Nicotine Withdrawal Symptoms and Utilization of Nicotine Replacement Therapy in Critically Ill Smokers

DISSERTATION

Presented in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy in the Graduate School of The Ohio State University

By
Carolyn Marie Carle, M.S.
Graduate Program in Nursing

The Ohio State University
2012

Dissertation Committee:
Professor Karen L. Ahijevych, Adviser
Professor Elizabeth R. Lenz
Professor Mary Ellen Wewers
Adjunct Assistant Professor Esther Chipps
Abstract

Cigarette smoking is an addictive behavior that contributes to the development of disease and subsequent mortality with more than 435,000 deaths attributable to smoking in the United States (U.S.) each year. Adult smoking prevalence in the U.S. is approximately 19.3%. This is much higher than the goal of $\leq 12\%$ established by the Healthy People 2020 initiative and is a concern when considering smoking related disease and associated health consequences.

Common diseases associated with cigarette smoking include lung cancer, chronic obstructive pulmonary disease, stroke, and coronary heart disease, all of which are associated with increased health care utilization and premature death. Severe exacerbations of these conditions trigger admissions to medical intensive care units. The unexpected disruption of cigarette smoking and nicotine intake in these patients may contribute to additional morbidity. Abrupt elimination of nicotine intake influences the development of nicotine withdrawal symptoms that may complicate recovery and prolong hospital stay.

The utilization of nicotine replacement therapy (NRT) in hospitalized smokers is a practice that decreases acute nicotine withdrawal symptoms, promotes smoking cessation after hospital discharge, and influences a positive recovery. However, many hospitals do not have specific policies regarding the use of NRT in critically ill smokers.
Provision of NRT to these patients is often at the discretion of the physician.

The characteristics of smokers admitted to intensive care settings and the use of NRT in this patient population has not been adequately explored. The purpose of this dissertation was to describe smokers admitted to an intensive care setting, explore their development of nicotine withdrawal symptoms (anxiety, agitation, cigarette craving), and to examine the relationships of these symptoms to delirium, ICU length of stay, and hospital length of stay. The use of NRT and relationship to symptoms was explored as well. Three manuscripts are presented in this dissertation document.

The assessment and treatment of unpleasant symptoms associated with nicotine withdrawal should be considered routine practice by intensive care nurses. The Theory of Unpleasant Symptoms (TOUS) provides a theoretical model that may facilitate this process. The first manuscript reviews the literature related to the TOUS. Based on this literature review, a preliminary model for unpleasant symptoms of nicotine withdrawal in critically ill smokers is proposed.

The second manuscript reports a description of the research design, study procedures, and results of the present pilot study with implications for future research. Nicotine withdrawal symptoms were evaluated in a sample of smokers admitted to an intensive care setting. Only one participant received NRT; therefore, the effects of NRT on withdrawal symptoms could not be examined. Relationships between influencing factors and symptoms as well as relationships among symptoms of nicotine withdrawal were explored.
The third manuscript reports recruitment outcomes of the present pilot study. Strategies to improve participation of critically ill patients in research are provided in this report. One hundred five critically ill smokers were screened for study participation and 10 critically ill smokers were determined to be eligible during a 20-month recruitment period. Eight critically ill smokers (80% of those eligible) were enrolled. The critical nature of patients admitted to the intensive care unit, unit characteristics, and medical center policies presented unique challenges to recruitment progress. This manuscript provides suggestions for consideration by researchers who are interested in recruiting critically ill patients for research studies.
Acknowledgments

This dissertation would not have been possible without the intellectual leadership and guidance of several individuals who have contributed and extended their valuable assistance in the preparation and completion of this study.

First and foremost, my sincerest gratitude is extended to my doctoral adviser, Dr. Karen Ahijevych, whose unwavering support, encouragement, patience, and belief in me has made the completion of this work possible. I would also like to thank Dr. Elizabeth Lenz and Dr. Mary Ellen Wewers as I have greatly benefitted from their expertise and guidance throughout my doctoral education. Special thanks is extended to Dr. Esther Chipps whose assistance in overcoming obstacles associated with this project allowed me to complete this dissertation research.

I would like to thank my husband, Kenneth Reed, for being steadfast in his patience, love, encouragement, and understanding throughout this endeavor. I would also like to acknowledge my parents, David and Clarice Carle, who taught me from a young age to believe in myself and that education can never be taken away from me. Finally, I would like to thank my miniature pinschers, Minnie and Midgie, for providing unconditional love and comic relief.

This research was supported by the Alumni Grant for Graduate Research and Scholarship.
Vita

2000..........................................................B.S.N., Mount Carmel College of Nursing
2003..........................................................M.S. Nursing, The Ohio State University
2000-2004 ..................................................Registered Nurse, Intensive Care Unit,

Doctors Hospital, Columbus, Ohio
2004-2005 ..................................................Registered Nurse, Emergency Department,

Riverside Methodist Hospital, Columbus, Ohio
2004-2007 ..................................................Graduate Teaching Associate, Department

of Nursing, The Ohio State University
2005-2006 ..................................................Nursing Education Coordinator, Doctors

Hospital, Columbus, Ohio
2006..........................................................Roadmap Training Program in Clinical

Research, T32 RR 023260-01, The Ohio

State University
2006-2008 ..................................................Clinical Research Nurse, Doctors Hospital,

Columbus, Ohio
2008-2009 ..................................................Graduate Research Associate, Department

of Nursing, The Ohio State University
vi
Publications


Fields of Study

Major Field: Nursing
Table of Contents

Abstract ........................................................................................................................................... ii

Acknowledgments ............................................................................................................................ v

Vita.................................................................................................................................................. vi

List of Tables ................................................................................................................................. xiii

List of Figures ............................................................................................................................... xiv

Chapter 1: The Theory of Unpleasant Symptoms: Theory Review and Application to Nicotine Withdrawal in Critically Ill Smokers ................................................................. 1

   Historical Development and Theory Origin .................................................................................. 2
   History of the TOUS .......................................................................................................................... 2
   Philosophical Origin of the TOUS ................................................................................................. 3

   Revolutionary Changes ................................................................................................................. 5

   Structural Elements of the Theory ............................................................................................... 6

   Concepts ....................................................................................................................................... 6
   Symptoms ....................................................................................................................................... 6
   Influencing Factors ......................................................................................................................... 7
   Performance .................................................................................................................................... 8

