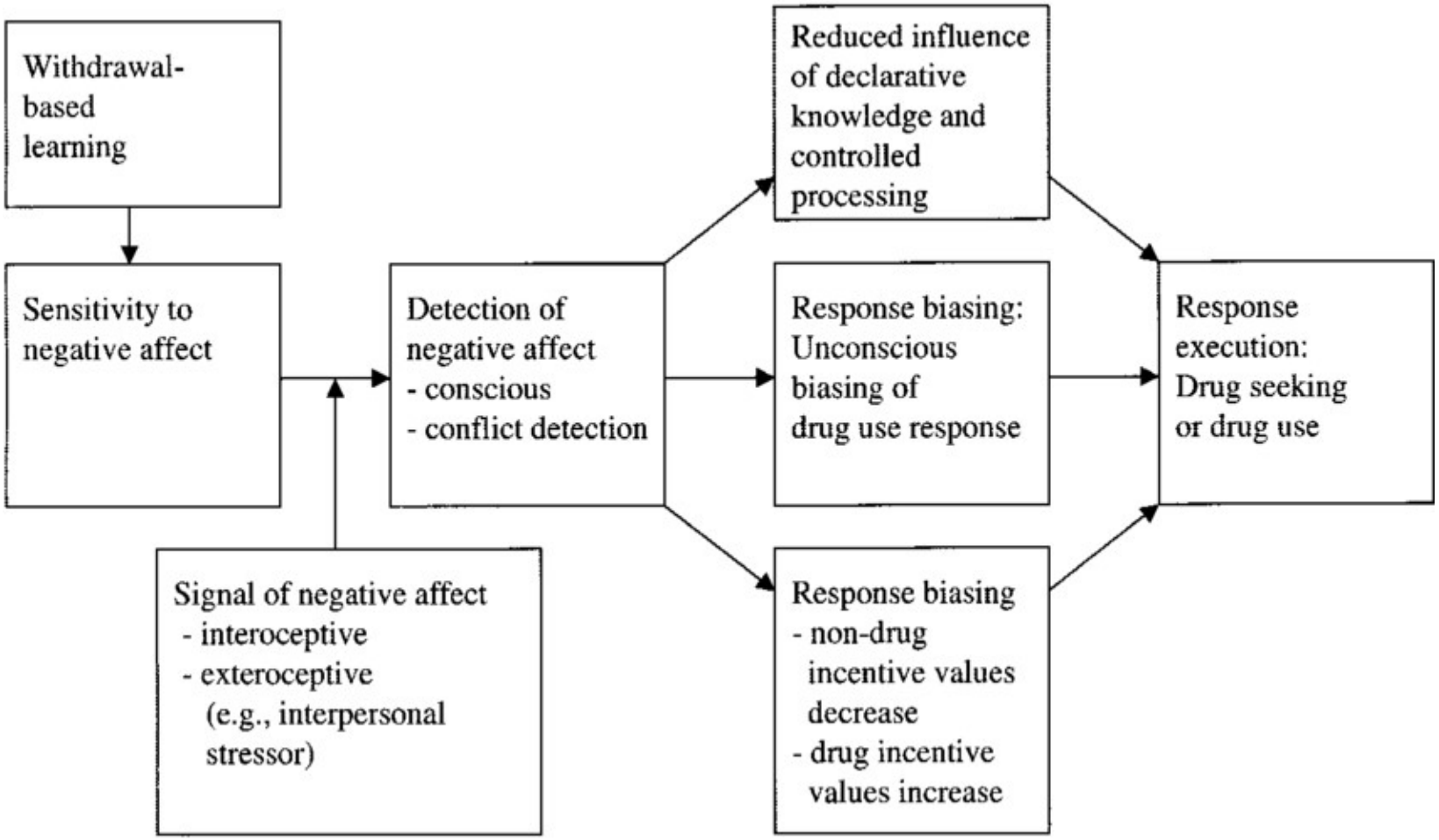
Chapter five is a synthesis and summary of the results found in this scholarly work. Implications of the findings for advancing the science of NW with tobacco users with MI are discussed. Recommendations for practice and policy are also offered for consideration.

Figure 1.1 Drug Motivational Processing at Low Levels of Negative Affect



Adopted from Baker, T. B., Piper, M. E., McCarthy, D. E., Majeskie, M. R., & Fiore, M. C. (2004). Addiction motivation reformulated: an affective processing model of negative reinforcement. *Psychological review*, *111*(1), 33.

Figure 1.2 Drug Motivational Processing at High Levels of Negative Affect



Adopted from Baker, T. B., Piper, M. E., McCarthy, D. E., Majeskie, M. R., & Fiore, M. C. (2004). Addiction motivation reformulated: an affective processing model of negative reinforcement. *Psychological review, 111*(1), 33.

CHAPTER 2. TOBACCO USE, NICOTINE WITHDRAWAL, AND MENTAL ILLNESS: A SYSTEMATIC REVIEW

2.1 Introduction

Significant accomplishments have been made in reducing the prevalence of the tobacco use epidemic in the U.S. over the past few decades. The Centers for Disease Control and Prevention (CDC) stated that the percentage of currently-smoking adults in the U.S. has declined from 20.9% in 2005 to 13.7% in 2018.[37,38] However, the percentage of current smokers with serious psychological distress in 2018 was 31.6%.[38] Further, the prevalence of smoking among people with serious psychological distress is greater now than among the general public 30 years ago.[39] This discernible gap in the smoking rates between these two groups may be attributed to the relatively high relapse rate among people with serious psychological distress who attempt to quit.[40] Therefore, it is crucial to assess factors hindering tobacco treatment services which contribute to high relapse rates among smokers with serious psychological distress.

Nicotine withdrawal (NW), a syndrome experienced by 21-50% of abstinent smokers,[12,41] is considered a primary obstacle to quitting smoking,[42,43] and a significant predictor of smoking relapse.[44-48] The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-V)[12] characterized NW diagnosis as the presence of four or more of the following symptoms: 1) irritability, frustration, or anger, 2) anxiety, 3) difficulty in concentration, 4) increased appetite, 5) restlessness, 6) depressed mood, and 7) insomnia. These symptoms can appear a few hours after quitting smoking[49,50] and peak during the first week of smoking abstinence and persist for 2 to 4 weeks or more.[14,44,45]

The emergence of these symptoms is the result of a sudden cessation or reduction of a tobacco-containing product after a prolonged period of use; and is often followed by clinical mood changes and impairments in various aspects of functioning.[12,13]

In addition to the symptoms outlined in the DSM-V diagnosis of NW,[12,13] this syndrome may also take the form of different clinical manifestations such as craving, fear, anhedonia, constipation, cough, dizziness, increased dreaming, mouth ulcers, and working memory deficit.[14-16] Moreover, reliable effect sizes in studies using a number of self-report measures (e.g., craving, subjective attentional bias towards smoking cues, negative affect), cognitive performance tasks (e.g., psychomotor processing, sustained attention), and physiological parameters (e.g., heart rate, electroencephalography power) were reported after only 12 hours of tobacco abstinence, indicating that acute NW is not merely a monotonic phenomenon.[17] Hence, given the potential mood changes, functional impairments, risk for relapse, and the volatile nature of NW,[12,17] this syndrome is of a particular concern to people with mental illness (MI).[11,19]

Admission of smokers to a smoke-free inpatient facility has been associated with greater likelihood for NW development.[12] This is particularly concerning for patients with MI, given the mounting trend of smoke-free campus policies in psychiatric institutions in the U.S..[3,24-27,51] The Centers of Medicare and Medicaid Services (CMS) has also mandated the provision of tobacco treatment during psychiatric hospitalization.[28] Quitting tobacco use among people with MI has been linked to better quality of life, lower likelihood of being discharged against medical advice, and several other positive physical and psychological health outcomes.[9-11] However, moderate to severe NW symptoms are reported in nearly two-thirds (65%) of psychiatric inpatients,[18] which, if

left untreated, could potentially lower the likelihood of successful quitting[19] and further compromise the efficacy of psychiatric care.[11]

Systematic reviews specifically examining NW are scarce and outdated.[52,53] To the best of my knowledge, no systematic reviews of NW among tobacco users with MI have been published. Therefore, the purpose of this systematic review was to synthesize the existing NW research literature among tobacco users with MI over the past 12 years, to outline the findings of the most recent literature addressing NW effects and correlates in this population, address the gaps in knowledge, and direct future research endeavors.

2.2 Methods

The PsycINFO, PubMed, and CINAHL databases were separately searched using Boolean logic (e.g., AND, OR) with a combination of medical subject headings, indexed terms, and keywords. Each database's subject headings or indexed terms, pertinent to this systematic review's topic, were identified before conducting articles search. The following phrases were used to conduct the search: smoking; cigarettes smoking; smoking cessation; smoking cessation assistance; nicotine; nicotine use; nicotine dependence; tobacco; tobacco smoking; tobacco use; tobacco abuse; tobacco use disorder; AND withdrawal; withdrawal symptoms; nicotine withdrawal; drug withdrawal; tobacco withdrawal; nicotine withdrawal syndrome; tobacco withdrawal syndrome; AND psychiatric; psychiatric disorders; psychiatric patients; psychiatric symptoms; mental disorders; chronic mental illness; chronic mental disorders; mentally ill patients; AND community mental health; mental health and illness assessment; community; community dwelling; public; hospitalization; hospital stay; psychiatric hospitalization; psychiatric

hospitals; psychiatric units; psychiatric institutions; community mental health centers; community mental health services; tobacco free hospitalization; and smoke free hospitalization. The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines and checklist for synthesizing and reporting evidence were adopted in this systematic review.[54]

Eligibility for articles selection were restricted to studies: 1) published in peer-reviewed academic journals; 2) written in English; 3) using human subjects (non-animal studies); 4) recruiting adult participants (≥ 18 years of age); and 5) published between 2008 and 2019. The selection process was limited to articles recruiting people with a history of mental illness or substance use problems, in addition to tobacco, in hospital, outpatient, or community settings, and addressing nicotine or tobacco withdrawal as a primary or secondary outcome measure. The search was not restricted by geographic location. However, research articles using qualitative methods and those tackling nicotine or tobacco withdrawal using genetic or neurobiological approaches were excluded. Data extracted from selected articles were obtained by the primary author, and the extracted data were reiterated by the same author one week later for verification of data accuracy. Findings are reported based on thematic categories of the selected articles that best reflect their sample sizes representativeness, setting, and tobacco users' MI diagnoses.

2.3 Results

Our search yielded 511 articles from the PubMed, CINAHL, and PsycINFO databases. After screening these articles for the eligibility criteria, a total of 239 articles were identified. Further, the resulting articles were examined by reviewing the titles

and/or abstracts for the inclusion of participants with histories of mental illness or substance use problems and addressing NW as a primary or secondary outcome measure. A total of 15 articles were included in this systematic review (see Figure 2.1). The selected articles are compared, and each described by their purpose/aims/hypothesis(es), design, sample, setting, instrument(s), intervention (if any)/procedure, main findings, and limitations (see Table 2.1).

2.3.1 Study designs

Six of the 15 studies (40%) adopted cross-sectional research designs; five of the six studies retrieved their data from secondary sources. Specifically, three studies used data from at least one nationally-representative survey[19,22,55] and two studies used secondary data from original research.[18,56] Another cross-sectional study retrieved data retrospectively from patients' chart review.[57] Nine studies (60%) used experimental research designs, two of which used secondary analysis of data from randomized-controlled trials (RCT),[21,58] and two studies were original RCTs.[59,60] One study reported data from a quasi-experimental design.[61] Moreover, two studies used a repeated measures approach,[62,63] and two used pre-posttest designs.[64,65]

2.3.2 Settings and sample sizes

Selected articles recruited participants from community-dwelling (n = 6), outpatient (n = 4), and psychiatric hospitalization settings (n = 5). Sample sizes of studies recruiting from community settings ranged between 81 and 9,913 participants.[21,22,55,58,59,66] Sample sizes of participants recruited from MI and/or substance use outpatient settings ranged from 19 to 225 patients;[60-62,65] and sample sizes of studies

recruiting from psychiatric units in general hospitals or psychiatric in-patient hospitals ranged between 100 and 754 inpatients.[18,56,57,63,64]

2.3.3 Participants' characteristics and psychiatric diagnoses

Studies recruiting from the community included only adult participants (≥18 years of age) and examined tobacco for current, recent, or at least lifetime use.[21,22,55,58,59,66] One of the six community studies stipulated that participants have at least one previous quit attempt that lasted for a minimum of 2 weeks.[22] All studies recruiting from community-dwelling participants used a self-report interview to establish a psychiatric diagnosis or problem.[21,22,55,58,59,66] Psychiatric problems in these studies included people with post-traumatic stress disorder (PTSD), psychotic (e.g., schizophrenia, schizoaffective, schizophreniform), mood, anxiety, alcohol use, and substance use disorders.[21,22,55,58,59,66] On the other hand, patients recruited from inpatient psychiatric settings had a wide range of documented psychiatric diagnoses (e.g., psychotic, depressive, adjustment, and substance use disorders). All participants recruited from inpatient psychiatric settings were in tobacco-free facilities.[18,56,57,63,64] The average reported number of cigarettes smoked per day by these inpatients ranged between 16 and 24; and all studies, but one,[63] indicated the use of NRT during hospitalization.[18,56,57,64] However, the majority of the inpatients demonstrated moderate to severe levels of nicotine dependency.[18,56,63] Of note, the average length of hospitalization ranged from six to 16 days and the majority of inpatients had co-morbid alcohol or drug use disorders.[56,57,64] Similarly, participants recruited from outpatient psychiatric settings reported smoking approximately 20 cigarettes per day and they had a wide variety of psychiatric diagnoses.[60-62,65] It is noteworthy to mention that one study recruited participants during psychiatric

hospitalization; however, their intervention took place outside the hospital with an allowance for participants to smoke.[65] Therefore, participants from this study were considered outpatients.

2.3.4 Experimental design interventions

All nine studies adopting experimental research designs incorporated tobacco use abstinence as the primary outcome, and the studies took place either in community, outpatient, or psychiatric hospitalization settings.[21,58-65] Three RCTs and one repeated measures study each randomly assigned their participants into two groups. These four studies each compared a group of smokers with psychiatric and/or substance use problems receiving tobacco treatment interventions (e.g., varenicline, NRT, cognitive behavioral therapy), to a treatment-as-usual or standard treatment group of smokers under the same tobacco deprivation conditions.[58-60,62] Another double-blinded RCT randomly assigned participants to five intervention groups and one control group, based on a combination of Bupropion and different forms of NRT administration coupled with individual counseling.[21] The remaining experimental studies (one quasi-experimental, one repeated measures, and two pre-posttest studies) were one-group designs with interventions including cognitive behavioral therapy, non-smoking positive experiences, varenicline, and sessions with tobacco treatment specialists.[61,63-65] Participants' follow-up for all experimental studies ranged between 1 and 27 weeks.[21,58-65]

2.3.5 Measures used to assess NW

Several measures were used to assess NW across the 15 selected studies. Seven studies used the Minnesota Nicotine Withdrawal Scale (MNWS),[18,56-58,60,62,66,67] two used

the Wisconsin Smoking Withdrawal Scale,[61,63,68] one study used the Ecological Momentary Assessment,[21,69] one used the Withdrawal Symptoms Checklist-weekly,[59,70] and one study used the Computerized Diagnostic Interview Schedule to assess for NW diagnosis.[64,71] In addition, some researchers merely introduced a list of NW symptoms to participants; one used a list based on DSM-IV criteria and two did not.[22,55,65] There was no similarity in choice of NW measure based on setting (i.e., inpatient, outpatient, or community). However, studies recruiting from out- and inpatient settings, in general, used more rigorous measures in assessing NW.[18,56,57,60-63]

2.3.6 Main findings of NW

For ease of presentation of findings, studies were clustered, based on similarities in setting or MI diagnoses in addressing NW, into the following categories:

2.3.6.1 Studies using national surveys data across different MI diagnoses

Two studies used nationally-representative data to address NW among tobacco users with different MI diagnoses.[19,55] Smith, Homish, Giovino, and Kozlowski (2014)[19] found that tobacco users with MI have higher likelihood to be diagnosed with NW compared to tobacco users without MI. In fact, they found that MI was responsible for more than 44% of NW diagnoses in the general population.[19] Also, they found that the likelihood for having NW was greater among tobacco users with psychotic disorders, mood and anxiety disorders with alcohol and drug use, mood and anxiety disorders, and alcohol and drug use and antisocial personality disorders, consecutively.[19] Similarly, Weinberger, Desai, and McKee (2010)[55] found that greater numbers of NW symptoms were found among tobacco users with substance or alcohol, mood, or anxiety disorders

during a quit attempt, compared to tobacco users without these conditions. While both studies assessed NW using self-report, cross-sectional approaches, the latter study[55] did not examine the severity of NW symptoms, nor include tobacco users with psychotic disorders.

2.3.6.2 Studies examining NW during psychiatric tobacco-free hospitalization

Six studies examined NW among tobacco users in the context of a tobacco-free hospitalization. These studies concluded that the following factors were correlated with greater NW experience during hospitalization: higher psychiatric symptoms severity; greater nicotine dependence; alcohol and drug use; race (i.e., African American); sex (i.e., women); timing of receiving NRT; low confidence in quitting; and providing tobacco treatment medication (i.e., varenicline) and counseling during the hospital stay.[18,56,57,63,64] Five studies used cross-sectional designs,[18,56,57,64,65] and only one examined NW prospectively during hospitalization.[63]

2.3.6.3 Studies targeting tobacco users with psychotic, mood, or anxiety disorders

Five studies examined NW among tobacco users with psychotic, depressive, or anxiety disorders. Piper, Cook, Schlam, Jorenby, and Baker (2011)[21] found that, compared to tobacco users who did not have anxiety disorders, greater pre-quit NW was found among those with panic attacks, generalized anxiety, or social anxiety disorders. Further, a significant positive association was found between having a post-traumatic stress disorder (PTSD) and NW symptoms.[22,59] Similarly, depression was associated with greater likelihood of having NW and NW-related relapse during a quit attempt.[22,58] Lastly, Schuster et al. (2017)[61] noticed that improvements in NW symptoms in a sample

of smokers with schizophrenia, schizoaffective, and bipolar disorders enhanced tobacco use abstinence, compared to those who did not have improvements in NW symptoms prior to a quit day.

2.3.6.4 Studies targeting tobacco users with substance use disorders

Two studies, primarily studied the association between NW and substance or alcohol use. Reid et al. (2008)[60] found that smoking cessation counseling and NRT administration decreased NW severity in a sample of tobacco users with substance abuse in general. On the other hand, Streck, Heil, Higgins, Bunn, and Sigmon (2018)[62] indicated that opioid-dependent smokers have greater NW severity compared to smokers without substance use disorders.