   Relational Elements of the Theory ............................................................................................... 8
Empirical Support for the TOUS .................................................................................................................. 9
Research Incorporating all TOUS Components .......................................................................................... 9
Incorporation of Influencing Factors and Symptoms ................................................................................. 13
Symptom Clusters ....................................................................................................................................... 17
Incorporation of Symptoms and Outcomes .................................................................................................. 19
Multidimensional Nature of Symptoms ...................................................................................................... 20
Summary ..................................................................................................................................................... 22
Application of the TOUS: Nicotine Withdrawal in Critically Ill Smokers ............................................... 22
Influencing Factor: Nicotine Dependence .................................................................................................. 23
Influencing Factor: Forced Abstinence ....................................................................................................... 23
Unpleasant Symptoms: Nicotine Withdrawal ............................................................................................... 24
  Anxiety ................................................................................................................................................... 25
  Agitation ................................................................................................................................................ 25
  Tobacco Craving .................................................................................................................................. 25
Cognitive Outcome: Delirium ..................................................................................................................... 26
Performance Outcome: Hospital Length of Stay ....................................................................................... 27
Nicotine Replacement Therapy ................................................................................................................ 27
Summary ..................................................................................................................................................... 27
References .................................................................................................................................................. 30
Chapter 2: Nicotine Withdrawal Symptoms and Utilization of Nicotine Replacement Therapy in Critically Ill Smokers

Review of the Literature

Theory of Unpleasant Symptoms

Influencing Factors

Nicotine Dependence

Smoking Abstinence

Unpleasant Symptoms: Nicotine Withdrawal

Anxiety

Agitation

Cigarette Craving

Performance Outcomes

Cognitive Outcome: Delirium

Secondary Outcome: Hospital Length of Stay

Nicotine Replacement Therapy

Purpose

Methods

Design

Sample and Setting

Measures
Anxiety........................................................................................................55
Cortisol Production..........................................................................................56
Agitation .............................................................................................................57
Cigarette Craving..............................................................................................57
Delirium ............................................................................................................58
Hospital Length of Stay ....................................................................................59
Cotinine ............................................................................................................59
Demographic and Clinical Variables ................................................................61
Procedure .........................................................................................................61
Data Analysis ....................................................................................................62
Results ..............................................................................................................62
Discussion .........................................................................................................66
Limitations .........................................................................................................69
Conclusion .........................................................................................................70
References .........................................................................................................71

Chapter 3: Research Challenges and Strategies to Improve Study Participation in
Critically Ill Patients ...........................................................................................89
Study Protocol ....................................................................................................91
Enrollment Progress ..........................................................................................94
Discussion .........................................................................................................95

xi
Patient Barriers to Recruitment..............................................................96
Unit Barriers to Recruitment..................................................................98
Organizational Barriers to Recruitment.............................................102
Summary ..............................................................................................103
Conclusion .........................................................................................105
References ..........................................................................................106
Bibliography .......................................................................................113
List of Tables

Table 2.1. Study Measures and Data Collection Time Points ............................................. 82
Table 2.2. Demographic and Clinical Characteristics of Study Participants ..................... 83
Table 2.3. Salivary Cortisol Mean Scores in µg/dL at Study Admission, Morning of Day 2, and Discharge ........................................................................................................... 84
Table 2.4. Collected and Missing Data for Cortisol and Cotinine Measures ................. 85
Table 2.5. Anxiety and Cigarette Craving Mean Scores at Study Admission, Morning of Day 2, and Discharge ........................................................................................................... 86
Table 2.6. Collected and Missing Data for Anxiety, Agitation, Cigarette Craving, and Delirium Measures ........................................................................................................... 87
Table 2.7. Kendall's tau Correlation Coefficients for Anxiety, Cigarette Craving, and Cortisol at 3 Study Time Points ........................................................................................................... 88
Table 3.1. Summary of Factors Impacting Study Progress ............................................. 109
Table 3.2. Demographic and Clinical Characteristics of Eligible and Enrolled Critically Ill Smokers ............................................................................................................................ 110
Table 3.3. Criteria on which Critically Ill Smokers were Excluded from Study Participation ........................................................................................................................ 111
Table 3.4. Barriers and Strategies to Improve Recruitment of Critically Ill Patients in Clinical Research ......................................................................................................................... 112
List of Figures

Figure 1.1. Illustration of the Original Theory of Unpleasant Symptoms ........................ 36
Figure 1.2. Illustration of the Updated Version of The Theory of Unpleasant Symptoms 37
Figure 1.3. The Theory of Unpleasant Symptoms as a Model for the Affects of Nicotine Replacement Therapy on Nicotine Withdrawal in Critically Ill Smokers ......................... 38
Figure 2.1. The Theory of Unpleasant Symptoms as a Model for the Affects of Nicotine Replacement Therapy on Nicotine Withdrawal in Critically Ill Smokers ......................... 81
Figure 3.1. Participant Recruitment and Enrollment Flow Chart ................................. 108
Chapter 1: The Theory of Unpleasant Symptoms:
Theory Review and Application to Nicotine Withdrawal in Critically Ill Smokers

The nicotine withdrawal symptom experience is one that may impact physiological and psychological morbidity in smokers admitted to intensive care settings and is an area that requires further investigation. Nicotine withdrawal produces a number of unpleasant symptoms, including anxiety, insomnia, irritability, restlessness/agitation, increased appetite, depressed mood, decreased heart rate, and difficulty concentrating (American Psychiatric Association, 1994). This syndrome has not been studied effectively in smokers admitted to intensive care, and the extent of these symptoms in this patient population is unknown. The occurrence of any of these symptoms in a hospitalized smoker may begin early in the treatment course and has the potential to compromise the therapeutic regimen and prolong hospital length of stay (Zack, 2001). Nicotine replacement therapy (NRT) utilization in hospitalized smokers is a practice that decreases acute nicotine withdrawal symptoms, promotes smoking abstinence after discharge, and influences a positive recovery (Rigotti, Munafo, & Stead, 2008; Fiore, et al., 2008); however, the provision of NRT or other interventions to smokers in intensive care settings has not been widely reported in the literature. Assessment and treatment of unpleasant symptoms associated with nicotine withdrawal should be considered routine practice by intensive care nurses, and the Theory of Unpleasant Symptoms (TOUS),
developed by Gift, Milligan, Pugh, and Lenz (Lenz & Pugh, 2003; 2008), provides a theoretical model that may facilitate this process.

To determine the appropriateness of the TOUS to guide nursing research and practice involving symptoms of nicotine withdrawal in intensive care patients, a critical analysis of the theory is presented. The historical development and origins of the theory will be discussed with respect to philosophy of science, it will be determined if the theory is revolutionary or evolutionary with respect to changes over time, and changes made to the theory will be identified. The meaning of the theory will be discussed with particular focus placed on theory concepts and relational elements. A synthesis of the research literature will then be presented to examine further the relational elements of the theory. Finally, the application of the TOUS to nursing research and practice involving nicotine withdrawal symptoms in critically ill smokers will be presented.