2.4 Discussion

The purpose of this systematic review was to synthesize, and outline NW correlates found in the literature among tobacco users with MI. The search yielded 15 research articles from the PubMed, CINAHL, and PsycINFO databases. The selected articles represented tobacco users with MI or substance use problems in community, outpatient, and inpatient psychiatric tobacco-free hospital settings. Also, the selected articles varied in designs, participants' diagnoses and characteristics, measures of NW, interventions tested, and findings related to NW. In summary, NW among tobacco users with MI is correlated with the following factors: 1) MI diagnoses (with varying severities across diagnoses); 2) psychiatric symptoms severity; 3) sex; 4) race; 5) previous or concurrent alcohol and drug use; 6) nicotine dependence; 7) timing of offering and use of NRT during psychiatric tobacco-free hospitalization; 8) confidence in quitting; 9) pre-

quit attempt anxiety and depression levels; and 10) pharmacological intervention (i.e., varenicline use). Below is a more detailed description of selected studies based on representativeness of studies' samples, settings, and MI diagnoses.

2.4.1 Nationally-representative studies

In a secondary analysis of data from two large national surveys including participants with and without MI, Smith et al. (2014)[19] classified MI diagnoses into the following categories: no disorder; internalizing disorders (i.e., past year mood and anxiety disorder); externalizing disorders (i.e., past year alcohol use disorders and drug use disorders, and lifetime antisocial personality disorder); internalizing and externalizing disorders; and psychotic episode or disorder. MI was responsible for 44.4% of the NW syndrome diagnoses in the total sample; and that across all MI categories, there was greater likelihood to be diagnosed with NW syndrome, compared to smokers without MI.[19] In addition, the relative risks of having NW for participants with MI, compared to those without MI, were 1.37, 2.37, 3.12, and 3.45 for externalizing disorders, internalizing disorders, internalizing and externalizing disorders, and psychotic disorders, respectively.[19] The symptom profiles of NW were, however, consistent across MI categories, and NW-related distress was higher among these categories, compared to people without MI.[19] Higher relative risk of experiencing NW among patients with psychotic, mood, and anxiety disorders than those with substance use and anti-social personality disorders is consistent with the affective nature of NW symptomatology (e.g., anxiety, restlessness, anger, depression) dictated by the DSM-IV-TR and DSM-IV criteria.[12,13] This affective nature is usually characteristic in these disorders, compared to the latent process of disinhibition usually encountered in drug and alcohol use and

personality disorders.[19,72] Similarly, Weinberger et al. (2010)[55] conducted a secondary analysis of data on a nationally-representative sample (n=8,213) from the National Institute of Alcohol Abuse and Alcoholism (NESARC) study. Having a current diagnosis of mood, anxiety, alcohol use, or substance use disorders was associated with greater number of reported NW symptoms during a quit attempt, compared to people without these conditions.[55] Further research is required to understand how affective symptoms observed in internalizing disorders may impede quit attempts among people with MI by virtue of greater NW severity.

2.4.2 Psychiatric tobacco-free hospitalization

Soyster, Anzai, Fromont, and Prochaska (2016)[18] employed a secondary data analysis to examine the characteristics and correlates of NW in a sample of 754 psychiatric inpatients from 3 mental health units in San Francisco. Using a general linear regression model, researchers indicated that being a woman, African American, having greater psychiatric symptoms severity, greater nicotine dependence, and having a diagnosis of both alcohol and other drug use disorders were associated with greater NW severity.[18] Furthermore, 65% of patients experienced moderate to severe NW symptoms.[18] Another study conducted in an inpatient psychiatric setting examined the associations between NW and NRT.[20] In this study, NW severity among patients receiving NRT on the unit was significantly greater than those receiving NRT at admission and those not provided NRT. Specifically, NW symptoms, such as restlessness, anxiety, anger, and depression, were significantly higher among patients receiving NRT on the unit, versus those receiving NRT at admission.[20] Furthermore, in a multivariate regression model to examine the predictors of NW severity during

psychiatric hospitalization, it was found that lower confidence in quitting and receiving NRT on the unit predicted greater NW symptoms severity.[20] Delayed administration of NRT during hospitalization was associated with greater NW symptoms.[20] This finding is particularly important among patients with higher likelihood of having greater NW symptoms, such as being African American.[18] However, Soyster et al. (2016)[18] stated that people of an African American ethnicity were less likely to be offered NRT, given that these patients did not refuse NRT at high rates. Greater attention is required to address disparities in providing smoking cessation services during psychiatric hospitalization.

Three more studies examined NW in the context of smoke-free hospitalization. Leyro et al. (2013)[56] characterized clinical management of tobacco withdrawal and dependence in a sample of 324 psychiatric inpatients, almost half of whom had unhealthy levels of alcohol consumption and/or illicit drug use. They found that offering NRT at admission was associated with greater likelihood of using it, compared to offering it later during hospitalization. This further supports the practice of adopting tobacco cessation treatment at the outset of psychiatric hospitalization, given that it not only increases the likelihood of using NRT,[56] but also decreases NW symptoms severity during hospitalization.[57] Leyro et al. (2013) also indicated that NRT use was higher among those with greater NW symptoms, tobacco dependence, and depressive symptoms.[56] Interestingly, patients with psychotic disorders were more likely to use a combination of NRT products (i.e., nicotine gum and patch) compared to patients with other psychiatric diagnoses.[56] This is consistent with Smith et al. (2014)'s[66] conclusion that psychotic patients experience greater NW severity compared to other psychiatric diagnoses. Pachas et al. (2012)[63] also found that NW symptoms among patients with stable schizophrenia,

who have moderate-to-severe nicotine dependence, progressively decreased over a 12-week period after providing varenicline and cognitive behavioral therapy during psychiatric tobacco-free hospital stay. This also resulted in a significant (47% of the sample; n=112) 2-week, biochemically-verified tobacco abstinence after 3 months.[63] However, NRT use was not reported in the paper. Finally, Shmueli, Fletcher, Hall, Hall, and Prochaska (2008)[64] studied whether smoking abstinence related to tobacco-free psychiatric hospitalization was associated with changing thoughts about quitting in a sample of 100 smokers. Prior to hospital discharge, there was a significantly higher perception of successful quitting and lower expectation of difficulty quitting smoking compared to those reported at admission.[64] Interestingly, NW did not seem to affect patients' desire to quit smoking, expectancy in successfully quitting, and staying quit in the period from hospital admission to discharge.[64]

2.4.3 Tobacco users with psychotic, mood, or anxiety disorders

Piper et al. (2011)[21] compared the NW characteristics of 579 community-dwelling participants who ever met life-time criteria for an anxiety diagnosis to 891 smoking counterparts who did not meet criteria. Before embarking on a quit attempt, participants who ever experienced a panic attack reported greater pre-quit negative affect and withdrawal and increases in post-quit intensity of cessation fatigue.[21] In addition, participants who ever met criteria for generalized anxiety or social anxiety disorders reported higher pre-quit levels of cravings, negative affect, and withdrawal symptoms, and greater quit-day cessation fatigue.[21] Ever experiencing generalized anxiety disorder, social anxiety disorder, or panic attack predicted poor smoking cessation outcomes almost up to 8 weeks after starting the quit attempt.[21] Also pertinent to anxiety disorders,

Weinberger, Maciejewski, Mckee, Reutenauer, and Mazure (2009)[22] conducted a secondary data analysis of sex differences in NW among a sample of 816 community-dwelling participants who made a quit attempt in the past lasting at least for 2 weeks. Investigators examined sex differences with regard to psychiatric diagnoses and found that, regardless of gender, having a life-time panic disorder increased the odds of experiencing recurrent NW symptoms by 3 times during multiple quit attempts.[22] In terms of smoking cessation outcomes, researchers found that women who had at least one PTSD in their lifetime were nearly 5 times more likely to relapse due to NW compared to men with the same condition.[22] Also, with regard to the association between PTSD, NW, and anxiety sensitivity (AS), Asnaani, Farris, Carpenter, Zandberg, and Foa (2015)[59] found that the association between AS and PTSD was only significant at low levels of NW severity.[59] Arguably, in a randomized, double-blinded study, Cosci, Bertoli, and Abrams (2013)[73] found no effect of NW on AS between groups receiving, versus not receiving, NRT. However, participants in this study did not have a diagnosis of panic disorder.[73] Finally, Attention Deficit Hyperactivity Disorder (ADHD) symptoms in adults were found correlated to NW symptoms.[74,75] In fact, tobacco users with ADHD experience higher NW symptoms severity during early abstinence, compared to those without ADHD.[76] However, ADHD medication was found to alleviate NW symptoms and cotinine levels in adult ADHD smokers, compared to those receiving placebo.[77] In summary, the effects experienced by people with a history of anxiety disorders may be related to similarities in the symptoms usually encountered by people with these diagnoses and the diagnostic criteria of NW (e.g., depression, anxiety, restlessness, irritability),[12] in addition to the proposed reduced coping skills to the challenge of

quitting faced by these smokers.[21] Future research is needed to address whether reducing anxiety symptoms pre-quit would yield better smoking cessation outcomes in this population.

As with the case of psychotic and anxiety disorders, several examinations also demonstrate higher NW with depressive symptoms. Reid and Ledgerwood (2016)[58] found that having higher levels of depression before a quit attempt affected the patterns of NW and urges to smoke over a 5-week period. Similar to this findings, another study confirms that having a history of life-time major depressive disorder is associated with a 2.5 times increased risk to relapse due to NW.[22] Alternatively in an examination of negative mood, depressive symptoms, and major depressive episodes in 179 smokers with a history of major depression, Kahler et al. (2002)[78] found that short and long-term smoking abstinence was associated with enhancement in depressive symptoms, but the incidence of major depressive episodes in these patients was independent of smoking abstinence.[78] Finally, varenicline was found effective in achieving 14-day smoking abstinence in a sample of 135 outpatients with psychotic or mood disorders.[61] This duration of abstinence was predicted by prior alcohol dependence, lower expectation of peer support on quitting, high vigilance and low reaction time variability, and improvement in NW prior to quitting day.[61] Thus, from these studies it may be surmised that future research needs to investigate the effects of therapeutic interventions to reduce pre-quit depressive symptoms on smoking cessation outcomes.

2.4.4 NW and tobacco users with alcohol or substance use disorders

A number of studies have demonstrated an important relationship in substance use effect on NW. For instance, in a multi-site RCT among 225 smokers, from community substance abuse rehabilitation centers, Reid et al. (2008)[60] found that NW and cravings decreased significantly in the treatment group (compared to control) and that craving for the designated abused substance simultaneously decreased with smoking reduction. Another study found that alcohol use disorder increased the odds of experiencing any NW symptoms during a quit attempt by 2.5 times.[22] However, men were found to have 2.5 times greater odds for relapse due to NW than women, if both had a life-time alcohol abuse or dependence.[22] Furthermore, in comparing 47 opioid-dependent smokers and 25 smokers without substance use disorder diagnoses on daily basis for a 2-week period, Streck et al. (2018)[23] found that after adjusting for age, education, number of regular-smoking years, CO level, and nicotine dependence, opioid-dependent smokers reported higher NW severity than non-substance use disorder smokers. Moreover, females in the non-substance use disorder group demonstrated steeper declines in nicotine craving over the study period, compared to females in the opioid-dependent group.[23] Nevertheless, the association between NW and patients with substance use disorders other than opioid and alcohol, to the best of our knowledge, has not been studied before in the literature and definitely merits systematic investigation. There remains a dearth of knowledge about how different substance use dependence levels affect NW experience and relapse outcomes. Considering the relatively high rates of substance use among patients with MI,[32] it is unknown whether substance use across different psychiatric diagnoses yields

different NW frequencies, severities, and relapse outcomes. Well-designed moderation studies can help scrutinize these relationships.

2.5 Limitations

The findings in our systematic review had some limitations that are worth mentioning. The heterogeneity of studies was our major limitation. That is, experimental and non-experimental studies were included, with different sample sizes, settings, interventions, and participants' diagnoses and tobacco use characteristics. This may affect the overall generalizability of our findings. Among experimental studies, RCTs, quasi-experimental, pre-posttest, and repeated measures research designs were included. While some studies included control or comparison groups, many did not, dictated by design. On the other hand, many non-experimental studies adopted cross-sectional and secondary analysis of data approaches, which may have resulted in missing significant factors associated with NW. In addition, inconsistencies in treatment modalities (e.g., varenicline, cognitive behavioral therapy, and NRT), participants' milieus (i.e., community-dwelling, inpatient, or outpatient settings) and participants' characteristics (e.g., different MI diagnoses) across studies may affect our results. Moreover, the trajectories of NW were not studied by different MI diagnoses. Noticeably, NW was not addressed for tobacco users with MI using more than one form of tobacco (e.g., smokeless tobacco), which represents a major a gap in the literature. Last, the majority of studies did not assess tobacco abstinence rates and NW-related relapse over time for more than 6 months.

2.6 Conclusion

Considering the high prevalence of tobacco use among people with MI, the purpose of this systematic review was to synthesize the research findings related to NW over the past 12 years. Several NW correlates among people with MI were identified across different settings and among different MI diagnoses. Identifying NW in this population can help nurses and other health care professionals, in community, inpatient and outpatient settings, identify patients of higher risk for developing NW and NW-related distress. The findings of this systematic review can also help tobacco treatment specialists develop and tailor evidence-based practices for patients to reduce barriers to tobacco use quit attempts. NW is a barrier that hinders a smoker's ability to quit tobacco and promotes relapse. More research is needed to scrutinize the nature and correlates of this phenomenon for more evidence-based recommendations, and guidance in tailoring effective interventions.

Table 2.1 Characteristics of Studies Addressing Nicotine Withdrawal among Tobacco Users with Mental Illness.

Authors	Purpose/Aims or hypotheses	Design	Sample	Setting	Instrument(s)	Intervention(if any) and/or Procedure	Main Findings	Limitations
Okoli, Al-Mrayat, Shelton, and Khara (2018)[57]	To examine the association between providing NRT upon admission with the motivation to quit and the severity of NW symptoms, in the context of smoke-free hospitalization.	Cross-sectional; retrospective chart review.	Two-hundred and fifty-five adult patients, 87-90% of whom admitted involuntarily ,who were assessed by a mental health professional.	Inpatient, tobacco-free psychiatric hospitalization.	Demographics. Tobacco use characteristics. Timing of providing NRT: admission vs. on the unit vs. not provided. Period between admission and receiving NRT. The motivation ruler – used to assess patients' perceived importance, confidence, and readiness to quit smoking or tobacco use. Stage of change in tobacco use – patients were classified into 2 groups: pre-contemplator/contemplator and preparers/action. The MNWS.	A retrospective analysis of data retrieved from medical records between January and December 2016 in a psychiatric hospital in Kentucky. Upon admission, every patient was assessed by a tobacco treatment nurse for NW, readiness to quit, and other aspects of patients' tobacco use. Then, the nurse provides practical counseling to encourage the patient to engage in the tobacco treatment services.	* Patients with cognitive disorders had the highest frequency of reporting at least 1 NW symptom, and patients with substance use disorders had the greatest NW severity. * NW severity among patients receiving NRT on the unit was significantly greater than those receiving NRT at admission and those not provided NRT. Specifically, patients provided NRT on the unit had higher mean scores of depression, anger, anxiety, and restlessness, compared to those not receiving NRT at admission. * Lower confidence in quitting and receiving NRT on the unit (vs. at admission) was associated with greater NW severity in a multivariate regression analysis.	Psychiatric symptoms severity was not assessed. NW symptoms severity was not assessed throughout the period of hospitalization. The effect of co-morbid psychiatric disorders was not assessed. The sample included only 15% of the tobacco users admitted to the hospital.

Table 2.1 Characteristics of Studies Addressing Nicotine Withdrawal among Tobacco Users with Mental Illness (continued).

Soyster, Anzai, Fromont, and Prochaska (2016)[18]	To examine the characteristics and correlates of NW severity among patients with MI during psychiatric hospitalization.	Cross-sectional; secondary analysis of data.	A total of 754 psychiatric inpatients from seven smoke-free units at 3 hospitals in San Francisco. Participants were adults smoking at least 5 cigarettes per day with no overly aggressive, somnolent, or disorganized behaviors.	Inpatient.	FTND. MNWS. Electronic version of the Mini International Neuropsychiatric Interview (eMINI) – to assess for current psychiatric disorders and previous trauma exposure. The Behavior and Symptom Identification Scale (BASIS-24) – used to assess past week overall psychiatric symptom severity score.	A secondary data analysis from the baseline survey of an interventional study. The analyses were performed prior to introducing the intervention.	* Having higher levels of nicotine dependence and prior use of NRT was associated with greater likelihood to be offered NRT. However, being African American and being older were associated with lower likelihood of being offered NRT. * Patients with no prior use of NRT, lower nicotine dependence, and milder cigarette craving were more likely to refuse NRT. * The prevalence of NW symptoms severity was described as follow: less than 1%, complete absence; 10% as slight; 24% as mild; 40% as moderate; and 25% as severe. * A general linear regression model has indicated that greater NW severity was associated with being a woman, African American, greater psychiatric symptoms severity, greater nicotine dependence, and having a diagnosis of both alcohol and other drug use disorders.	The absence of randomization of the covariates increased the ecological validity of the findings. However, it prevented deriving causal mechanisms.

Table 2.1 Characteristics of Studies Addressing Nicotine Withdrawal among Tobacco Users with Mental Illness (continued).