**Historical Development and Theory Origin**

**History of the TOUS**

The TOUS was presented in 1995 by nurse researchers (Gift, Milligan, Pugh, & Lenz) involved in research regarding dyspnea or fatigue experienced in select patient populations. Pugh and Milligan collaborated initially, as their research centered on fatigue during the different phases of the perinatal period (Lenz & Pugh, 2003). This work eventually produced a conceptual framework on fatigue during childbearing (Pugh & Milligan, 1993). Pugh then worked with Gift and together they developed a model of dyspnea and fatigue that incorporated components of the fatigue framework with Gift’s conceptualization of dyspnea (Gift & Pugh, 1993). Lenz, who was familiar with the work
of all three nurse researchers, began collaborating with them and together they developed a generic middle range theory that evolved into the first version of the TOUS (Lenz, Suppe, Gift, Pugh, & Milligan, 1995). Through continued group effort, the TOUS was refined and an updated version presented in 1997 (Lenz, Pugh, Milligan, Gift, & Suppe, 1997). The theory is considered a work in progress and efforts to improve and refine the theory are continually being made by the authors (Lenz & Pugh, 2008; Lenz, Gift, Pugh, & Milligan, 2013).

**Philosophical Origin of the TOUS**

The philosophical origin of the TOUS is contemporary empiricism or scientific realism. According to Schumacher and Gortner (1999), scientific realism allows for affirmation of subjective client states and evaluation of data that are not observable, as well as those which are observable, where it is thought that unobservable processes often contribute to the overt expression of observable phenomenon. Other tenets pertinent to scientific realism are that data collected may be quantitative or qualitative in nature, context varies between individual researchers, causality is multifaceted and multidirectional, and description, prediction, and explanation are key for the practice of science.

The TOUS is underpinned by contemporary empiricism in several ways. Examples of unobservable entities within the model include the symptom or symptom experience and psychological factors. These variables, though not directly measurable or observable, can be quantified when using reliable and valid measurement tools. Also, depending on the symptom, there may be chemicals produced by the human body that are...
measureable. An example of this is the symptom of anxiety. Anxiety is a subjective state; however, when an individual experiences anxiety, hormones such as epinephrine, norepinephrine, and cortisol may be released. Measurement of these chemicals is possible; this allows for quantitative analysis of the phenomenon. The patient’s perception of anxiety also justifies qualitative components describing the symptom.

Causality in the TOUS is also consistent with contemporary empiricism, in that theoretical or unobservable components of the theory are causally responsible for and explain observable phenomena (Schumacher & Gortner, 1999). Other components of the theory supported by contemporary empiricism are physiological factors, environmental factors, and performance outcomes. These areas may be directly observable, are measurable, and may be influenced by unobservable phenomena. An example of this would be elevation in heart rate, a physiological factor, which is caused or explained by perceived anxiety, which can be either a symptom or psychological factor.

The TOUS also is consistent with the description, prediction, and explanation components of scientific realism. First, it provides a model that describes the interaction of psychological, physiological, and environmental factors and how they influence the symptom experience, as well as performance or outcome. Second, it predicts that psychological, physiological, and environmental factors will influence the symptom experience, that a symptom or combination of symptoms will influence performance, and that performance has reciprocal influences on factors and the symptoms experience. Third, it explains this phenomenon by identifying the roles that certain factors
(psychological, physiological, environmental) exhibit on symptoms and how symptoms affect performance outcome.

**Revolutionary Changes**

A theory that is revolutionary is inductive in origin as the theory is developed from observations in clinical practice, literature, or other data (Walker & Avant, 2005). A theory that is evolutionary or deductive in origin is developed from a pre-existing theory or hypothesis. Considering this distinction, the TOUS is revolutionary and inductive, as it was developed through observation of specific symptoms in clinical practice. Initial work was conducted on dyspnea, by Gift, and on fatigue, by Milligan and Pugh; and through collaborative efforts with Lenz, common elements across both symptom experiences were identified and inductively moved their ideas to the level of middle range theory (Lenz & Pugh, 2003). The first version of the TOUS presented in 1995 (see Figure 1.1) consisted of a linear model identifying relationships between physiological (normal systems, pathologic problems, and energy substrates), psychological (mental state and reaction to illness), and situational (life style and personal resources/experiences) factors with one symptom. The experience of one symptom, incorporating the dimensions of quality, duration, distress, and intensity, was hypothesized to influence performance (functional status, cognitive functioning, and physical performance). This model did not acknowledge the interactive nature of the influencing factors or feedback effects between the influencing factors, the symptom, and performance (Lenz et al., 1997). Publication of the theory generated correspondence to the authors that helped them identify weaknesses and prompted changes in the theory yielding an updated version of the TOUS in 1997.
Main revisions were the inclusion of multiple symptoms that have the capability of interacting with each other, interactions among the influencing factors, feedback influences from performance outcomes on both symptoms and influencing factors, feedback influences from symptoms on influencing factors, and ability of interacting influencing factors to impact the symptoms experience (Lenz et al., 1997).

Several underlying assumptions can be inferred in the TOUS. First, a number of symptoms have sufficient commonalities to warrant the development of a theory that can cross a number of unpleasant symptoms. Second, symptom experiences are multidimensional. Third, symptoms are subjective, but can be described and measured. Fourth, multiple symptoms can occur together and influence one another. A final assumption is that performance outcomes can encompass behavior and cognition.

**Structural Elements of the Theory**

The structural elements of the TOUS will now be identified. Specifically, the concepts of symptoms, influencing factors, and performance outcomes will be discussed.

**Concepts**

**Symptoms.** Symptom(s) and an individual’s symptom experience are the central components of the TOUS. According to Lenz and Pugh (2003) and Lenz et al. (2013), for the purposes of the TOUS, symptoms are defined as “the perceived indicators of change in normal functioning as experienced by patients” (Rhodes & Watson, 1987). Symptoms may occur alone, in combination with other symptoms, precede or cause other symptoms to develop, and may be additive, multiplicative, and interactive where the occurrence of a symptom with other symptoms is perceived as different than its occurrence in isolation.
(Lenz & Pugh, 2003). Symptoms are also described by intensity, perceived distress, timing, and quality. These variable dimensions allow patients to describe symptoms as they perceive them; and symptoms, due to their subjective nature, may be described only by the individual experiencing them. Intensity is the strength or severity of the symptom, and timing is the duration and frequency of the symptom experience. The distress dimension refers to the degree that the individual is bothered by the symptom, with the meaning of the symptom to the individual contributing to the assessment of distress. The quality dimension is the description an individual uses to express how the symptom experience feels. One or more of these dimensions may be measured when assessing a symptom; and measurement of one or two of these dimensions, though not as descriptive as all four dimensions, is still a valid option for assessment and management of unpleasant symptoms (Lenz & Pugh, 2003).

**Influencing Factors.** The conceptualization of influencing factors encompasses three categories of factors: physiological, psychological, and situational. Physiological factors include normal functioning body systems, pathologic changes, genetic makeup, hormonal fluctuations, and age among others (Lenz & Pugh, 2003). Psychological factors include cognitive and affective variables such as coping patterns, mood/mental state, and response to a diagnosis or to the symptom experience itself. Situational factors are associated with an individual’s physical and social environment. Physical environment characteristics that may influence the symptom experience include temperature, noise level, and air or water pollutants among others (Lenz & Pugh, 2003). Social environment consists of variables such as culture, neighborhood context, social networks and support,
socioeconomic status, and access to resources and health care. Influencing factors may interact with each other in relation to the symptoms, relate to each other over and above their relationship with the symptoms, and may influence the variability of the symptom experience (Lenz & Pugh, 2003).

**Performance.** The concept of performance consists of a number of dimensions that include physical activity/imimpairment, cognitive functioning/impairment, social functioning, and role performance. Functional performance encompasses activities of daily living, social interaction, and role-related tasks, whereas cognitive performance is associated with activities such as concentrating and problem solving (Lenz & Pugh, 2008). An alteration in any of these areas represents the outcome or consequence of the symptom experience.

**Relational Elements of the Theory**

Several relationships between and within theory concepts identified by Lenz and Pugh (2008) are depicted in Figure 1.2. The first is that the three categories of influencing factors are related to and may interact with each other while also influencing the symptom experience. A second relationship is each of the symptoms experienced by an individual interacts with or relates to the others and may induce an additive or multiplicative effect. The symptom experience then influences performance outcome. The symptom experience may also serve as mediator/moderator between influencing factors and performance (Lenz & Pugh, 2008). Other relationships are that performance outcomes provide feedback to the symptom experience and both performance outcomes and symptom experience provide feedback to influencing factors.
Empirical Support for the TOUS

The TOUS has guided research on symptoms across a variety of patient populations and disease entities (Carpenter et al., 2004; Corwin, Klein, & Rickelman, 2002; Corwin, Brownstead, Barton, Heckard, & Morin, 2005; Crane, 2005; De Vito Dabbs et al., 2003; Gift, Stommel, Jablonski, & Given, 2003; Gift, Jablonski, Stommel, & Given, 2004; Huth & Bromme, 2007; Jurgens et al., 2009; Kapella, Larson, Patel, Covey, & Berry, 2006; Kim, Oh, & Lee, 2006; Kim, Oh, Lee, Kim, & Han, 2006; Lee, Chung, Park, & Chun, 2004; Liu, 2006; McCann & Boore, 2000; Motl & McAuley, 2009; Oh, Kim, Lee, & Kim, 2004; Parks, Lenz, Milligan, & Han, 1999; Parshall et al., 2001; Redeker, Lev, & Ruggiero, 2000; Reishtein, 2005; Rychnovsky, 2007; Scordo, 2005; Spector, Hicks, & Pickleman, 2002; Tyler & Pugh, 2009; Woods, Kozachik, & Hall, 2010) including cancer, cirrhosis, chronic obstructive pulmonary disease (COPD), cardiac disease, postpartum depression, renal failure in hemodialysis patients, and multiple sclerosis. It has also guided research with surgical patients (lung and heart-lung transplant, bariatric surgery, tonsillectomy, and resection for gastroesophageal cancer), healthy young adult smokers, and women experiencing intimate partner violence. A synthesis of the research will now be presented to provide support for or to question the relational elements of the theory.

Research Incorporating all TOUS Components

The majority of published studies guided by the TOUS have incorporated two or more conceptual elements of the theory; however, the number of studies incorporating all theory components is few (Rychnovsky, 2007; Scordo, 2005; Crane, 2005; Kapella et al.,
Support for relational elements of the theory varies. Rychnovsky’s (2007) work with postpartum women incorporated all theory components and determined that delivery type and degree of lactogenesis (physiological factors), depression and anxiety (psychological factors), and maternal sleep disturbance and infant mood (situational factors) influenced the development of fatigue (symptom) with greater levels of fatigue causing lower functional status (performance outcome), thus supporting elements of the TOUS where influencing factors impact the symptom experience with resulting alterations in performance outcome. However, the use of maternal sleep disturbance as a situational influencing factor is incongruent with the conceptualization of the concept, unless it is an indirect measure for maternal support systems.

Crane’s (2005) study of older women after myocardial infarction and Scordo’s (2005) study of individuals experiencing mitral valve prolapse syndrome (MVPS) also utilized all theory components, but support for relationships between components varied. Crane (2005) examined the symptom of fatigue and found strong relationships between depression (psychological factor) and fatigue as well as sleep (physiological factor) and fatigue thus supporting relational elements of the TOUS. However, no relationship existed between the physiological factor variables of body mass index (BMI), co-morbidities, and beta blocker use and fatigue, which contradicts the hypothesized relationship between physiological influencing factors and the symptom experience. This indicates that support for relational elements of the TOUS can vary within the same research depending on the number and type of influencing factors evaluated.
Scordo (2005) examined symptoms of MVPS, but found that the influencing factors used in the model accounted for a small portion of variance in symptoms scores and the outcome variables did not significantly predict symptoms scores. These findings may have contributed to a lack of fit of the study model with the TOUS framework; it could also be related to the variables selected for the study and instruments used to measure study variables.

Kapella et al. (2006) used the TOUS to assess dimensions of fatigue in COPD patients as well as relationships between fatigue and dyspnea in relation to functional performance and influencing factors. The interactive nature of fatigue, dyspnea, anxious and depressed moods, and sleep quality suggested support for relational elements of the TOUS; however, independent effects of variables could not be determined. Of note, a strong relationship existed between sleep quality and fatigue. In this study, sleep quality was categorized as a situational influencing factor; however, it is often considered as part of a symptom cluster with fatigue (Barsevick, 2007a; Barsevick, 2007b), thus possibly explaining the strong relationship in this study.

Kim et al. (2006) examined the symptom experience in patients with cirrhosis where persons with lower levels of psychological distress (psychological factor) and who were employed (situational factor) had lower levels of symptoms and had a better quality of life. These relationships support the TOUS where symptoms are hypothesized to be affected by influencing factors which in turn impact performance outcomes; however, the relationship between symptoms and performance outcome in this study may not
adequately support the TOUS, as quality of life may not fit with the theory’s definition of performance outcome.

A case study by Tyler and Pugh (2009) used all theory concepts to assess symptoms, influencing factors, and performance outcome in a bariatric surgery patient. Physiological factors, including altered gut function and absorption, caused dehydration and malabsorption, which affected symptoms of constipation, nausea with vomiting, and abdominal pain. Psychological factors, including food cravings and depressed mood, influenced the symptoms of irritability and fatigue. Situational factors, including poor social support and occupational stress influenced the development of fatigue as well. The interaction of influencing factors and symptoms impacted performance resulting in delayed recovery, delayed return to work, poor problem solving, and prolonged malnutrition. This clinical exemplar shows support for relationships among TOUS concepts and demonstrates how the theory can be used to guide nursing practice.