Piper, Cook, Schlam, Jorenby, and Baker (2011)[21]	To examine how NW, dependence, treatment response, and cessation success relate to specific anxiety diagnoses: Generalized Anxiety Disorder (GAD), Social Anxiety Disorder (SAD), and panic attacks.	Secondary analysis of data of a randomized-controlled trial.	A secondary analysis of data including 1504 smokers who reported smoking 10 or more cigarettes per day for the past 6 months with a motivation to quit. Smokers also were mild alcohol drinkers with no history of a psychotic or eating disorder.	Community dwelling.	FTND. The Wisconsin Inventory of Smoking Dependence Motives (WISDM). Ecological Momentary Assessment (EMA) – used to assess for various smoking-related measures for the past 15 minutes, including cessation fatigue. The World Mental Health Survey Initiative, version of the Composite International Diagnostic Interview – used to provide, past year and ever, diagnoses for various diseases, including SAD, GAD, and Panic disorder. Cessation outcomes at 8 weeks and 6 months (e.g., CO levels).	At baseline, participants underwent CO, vital signs, and medical history screening with the world mental health survey initiative version of the composite international diagnostic interview. Participants were then double-blinded and randomized into one of 6 treatment conditions: bupropion SR; nicotine lozenge; nicotine patch; nicotine patch + nicotine lozenge; bupropion SR + nicotine lozenge; or placebo. All medications were provided for at least 12 weeks post-quit. The EMA was reported twice a day (once before going to bed and once after waking). The EMA data of cessation fatigue and withdrawal measures were analyzed and depicted on a graph illustrating patients' pre-quit level, pre-quit slope, and post-quit slope. All participants received 6, 10-20 minutes, individual counseling session in social support, coping, and problem solving.	* Five hundred and seventy-nine participants ever met criteria for an anxiety diagnosis, and 205 met that criterion for the past 12 months. The comparisons were made relative to participants with no anxiety diagnosis (n=891). Compared to participants with no anxiety diagnosis: 1. Smokers who experienced a panic attack anytime in the past reported higher levels of pre-quit negative affect and withdrawal and increases in post-quit slope of cessation fatigue. 2. Smokers who ever had GAD reported greater levels of pre-quit cravings, negative affect, withdrawal symptoms, and more intense pre-quit and quit-day cessation fatigue. 3. Smokers who ever had SAD reported higher pre-quit levels of cravings, negative affect, withdrawal symptoms, and cessation fatigue, in addition to greater quit-day cessation fatigue. * In general, and after adjusting for age, gender, race, and treatment, ever having a panic attack, multiple anxiety diagnoses, SAD, or GAD predicted poor smoking abstinence outcomes over an 8-week period.	The study sample was highly motivated and willing to engage in a smoking treatment plan. The baseline assessment did not account for current symptomatology. Other anxiety disorders were not accounted for (e.g., obsessive-compulsive disorder, specific phobias). Patients were not randomly assigned to the treatment groups.

Table 2.1 Characteristics of Studies Addressing Nicotine Withdrawal among Tobacco Users with Mental Illness (continued).

Weinberger, Maciejewski, Mckee, Reutenauer, and Mazure (2009)[22]	To examine whether the interaction between gender and psychiatric diagnosis (major depressive disorder, panic disorder, PTSD, and alcohol use or dependence) has an effect on reporting NW, and relapse in response to NW.	Cross-sectional; secondary analysis of data of a subsample of the National Comorbidity Survey.	A total of 816 community-dwelling participants who reported current tobacco use with 1≥ attempts to quit smoking, which lasted for at least 2 weeks.	Community dwelling.	Modified version of the Composite International Diagnostic Interview – used to assess the presence of psychiatric disorders. Number of quit attempts. Any withdrawal symptom – participants were provided a list of NW symptoms (e.g., difficulty sleeping, cravings, headache) and asked to report if they experienced any symptom in that list. Longest period of withdrawal (in days). Any recurring withdrawal symptoms – whether NW symptoms experienced during multiple attempts to quit. Relapse to alleviate withdrawal symptoms.	A retrospective analysis of data from a study conducted between 1991 and 1992 by the National Co-morbidity Survey (CNS). Analyses were adjusted for demographic variables (i.e., age, race, income, education, marital status).	* Approximately equal proportions of men and women reported experiencing NW during their quit attempts (women, 68%; men, 67.7%). * Approximately equal proportions of men and women reported relapsing to smoking, seeking relief of NW (women, 60%; men, 59%). * The number of life-time quit attempts was not different between genders. * Women with major depressive disorder and alcohol abuse/dependence reported longer periods of experiencing NW compared to men. * Regardless of gender, having a history of alcohol use disorder increased the odds of experiencing any NW during a quit attempt by 2.5 times. * Regardless of gender, having a life-time panic disorder increased the odds of experiencing recurrent NW symptoms by 3 times for multiple quit attempts. * Women with life-time major depression disorder reported experiencing 2.7 times greater NW recurring symptoms compared to men with the same condition. * Regardless of gender, having a history of life-time major depressive disorder was associated with increasing the risk to relapse due to NW by 2.5 times. * Men reported 2.5 times greater the odds to relapse due to NW than women, if both had a life-time alcohol abuse/dependence.	Recall bias because, NW was assessed retrospectively. Inclusion to the study was restricted by those whose quit attempts lasted at least for 2 weeks. Information regarding severity of alcohol abuse/dependence and psychiatric symptoms were not assessed. Other psychiatric illnesses with high relevance to smoking were not assessed (e.g., schizophrenia).

							* Women who had life-time PTSD were nearly 5 times more likely to relapse due to NW than men with the same condition.	

Table 2.1 Characteristics of Studies Addressing Nicotine Withdrawal among Tobacco Users with Mental Illness (continued).

Asnaani, Farris, Carpenter, Zandberg, and Foa (2015)[59]	To examine the relations between Anxiety Sensitivity (AS) (i.e., having a tendency towards greatly misinterpreting internal anxiety-related sensations), NW, and PTSD symptoms among smokers seeking tobacco treatment. To examine whether higher NW severity moderates the association between AS and PTSD symptom severity.	Randomized-controlled trial.	A total of 117 adult participants who smoked at least 10 cigarettes per day and have a diagnosis of PTSD. Participants did not have substance use disorders other than nicotine, and no psychosis or prominent suicidal ideations.	Community dwelling.	Anxiety Sensitivity Index (ASI). Withdrawal Symptoms Checklist – Weekly (WSC-W) – used to assess the severity of NW over the past week. PTSD Symptom Scale Interview (PSS-I) – used to assess the severity of PTSD symptoms. It includes a total score and 3 subscales: re-experiencing, avoidance, and hyperarousal. CO levels.	At baseline (week 0), participants were screened for PTSD symptoms using the structured clinical interview and were randomized into standard smoking cessation treatment (varenicline and supportive counseling) and standard smoking cessation with PTSD treatment (varenicline, supportive counseling, and prolonged exposure therapy). The treatment sessions lasted for 12 weeks. Participants were assessed for the battery of instruments at baseline, 12 weeks, and 27 weeks later. Cross-sectionally random sampling (without replacement) of cases for analyses included all three times of assessment.	* Adjusting for gender, time of assessment, expired CO, and negative affect, the main effects of AS and NW were significant on total PTSD symptom severity, and the interaction of both, AS and NW, was significant as well. * The moderations models revealed that the association between AS and PTSD was only significant at low levels of NW severity.	Nicotine dependence was not included in the analyses because it was assessed only at baseline. The varying levels of AS were not assessed. Other cognitive-affective risk processes were not controlled for, which might have affected PTSD symptoms severity.

Table 2.1 Characteristics of Studies Addressing Nicotine Withdrawal among Tobacco Users with Mental Illness (continued).

Streck, Heil, Higgins, Bunn, and Sigmon (2018)[62]	To examine the effect of NW between smokers with Opioid Dependency (OD) and smokers without co-morbid Substance Use Disorder (SUD), and to examine whether gender moderates NW.	Secondary analysis of data from 5 studies; two-group, repeated measures.	Forty-seven OD adult smokers who used methadone or buprenorphine and who reported smoking at least 10 cigarettes per day, and 25 non-SUD adult smokers who also smoked at least 10 cigarettes per day.	Outpatient.	FTCD. MNWS – the desire to smoke item (i.e., craving) was analyzed separately.	A retrospective analysis of data gathered from 3 studies. Participants visited the laboratory for 14 consecutive days, and nicotine abstinence was biochemically verified. Participants completed the FTCD at baseline and the MNWS in every visit. Participants selected if more than 85% of the biochemically-verified samples indicated abstinence.	* Before embarking on the quit attempt, and after adjusting for age, education, number of years of regular smoking, CO level and nicotine dependence, OD smokers reported higher NW severity than non-SUD smokers. * There was a significant decline in NW for both groups over the period of 14 days. However, NW was not different between the groups. * Smokers with OD had higher desires to smoke at baseline, compared to those without SUD. * There was a significant time × gender × group interaction in craving over the 14-day period. * Compared to males, females showed a significant group × visit interaction, with females in the non-SUD group demonstrating a steeper decline in tobacco craving relative to females in the OD group.	Participants' anticipation of increases in anxiety or withdrawal might have affected NW during study period. Small sample size. Timing and doses of medication among participants in the OD group was not assessed.

Table 2.1 Characteristics of Studies Addressing Nicotine Withdrawal among Tobacco Users with Mental Illness (continued).

Reid and Ledgerwood (2016)[58]	To examine whether the effect of elevated depression scores prior to a smoking quit attempt predicts patterns of NW and urges to smoke, in a group of nicotine-dependent smokers undergoing smoking cessation treatment.	Secondary analysis of a randomized controlled trial.	A total of 81 smokers who did not have severe or uncontrolled psychiatric disorders or current substance dependence issues.	Community dwelling.	Structural Clinical Interview for DSM-IV-TR – to assess for suicidality, psychosis, and substance use. Smoking history. FTND – administered at baseline and every week. Beck Depression Inventory, second edition (BDI-II) – participants were dichotomized into high and low depressive symptoms – administered at baseline and every week. Questionnaire of Smoking Urges -Brief – administered at baseline and every week. MNWS – administered at baseline and every week. CO – administered twice daily at baseline and throughout the treatment weeks.	Participants attended the treatment clinic for 5 weeks, twice daily, 5 days per week. The first week was for baseline measurements and to prepare participants for quitting. Participants were then randomized into standard care and reward-motivated treatment groups.	Linear mixed model analyses were performed for all the analyses. * The main effects of depression scores and time were significant on NW symptoms severity. * Reporting higher depression at the onset of treatment was associated with greater NW throughout treatment. * The main effect of the treatment condition on NW was insignificant. * Main effects of depressive scores and time revealed significant effect on smoking urges. * Interaction of depressive scores and time on NW was also significant. * Reporting higher levels of depression was associated with increased levels in urges to smoke during the first week followed by progressive reduction in those urges in the remaining treatment period. * No significant effect of treatment condition was found on urges to smoke.	Small sample size. The high-depression (n=18) and low-depression (n=63) groups were unevenly distributed. Finding were pertinent to smokers reporting depression rather than smokers with major depressive disorder.

Table 2.1 Characteristics of Studies Addressing Nicotine Withdrawal among Tobacco Users with Mental Illness (continued).

Smith, Homish, Giovino, and Kozlowski (2014)[19]	To compare the severity and likelihood of having NW syndrome across mental illness diagnoses and in relation to those without MI. To compare NW symptoms among MI diagnoses. To estimate the proportion of NW syndromes caused by MI. To estimate whether smokers with MI have higher levels of motivation to quit and greater quitting attempts, compared to smokers without MI. To examine the influence of NW and nicotine dependence on cessation efforts among smokers with MI.	Cross-sectional; secondary analysis of data from 2 national surveys.	Study 1: Wave-1 of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). A sample of 9,913 individuals who reported smoking 100 cigarettes during their lifetime, including last year. Data was collected between 2001-2002. Study 2: Data was retrieved from a 2-wave national telephone survey of U.S. smokers 25 years of age or more between May 2004 and March 2005. A total of 751 smokers were included in the analyses.	Community dwelling.	Study 1: 1. Mental illness. MI was assessed using the Alcohol Use Disorder and Associated Disabilities Interview Schedule. 2. Nicotine Withdrawal. NW was assessed based on the DSM-IV criteria for its diagnosis. 3. Withdrawal-Related Distress. This distress was assessed using surveyors-generated questions. Study 2: 1. Nonspecific Psychological Distress – using Kessler's K6 screening tool. 2. Nicotine Dependence – using the Heaviness of Smoking Index (HSI). 3. Nicotine Withdrawal – using the MNWS. 4. Quitting Motives, quit attempts, and quit success – using surveyors generated questions. Successful quitting was defined as having 30 days of abstinence from all tobacco products.	A retrospective analysis of data was employed. In order to make a theoretically-sound diagnostic groupings of MI, researchers classified MI diagnoses in their samples into the following categories: 1. No disorder. 2. Internalizing disorder – past year mood and anxiety disorder. 3. Externalizing disorder – past year alcohol use disorders and drug use disorders and lifetime antisocial personality disorder. 4. Internalizing and externalizing disorders. 5. Psychotic episode or disorder.	* Among all MI categories, there was greater likelihood to be diagnosed with NW syndrome, compared to smokers without MI. The relative risks (RR) were 1.37, 2.37, 3.12, and 3.45 for externalizing disorders, internalizing disorders, internalizing and externalizing disorders, and psychotic disorders, respectively. * Mental illness was responsible for 44.4% of the NW syndrome diagnoses of the total sample. * compared to smokers with no MI, and after adjusting for sociodemographic variables, the RRs of having NW-related distress were 1.26, 1.65, 1.97, and 2.47 for externalizing, internalizing, internalizing and externalizing, and psychotic disorders, respectively. * Symptoms profiles of NW were consistent across the MI categories. However, anxiety was a better marker for internalizing disorders, and restlessness was a better marker for internalizing and externalizing disorders. * Smokers with nonspecific psychological distress were more motivated to quit, reported more severe NW, have higher nicotine dependence, and were less likely to successfully quit compared to those without nonspecific psychological distress. * Nonspecific psychological distress and quit success were mediated by NW and dependence.	Due to using cross-sectional design in study 1, the occurrence and time course of NW was never determined. Measures of smoking cessation were not biochemically verified. A significant number of smokers with MI might not have participated in the surveys in the first place.

Table 2.1 Characteristics of Studies Addressing Nicotine Withdrawal among Tobacco Users with Mental Illness (continued).

Reid et al. (2008)[60]	Researchers hypothesized that a smoking cessation program, given to participants in community substance abuse rehabilitation centers, will be acceptable by participants, effective in promoting smoking abstinence, and not worsening the concurrent drug alcohol treatment.	Multi-site Randomized controlled trial.	A total of 225 participants (153 in the smoking cessation treatment group and 72 in the treatment-as-usual group). All participants met substance dependence criteria, smoked around a pack of cigarettes, and have moderate to high levels of nicotine dependence.	Outpatient	Baseline: 1. Demographics 2. Smoking status. 3. Exhaled carbon CO results. 4. Urine cotinine results. 5. Fagerstrom nicotine tolerance questionnaire. 6. Smokers' belief questionnaire. 7. reasons for quitting questionnaire. 8. Abbreviated version of the addiction severity index. 9. Urine drug screen results. 10. alcohol breathalyzer results. 11. Vital signs. Weekly and follow-up at weeks 13 and 26: 1. self-reported average cigarettes per day. 2. Exhaled CO levels. 3. compliance with smoking cessation and drug rehabilitation treatment. 4. Modified MNWS. 5. Urine drug screen. 6. Alcohol breathalyzer test. 7. self-reported substance abuse. 8. vital signs, weight, adverse events, and concomitant medication information.	For the treatment group: 1. Smoking cessation counseling of 9 sessions, which was tailored for patients undergoing substance use treatment. Sessions started 1 week before the target quit day and continued for 6 weeks after the quit day. 2. NRT, consisted of 2 forms of transdermal nicotine patches (21 and 14mgs), which were tapered over time.	* Adherence to taking the NRT was highest in the first 3 weeks after the quit date. * Adherence to NRT use was higher among patients in the methadone program compared to patients in the non-methadone program. * Smoking abstinence was 10-11% during weeks 2-7 in the treatment group/ * Smoking abstinence rates were 5.5% and 5.7% at weeks 13 and 26 for the treatment group, respectively. Compared to 0% and 5.2% for the control groups at weeks 13 and 26, respectively. * During treatment period, the treatment group had around 75% reduction in the number of daily smoked cigarettes and a decrease in CO levels, compared to the control group. At weeks 13 and 26, patients in the treatment group had significantly less cigarettes per day compared to control. * NW and cravings decreased significantly in the treatment group, compared to control. * Drug and alcohol abstinence rates between treatment and control groups were similar over the course of smoking cessation, with no main effect of treatment condition. * Fewer number of cigarettes smoked per day were associated with lower craving for the primary abused substance.	Most participating sites (80% of the sample) adopted methadone-based treatment programs. Applicability of the program was considered unfeasible for many sites that chose to drop from this study. Contribution in the reduction in smoking and smoking abstinence rates were not separately attributed to counseling or NRT intervention.

Table 2.1 Characteristics of Studies Addressing Nicotine Withdrawal among Tobacco Users with Mental Illness (continued).

Schuster et al. (2017)[61]	To identify predictors of smoking abstinence among smokers with bipolar or schizophrenia, who were treated with a combination of cognitive behavioral therapy and varenicline for 12 weeks.	Quasi-experimental; secondary analysis of data.	One hundred and fifty-three outpatients from 10 community mental health centers in 6 states. Patients had a DSM-IV-TR diagnosis of schizophrenia, bipolar, or schizoaffective disorders. Patients were clinically stable for the past month, smoked at least 10 cigarettes per day, and had an expired CO levels of at least 9 ppm.	Outpatient.	Demographics. Cognitive performance (e.g., accuracy, vigilance, speed of processing). Treatment characteristics (e.g., antipsychotic regimen). Smoking characteristics (e.g., expired CO levels, FTND, Wisconsin Smoking Withdrawal Scale [WSWS]). Smoking environment (e.g., number of people smoking in household, support from others in quitting smoking). Psychopathology (e.g., Barrett impulsiveness scale, brief psychiatric rating scale, and the schedule for assessment of negative symptoms). Physical health (BMI and Framingham score).	Open-label varenicline started at 0.5mg once daily, which was gradually increased to 1mg twice daily for 11 weeks. In addition, cognitive behavioral therapy sessions of 1 hour given on weekly basis for 12 weeks. Quit day was determined after 4 to 5 weeks of taking the medication.	* Around 50% of the sample managed to achieve 14 days of biochemically-verified continuous abstinence at week 12 of the study. * A multivariate model identified the following predictors of a 14-day abstinence in our sample: number of cigarettes per day, prior alcohol dependence, lower expectation of peer support on quitting, high vigilance and low reaction time variability, and improvement in NW prior to quitting day.	Lack of control group. Findings cannot be generalized to patients with psychiatric or medical instability or have substance use disorders. All patients included in analyses completed at least 3 weeks in the study. Therefore, study findings cannot be generalized to patients not completing at least 3 weeks of treatment.

Table 2.1 Characteristics of Studies Addressing Nicotine Withdrawal among Tobacco Users with Mental Illness (continued).