Additional studies using all theory concepts were conducted by Redeker et al. (2000) and De Vito Dabbs et al. (2003), but assessed only the relationships of a psychological influencing factor with symptoms and performance outcome. Redeker et al. (2000) evaluated the influence of depression and anxiety (psychological factors) with symptoms of insomnia and fatigue on quality of life in cancer patients. Patients with high levels of depression were more likely to have insomnia, fatigue, anxiety, and a poorer quality of life; however, due to study design, a temporal relationship between the influencing factors, symptoms, and outcome could not be established. This study also utilized quality of life as a performance outcome which, depending on the measure used,
may not encompass the functional and cognitive outcomes presented in the TOUS. De Vito Dabbs et al. (2003) examined the effect of psychosocial stress (psychological factor) on physical symptoms and physical impairment (performance outcome) in patients after lung or heart-lung transplantation. Strong relationships were found between psychosocial factors, symptoms, and impairment where patients with higher levels of psychological morbidity had an increased number of symptoms and levels of impairment. These relationships support the elements of the TOUS; however, due to study design, predictive relationships between variables could not be established.

**Incorporation of Influencing Factors and Symptom Components**

Several studies have incorporated the concepts of influencing factors as they relate to the symptom of fatigue, but did not address performance outcomes (Carpenter et al., 2004; Corwin et al., 2002; Corwin et al., 2005; Lee et al., 2004; Liu, 2006; McCann & Boore, 2000; Oh et al., 2004; Woods et al., 2010). Carpenter et al. (2004) evaluated sleep quality and fatigue as influenced by depression (psychological factor), age and menopausal status (physiological factor), and night-time hot flashes (situational factor) in breast cancer survivors. Significant correlations found among global sleep quality, fatigue, and depressive symptoms provided support for the effect of a psychological influencing factor on a symptom experience as well as evidence for the presence of a symptom cluster. The hypothesized relationship between hot flashes and the symptom experience was not supported. Of note, hot flashes would have been more appropriately categorized as a physiological than as a situational factor.
Corwin et al. (2002) examined fatigue in relation to physiological factors (age, gender, blood pressure, inflammatory status, immune status, and BMI), psychological factors (depression and anxiety), and situational factors (sleep quantity and sleep quality) in healthy smokers. A significant correlation was present between age and fatigue, wherein younger individuals reported greater fatigue; however, fatigue was not related to other physiological factors. Fatigue was also positively correlated with anxiety, depression, sleep quality, and sleep quantity. Sleep quality and sleep quantity may have been more adequately categorized as symptoms, because they are internal rather than environmental variables. In another study, Corwin et al. (2005) evaluated postpartum depression as a symptom influenced by several physiological, psychological, and situational variables. Fatigue (physiological factor) and stress (psychological factor) were significantly correlated with symptoms of depression and with each other. There were no correlations between salivary cortisol (psychological factor) and depressive symptoms, postpartum fatigue (physiological factor) or stress or between age and depression, fatigue, or stress. These results both support and question relationships among concepts in the TOUS. In addition, fatigue would have been more appropriately categorized as a symptom instead of a physiological factor and cortisol as a physiological factor instead of a psychological factor. Fatigue is a subjective state experienced by an individual and is more congruent within the symptom concept. Cortisol, as a measurable chemical produced by normal body functions and pathologic states, is more congruent with the physiological influencing factor concept.
Liu (2006) and McCann and Boore (2000) conducted research studying fatigue in hemodialysis patients. Liu’s (2006) findings both support and question the proposed relationships among influencing factors and symptoms in the TOUS. Individuals who were unemployed (situational factor) and who were depressed (psychological factor) had higher levels of fatigue; however, levels of fatigue were not affected by physiological factors. Age and gender were also categorized as situational factors in this study, whereas the TOUS portrays them to be physiological factors. McCann and Boore (2000) found relationships between physiological and psychological factors and fatigue, but no relationship between situational factors and fatigue. Of note, several variables were conceptualized as factors other than those proposed by the TOUS. Length of time receiving hemodialysis was conceptualized as a situational factor and physical health status (measured as physical functioning and role performance) as a physiological factor, whereas the TOUS portrays them as a physiological factor and performance outcome respectively. Also, sleep problems was conceptualized as a physiological influencing factor instead of as a symptom. The latter approach would have allowed evaluation of the symptom cluster with fatigue.

The symptom of fatigue in Koreans with lung cancer was evaluated by Oh et al. (2004). They found that overall fatigue was significantly correlated with dyspnea (physiological factor) and mood state (psychological factor), but sleep quality (situational factor) did not significantly contribute to fatigue scores. These findings provide inconsistent support for the relationships proposed between physiological, psychological, and situational factors and symptoms in the TOUS; however, sleep quality was used as a
situational factor and may have been more appropriately utilized as a symptom interacting with fatigue.

In their research on sleep quality in women experiencing intimate partner violence, Woods et al. (2010) found relationships between depression (psychological factor) and global sleep quality (symptom) that were significant when depression was considered alone, but not when combined with post traumatic stress disorder (psychological factor) and physical health symptoms (physiological factors). In addition, stress health symptoms was the only physiological factor that was positively associated with poor sleep quality. These findings show varying support for relationships between concepts in the TOUS, as relationships varied with the number of variables examined for each influencing factor.

Another study incorporating concepts of influencing factors and symptoms was conducted by Lee et al. (2004). They assessed only two influencing factors with symptoms experienced in Korean women with breast cancer. Mood disturbance (psychological factor) was significantly related to symptoms experienced; however, social support (situational factor) was not related to the symptoms experience. A significant negative relationship was found between social support and mood disturbance, but was a low correlation. These findings support the TOUS’s proposed relationships between psychological and situational influencing factors, and also suggest that one set of influencing factors (in this case psychological) can mediate the relationship of another influencing factor (in this case situational) to the symptom experience. The proposed direct influence of social support on the symptom experience was not supported.
Symptom Clusters

The presence and interaction of one or more symptoms, as presented in the revised TOUS (Lenz et al., 1997) informed the conceptual development of the symptom cluster. The challenge to study symptoms as a symptom cluster was issued by Dodd, Miaskowski, and Paul in 2001 and several researchers have utilized the TOUS to guide their symptom clusters research (Gift et al., 2003; Gift et al., 2004; Jurgens et al., 2009; Motl & McAuley, 2009; Reishtein, 2005). In their research on symptoms experienced by patients with lung cancer, Gift et al. (2004) found that symptoms of fatigue, nausea, weakness, appetite loss, weight loss, altered taste, and vomiting occurred together to form a symptom cluster. Of note, the symptom cluster in this study was found to be strongly related to advanced stage of lung cancer, chemotherapy treatment, and increased number of co-morbidities (physiological factors). The number of symptoms was also strongly associated with functional limitations (performance outcome). These findings support the TOUS’s assumption that symptoms may co-occur, may be influenced by antecedent variables, and are capable of impacting performance. Further research evaluated the symptom cluster over the lung cancer illness course (Gift et al., 2003). The symptom cluster established at cancer diagnosis was present at 3 and 6 months, with decreasing severity of symptoms at each time point and was an independent predictor of death (performance outcome), as patients with more severe symptoms were more likely to die within a 13 month period. The stage of cancer at diagnosis (physiological factor) predicted the number of symptom clusters reported and age (situational factor) and stage of cancer were independent predictors of death. No significant relationships were found
between therapy type and number of co-morbid conditions (physiological factors) and gender (situational factor) and the dependent variable symptom clusters. These findings indicate inconsistent support for the relationships proposed in the TOUS, perhaps in part because of the number of variables used as indicators of each concept. Of note is that, no psychological influencing factors were included, even though they may have been more predictive of the symptom experience in patients with cancer. On the other hand, gender and age, which are categorized as physiological factors in the TOUS, were considered situational factors in this study.