Leyro et al. (2013)[56]	1. Characterizing clinical management pertinent to tobacco withdrawal and dependence among smokers hospitalized with MI. 2. Determination of provider practices and patient utilization of NRT predictors in terms of smoking-related, demographics, psychiatric, and substance use factors.	Cross-sectional; secondary analysis of data; exploratory design.	A total of 324 psychiatric inpatients from 2 hospitals. Patients reported smoking for 21 years, with an average of 19 cigarettes per day. They also reported moderate levels of nicotine dependence and almost half of the sample having hazardous alcohol consumption and/or current illicit drug-related problems.	Inpatient, smoke-free psychiatric hospitalization.	Demographics. Tobacco use characteristics (e.g., age of onset, years smoking). The seven-item MNWS. Heaviness of smoking index. Authors-developed NRT questionnaire. The 10-item Center for Epidemiologic Studies Depression Scale (CES-D-10). The 10-item Alcohol Use Disorders Identification Test (DAST). Mental health characteristics (e.g., Global Assessment Functioning [GAF] score, reason for hospitalization).	Charts of newly admitted patients were reviewed by research staff. Eligible patients who are interested in participation were approached and consented.	* The majority of participating patients (73%) were offered NRT at admission. * Around 50% of participants used NRT during hospitalization. * Participants who were offered NRT at admission were more likely to use it, compared to participants who were offered NRT later during hospitalization. * Timing of offering NRT was undiscriminating regardless of demographics, psychiatric diagnosis, hospital site, substance use characteristics, and length of hospital stay. * Compared to patients who did not use NRT, patients who used NRT had higher depressive symptoms, were heavier smokers, and had greater NW. * Unlike nicotine gum, prior use of nicotine patch was related to NRT patch use during hospitalization. * Participants' belief that NRT was helpful for quitting, decreases NW, and represents a substitution when he/she cannot smoke were associated with greater likelihood of using NRT. * Patients with psychotic disorders were more likely to use a combination of NRT products (i.e., gum and patch), compared to patients with mood disorders or other psychiatric diagnoses.	Cross-sectional design. Limited generalizability due to limited geographical disposition of the study. Since patients were given the freedom to choose their own NRT type, heavy smokers may not have chosen a combination of NRT products, regardless of their effectiveness.

Table 2.1 Characteristics of Studies Addressing Nicotine Withdrawal among Tobacco Users with Mental Illness (continued).

Weinberger, Desai, and McKee (2010)[55]	1. Comparing smokers with current axis I psychiatric disorders to smokers without, in terms of different NW aspects. 2. comparing the NW experience among smokers with comorbid psychiatric and substance/alcohol use disorder and smokers with a single psychiatric or substance/alcohol use disorders.	Nationally-representative survey; secondary analysis of data.	A subsample of current smokers (8,213) from the National Institute of Alcohol Abuse and Alcoholism (NESARC) study. Participants were adults (≥ 18 years of age), were at least high school graduates, with 53% having current nicotine dependence.	Community dwelling.	Demographics and smoking information (e.g., marital status, age of smoking onset). Psychiatric diagnosis; using the Alcohol Use Disorder and Associated Disabilities Interview Schedule – Version for the DSM-IV. NW; by reporting any of the DSM-IV-TR signs and symptoms of NW over the past 12 months (yes/no). Tobacco use relapse because of NW.	Secondary analysis of data.	* Having a current mood, anxiety, alcohol use, or drug use disorder was associated with younger age of smoking onset, higher likelihood of reporting nicotine dependence, and reporting at least one NW symptom. * Having a current diagnosis of mood, anxiety, alcohol use, or substance use disorders was associated with greater number of reported NW symptoms during a quit attempt, compared to people without these conditions. * Comorbidity between mood or anxiety disorders and alcohol use or substance use disorders was found insignificant in reporting NW, compared to smokers without comorbidity. * NW-related distress, discomfort, and NW-smoking relapse were found more likely among smokers with current mood, anxiety, or substance use disorders, but not alcohol use disorder.	Cross-sectional data. Self-report. Retrospective recall bias of NW. The following pertinent information were not assessed: NW symptoms severity, number of quit attempts, duration of quit attempts, and smoking cessation treatment utilized.

Table 2.1 Characteristics of Studies Addressing Nicotine Withdrawal among Tobacco Users with Mental Illness (continued).

Shmueli, Fletcher, Hall, Hall, and Prochaska (2008)[64]	To examine whether thoughts about quitting smoking were associated with smoking abstinence related to psychiatric smoke-free hospitalization.	Pre-posttest design; secondary analysis of data.	A total of 100 patients who smoked more than 100 cigarettes over their lifetime, and who smoked at least one cigarette the week preceding hospitalization. Patients were hospitalized, on average, for 7.5 days.	Inpatient, smoke-free psychiatric hospitalization	The Smoking History Questionnaire. FTND. The Computerized Diagnostic Interview Schedule-IV (CDIS-IV). The Secondhand Smoke Exposure Survey. The Stages of Change Scale. The Commitment to Abstinence Scale. Chart review (e.g., length of stay, NRT use).	First assessment was conducted within 48 hours of admission; and the second assessment was conducted before patients' discharge. After hospitalization, patients were followed up at 1 week, 1 month, and 3 months.	* Compared to assessment at hospital admission, patients had both statistically significant higher perception of successfully quitting and lower expectation of difficulty in quitting smoking prior to hospital discharge. * Psychiatric diagnoses (62% of patients were diagnosed with NW using the CDIS-IV) did not seem to affect patients' desire to quit smoking, expectancy in successfully quitting, and staying quitted; from hospital admission to discharge. * Compared to the number of cigarettes smoked before hospitalization, this number was significantly lower at the 3-month follow up. However, all patients reported returning to smoking. * After hospital discharge, 48% of participants reported conducting a quit attempt.	Recruitment from 1 clinical site.

Table 2.1 Characteristics of Studies Addressing Nicotine Withdrawal among Tobacco Users with Mental Illness (continued).

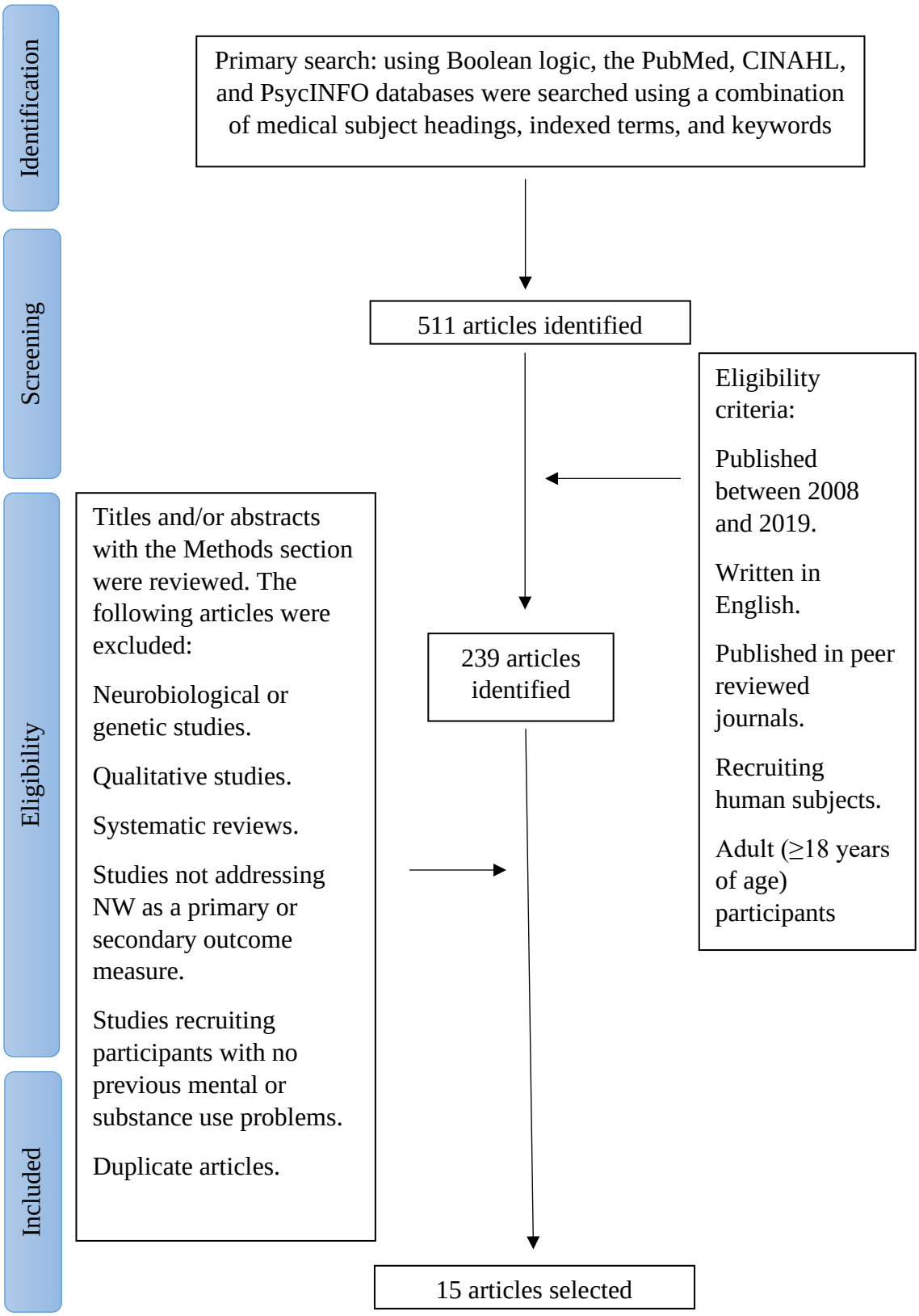
Keizer et al. (2012)[65]	To describe the feasibility of an intervention, based on the association of temporary smoking abstinence with positive experiences.	Pre-posttest.	Nineteen smoking patients admitted to a tobacco-free psychiatric hospital in Geneva, Switzerland. Participants were generally heavy smokers, consuming around 1 pack per day.	Outpatient.	Cigarettes per day (CPD). HSI. Stage of motivation to quitting. Self-efficacy about smoking cessation. 7 withdrawal symptoms. Expired CO levels.	Patients left the hospital in the morning; were encouraged to stay smoke-free, and were engaged in positive experiences associated with non-smoking, such as outdoor restaurant lunch, informal discussion about the smoking abstinence experience, group sessions with a tobacco treatment specialist, thermal baths, and afternoon tea with music. NRT was offered free of charge during hospitalization and during intervention. Participants returned in at night. CO levels was measured in the morning, afternoon, and the next morning of the intervention day. Follow up, after 1 week, including assessment of CPD over the past week after the intervention, HSI, and stage of motivation and self-efficacy.	* Around 80% of participants were abstinent at 10-hour period and 47% were abstinent the next morning. * CO levels decreased significantly throughout the intervention day. * Reporting of NW was low. Actually, around one-third of participants reported perceived benefits of abstinence with regard to concentrating, depression, craving, and anxiety. * Significant reduction in the number of smoked cigarettes was found 1 week before and after the intervention.	Lack of a control group. Sample size. Non-validated instruments. Short period of observation.

Table 2.1 Characteristics of Studies Addressing Nicotine Withdrawal among Tobacco Users with Mental Illness (continued).

Pachas et al. (2012)[63]	To prospectively evaluate smoking outcomes, adverse events, and psychiatric symptoms among patients with stable schizophrenia during treatment with varenicline and cognitive behavioral therapy.	One-group repeated measures.	A total of 112 adult patients with stable schizophrenia. Participants were on average 47 years of age, smoked more than 1 pack of cigarettes per day, and had moderate to severe nicotine dependence.	Inpatient psychiatric hospitalization.	Baseline: 1. Smoking and medical history. 2. Expired CO. 3. FTND. 4. Cotinine and drug screen test results. Weekly assessment: 1. Self-report smoking behavior. 2. End-expiratory CO measurement. 3. NW, using the WSWS. 4. Calgary Depression Scale for schizophrenia. Baseline and end-of-treatment assessment: 1. Brief psychiatric Rating Scale. 2. Schedule for the Assessment of Negative Symptoms.	Varenicline 0.5mg once daily, increased gradually to 1mg twice daily for 11 weeks. In addition, 1-hour session of cognitive behavioral therapy on weekly basis. The quit day was set between weeks 4 and 5.	* From week 1 to week 12 or early termination, there was significant improvements in NW symptoms and psychosis ratings. * Similarly, the repeated measures analyses revealed increases in abstinence rates and decreased NW symptoms. * The progressive increase in abstinence rates was associated with progressive decreases in depressive and CO levels as well. * By the end of week 12, around 47% of participants achieved 2 consecutive weeks of smoking abstinence that was biochemically verified. Also, at the same timepoint, 34% of participants achieved 4 or more consecutive weeks of, biochemically-verified, smoking abstinence.	Absence of control group. Limited statistical power related to sample size. Around one-third of participants dropped out early.

Abbreviations used across studies: NRT=Nicotine Replacement Therapy; NW=Nicotine Withdrawal; MI=Mental Illness; FTND/FTCD=Fagerstrom Test for Nicotine Dependence/Fagerstrom Test for Cigarettes Dependence; CO=Carbon Monoxide; PTSD=Post Traumatic Stress Disorder.

Figure 2.1 A Diagram of Articles Selection Process.



CHAPTER 3. THE PSYCHOMETRIC PROPERTIES OF THE MINNESOTA TOBACCO WITHDRAWAL SCALE AMONG PATIENTS WITH MENTAL DISORDERS[79]

3.1 Introduction

People with serious mental illness (SMI) are disproportionately affected by tobacco use compared to the general population.[1] About 21% to 59% of people with SMI are current tobacco users.[2-6] In particular, those diagnosed with schizophrenia, mood, anxiety, and substance use disorders have the highest smoking prevalence rates.[66,80] During the first decade of the 21st century, there was a significant decline in the sales and rates of cigarette smoking in the general population.[81,82] On the other hand, the rates of smoking among people with SMI remain high, with an increasing gap in smoking prevalence between people with and without SMI in the general population.[82] In fact, people with SMI consume around 44% of all cigarettes smoked annually in the United States.[7] Consequently, and in addition to the negative social and economic effects of smoking, people with SMI have higher risk for cancer, heart, and lung diseases, have 10 to 25-year shorter life expectancy, and constitute more than one-third of the U.S. annual smoking-attributed mortalities.[1,8] Therefore, it is crucial to identify and assess factors that may compromise tobacco treatment (TT) among people with SMI.

An important factor that often hinders successful TT is the nicotine withdrawal (NW) syndrome. This syndrome is a set of symptoms appearing within 24 hours after an abrupt cessation or reduction in the consumption of tobacco-containing products, for those using nicotine on a daily basis for at least a couple of weeks.[12] The *Diagnostic and*

Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), requires four or more of the following eight symptoms for a NW syndrome diagnosis: dysphoric/depressed mood, insomnia, irritability/frustration/anger, anxiety, difficulty concentrating, restlessness, or increased appetite/weight gain.[12] Around 65% of psychiatric inpatients report moderate to severe NW, which has been correlated to gender (i.e., women), polysubstance use, and being African American.[18] In fact, people with SMI have higher NW symptom severity during a quit attempt as compared to the general population;[19] which may compromise successful quit attempts and the efficacy of the provided psychiatric care, if left untreated.[11,19] Given the current trend towards tobacco-free psychiatric hospitalizations in the United State,[25-27,51] it is important to have valid and reliable tools for capturing NW syndrome among patients with SMI.

Identifying and treating NW during a tobacco-free psychiatric hospitalization could enhance the provision of psychiatric care and may increase the likelihood of engaging in TT among patients with SMI. The Minnesota tobacco withdrawal scale (MTWS), previously named the Minnesota nicotine withdrawal scale,[83,84] is a widely used instrument for detecting NW. It has been translated into several languages, applied in different populations, used to assess the efficacy of nicotine replacement therapy (NRT) and withdrawal symptomatology to smokeless tobacco, and has also been used to predict smoking relapse.[62,85-88] Compared to other scales used to measure NW such as the mood and physical symptoms scale,[89] the Shiffman-Jarvik scale,[90] the Wisconsin withdrawal scale (WWS),[68] and the cigarette withdrawal scale (CWS), the MTWS showed high sensitivity in detecting certain NW symptoms (irritability, difficulty concentrating, craving, restlessness, and anxiety), but low sensitivity to depression and

insomnia after 24 hours of tobacco use abstinence.[91] When test-retest reliability and Cronbach's alpha were compared between the MTWS, the CWS, and the WWS in an internet cohort sample, the MTWS showed a high Cronbach's alpha coefficient (≥0.85); and a moderate intraclass correlation coefficient (r = 0.71) compared to the CWS (r = 0.79) and the WWS (r = 0.80).[92] Validity testing of the MTWS was examined through confirmatory factor analysis, which concluded that a unidimensional model of the 8-item MTWS best fitted their data, which was derived from three separate clinical trials.[93]

Among outpatient clients with schizophrenia who demonstrated a stable psychiatric state, Weinberger et al. (2007)[94] examined the internal consistency and test-retest reliability of the MTWS and the Tiffany questionnaire for smoking urges (TQSU). Researchers found that the internal consistency reliability coefficient of the MTWS was 0.88 compared to 0.79 and 0.88 for the TQSU factor 1 (urges to smoke in response to positive reinforcement) and factor 2 (urges to smoke in response to negative reinforcement), respectively. Also the test-retest reliability coefficient was 0.58 for the MTWS compared to 0.65 and 0.69 for the TQSU factors 1 and 2, respectively.[95] However, the validity and reliability of the MTWS has not been examined extensively among patients with SMI in a hospitalized tobacco-controlled setting.

The purpose of this study was to examine the psychometric properties of the MTWS among patients with SMI in the context of a tobacco-free psychiatric hospitalization. The specific aims of this study were to:

(1) test the reliability of the MTWS (i.e., internal consistency/item analysis reliabilities) and to (2) support the MTWS's validity by:

(a) hypothesizing that patients with higher tobacco consumption would report higher NW severity on the MTWS; and

(b) examining exploratory factorial analysis of the MTWS.

3.2 Methods

3.2.1 Sample and setting

Data were obtained from Eastern State Hospital (ESH), a 239-bed State-operated and owned psychiatric hospital serving 50 counties in Kentucky. Starting January 1st, 2016, ESH enhanced its existing inpatient services to include evidence-based TT services[96,97] in compliance with the inpatient psychiatric facility quality report requirements.[28] These TT services are comprised of assessing patients' tobacco use characteristics (e.g., tobacco type used and number of packs used per day), offering TT and practical counseling, and administering Food and Drug Administration (FDA) approved medication. In addition, the services included monitoring and management of NW by a qualified registered nurse for all tobacco users able to engage in this treatment service. Since the ESH is covered by a 100% tobacco-free campus policy, patients are unable to leave the units to use any tobacco products as per the policy.

3.2.2 Design

This study was a secondary analysis of data from a retrospective review of medical records from 255 admissions to ESH between January 1st, 2016 and December 31st, 2016. Of the total 2751 admissions in 2016, 1073 patients were current tobacco users. Two hundred and fifty-five (23.8%) of these tobacco users were able to respond to

the administration of the MTWS. Those who did not respond were unable to do so because of their psychiatric symptom severity, stayed in the hospital for a short duration, or refused to respond. Data were derived from the records of tobacco-using psychiatric patients, 18 years of age and older, who engaged in the TT services in the specified time period. The original study examined the relationships between the provision of NRT at admission, patients' motivation to quit smoking, and NW severity.[99] Approval for this study was obtained from the University of Kentucky medical institutional review board (Exemption Certification for Protocol No. 17-0064-X2B).