Motl and McAuley (2009) examined the symptoms of fatigue, pain, and depression as a possible symptom cluster and the effect on physical activity behaviors in patients with multiple sclerosis. Symptoms experienced by patients formed a symptom cluster as determined by factor analysis, bivariate correlations, and co-variance modeling, thus supporting the symptom component of the TOUS. In addition, the symptom cluster had a moderate and negative relationship with physical activity behavior, providing support for the relational element of symptoms affecting performance outcome.

The notion of co-occurring symptoms was also supported by Jurgens et al. (2009), who discerned the presence of acute and chronic symptom clusters in patients hospitalized with decompensated heart failure. Three unique symptom clusters were found: acute volume overload, chronic volume overload, and emotional symptoms. An explanation of the multidimensional nature of symptoms was also proposed by the authors; however, it was unclear how this analysis was applied to the symptom clusters.
A study by Reishtein (2004) evaluated the symptoms of dyspnea, fatigue, and sleep difficulty and their effect on functional performance in persons with COPD. Findings indicated that the three symptoms were related to one another. The symptoms of dyspnea and fatigue were also strongly and negatively related to functional performance. This finding supports the TOUS hypotheses that symptoms can co-occur, and that symptoms influence performance outcome; however, the three symptoms together did not explain more of the variance in functional performance than one symptom alone (dyspnea). The finding that there was no relationship between sleep difficulty and functional performance indicates that all of the symptoms in a cluster can be related to one another, but may differ in the strength and nature of the individual relationships to performance.

**Incorporation of Symptoms and Outcomes**

Studies focusing on the relationship between the symptom experience and performance outcome were conducted by Parks et al. (1999) and Spector et al. (2002). The symptom of fatigue and its influence on the performance outcomes of maternal health and infant health and development was the focus of the research by Parks et al. (1999). Consistent fatigue was hypothesized to contribute to lower levels of maternal health, infant health, and infant development. Findings were inconsistent in their support of relationships proposed by the TOUS. The combination of mental and physical fatigue was associated with maternal health, with mental fatigue explaining a greater proportion of the variance in maternal health scores. Persistent fatigue was not associated with infant health, but was associated with infant development when mental and physical fatigue
were combined. No difference was found in infant development when mental and physical fatigue were considered alone. Of note, using infant health and development as outcomes of maternal fatigue does not support the TOUS’s conceptualization of performance outcome; however, this does show that more proximate outcomes, such as maternal health, can impact other outcomes that are likely linked to maternal health. Spector et al. (2002) evaluated symptoms experienced in patients with gastrointestinal malignancies post-surgical intervention, and examined relationships between symptoms and health-related quality of life. Patients with increased symptom frequency had lower health-related quality of life scores as measured by the Gastroenterology Quality of Life Index; however, this tool assessed symptom, emotion, function, and social domains. The inclusion of function and social domains only would have been more congruent with performance outcome and would have eliminated the problem of symptom measures being included for both independent and dependent variables. The overlap between the measures of symptoms and health-related quality of life cannot be eliminated as contributing to the relationship found.

**Multidimensional Nature of Symptoms**

Three studies focused on the multidimensional nature of symptoms (Parshall et al., 2001; Kim et al., 2006; Huth & Broome, 2007). Parshall et al. (2001) evaluated the distress, intensity, and duration of dyspnea in patients presenting to the emergency department (ED) with heart failure and whether symptom dimensions were associated with hospital admission. Dyspnea was the most distressing symptom prompting the decision to go to the ED, the intensity and distress of dyspnea when deciding to come to
the ED was comparable for all patients despite dyspnea duration, and there was no association between dyspnea duration and hospital admission. These findings support the multidimensional nature of a symptom as proposed in the TOUS.

In their study of patients with cirrhosis, Kim et al. (2006) examined the multidimensional nature of 18 symptoms and the influence of physiological factors (disease severity, disease etiology, and hepatocellular carcinoma status) on the symptom experience. Disease etiology and cancer status were not significantly related to the symptom experience; however, disease severity was significantly related to the overall symptom experience. The findings provided inconclusive evidence for the relationship between physiological antecedents and symptoms in the TOUS. The multidimensionality of symptoms as proposed by the TOUS was supported by the research, as certain symptoms (muscle cramps, dark urine) varied in their importance to the patient as reflected in patients’ identification of the symptom dimension that had the most impact.

Huth and Broome (2007), in their study of post-operative tonsillectomy patients, evaluated the use of guided imagery on the symptoms of pain and vomiting, as well as the intensity and distress of these symptoms on fluid intake (performance outcome). In addition, pharmacologic intervention, type of surgery, and anxiety level were factors influencing the symptom experience. There were no significant differences between the intervention and control groups on any of the study variables; however, intensity and distress of pain were described as moderate. Pain, therefore, seemingly had a reciprocal influence on the psychological factor of anxiety, which subsequently may have affected the ability of the imagery group to concentrate on the intervention. In addition, to support
for the reciprocal link between symptoms and influencing factors as proposed in the TOUS, the study demonstrated other evidence of reciprocity. For example, pain level influenced fluid intake and vomiting, which in turn resulted in lower analgesic use and corresponding increase in pain level.

**Summary**

The aforementioned research has provided mixed support for the relational elements of the TOUS, with the majority of evidence supporting the proposed relationships in the theory. A number of issues were revealed concerning the categorization of variables and overlap of measures used to study concepts and relationships in the theory. Application of the TOUS in the evaluation of nicotine withdrawal symptoms in critically ill smokers is now presented.

**Application of the TOUS: Nicotine Withdrawal in Critically Ill Smokers**

The TOUS presents a framework that provides an appropriate underpinning for the evaluation of nicotine withdrawal symptoms in critically ill smokers (see Figure 1.3). Smokers admitted to intensive care settings are forced to abstain from cigarette smoking (situational factor) and subsequent nicotine intake. This, in combination with the patient’s physiological nicotine dependence (physiological influencing factor), should contribute to the possible development of unpleasant symptoms of nicotine withdrawal. If not treated appropriately, these symptoms may then predispose the patient to the development of delirium (cognitive outcome), and ultimately increase hospital length of stay (LOS), most often interpretable as a physiological outcome. Hypothetically, the use of nicotine replacement therapy (NRT) in these patients may decrease the development of
nicotine withdrawal symptoms. Of note, the unpleasant symptoms of nicotine withdrawal, for the purposes of this paper, are anxiety, agitation, and cigarette craving. An overview of how the relational elements of the TOUS may be applied to this area of inquiry is now presented.

**Influencing Factor: Nicotine Dependence**

Tobacco dependence, a physiological influencing factor (see Figure 1.3), is exhibited by a relapsing and remitting series of quit attempts followed by re-initiation of tobacco use and is also present when a person does not attempt to quit smoking. Nicotine influences the development of cognitive, behavioral, and physiological symptoms associated with dependence (Henningfield, 1995; USDHHS, 2001). Psychopharmacological properties of nicotine are highly addictive and implicated in maintaining cigarette smoking due to positive reinforcement mechanisms (Watkins, Koob, & Markou, 2000; Bergen & Caporaso, 1999). The need to maintain these feelings and prevent unpleasant symptoms of nicotine withdrawal, or negative feedback mechanisms, promotes repeat use of nicotine-containing products. A smoker admitted to intensive care is unable to continue this cycle. The longer the period of smoking abstinence, the more likely nicotine withdrawal will occur and the unpleasant symptoms will be experienced.

**Influencing Factor: Forced Abstinence**

Smoking abstinence is usually operationalized as the duration of time from the last cigarette smoked until re-initiation of smoking behavior. This occurs as a conscious effort to refrain from smoking or when a smoker is forced to abstain due to no-smoking
policies in the environment or physical incapacity that precludes smoking. In the current study, smoking abstinence was categorized as a situational variable because of the patient’s location in the intensive care unit. The longer the period of abstinence, the more likely the individual will develop unpleasant symptoms of nicotine withdrawal. Smokers admitted to intensive care settings are forced to abstain from smoking due to critical care unit policies or medical conditions/treatments that prevent them from leaving the unit to smoke. A patient who is physiologically dependent on nicotine will begin to develop nicotine withdrawal symptoms if nicotine replacement is not initiated; however, reports of standardized protocols for nicotine replacement therapy in critically ill smokers have not been found in the literature and the practice is at the physician’s discretion.

**Unpleasant Symptoms: Nicotine Withdrawal**

The combination of nicotine dependence and smoking abstinence influences the development of unpleasant symptoms of nicotine withdrawal. Nicotine withdrawal symptoms include anxiety, insomnia, irritability, restlessness/agitation, increased hunger, depressed mood, difficulty concentrating, and tobacco craving (Benowitz, 2008; American Psychologic Association, 1994) in association with termination or reduction of nicotine use after several weeks of daily use of nicotine-containing products. Symptoms of nicotine withdrawal typically have a rapid onset within 24 to 36 hours (Padua & Wiley, 1993). This is an important consideration for smokers admitted to the hospital, and specifically to intensive care, as nicotine withdrawal may begin early in the treatment course, adversely affect therapeutic outcomes, and increase hospital LOS (Zack, 2001).

The unpleasant symptoms of anxiety, agitation, and craving, three of the most commonly
reported symptoms of nicotine withdrawal in hospitalized smokers (Rigotti et al, 2000),
will now be discussed.

**Anxiety.** Anxiety is an unpleasant symptom characterized by subjective and
consciously perceived feelings of tension and apprehension or dread and foreboding
(Zack, 2001; Dejong, Moser, An, and Chung, 2004). Anxiety occurs in approximately
70% to 87% of patients admitted to critical care environments (Bone et al., 1995) and is
also a common symptom of nicotine withdrawal. Patients with signs/symptoms of anxiety
may exacerbate the condition requiring their intensive care admission, increase their risk
of developing other physiological or psychological sequelae, and compromise their
therapeutic regimen.

**Agitation.** Agitation, another unpleasant symptom, is an overt expression of
organic or psychological illness characterized by excessive motor or verbal behavior
(Haskell, Frankel, & Rotondo, 1997). Agitation occurs in 52% to 71% of critical care
patients (Jabir et al., 2005; Fraser, Prato, Riker, Berthiaume, & Wilkins, 2000) and may
be caused by multiple factors including stress associated with hospital/intensive care
admission, alcohol/drug intoxication or withdrawal, pain, anxiety, and delirium/dementia
(Haskell et al, 1997; Jabir et al, 2005). The risk for agitation increases with nicotine
withdrawal and may be influenced by tobacco craving.

**Tobacco craving.** Tobacco craving, an early unpleasant symptom of nicotine
withdrawal (Tiffany & Drobes, 1991), is a function of psychological and physiological
nicotine dependence and is defined as the smoker’s desire or compulsion to use tobacco
to produce a desired effect previously experienced (Etter, Houezec, & Perneger, 2003;
Miyatta & Yanagita, 2001). The intensity of tobacco craving increases during the first hour of abstinence and peaks within 6 to 24 hours after smoking the last cigarette. The prevalence of tobacco craving in hospitalized smokers was evaluated by Rigotti et al. (2000) who found that 89% of patients reported at least one symptom of nicotine withdrawal, over half reported three symptoms (restlessness/agitation, craving, difficulty sleeping), 49% reported anxiety, and 55% reported craving for a cigarette since admission. Thus, craving occurs alone or in combination with other nicotine withdrawal symptoms and should be considered in smokers experiencing anxiety or agitation.

**Cognitive Outcome: Delirium**

Delirium, a cognitive performance outcome (see Figure 1.3), is an acute disorder of attention and cognition (Mayer et al., 2001) characterized by fluctuations in impaired cognitive functioning over time (Ely et al., 2001) often associated with anxiety and agitation. The incidence of delirium in intensive care settings varies from 16% to 85% (Teneggi et al., 2002) and is related to patient co-morbidities, the unit providing care (neurological vs. surgical vs. medical), and the measurement tool used to assess delirium. Only one study has gathered data on patient smoking status and identified smoking as an independent risk factor for delirium in the ICU (Dubois, Bergeron, Dumont, Dial, & Skrobik, 2001). Findings were that smoking a minimum of 20 cigarettes a day prior to admission, independent of other co-morbidities, doubled the risk for delirium. This indicates that smoking status and unpleasant symptoms of nicotine withdrawal increase the risk for delirium in ICU patients.
**Performance Outcome: Hospital LOS**

Hospital LOS is the time extending from hospital admission to discharge or death. Symptoms of withdrawal, such as anxiety and agitation, contribute to the development of delirium which prolongs hospital LOS (Ely et al., 2001; Marshall & Soucy, 2003). One study evaluated delirium as an independent predictor of LOS in 261 non-ventilated ICU patients and found that 48% experienced delirium that was associated with one extra day in the ICU and two extra days in the hospital (Thomason et al., 2005). Treatment of nicotine withdrawal symptoms has the potential to decrease or eliminate delirium and decrease hospital LOS.