3.2.3 Measures

Demographics and clinical characteristics. Patients' demographics retrieved from medical records included age, race (i.e., White vs. non-White), sex (i.e., male vs. female), and education level (i.e., less than high school vs. high school/GED vs. associate degree or higher). In addition, the following clinical variables were also retrieved from the medical records: psychiatric diagnosis, duration of hospitalization (in days), tobacco use type (i.e., cigarettes vs. non-cigarettes), substance use history (i.e., yes vs. no), cigarette-equivalents per day (CPD), and the use of NRT during hospitalization (yes vs. no). CPD was calculated based on converting different tobacco products to the cigarette equivalent based on approximate nicotine content, such that 1 can of chew tobacco was equivalent to 1 pack of cigarettes, 1 cigar was equivalent to 4 cigarettes, and 1 can/tin of moist tobacco was equivalent to 2.5 packs (i.e., 50 cigarettes/day equivalent).[81,100] One individual was an e-cigarette user for whom the amount of nicotine consumed was not available in the charts; thus, for the cigarette equivalent per day calculations, it was conservatively assumed that the individual used a pack of cigarettes per day. For ease of analysis,

patients' discharge diagnoses were categorized into clinically-driven psychiatric groups; including psychotic (i.e., schizophrenia, schizoaffective, psychotic disorder not otherwise specified etc.), mood and anxiety (i.e., major depressive disorder, bipolar disorder, post-traumatic stress disorder etc.), substance use (i.e., alcohol, cocaine, marijuana, opiate etc.), or other (i.e., personality, malingering, cognitive, or altered mental status not otherwise specified) disorders. Patients with psychotic disorders have been grouped separately in the literature.[19] Patients with mood and anxiety disorders were grouped together because they were postulated to represent a higher-order factor (i.e., internalizing disorder).[101] Similarly, patients with substance use disorders were grouped separately because they were postulated to represent another higher-order factor (i.e., externalizing disorders).[101]

The Minnesota Tobacco Withdrawal Scale. The MTWS is a self-report 8-item scale based on the diagnostics criteria for NW in the DSM-IV-TR (i.e., irritability/frustration/ or anger, anxiety, difficulty concentrating, increased appetite, restlessness, depressed mood, and insomnia), in addition to craving.[13,83] For this study, the MTWS scores were obtained from patient record review. Item responses ranged between 0 (i.e., no symptoms) and 4 (i.e., severe symptoms), with a total potential score of 32. The MTWS was administered to patients as close to admission as possible. However, there were instances, in which, at admission, patients were unwilling or unable (due to psychiatric symptom severity) to provide responses to the MTWS. In such cases, the MTWS was administered by nursing staff at a time when the patient was stable enough to provide an adequate response (often within 1 to 4 days of admission). In fact, only 2 (0.8%) patients were assessed on the day of admission, 106 (41.5%) within 1-2

days of admission, 55 (21.6%) within 3-4 days of admission, and 92 (36.1%) after 5 days of admission.

3.2.4 Data analysis

Means (M) and standard deviations (SD) were used to describe interval- and ratio-level variables, and frequencies and percentages (%) were used to describe ordinal and nominal level variables. Differences in patients' demographics, duration of hospitalization, type of tobacco used, substance use history (yes vs. no), MTWS scores, and the administration of NRT (yes vs. no) were examined by the CPD values (i.e., above and below the median, 20.00) using Chi square for nominal and ordinal level variables, and *t*-test or analysis of variance (ANOVA) for interval and ratio level variables. SPSS version 24 was used for all analyses, and α was set at 0.05.

3.2.5 Reliability testing

Cronbach's alpha was calculated to assess the internal consistency reliability of the MTWS. In addition, item analysis was further employed to assess the homogeneity of the instrument in terms of its item-total and inter-item correlations. Item-total and inter-item correlations between 0.2 and 0.8 are desirable. However, correlation coefficient values more than 0.8 are considered redundant.[102] Test-retest reliability examination was inappropriate due to the rapidly changing nature of NW over a relatively short period of time,[13] and the limited number of readmissions in our sample (n=22).

3.2.6 Validity testing

Hypothesis testing and exploratory factor analysis were employed to assess the construct validity of the MTWS among patients with SMI during a psychiatric smoke-free hospitalization. First, based on the evidence in the literature confirming that individuals experiencing higher NW symptom severity after 24 hours of abstinence also report higher consumption rates of nicotine,[103,104] we hypothesized that patients with higher CPD scores would report higher NW severity on the MTWS (as a proxy of the amount of nicotine consumption). To test this hypothesis, a general linear regression model was used to examine whether the CPD score was an independent associative factor with the MTWS scores, adjusting for the dosage of NRT (none vs. 14mg vs. 21mg), race, duration of hospitalization, and discharge diagnosis. These covariates were included for control in the regression model due to their association with NW as previously evident in the literature. Specifically, the duration of hospitalization is a significant correlate of tobacco use in this population,[105] the administration of NRT is associated with lesser NW severity scores among patients with SMI during hospitalization,[99] and African American patients with SMI have higher NW severity compared to their Caucasian counterpart.[18] Lastly, patients with different SMI diagnoses have varying probabilities of being diagnosed with NW syndrome.[19] Because the MTWS scores were skewed, we performed regression analyses with both raw and log-transformed MTWS values.

Second, an exploratory factor analysis was used to examine the structure and construct validity of the MTWS. The suitability of the data for factor analysis was verified using the Kaiser-Mayer-Oklin and the Bartlett's sphericity tests. Distinct dimensions/factors of the instrument were identified using the scree plot and eigenvalues

of 1 and more, and each dimension's items were distinguished by 0.4, or more, Varimax-rotated loading values when applicable.[106]

3.3 Results

3.3.1 Sample characteristics

Our sample consisted primarily of White (89.4%) males (55.7%), with a mean age of 42 years (SD=14). On average, patients had a 16-day hospitalization period and a 3.2 (SD=4.2) score on the MTWS. Patients primarily were diagnosed with psychotic (38.4%) or mood and anxiety (31.8%) disorders, had at least a high school/GED education level (72.6%), were cigarette smokers (89.4%) who consumed on average 23.7 (SD=16.7) CPD, had a substance use history (69.5%), and had received NRT during their current hospitalization (92.5%). Moreover, males and White patients were more likely to have CPD values of more than 20 compared to females and non-White patients (*Ps*=0.11 and 0.027, respectively). Furthermore, patients with greater MTWS scores were more likely to have CPD values of more than 20 ($P<0.001$), as were patients who were non-cigarette users ($P<0.001$) (see Table 3.1).

3.3.2 Reliability testing

The reliability analysis yielded a Cronbach's alpha coefficient of 0.763, interitem correlations coefficient of 0.393, and item-total correlations between 0.291 and 0.691. Item-item correlations, between 7 items (excluding the craving item), ranged between 0.21 and 0.717. However, craving was poorly correlated with insomnia, difficulty concentrating, and weight gain/increased appetite in our sample, with correlation coefficient values of 0.183, 0.177, and 0.081, respectively. Anyhow, the overall

Cronbach's alpha of the instrument did not decline below 0.698 when any of its items were deleted, including the craving item (see Table 3.2).

3.3.3 Validity testing

A general linear regression model, using data from 255 patients was used to examine whether the CPD scores would be independently associated with higher MTWS scores. The general regression model identified race (i.e., being non-White) (β: 0.240, CI: 0.277-1.104, *p*-value = 0.001) and the CPD values (β: 0.147, CI: 0.000-0.015, *p*-value = 0.048) as independent, statistically significant associative factors with the MTWS scores. That is, considering the dosage of NRT (i.e., none vs. 14 mg vs. 21mg), race, hospitalization period (in days), and the psychiatric diagnosis at discharge as adjusted covariates, the mean score of the MTWS would increase by 0.147 for each 1 unit increase on the CPD scores. No other variables were significantly associated with the MTWS scores, and the overall model explained 8.7% of the total variance in the dependent variable (see Table 3.3). We performed the same analysis with the MTWS scores that were log-transformed and still had the CPD as a statistically significant associative factor in both models.

The exploratory factor analysis identified one factor with an eigenvalue of 3.920, which explained 49% of the total variance in the MTWS scores. Most of the items loaded significantly on this factor with item loadings ranging between 0.452 and 0.835. However, the item measuring cravings to smoke in this population had the least loading on this factor (0.377) (see Table 3.4). The fitness of the data for factor analysis was confirmed by the Kaiser-Mayer-Oklin statistic of 0.865 and the Bartlett's test of

sphericity (*P*-value < 0.001). No rotation of loadings was performed due to lacking more than one factor.

3.4 Discussion

The purpose of this study was to examine the psychometric properties of the MTWS among patients with SMI during a tobacco-free psychiatric hospitalization. Although the MTWS has been extensively validated in other samples, it has not been examined among psychiatric inpatients during a tobacco-free hospitalization. Our findings indicate adequate validity and reliability psychometric properties of the MTWS in this population in terms of its internal consistency, homogeneity of items, and measurement of the intended construct. These findings have some important implications for TT in this population.

We found that all items of the MTWS had fair to moderate correlations with the total scale score; and that all items representing the diagnostic criteria of NW, as indicated by the DSM-IV-TR, demonstrated good item-to-item correlation coefficients. Also, the Cronbach's alpha correlation coefficient of the scale exhibited good internal consistency when any of its items were deleted. Comparable findings were reported previously in the literature among patients with SMI. For example, in a sample of 151 psychiatrically stable smokers with schizophrenia, a 0.88 Cronbach's alpha coefficient was obtained on the MTWS, as compared to 0.90 in a control group of smokers without schizophrenia (n=181).[95] Similarly, in an internet-based study involving participants from the United States, Canada, and Europe, the Cronbach's alpha coefficient of the MTWS in 2043 ex-smokers was reported to be 0.85.[92] The relatively lower Cronbach's alpha

observed in our sample (i.e., 0.76) as compared to prior studies may be due to differences in sample characteristics. For example, as compared to our sample of acutely hospitalized psychiatric patients, a study by Weinberger et al. (2007)[107] was based on a sample of psychiatrically-stable outpatients and the study by Etter and Hughes (2006)[92] was derived from a sample of non-psychiatric patients. Thus, the internal consistency finding of the MTWS in our sample seems adequate to support the homogeneity of the scale for acutely hospitalized psychiatric patients during a tobacco-free hospitalization.

Furthermore, we hypothesized and found, through adjusted multivariate regression analyses, that greater tobacco consumption was associated with higher NW symptom severity in our sample. This association may lend support for the construct validity of the MTWS. The construct validity of the MTWS has also been scrutinized previously using hypotheses testing. Evidence to support the validity of the MTWS was also demonstrated in other studies when it was used to test the differences in NW symptoms severity between recent (≤31 days) and long term (32-365days) ex-smokers, recent ex-smokers (≤31days) and daily smokers, and recent (≤31 days) ex-smokers and never smokers.[92] The finding in our sample, along with results found in the aforementioned study, further strengthens the validity of the MTWS in measuring the construct of NW. Moreover, a unidimensional construct was identified through our factor analysis of the MTWS, as indicated by an eigenvalue of 1 and more, and a scree plot (not shown). Nonetheless, an exploratory factor analysis of a Korean translated version of the MTWS suggested that this scale may have two dimensions (i.e., the early-occurring disturbances in mental functioning, and the disturbances in physiological functioning and late-occurring disturbances in mental functioning dimensions), that explained 66% of the

variation in the NW scores.[108] Yet, other studies have found that the MTWS is unidimensional.[92,93] Hence, more research may be warranted to confirm the dimensionality of the instrument.

Several limitations should be taken into consideration in properly interpreting the findings of our psychometric analysis. Primarily, this study was limited by the fact that some potential factors affecting NW were not included in our regression model (e.g. co-occurring substance use). Second, the effect of classifications and dosages of the prescribed antipsychotic medication during hospitalization on NW were not available and could not be addressed in this study. Third, the data for this secondary analysis was based on a convenience sample of participants who were willing and able to provide responses on the MTWS. This sample represented only about 23.8% of all tobacco users who were admitted to the hospital during the data collection time frame, which may limit the generalizability of the findings. Fourth, our sample had relatively low average scores on the MTWS with 27.8% reporting no NW symptoms. These low scores may have been a result of patients being administered NRT at admission per hospital protocol. This administration of NRT potentially mitigated the severity of NW in our sample and may not represent the typical profile of NW among psychiatric patients who do not receive NRT during hospitalization. Fifth, the measurement of the MTWS occurred at variable times after admission, which may have skewed the MTWS scores. Hence, it is possible that alpha and factor analyses may have exaggerated the internal consistency and factor loadings because of the distribution of the MTWS. This limitation is particularly of note because the eigenvalues on the scree plot were very close to having a second dimension of the scale (0.969). Moreover, because of the low subsample proportion of the diagnostic

groups, we were unable to examine the validity and reliability of the MTWS for individual diagnoses; however, future studies with robust sample sizes should be considered to assess the reliability and validity of the MTWS among different diagnostic groups. Finally, the adequacy of the MTWS in measuring NW has not been examined longitudinally throughout the period of hospitalization. Future studies may examine changes in NW scores over time to better understand the time-course of the symptom severity among patients with SMI during a tobacco-free hospitalization.

3.5 Conclusion

Addressing factors, such as NW, which may hinder engagement in TT among people with SMI remains a critical area of research. Evaluating the psychometric properties of the MTWS can lend confidence in its use as an assessment tool for assessing NW by nurses and other health professionals. We found that the MTWS demonstrated reliable and valid psychometric properties for measuring NW among patients with SMI during a psychiatric tobacco-free hospitalization. This instrument may be recommended in clinical practice to identify patients with high NW severity, in order to take necessary measures in managing withdrawal during a tobacco-free hospitalization. Future research should examine the efficacy in measuring NW in this population over an extended period of hospitalization. Such research is crucial in addressing ways to curb the hidden tobacco use epidemic among people with SMI.

Table 3.1 Differences in Sample Demographics and Clinical Variables by Cigarette Equivalents per Day (*N*=255)

Variable	Mean ± SD or N (%)			
	Whole sample 255 (100%)	**CPD[a] 0-20** 180 (70.6%)	**CPD[a]>20** 75 (29.4%)	***P*-Value**
Age (in years)	42 ± 14	42.5 ± 14.3	40.9 ± 13.5	0.405
Sex				0.011*
Males	142 (55.7%)	91 (50.6%)	51 (68%)	
Females	113 (44.3%)	89 (49.4%)	24 (32%)	
Race				0.027*
White	228 (89.4%)	156 (86.7%)	72 (96%)	
Non-White	27 (10.6%)	24 (13.3%)	3 (4%)	
Diagnosis categories				0.680
Psychotic disorders	98 (38.4%)	71 (39.4%)	27 (36%)	
Mood and anxiety	81 (31.8%)	58 (32.2%)	23 (30.7%)	
disorders	40 (15.7%)	25 (13.9%)	15 (20%)	
Substance use disorders	36 (14.1%)	26 (14.4%)	10 (13.3%)	
Other disorders				
Hospitalization period	16.2 ± 28.2	15.1 ± 25.9	18.8 ± 33.3	0.339
MTWS[b] scores	3.2 ± 4.2	2.6 ± 3.2	4.7 ± 5.6	<0.001*
Education level				0.565
Less than high school	70 (27.5%)	46 (25.6%)	24 (32%)	
Highschool/GED	82 (32.2%)	60 (33.3%)	22 (29.3%)	
Associate degree or	103 (40.4%)	74 (41.1%)	29 (38.7%)	
higher				
Tobacco use form				<0.001*
Cigarettes	288 (89.4%)	169 (93.9%)	59 (78.7%)	
Non-cigarettes	27 (10.6%)	11 (6.1%)	16 (21.3%)	
Substance use history				0.988
Yes	171 (69.5%)	121 (69.5%)	50 (69.4%)	
No	75 (30.5%)	53 (30.5%)	22 (30.6%)	
Nicotine replacement therapy				0.176
Yes	236 (92.5%)	164 (91.1%)	72 (96%)	
No	19 (7.5%)	16 (8.9%)	3 (4%)	

[a] Cigarettes equivalents per day. [b] Minnesota Tobacco Withdrawal Scale. * Statistically significant at α equals 0.05.

Table 32.2 Item-total and Inter-item Correlations for the MTWS (*N*=255)

MTWS Item	Corrected item-total correlation	Craving	Depressed mood/sad	Insomnia/ sleep problems/ awakening at night	Anger/ irritable/ frustrated	Anxious/ nervous	Difficulty concentra-ting	Restlessness	Increased appetite/ hungry/ weight gain	Cronbach's alpha if item deleted
Craving	0.291	1.00								0.853
Depressed mood/sad	0.548	0.243	1.00							0.730
Insomnia/sleep problems/awakening at night	0.576	0.183*	0.423	1.00						0.732
Anger/irritable/frustrated	0.691	0.288	0.465	0.530	1.00					0.698
Anxious/nervous	0.636	0.223	0.527	0.438	0.717	1.00				0.711
Difficulty concentrating	0.589	0.177*	0.415	0.514	0.519	0.476	1.00			0.732
Restlessness	0.689	0.260	0.413	0.602	0.638	0.584	0.625	1.00		0.702
Increased appetite/hungry/weight gain	0.312	0.081*	0.264	0.292	0.229	0.210	0.330	0.350	1.00	0.761

***** Less than 0.20. Cronbach's alpha = 0.763. Interitem correlations = 0.393.

Table 3.3 Summary of Multivariate Regression Model (*N*=255)

Variable	B	β	Confidence Interval (CI)	*p*-Value
CPD	0.008	0.147	(0.000-0.015)	0.048*
Dosage of NRT				
Not given NRT	---	---	---	---
(reference)	0.115	0.059	(-0.244-0.474)	0.529
14mg	0.192	0.119	(-0.116-0.500)	0.221
21mg or more				
Race				
White (reference)	---	---	---	---
Non-White	0.690	0.240	(0.277-1.104)	0.001*
Hospitalization period (in days)	-0.001	-0.032	(-0.006-0.004)	0.667
Discharge diagnosis				
Other disorders	---	---	---	---
(reference)	0.188	0.114	(-0.165-0.541)	0.295
Depressive disorders	0.055	0.033	(-0.294-0.404)	0.756
Psychotic disorders	0.175	0.083	(-0.233-0.583)	0.399
Substance use disorders				

Dependent variable: Nicotine withdrawal severity, measured using the MTWS. β: Standardized coefficients. B: Unstandardized coefficients. Adjusted R^2: 0.087. CPD: Cigarettes equivalents per day. * Significant at α = 0.05.

Table 3.4 Loadings of the MTWS Items on the Identified Factor

Item of the MTWS	Item Loadings on The Identified Factor
Restlessness	0.835
Anger/Frustration/Irritability	0.825
Anxiety	0.787
Difficulty Concentrating	0.754
Insomnia	0.740
Depressed Mood	0.678
Increased Appetite	0.452
Craving	0.377

MTWS: Minnesota Tobacco Withdrawal Scale.

CHAPTER 4. NICOTINE WITHDRAWAL AND SUBSTANCE USE AMONG TOBACCO-USING PATIENTS WITH MENTAL ILLNESS

4.1 Introduction

Despite the major strides accomplished in reducing adult tobacco use over the past few decades, people with mental illness (MI) remain disproportionately affected by tobacco use prevalence when compared to the general population.[1,82,109,110] In fact, people with MI are twice as likely to use tobacco compared to the general population, ostensibly consuming roughly 44% of all cigarettes produced annually in the United States.[6,7] Because of this staggering inclination toward tobacco use, people with MI have a higher risk for heart, cerebrovascular disease, and chronic respiratory diseases and cancers.[111] Actually, people with MI account for more than one-third of the U.S. annual deaths attributed to tobacco use.[1,8] Hence, efforts to promote tobacco treatment with this population are critically important.

Tobacco dependence treatment efforts among people with MI are associated with lowering the likelihood of being discharged against medical advice in the psychiatric hospital setting, enhancing quality of life, and several other positive physical and psychological health outcomes.[10,11,111] Importantly, tobacco users with MI report motivation levels to quit tobacco comparable to those of the general population.[1,112] To support patients' increased motivation to stop tobacco use, psychiatric institutions in the United States have increasingly endorsed tobacco-free policies and enhanced tobacco treatment services during inpatient hospitalizations.[3,51,113,114] These tobacco-free policies have been shown to have positive tobacco cessation outcomes.[3,51,113,114]

Nicotine withdrawal (NW) is an important barrier that impedes tobacco dependence treatment and is often an unintended consequence of tobacco-free policies in acute hospitalizations. NW is a set of symptoms that occur after abstaining from or reducing the amount of tobacco normally consumed.[12] NW syndrome is characterized by the presence of four or more of the following symptoms within a 24 hour period of tobacco abstinence: anxiety; irritability, frustration, or anger; increased appetite; difficulty concentrating; depressed mood; restlessness; and insomnia.[12] NW is an under studied issue, and it is associated with the likelihood of unsuccessful quit attempts in the tobacco-using MI population.[11,19] As compared to those without, tobacco users with substance use disorders (SUD; e.g. cannabis, cocaine, and alcohol) tend to experience greater NW.[19] Moreover, there are high rates of lifetime co-occurring SUDs observed in tobacco-using patients with MI (11% to 52%).[29-31] Yet in consideration of the high prevalence of tobacco use among those with co-occurring substance use disorders and MI, the relationship between SUD and NW in this population is poorly studied. Thus, in order to guide treatment in tobacco-free psychiatric institutions, it is crucial to understand the experience of NW among tobacco users with concurrent MI and SUDs during hospitalization.

NW is experienced by up to 65% of tobacco users with MI.[18] In fact, MI is associated with at least 44% of all NW diagnoses in the general population.[19] Among those at greatest risk for NW are tobacco users with psychotic disorders and mood or anxiety disorders, compared to other MI diagnoses.[19] NW has been linked to a number of factors among tobacco users with MI, such as sex, level of nicotine dependence, severity of psychiatric symptoms, alcohol and drug use, and anxiety and depression levels.[18,21,58,62]

If left untreated, NW can hinder the provided psychiatric care and lower the success rate in quitting tobacco use through relapse.[11,19]

Given the scarcity of studies examining NW among people with concurrent substance use and MI, the purpose of this study was to examine the nature of the relationships between psychiatric diagnoses, substance use, and NW severity among psychiatric inpatients. Specifically, among inpatients in a tobacco-free psychiatric facility, this study aimed to evaluate whether co-occurring substance use moderates the relationship between psychiatric diagnosis and NW severity. The psychiatric diagnoses considered in this analysis includes psychotic disorders (yes/no) and mood or anxiety disorders (yes/no). The hypotheses were:

i. Among tobacco-using patients diagnosed with psychotic disorders (e.g., schizophrenia, schizoaffective, or psychotic disorder not otherwise specified), the concurrent use of each of the following substance classes: alcohol; cannabis; hallucinogens; inhalants; stimulants; opiates, pain killers, or heroin; sedatives, hypnotics, or anxiolytics; or poly-substances, within the past 12 months prior to admission, would serve as a moderator to NW severity (See Figure 4.1, A).

ii. Among tobacco-using patients diagnosed with mood or anxiety disorders (e.g., major depressive disorder, bipolar disorder, or post-traumatic stress disorder), the concurrent use of each of the following substance classes: alcohol; cannabis; hallucinogens; inhalants; stimulants; opiates, pain killers, or heroin; sedatives, hypnotics, or anxiolytics; or poly-substances, within the past 12 months prior to admission, would serve as a moderator to NW severity (See Figure 4.1, B).

4.2 Methods

4.2.1 Design

This observational, retrospective study used longitudinal data to perform a secondary data analysis of patients' chart records from a regional psychiatric hospital in Kentucky. The original research, from which these data were obtained, examined NW symptoms and motivation to quit smoking after offering nicotine replacement therapy (NRT) at admission for newly admitted psychiatric inpatients.[57]

4.2.2 Sample and setting

Data for this analysis were derived from psychiatric hospital admission charts between January 1 and December 31, 2016. The psychiatric hospital is a tobacco-free, 239-bed state-owned institution in Kentucky, which provides tobacco treatment services consistent with evidence-based practices.[96,115] These services include assessing patients' tobacco use characteristics and readiness to quit, NW symptoms; and providing practical cessation counseling and U.S. Food and Drug Administration (FDA)-approved smoking cessation medication (i.e., NRT), as needed, during hospitalization. This tobacco treatment service is provided by a nurse certified in tobacco treatment. Data from all tobacco-using patients who had been assessed for NW by the tobacco treatment nurse, after at least 24 hours of admission, were included in the analyses. Data from patients who were unable to respond to the tobacco treatment nurse due to impaired cognitive ability (often related to the psychiatric illness for which they were admitted) or who refused to respond were excluded from the analyses.

4.2.3 Measures

4.2.3.1 Demographics and mental illness diagnosis

Information retrieved from medical records included age (in years), sex, ethnicity (White vs. non-White), and educational status (less than high school/special education vs. GED vs. Associate or higher degree). In addition, each patient's primary discharge diagnosis for this admission, hospitalization period (in days), time till assessment for NW (in days) after admission, and the number of lifetime prior hospitalizations to that facility were obtained. Patients' primary discharge diagnoses, which were based on the ICD-10 criteria,[116] were categorized into psychotic (e.g., schizophrenia, schizoaffective disorder, psychosis not otherwise specified) vs. mood or anxiety (e.g., major depressive disorder, bipolar disorder, generalized anxiety disorder, mood disorder not otherwise specified) vs. substance use (e.g., substance-induced mood or psychotic disorder, alcohol use, cocaine use, opiate use, etc.) vs. other (i.e., personality/malingering, cognitive/traumatic brain injury, adjustment disorders, or altered mental status not otherwise specified) disorders. We adopted this categorization of psychiatric disorders because patients with mood or anxiety disorders were found to be best conceived as subfactors for a higher-order factor (i.e., internalizing disorders), and patients with psychotic and substance use disorders have been categorized separately in the literature.[19,101,117]

4.2.3.2 Tobacco use characteristics

Data on type of tobacco use (cigarettes vs. non-cigarettes) and timing of receiving NRT during hospitalization (i.e., not given vs. at admission vs. on the unit) were retrieved from patients' charts. Due to the poly-tobacco products used by patients (i.e., cigarettes,

chew tobacco, electronic cigarettes, cigars, and pipes), cigarette-equivalents per day (CePDs) were calculated; i.e., four cigarettes were deemed equivalent for every cigar, 20 cigarettes was conservatively imputed for one electronic cigarette used per day, and 2.5 packs of cigarettes were equivalent to one can/tin of moist tobacco per day.[81,100]

4.2.3.3 Substance use classes

Self-reported substances used by patients in the 12 months prior to admission were categorized into the following classes: alcohol; cannabis – including synthetic cannabinoids (also known as spice);[118] hallucinogens – including lysergic acid diethylamide (LSD), phencyclidine (PCP), ecstasy, and psilocybin mushroom; inhalants – including gasoline, glue, paint, and butane; stimulants – including cocaine, methamphetamines, Adderall, and synthetic cathinones (also known as bath salts);[119] sedatives, hypnotics, or anxiolytics – including barbiturates, antihistamines, and benzodiazepines; and opiates – conventionally including pain killers and heroin. This categorization of drugs classes was adopted from the DSM-V classification of substance-related and addictive disorders.[12] In addition, patients were grouped in terms of any substance use and poly-substance use (defined as the use of more than one drug regardless of class) over the past year prior to admission.

4.2.3.4 NW and NW syndrome

The Minnesota Tobacco Withdrawal Scale (MTWS) is a self-report questionnaire consisting of 8 items, based on the *Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition, Text Revision,* (DSM-IV-TR) criteria for the diagnosis of NW (i.e., dysmorphic/depressed mood, insomnia, irritability/frustration/anger, anxiety,

difficulty concentrating, restlessness, increased appetite/weight gain), in addition to craving – excluding the sign of decreased heart rate.[13,83] Each of the eight items represents a specific symptom of the NW syndrome, scored from 0 (no symptoms) to 4 (severe symptoms), with a summative total score ranging between 0 and 32. The MTWS has demonstrated adequate internal consistency (alpha=0.77) in previous studies.[92,93] Of note, the DSM-IV-TR indicates that four or more of the aforementioned symptoms are required for a NW syndrome diagnosis.[13]

4.2.4 Data analysis

During the time-frame of this evaluation, chart data indicated that 1,702 patients were tobacco users. Of the total number of patients admitted during this time (N = 2751), 115 (4.2%) refused to be assessed for NW; and 1,231 (44.7%) were not assessed because of the severity of their psychiatric symptoms, were not available for assessment when the tobacco treatment nurse attempted to visit them, or stayed in the hospital for fewer than 3 days. Moreover, 101 of those assessed were repeated visits in the same year and were excluded from the analysis to prevent potential confounding from prior assessments. Hence, the study sample consisted of 255 tobacco-using patient records with single admissions in the past 12 months, for whom the MTWS was completed.

Nominal and ordinal level variables were described using frequencies and percentages, while means (M) and standard deviations (SD) were used to describe ratio and interval level variables. Differences in sample demographics, history and treatment of substance use, type of tobacco product consumed, length of hospital stay, time until NW assessment, timing of receiving NRT, cigarette-equivalents per day (referred to in

this paper as CePDs), number of prior hospitalizations, and the MTWS scores were examined by MI diagnosis categories using Chi-square for nominal and ordinal level variables, and Analysis of Variance (ANOVA) with Levene's test of homogeneity of variances (or Kruskal-Wallis test as appropriate) for interval and ratio level variables. In addition, differences in proportions of use for each of the substance use classes across MI diagnoses were examined using Chi-square.

The PROCESS macro for SPSS[120] was used to assess the moderation effect for each substance use class (categorical moderators: having used each substance use class within the 12 month prior to admission vs. not) separately with each of the independent variables ('psychotic disorder' compared to all other patients; and 'mood or anxiety disorder' compared to all other patients). Moreover, throughout the moderation analyses, race, sex, CePD, and the timing of NRT administration were included as covariates due to their association with NW among patients with MI. Explicitly, among tobacco-using patients hospitalized with MI, those who are African American and female experience greater NW severity compared to their Caucasian and male counterparts.[18] In addition, the timing of NRT administration during hospitalization (not given vs. upon admission vs. on the unit) has been associated with varying experiences of NW in this population.[57] Finally, the amount of nicotine consumed per day can affect the NW experience.[103,104] The alpha level was .05 for all inferential testing and the IBM SPSS statistical package software (v. 24) was used for all calculations.

4.3 Results

4.3.1 Sample characteristics

The study sample (*N* = 255) primarily consisted of White adults (89%) who had at least a GED degree or higher level of education (72%) and were cigarette smokers (89%) with a mean score of 3.2 (*SD* = 4.2) on the MTWS. Ninety-eight patients (38.4%) had psychotic disorders and 81 patients (31.7%) had mood or anxiety disorders. Participants reported a relatively high CePD (M = 23.7, SD = 16.7), and a most received NRT during their hospitalization (82%). In addition, almost half the sample used cannabis (49%) and roughly one third used either alcohol, stimulants, opiates, or sedatives. More than half were poly-substance users, with more than two-thirds reporting the use of any type of substances. Notably, only 29% of patients reported receiving substance use treatment in the past. Based on the MI diagnosis categories, patients had significant differences in the level of their education, χ^2 (6, N = 255) = 13, p = .043, hospitalization duration in days, χ^2 (3, N = 255) = 45.8, p < .001, number of prior hospitalizations, χ^2 (3, N = 255) = 16.8, p = .001, time til NW was assessed after admission, χ^2 (3, N = 255) = 11.8, p = .008, having received substance use treatment in the past, χ^2 (3, N = 248) = 14, p = .003, and their MTWS scores, F (3, 251) = 1.8, p = .015. In terms of substance use per class, significant differences across MI diagnoses were found in terms of hallucinogens use, Likelihood Ratio test statistic χ^2 (3, N = 203) = 15, p = .003, stimulants use χ^2 (3, N = 203) = 23, p <.001, opiates use χ^2 (3, N = 204) = 36, p < .001, sedatives use χ^2 (3, N = 203) = 15, p = .002, poly-substance use χ^2 (3, N = 202) = 21, p < .001, and any substances use, χ^2 (3, N = 202) = 16, p = .001. No other significant differences in demographics or clinical variables were observed (see Table 4.1).

4.3.2 Psychotic disorders and NW

Significant interaction effects on NW severity were found between having a psychotic disorder and the concurrent use of the following substance classes: hallucinogens (p = .002), inhalants, (p = .036), opiates, (p = .05), sedatives, hypnotics, and anxiolytics (p < .001), stimulants (p = .012), and poly-substance use (p = .024) (see Table 4.2). Specifically, among patients with psychotic disorders compared to patients without, simple slopes analyses revealed significant negative relationships with NW severity when the use of each of the following substances was reported: hallucinogens, b = -1.09, 95% CI [-1.73, -.44], t = -3.32, p = .001; inhalants, b = -1.10, 95% CI [-1.97, -.23], t = -2.50, p = .013; opiates, b = -.62, 95% CI [-1.16, -.09], t = -2.29, p = .023; sedatives, hypnotics, and anxiolytics, b = -1.13, 95% CI [-1.56, -.70], t = -5.14, p < .001; stimulants, b = -.71, 95% CI [-1.22, -.20], t = -2.77, p = .006; and poly-substance use, b = -.43, 95% CI [-.80, -.06], t = -2.30, p = .022 (see Table 4.3 and Figure 4.2). This indicates that the use of any of these substances was associated with lower severity in NW symptoms. No significant moderation effect on NW was found between having a psychotic disorders and alcohol or cannabis use.

4.3.3 Mood or anxiety disorders and NW

Significant interaction effects on NW severity were found between having a mood or anxiety disorder and the concurrent use of hallucinogens (p = .021), and sedatives, hypnotics, and anxiolytics (p = .022) (see Table 4.4). Specifically, among patients with mood or anxiety disorders, compared to patients without, simple slopes analyses revealed a significant positive relationship on NW severity when hallucinogens, b = .83, 95% CI

[.23, 1.43], $t = 2.74$, $p = .007$, and sedatives, hypnotics, and anxiolytics use, $b = .61$, 95% CI [.11, 1.11], $t = 2.40$, $p = .017$, were reported (see Table 4.5 and Figure 4.3). This indicates that the use of any of these substances was associated with greater severity in NW symptoms. No significant moderation effect on NW was found between having a mood or anxiety disorders and alcohol, cannabis, inhalants, stimulants, opiates, or poly-substance use.

4.4 Discussion

The purpose of this study was to examine the nature of the relationship between the co-occurring use of different classes of substances on NW severity among inpatient tobacco users with psychotic or mood or anxiety disorders diagnoses. Among patients with psychotic disorders, as compared to patients without, there was significantly lower NW severity among those who reported past 12-month use of hallucinogens; inhalants; opiates; sedatives, hypnotics, and anxiolytics; stimulants; or poly-substance use. On the other hand, patients with mood or anxiety disorders, compared to patients without, reported significantly higher NW severity when they reported past 12-month use of hallucinogens or sedatives, hypnotics, and anxiolytics.

Previous research has reported differences in the NW experience among people with and without MI. Smith, Homish, Giovino, and Kozlowski (2014)[19] conducted a secondary analysis of data on a nationally-representative sample of more than 43,000 civilian, non-institutionalized adults in the U.S., which were collected using face-to-face computer-assisted interviews. Researchers found that people with both psychotic disorders and mood or anxiety disorders were more likely to experience higher NW

symptoms severity compared to the general public. These findings, however, do not necessarily contradict ours (i.e., patients with psychotic disorders, may experience lower NW severities, considering substance use profiles) in light of differences in samples' characteristics. For instance, Smith et al. (2014)[19] designated community-dwelling people without MI as a comparison group of reference for NW severity, compared to hospitalized patients with other MI diagnoses in our sample. In addition, substance use profiles across MI groups in Smith et al. (2014)'s[19] study were not accounted for in their analyses. Nonetheless, it is worth mentioning that researchers found that patients with past year alcohol use and drug use disorders had the lowest relative risk of having more severe NW, in comparison to patients with psychotic and mood or anxiety disorders.[19]

We found that patients with mood or anxiety disorders may demonstrate higher NW severities when hallucinogens or sedatives, hypnotics, and anxiolytics use was reported. Similarly, in a sample of 8,213 community-dwelling current smokers, Weinberger, Desai, and McKee (2010)[55] found that participants with mood, anxiety, alcohol, or substance use disorders were more likely to have greater NW symptoms, with an increased likelihood for withdrawal-related discomfort and relapse, compared to people without these conditions. However, researchers also found no interaction effect on NW severity between having current mood or anxiety diagnoses and the co-morbidity of alcohol or substance use disorder.[55] Again, the resulting discrepancy in the interaction effect between substance use and MI on NW severity between ours and Weinberger et al. (2010)'s[55] study can be attributed to using different reference groups for comparison, with dissimilar MI conditions. Explicitly, psychiatric hospitalization for patients with MI

is indicative of greater influence of MI on functioning and general wellbeing of the individual, compared to community-dwelling people with MI.

In addition, different interaction outcomes between substance use and MI on NW can also be attributed to varying substance use profiles of the comparison groups used as reference (i.e., community-dwelling people with substance use problems vs. patients with MI and co-morbid substance use). For instance, while the lifetime prevalence rates of substance use among patients with a diagnosed MI and the general public are both considerably high, 36-58% and up to 83%, respectively,[29,31,121,122] only 12-20% of people in the community with MI and substance dependence used mental health services, compared to up to 50% among patients with severe MI and substance dependence.[123,124] Significant differences in the utilization of mental health services have also been recognized across patients with MI diagnosis, based on their substance use profiles. Specifically, among patients with psychotic, mood, or anxiety disorders who required psychiatric hospitalization during the course of their MI, an overall significantly higher annual contact with outpatient clinics, emergency departments, and days of hospitalization were observed among those with concurrent substance use disorders.[32] Moreover, a higher percentage of patients with MI and co-morbid substance use disorders were found utilizing specialty tertiary inpatient mental health programs, in comparison to utilizing specialty outpatient and community mental health services.[125] This inconsistency in utilizing mental health services among people with and without MI, who also have substance use problems, can be perceived as an indicator of the severity of the underlying substance use problem in patients with MI. Such underlying severity may potentially

explain NW experience during psychiatric hospital stays compared to NW experienced among people with MI and substance use problems in the community setting.

In a study examining NW severity correlates among patients with MI during psychiatric hospitalization, who also received NRT during their hospital stay (70%), Soyster, Anzai, and Prochaska (2016)[18] found that NW severity was positively associated with alcohol and drugs use. However, around only 25% of their sample had psychotic disorders, while patients with mood disorders constituted 60% of their sample. While Soyster et al. (2016)[18] did not assess NW severity by MI diagnoses or specified substance use classes in their sample, their results are comparable to our finding of higher NW among patients with mood or anxiety disorders.[18]

Positive symptoms found in patients with psychotic disorders have been linked to hyperactivity in the dopaminergic cerebral mesolimbic neural pathway.[126,127] Nicotine exposure is also believed to increase the firing of dopamine neurons in the mesolimbic tract.[128] On the other hand, NW is associated with decreased levels of dopamine in the nucleus accumbens (i.e., mesolimbic tract).[128-130] One possible interpretation of the lower severities in NW observed among patients with psychotic disorders in our study is the associated, either direct or indirect, increased activity in different dopaminergic neuronal pathways coupled with hallucinogens; inhalants; opiates; sedatives, hypnotics, and anxiolytics; stimulants; or poly-substances use.[131-137] Moreover, non-adherence to antipsychotic medications is common in this patient group, especially when accompanied with substance use.[138,139] This non-adherence to antipsychotics is associated with rebound activation of the dopaminergic response, leading to increased effects of dopamine,[140] and

potentially to fewer NW symptoms. But these findings are speculative at best and require further investigation.

Patients with mood or anxiety disorders are characterized by having decreased levels of serotonin, among others, from the brain stem.[141,142] Nicotine exposure has been linked to elevated levels of serotonin among both, smokers and nonsmokers.[143] Alternatively, NW is believed to decrease serotonin release in the forebrain and limbic system.[130,144] A possible rationale of the higher NW severity found among mood or anxiety disorder patients reporting sedative, hypnotic, and anxiolytic use in our sample is that these drugs work on further decreasing serotonin levels in the brain.[145,146] Hallucinogen use, on the other hand, is associated with increased levels of serotonin in the brain.[131,147] However, antipsychotic use, which is common among patients with mood or anxiety disorders, is linked to reversing hallucinogen-induced increases in serotonin levels,[148] possibly leading to higher NW symptoms.

The interpretation of the results of the study reported here need to be considered in light of a number of limitations. Approximately 35% and 62% of patients with psychotic and mood or anxiety disorders, respectively, were poly-substance users. Further, approximately 50% within each MI diagnoses category used either alcohol or cannabis. Drug-drug overlap and effect on NW for each substance use category was not analyzed in this study. Also, due to a lack of data from the parent study, the impact of treatment of substance use withdrawal could not be assessed. Furthermore, duration and frequency of substance use class data was not available in the dataset. Importantly, treatment for and last dose of the used substance prior to hospitalization was also unavailable. Moreover, the similarity of NW symptoms with signs and symptoms of MI

and antipsychotic side effects may have affected the NW scores; thus, longitudinal research on NW in this population is warranted, along with the effects of the sensitivity of NW across different MI diagnoses. The generalizability of our results is affected by the fact that our sample constituted only 24% of the total tobacco users admitted to the psychiatric facility over one year. The remaining majority of eligible patients were either unable to respond due to psychiatric symptoms severity, being hospitalized for a short duration of time, or refusing to be assessed for NW. Finally, since multiple comparisons were performed for each independent variable from the same dataset, there was a risk for inflating type 1 error. When Bonferroni corrections were applied for each independent variable tested, the new p – value was set at .00625 (i.e., .05 divided by the 8 substance use classes for each independent variable). Accordingly, the only significant interaction effects on NW severity were found among patients with psychotic disorders who used hallucinogens or sedatives, hypnotics, or anxiolytics.

4.5 Conclusion

Notwithstanding the inherent limitations in this secondary data analysis, we found that concurrent substance use among patients with psychotic and mood or anxiety disorders resulted in varying NW experiences. Moreover, the findings provide insight on the vulnerability to NW among patients with substance use admitted to psychiatric institutions. Hence, an emphasis on early detection of NW after psychiatric admission, particularly among tobacco-using patients with substance use disorders, is warranted. Future research is needed to examine the longitudinal trajectory of NW symptoms during hospitalization for different substance use classes across different MI diagnoses. Such studies can provide important directions for tailoring tobacco dependence treatment

among psychiatric inpatients to curb the disproportionate tobacco-related disease burden and mortality in this population.

Table 4.1 Differences in Sample Characteristics by Primary Psychiatric Diagnosis Categories at Discharge

Variable	Mean ± SD, Median [25th percentile, 75th percentile], or N (%)					
	Total sample (*N* = 255)	**Psychotic disorders (*n* = 98)**	**Mood or anxiety disorders (*n* = 81)**	**Substance use disorders (*n* = 40)**	**Other disorders[9] (*n* = 36)**	***p*-Value**
Age (in years)[§]	41 [31, 54]	46 [33, 54]	38 [31, 53]	36 [27, 49]	48 [28, 60]	.06
Gender						.363
Males	142 (56)	60 (61)	39 (48)	22 (55)	21 (58)	
Females	113 (44)	38 (39)	42 (52)	18 (45)	15 (42)	
Ethnicity						.093
White	228 (89)	82 (84)	76 (94)	38 (95)	32 (89)	
Non-White	27 (11)	16 (16)	5(6)	2 (5)	4 (11)	
Education						.043*
Less than high school	70 (26)	26 (27)	15 (19)	14 (35)	15 (42)	
GED	82 (32)	26 (27)	30 (37)	16 (40)	10 (28)	
Associate or higher degree	103 (40)	46 (47)	36 (44)	10 (25)	11 (31)	
Hospitalization period (in days) [§]	8 [5, 15]	13 [8, 24]	6 [4, 10]	6 [4, 7]	9 [5, 18]	<.001*
Number of prior hospitalizations[§]	1.4 ± 3.5	2.2 ± 4.4	1.2 ± 2.9	0.6 ± 2.9	0.5 ± 1.1	.001*
Tobacco use type						.974
Cigarettes	228 (89)	88 (89)	73 (90)	35 (88)	32 (89)	
Non-cigarettes	27 (11)	10 (10)	8 (10)	5 (13)	4 (11)	
Cigarettes equivalent per day (CePD)	23.7 ± 16.7	22.5 ± 14.6	23.9 ± 19.5	26.6 ± 16.9	23.2 ± 14.7	.613
Time till NW assessment[§]	3 [2, 6]	4 [2, 9]	2 [1, 5]	3 [2, 5]	3 [2, 6]	.008*
Receiving NRT						
Not given	48 (19)	26 (27)	10 (12)	5 (13)	7 (19)	.069
At admission	175 (69)	62 (63)	60 (74)	26 (65)	27 (75)	.341
On the unit	32 (13)	10 (10)	11 (14)	9 (23)	2 (6)	.123
Substance use class						
Alcohol[ǀǀ]	86 (42.4)	27 (39)	31 (48)	14 (38)	14 (45)	.664
Cannabis[ǀ]	99 (49)	33 (47)	33 (51)	21 (55)	12 (39)	.558
Hallucinogens[ǀǀ]	22 (11)	3 (4)	8 (12)	10 (27)	1 (3)	.003*.◆
Inhalants[ǀǀǀ]	6 (3)	2 (3)	3 (5)	1 (3)	0 (0)	.493◆
Stimulants[ǀǀ]	60 (30)	9 (13)	20 (31)	21 (57)	10 (32)	<.001*
Opiates – including pain killers and heroin[ǀ]	64 (31)	8 (11)	26 (39)	24 (65)	6 (19)	<.001*
Sedatives, hypnotics, and anxiolytics[ǀǀ]	55 (27)	12 (17)	22 (34)	17 (46)	4 (13)	.002*
Poly-substance Use [ǀǀǀ]						<.001*
Yes	107 (53)	24 (35)	40 (62)	29 (78)	14 (45)	
Any substances use [ǀǀǀ]						.001*
Yes	153 (76)	44 (64)	52 (80)	36 (97)	21 (68)	
Substance use treatment[‡]						.003*
Yes	73 (29)	26 (28)	23 (29)	20 (50)	4 (11)	
MTWS scores	3.2 ± 4.2	2.4 ± 3.6	3.9 ± 4.7	4.1 ± 4.8	3.0 ± 4.3	.015*

[ǀ] 51 missing cases.
[ǀǀ] 52 missing cases.
[ǀǀǀ] 53 missing cases.
◆ Pertinent to the Likelihood Ratio *p* – value.

[‡] Seven missing cases.
* Significant at $\alpha = 0.05$.
[§] Analyzed using Kruskal-Wallis test.
NRT: Nicotine Replacement Therapy.
MTWS: Minnesota Tobacco Withdrawal Scale.
[ϑ] Includes personality/malingering, cognitive/traumatic brain injury, adjustment disorders, or altered mental status (not otherwise specified) disorders.

Table 4.2 Parameters of Significant Interaction Terms for Separate Regression Models Examining the Interaction of Psychotic Disorder Status and Different Substance Use Classes on NW

Substance use class used in the moderation analysis model	Interaction term coefficient	*t* – value	95% CI	*p* – value of interaction term	R^2 of the model	*p* – value of the model
Hallucinogens	-1.04	-3.01	-1.72, -.36	.002	.125	< .001
Inhalants	-.96	-2.11	-1.87, -.06	.036	.117	< .001
Opiates	-.57	-1.94	-1.18, .00	.05	.106	< .001
Sedatives, Hypnotics, and Anxiolytics	-1.27	-4.99	-1.77, -.77	< .001	.178	< .001
Stimulants	-.74	-2.55	-1.30, -.17	.012	.121	< .001
Poly-substance use	-.55	-2.27	-1.03, -.07	.024	.124	< .001

Note: Dependent variable for all models was NW severity. Covariates included in all models: psychotics disorder diagnosis vs. not; substance use class (yes vs. no); race (white vs. non-White); sex, CePD; timing of NRT administration; and interaction term of specific substance use class by psychotic disorder diagnosis.

Table 4.3 Substance Use Moderators of The Relationship Between Psychotic Disorder Status and NW

Substance Use Class	*b*	Standard Error (S.E.)	*t*	95% Confidence Interval (CI)	*p* - Value
Hallucinogens Use					
Reported	-1.09	.33	-3.32	-1.73, -0.44	.001*
Not Reported	-0.047	.12	-0.38	-0.29, 0.20	.707
Inhalants Use					
Reported	-1.10	.44	-2.50	-1.97, -0.23	.013*
Not Reported	-0.14	.12	-1.17	-0.37, 0.10	.244
Opiates Use					
Reported	-0.62	.27	-2.29	-1.16, -0.09	.023*
Not Reported	-0.04	.14	-0.28	-0.31, 0.23	.784
Sedatives, Hypnotics, and anxiolytics					
Reported	-1.13	.22	-5.14	-1.56, -0.70	< .001*
Not Reported	0.14	.13	1.10	-0.11, 0.39	.275
Stimulants Use					
Reported	-0.71	.26	-2.77	-1.22, -0.20	.006*
Not Reported	0.02	.13	0.17	-0.24, 0.29	.866
Poly-substance Use					
Reported	-0.43	.19	-2.30	-0.80, -0.06	.022*
Not Reported	0.16	.15	0.75	-0.19, 0.42	.454

Note: all analyses controlled for sex, race, CePD, and timing of NRT administration. * Significant at α equals 0.05.

Table 4.4 Parameters of Significant Interaction Terms for Separate Regression Models Examining the Interaction of Mood or Anxiety Disorder Status and Different Substance Use Classes on NW

Substance use class used in the moderation analysis model	Interaction term coefficient	*t* – value	95% CI	*p* – value of interaction term	R^2 of the model	*p* – value of the model
Hallucinogens	.77	2.32	.12, 1.42	.021	.128	< .001
Sedatives, Hypnotics, and Anxiolytics	.66	2.30	.01, 1.23	.022	.125	< .001

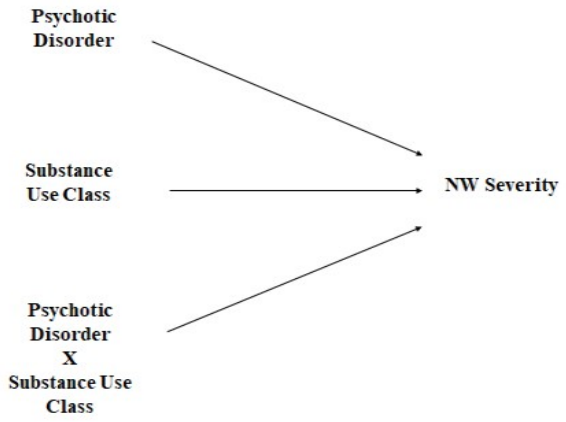
Note: Dependent variable for all models was NW severity. Covariates included in all models: psychotics disorder diagnosis vs. not; substance use class (yes vs. no); race (white vs. non-White); sex, CePD; timing of NRT administration; and interaction term of specific substance use class by Mood or Anxiety disorder diagnosis.

Table 4.5 Substance Use Moderators of the Relationship Between Mood or Anxiety Disorder Status and NW

Substance Use Class	*b*	Standard Error (S.E.)	*t*	95% Confidence Interval (CI)	*p* - Value
Hallucinogens Use					
Reported	0.83	.30	2.74	0.23, 1.43	.007*
Not Reported	0.61	.13	0.46	-0.20, 0.31	.648
Sedatives, Hypnotics, and anxiolytics					
Reported	0.61	.25	2.40	0.11, 1.11	.017*
Not Reported	-0.05	.13	-0.41	-0.32, 0.21	.684

Note: all analyses controlled for sex, race, CePD, and timing of NRT administration. * Significant at α equals 0.05.

A. Hypothesis 1



B. Hypothesis 2

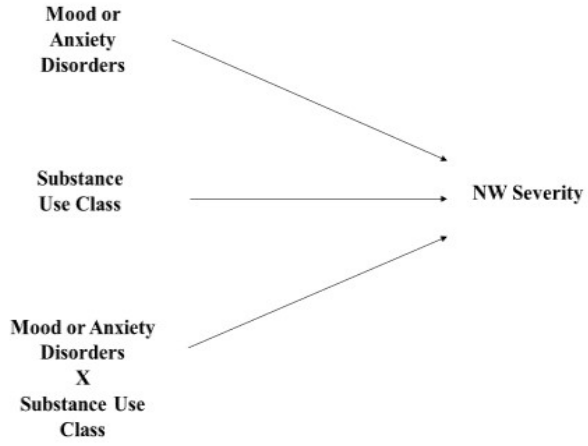


Figure 4.1 Moderation analyses models for hypotheses 1 and 2. Substance use classes include: alcohol; cannabis; hallucinogens; inhalants; stimulants; opiates – including pain killers and heroin; sedatives, hypnotics, and anxiolytics; and poly-substance use. note: a series of separate moderation models were rendered for each substance use class.

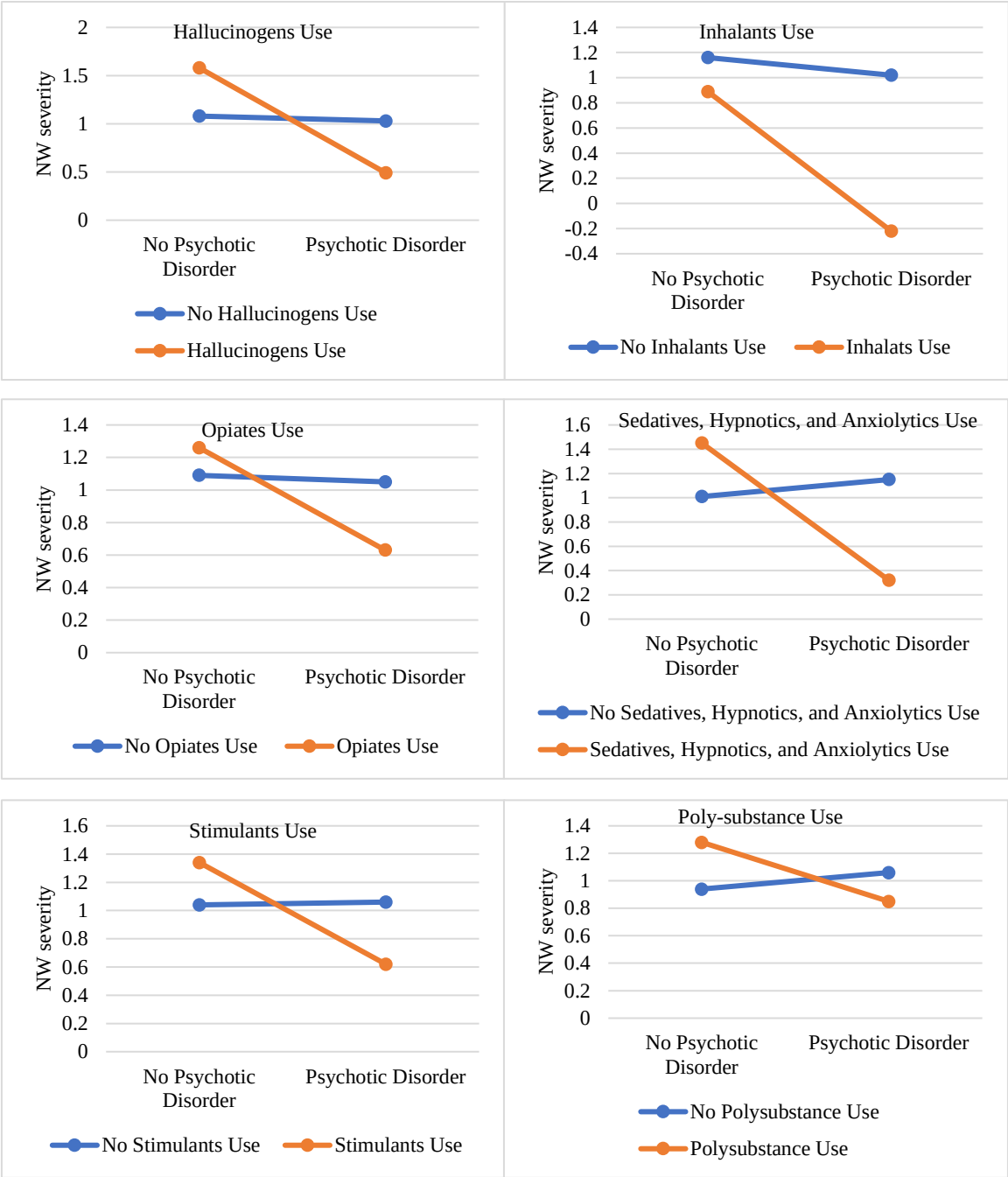


Figure 4.2 Simple Slopes Analyses of Different Substance Use Classes for Patients with Psychotic Disorders.

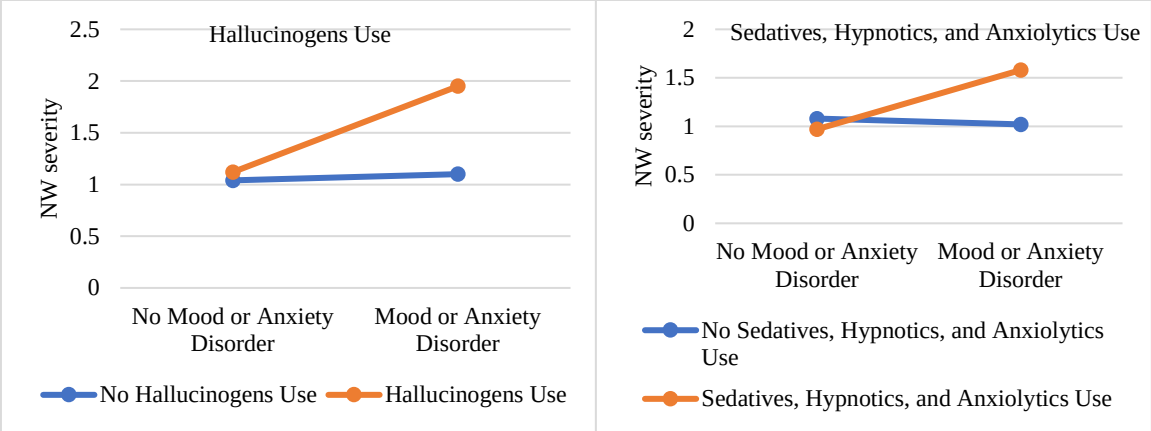


Figure 4.3 Simple Slopes Analyses of Different Substance Use Classes for Patients with Mood or Anxiety Disorder.

CHAPTER 5. SUMMARY

5.1 Background and Purpose

The primary goal of this dissertation is to enhance understanding of nicotine withdrawal (NW) among tobacco users with mental illness (MI). A significant proportion of tobacco users with MI experience NW,[18] which is linked to lowering the likelihood of their successful quit attempts;[11,19] and further predisposing them to health and economic adversities, and maintaining high mortality tobacco-related rates.[1,8,9] Since NW is experienced in greater intensity among people with MI,[19] this unique feature of NW relative to those with MI may also serve as a contributing factor for the staggering gap in the proportion of tobacco use between those with- and without MI.[37,38]

Three manuscripts are introduced in this dissertation: 1) a systematic review of the research literature published from 2008 to 2019, to synthesize and summarize factors associated with NW among tobacco users with MI; 2) a psychometric properties evaluation of the Minnesota Tobacco Withdrawal Scale (MTWS) in a sample of tobacco users with MI; and 3) an observational, retrospective study of longitudinal data using moderation analysis to examine the nature of the relationships between psychiatric diagnoses and substances of abuse with NW severity among psychiatric inpatients.

Quitting tobacco use is associated with lowering the likelihood of being discharged against medical advice among hospitalized psychiatric patients, reporting better quality of life, and reducing anxiety, depression, and stress levels compared to those who sustain tobacco use.[9-11] Quitting tobacco use is hindered by relapse, which is associated with NW.[42-48] This chapter summarizes the findings from each manuscript in

this dissertation and how these findings may help guide clinical practice, promote policy development, and steer future research.

5.2 Summary of findings

Chapter 2 in this dissertation presented a systematic review of the literature. Fifteen articles published from 2008 to 2019 studying NW among tobacco users with MI as a primary or a secondary outcome measure were identified. The identified articles employed experimental and non-experimental designs, and they summarized the correlates of NW experienced by tobacco users with MI. These correlates include: MI diagnoses of psychotic and mood or anxiety disorders, higher severity of psychiatric symptoms, race (i.e., African Americans), sex (i.e., women), higher nicotine dependence, previous or concurrent drug and alcohol use, low confidence in one's ability to quit, pharmacological interventions to treat tobacco use (i.e., varenicline), high pre-quit anxiety and depression levels, and timing of offering and use of nicotine replacement therapy (NRT) during a tobacco-free psychiatric hospitalization (i.e., upon admission vs. later during hospitalization). These findings outline the importance of assessing the correlates of NW among tobacco users with MI. For example, research shows that people with psychotic disorders have higher odds of having NW compared to other psychiatric diagnoses.[19] This may suggest that tobacco treatment for tobacco users with psychotic disorders may need diagnostic-tailored approaches for minimizing NW. Also, these correlates discern a form of disparity in offering NRT during psychiatric hospitalization against African Americans.[18] The fact that African Americans are less likely to be offered NRT is critically important as we change standards of practice for tobacco treatment in psychiatric hospitals. Give what we know about NW and psychotic disorders, it would be

especially important to ensure access to NRT for African Americans with psychotic disorders to promote successful tobacco cessation outcomes.

Chapter 3 in this dissertation examined the psychometric properties of the MTWS in a sample of 255 patients admitted to a tobacco-free, state psychiatric facility in Kentucky. Reliability testing was conducted using the Cronbach's alpha, item-total, and inter-items correlation coefficients. Further, validity testing was examined using hypothesis testing and exploratory factor analysis. We hypothesized that higher number of cigarettes smoked per day were predictive of greater NW symptoms severity when measured using the MTWS. The reliability analysis yielded a Cronbach's alpha coefficient of 0.763, inter-item correlation coefficient of 0.393, and item-total correlations between 0.291 and 0.691. The overall Cronbach's alpha of the instrument did not decline below 0.698 when any of its items were deleted. A multivariate general linear regression was used to test the validity of the MTWS. The regression model showed that the number of cigarettes smoked per day increased NW symptoms severity, when measured using the MTWS, by 0.147 for each reported cigarette smoked per day, confirming the validity of using the MTWS in this population. Also, an exploratory factor analysis identified one factor with an eigenvalue of 3.920, which explained 49% of the total variance in the MTWS scores. Most of the MTWS's items loaded significantly on this factor with item loadings ranging between 0.452 and 0.835. Briefly, this manuscript concluded that the MTWS demonstrated reliable and valid psychometric properties for measuring NW among tobacco users with MI during a psychiatric tobacco-free hospitalization. This instrument is recommended for use in clinical psychiatric practice to identify NW in tobacco-using patients.

Chapter 4 examined whether co-occurring use of substances of certain classes moderate the relationship between psychiatric diagnosis and NW severity. The psychiatric diagnoses considered in this manuscript included psychotic disorders (yes/no) and mood or anxiety disorders (yes/no). The substance use classes that each served as a moderator included: alcohol; cannabis; hallucinogens; inhalants; stimulants; opiates, pain killers, or heroin; sedatives, hypnotics, or anxiolytics; or poly-substances. Throughout the moderation analyses, race, sex, cigarette-equivalents smoked per day, and the timing of NRT administration were included as covariates due to their association with NW among tobacco users with MI.[18,57,103,104]

Among study participants with psychotic disorders, as compared to those without, our moderation analyses revealed significantly lower NW severity among those who reported the past 12-month use of hallucinogens; inhalants; opiates; sedatives, hypnotics, and anxiolytics; stimulants; or poly-substance use. On the other hand, participants with mood or anxiety disorders diagnoses, compared to those without, reported significantly higher NW severity when reporting the past 12-month use of hallucinogens or sedatives, hypnotics, and anxiolytics. This manuscript indicated that, in addition to differences in NW among varying MI diagnoses,[19] NW experiences can vary within patients with the same MI diagnosis by different histories of substances used.

5.3 Contribution of dissertation

This dissertation contributes to research and practice in a number of ways. First, the findings identify a number of factors correlating to NW among tobacco users with MI. These findings can help clinicians identify tobacco users with MI who are at greater

risk for developing NW. Once these high-risk patients are identified, clinicians can plan and evaluate intervention strategies to minimize NW and promote tobacco abstinence. For example, a heavy smoker African American woman newly admitted to a tobacco-free psychiatric facility with a diagnosis schizophrenia is expected to experience high levels of NW. Second, this dissertation adds to the research literature that supports the use of the MTWS with tobacco users to assess NW during psychiatric tobacco-free hospitalization. This gives clinicians and researchers a reliable and valid assessment tool to guide actions that could alleviate or reverse these symptoms, leading to more successful cessation and lower chance of relapse. Last, this dissertation discovered significant differences in NW in tobacco users with the same MI diagnoses (i.e., psychotic and mood or anxiety disorders), based on the use of certain classes of substances. This finding provides support for tailoring tobacco treatment and relapse prevention based on particular patients with certain MI diagnoses, and also taking into consideration use of certain substances. For example, a tobacco-using patient with major depression disorder, who also abuses anxiolytics, may experience higher NW compared to another patient with major depressive disorder who does not.

5.4 Limitations

This dissertation has a number of limitations. The systematic review included experimental and non-experimental studies, with varying research designs, from various settings and with distinct participants' diagnoses and characteristics. This may have affected the generalizability of our conclusions. However, it is a strength that studies used different designs and methods with different populations and in different settings, providing a more robust understanding of the factors that impact NW in this high-risk

population. Chapters 3 and 4 involved secondary data analysis from a parent study which adopted a cross-sectional research design using a convenience sample.[57] That sample represented around one-quarter of the total number of tobacco-using patients admitted to a psychiatric hospital over a 1-year period.[57] Also, the majority of that sample received NRT during hospitalization, which may have resulted in lower than average NW scores during hospitalization. Thus, the studies using this data set may have been subject to selection bias, threatening internal validity. With regard to Chapter 4, an important limitation was repeated analyses from the same dataset and the fact that around one- to two-thirds of participants reported using more than one substance use class (i.e., overlap of use across classes), with around 50% of participants within each MI category using either alcohol or cannabis. This may have limited the isolated effect of a specific substance use class on NW.

5.5 Recommendations for future research

We recommend that nurses and researchers offer and evaluate the impacts of offering NRT as part of evidence-based tobacco treatment services during psychiatric hospitalization to reduce disparities in tobacco use. Research is needed to study whether reducing depression and anxiety levels before embarking on a quit attempt would lead to different tobacco abstinence outcomes among the MI population. Future research needs to examine the efficacy of different instruments in measuring NW over an extended period of psychiatric hospitalization. Finally, research to understand the longitudinal trajectory of NW symptoms during hospitalization for patients who use different classes of substances with different MI diagnoses is needed.

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VITA

Yazan Daher Al-Mrayat

Education

Institution	Degree	Date Conferred	Field of Study
Hashemite University, Jordan	MSN	May 2014	Nursing
Mutah University, Jordan	BSN	February 2007	Nursing

Professional Experiences

Date	Institution and Location	Position
December 2019 – Present	University of Kentucky Healthcare – Good Samaritan Hospital, USA	Registered Nurse
February 2017 – December 2019	University of Kentucky, USA	Graduate Research Assistant, College of Nursing
September 2008 – July 2016	King Abdullah University Hospital, Jordan	Registered Nurse, Medical Intensive Care Unit
July 2007 – August 2008	King Abdullah University Hospital, Jordan	Registered Nurse, Surgery Ward

Awards

October 19, 2015 Sponsorship for a doctorate education in Nursing – Mutah University, Jordan.

October 10, 2018 Travel award by the College of Nursing, University of Kentucky ($1,148) to attend the 32nd Annual APNA conference of the American Psychiatric Nurses Association in Columbus, Ohio.

March 22, 2019 Best poster presentation at the annual American Psychiatric Nurses Association – Kentucky Chapter conference, Louisville, Kentucky.

April 15, 2019 Travel award by the Delta Psi – At Large Chapter of the Sigma Theta Tau International ($1,200) to attend the National Conference on Tobacco or Health (NCTOH) held in Minneapolis, Minnesota August 27-29, 2019.

August 26, 2019 The Katherine Tenore Girone Scholarship Fund Award ($500).

January 15, 2020 The Katherine Tenore Girone Scholarship Fund Award ($500).

Professional Publications

Abstracts

Al-Mrayat, Y., *Okoli, C.T.C., (2017, March). Changes in Tobacco Treatment After Introducing A Service in A State Psychiatric Facility. American Psychiatric Nurses Association, Kentucky Chapter, Lexington, KY, U.S.A (Poster).**

Al-Mrayat, Y., *Okoli, C.T.C., (2018, October). The Effect of Substance Use History on Nicotine Withdrawal Severity During Psychiatric Smoke-Free Hospitalization. The 28th Annual Nursing Research Papers Day, University of Kentucky, Lexington, KY, U.S.A (Poster).**

Al-Mrayat, Y., *Okoli, C.T.C., Shelton, C., Khara, M., (2018, October). A Retrospective Analysis of The Association Between Providing Nicotine Replacement Therapy at Admission and Motivation to Quit and Nicotine Withdrawal Symptoms During an Inpatient Psychiatric Hospitalization. The 32nd Annual American Psychiatric Nurses Association conference, Columbus, OH, U.S.A (Poster).**

Al-Mrayat, Y., *Okoli, C.T.C., (2019, March). Nicotine Withdrawal and Substance Use among Psychiatric Patients: A Retrospective Analysis. American Psychiatric Nurses Association, Kentucky Chapter, Louisville, KY, U.S.A (Poster).**

Al-Mrayat, Y., *Okoli, C.T.C., Studts, C., Rayens, M., Hahn, E., (2019, April). Psychological and Mental Illness correlates of Nicotine Withdrawal. The 14th Annual Center for Clinical and Translational Science conference & College of Nursing Scholarship Showcase, University of Kentucky, Lexington, KY, U.S.A (Poster).**

Williams, L., Gomez, M., Shelton, B., Mullet, T., ***Al-Mrayat, Y.***, *Studts, J., (2019, April) Kentucky-Community Cancer Awareness Research and Education (K-CARE): Community Engagement to Reach Disparate Populations in Western Kentucky. The 14th Annual Center for Clinical and Translational Science conference & College of Nursing Scholarship Showcase, University of Kentucky, Lexington, KY, U.S.A (Poster).**

Al-Mrayat, Y., *Okoli, C.T.C., (2019, June). Estimating Nicotine Consumption among Poly-Tobacco Users. Compassion: Research and Practice Initiatives Day (RAPID), Eastern State Hospital, Lexington, KY, U.S.A (Podium).*

Al-Mrayat, Y., *Okoli, C.T.C., Studts, C., Rayens, M., Hahn, E., (2019, August). The Psychometric Properties of the Minnesota Nicotine Withdrawal Scale Among Patients with Mental Illness. National Conference on Tobacco or Health (NCTOH), Minneapolis, MN, U.S.A (Poster).**

Al-Mrayat, Y., *(2019, Oct). The Psychometric Properties of The Minnesota Tobacco Withdrawal Scale, Delta Psi At-Large Evidence-Based Practice Presentations and Fall Meeting, Sigma Theta Tau International. Lexington, KY, U.S.A (Podium).*

***Al-Mrayat, Y.**, Okoli, C.T.C., Williams, L. (2019, Nov). Using Cigarette-Equivalents to Estimate Nicotine Consumption Among Poly Tobacco Users. American Public Health Association, Philadelphia, PA, U.S.A (Poster).**

*Daniels, L., Okoli, C.T.C., **Al-Mrayat, Y.**, Williams, L., (2019, Nov). Changes in tobacco treatment measures in a state psychiatric hospital in Kentucky: A forty-month trajectory. American Public Health Association, Philadelphia, PA, U.S.A (Poster).**

*Jones, D., Dungan, J., **Al-Mrayat, Y.**, Okoli, C.T.C (2020, March). A psychometric analysis of an organization-developed tool: The KVC Kentucky consumer and family member experience and satisfaction surveys. 33rd Research & Policy Conference on Child, Adolescent, and Young Adult Behavioral Health, Tampa, Florida http://www.cmhconference.com/ (conference canceled)*

*Peer reviewed.

Publications

Okoli, C. T., **Al-Mrayat, Y. D**., Shelton Jr, C. I., & Khara, M. (2018). A retrospective analysis of the association between providing nicotine replacement therapy at admission and motivation to quit and nicotine withdrawal symptoms during an inpatient psychiatric hospitalization. Addictive Behaviors(85), 131-138.

Okoli, C. T., **Al-Mrayat, Y. D.**, & Stead, B. (2018). Brief Report: The effect of implementing a tobacco treatment service on adherence to evidence-based practice in an inpatient state-owned psychiatric hospital. The American Journal on Addictions, 27(5), 368-371.

Al-Mrayat, Y. D., Okoli, C. T., Studts, C. R., Rayens, M. K., & Hahn, E. J. (2019). The Psychometric Properties of the Minnesota Tobacco Withdrawal Scale Among Patients with Mental Illness. Biological Research for Nursing, 1099800419895573.

Lovoria B. Williams, Brent J. Shelton, Maria L. Gomez, **Yazan D. Al-Mrayat**, Jamie L. Studts. (2020). Using Implementation Science to Disseminate a Lung Cancer Screening Education Intervention through Community Health Workers. Journal of Community Health (Under Review).

Williams, L.B., Gomez,M. L., Shelton, B. J., **Al-Mrayat, Y. D.**, Zuerner-Johnson, D. Studts, J. L. (2020). Community Partnership to Implement a Lung Cancer Screening Education Progam Through Community Health Workers. Progress in Community Health Partnerships: Research, Education and Action (under review).