**Nicotine Replacement Therapy**

NRT is a pharmacologic intervention used to reduce or eliminate cigarette smoking behavior and prevent the development of unpleasant nicotine withdrawal symptoms. The use of NRT in intensive care patients is at the discretion of the physician and is an infrequent practice, but may be of benefit to critically ill patients (Cartin-Ceba, Warner, Hays, & Afessa, 2011; Honisett, 2001; Mayer et al., 2001, Panos, Tesoro, Kim, & Mucksavage, 2010; Seder et al., 2011; ) Carle and colleagues conducted a descriptive pilot study exploring unpleasant symptoms of nicotine withdrawal in intensive care patients and the use of NRT in this patient sample.

**Summary**

The TOUS has stimulated a large amount of research in a variety of patient (postpartum, cancer, cardio-pulmonary, hemodialysis, multiple sclerosis, cirrhosis, post-operative), and healthy adult populations (intimate partner violence, healthy smokers).
Several unpleasant symptoms have been studied; most notable are fatigue and dyspnea. The majority of research has not formally tested the TOUS; however, a mixed pattern of support has been revealed for theory concepts and relationships.

Strengths of the TOUS have been proposed by Brant, Beck, and Miaskowski (2009). First, the theory considers multiple symptoms occurring simultaneously and possible interactions among those symptoms. Studies on symptom clusters (Motl and McAuley, 2009; Jurgens et al., 2009; Reishtein, 2004) have lent support for these relationships. A second strength is the temporal relationship between concepts as exhibited by feedback loops. An example of this reciprocity was demonstrated in Huth and Broome’s (2007) study of post-operative tonsillectomy patients. A final strength is that the TOUS is not only relevant to nursing research, but may also be used to guide nursing practice (Lenz et al., 2013) as presented in Tyler and Pugh’s (2009) case study of a bariatric surgery patient.

Several limitations of the theory have also been acknowledged by Brant et al. (2009) and Lenz et al. (2008). First, the influencing factors and outcome categories are not well-defined and variables within each category require further clarification. This leads to inappropriate conceptualization of study variables, such as sleep quality and maternal sleep as a situational influencing factors (Oh et al., 2004; Rychovsky, 2007), sleep quality as a physiological influencing factor (Kapella, 2006), salivary cortisol response as a psychological influencing factor (Corwin et al., 2005) and quality of life as a performance outcome (Kim et al., 2006; Redeker, 2000) among others. Second, there is no intervention component among theory concepts. Another limitation identified by
Brant et al. (2009) is the TOUS does not consider the exacerbation or resolution of a symptom experience. A final limitation acknowledged by Lenz et al. (2008) is the outcomes component does not consider primary and secondary outcomes or the temporal relationship between a proximal outcome and a distal outcome.

The TOUS provides a useful framework for the evaluation of unpleasant symptoms associated with nicotine withdrawal in smokers admitted to intensive care settings as it has guided symptom research across a variety of patient populations and nursing disciplines. The nicotine withdrawal symptom experience is one that has not been thoroughly explored in critically ill smokers and determining the presence of nicotine withdrawal symptoms in these patients is a crucial nursing assessment. It is also important to determine potential influencing factors that impact the development of nicotine withdrawal symptoms as well as how withdrawal symptoms influence patient outcomes. Research is needed to determine the presence of these symptoms in this patient population so that interventions may be considered. This paper presents a preliminary model, based on the TOUS, conceptualizing unpleasant symptoms of nicotine withdrawal as experienced in critically ill smokers. The proposed model provides a preliminary guide for the exploration of factors influencing the nicotine withdrawal symptom experience, the presence and interaction of multiple withdrawal symptoms, and the influence of the symptom experience on performance outcome in critically ill smokers.
References


Crane, P. (2005). Fatigue and physical activity in older women after myocardial


373-384.


Panos, N., Tesoro, E., Kim, K., & Mucksavage, J. (2010). Outcomes associated with


Figure 1.3. The Theory of Unpleasant Symptoms as a Model for the Affects of Nicotine Replacement Therapy (NRT) on Nicotine Withdrawal in Critically Ill Smokers. Adapted from “The middle-range theory of unpleasant symptoms: An update,” by E. Lenz, L. Pugh, R. Milligan, A. Gift, and F. Suppe, 1997, Advances in Nursing Science, 19, p. 17. © 1997 Aspen Publishers, Inc.
Chapter 2: Nicotine Withdrawal Symptoms and Utilization of Nicotine Replacement Therapy in Critically Ill Smokers

Cigarette smoking is an addictive behavior that is a common contributor to the development of disease and subsequent mortality. There are over 435,000 deaths attributable to smoking that occur in the United States each year (King, Dube, Kaufman, Shaw, & Pechacek, 2011; U.S. Department of Health and Human Services [USDHHS], 2004; Fiore, et al., 2008). The prevalence rates for smoking in the United States did not meet the Healthy People 2010 goal of reducing smoking levels to ≤ 12%; therefore, this goal has been renewed for Healthy People 2020 (USDHHS, 2011). The prevalence for adult smokers in the United States for the year 2010 indicated that approximately 19.3% of adults were current smokers (King et al., 2011) which is a cause for concern when considering smoking related disease and associated health consequences.

Common diseases associated with cigarette smoking include lung cancer, chronic obstructive pulmonary disease, stroke, and coronary heart disease (Adhikari, Kahende, Malarcher, Husten, & Asman, 2009). These illnesses contribute substantially to increased health care utilization and premature death. Severe exacerbations of chronic conditions trigger admissions to medical intensive care units. While the prevalence of smokers in these settings is unknown, the most common diagnoses for all patients admitted to
Medical intensive care units include respiratory failure or insufficiency, ischemic heart disorders, congestive heart failure, sepsis, gastrointestinal bleeding, and multiple organ system failure (Society of Critical Care Medicine, 2012), the majority of these being closely associated with cigarette smoking. The unexpected disruption of cigarette smoking and nicotine intake during critical care admission may contribute to additional morbidity due to the potential development of nicotine withdrawal symptoms. Nicotine is a drug found in cigarettes that induces psychological and physiological dependence and when consumption is abruptly eliminated, withdrawal symptoms may complicate recovery as they can result in delirium, which in turn, can lead to prolonged length of hospital stay.

Hospitals have been mandated to be smoke free since 1992 when the Joint Commission on Accreditation of Healthcare Organizations required the institution and enforcement of hospital-wide, smoke-free policies as an accreditation standard (Fiore & Jorenby, 1992). This atmosphere leads to forced smoking abstinence and subsequent withdrawal symptoms among patients. Hospitalized smokers who are ambulatory may smoke in designated smoking areas. Smokers admitted to intensive care settings, though, are forced to abstain from cigarette smoking. Abrupt cessation of nicotine intake increases the potential for the development of withdrawal symptoms and associated psychological morbidity (Honisett, 2001). More hospitals have implemented tobacco-free campus policies extending from indoor to outdoor environments (Williams et al., 2009; Fiore et al., 2008) and have implemented smoking cessation interventions as a quality of care measure (Rigotti, Munafo, & Stead, 2008); however, many hospitals do not have
specific policies regarding the provision of nicotine replacement therapy to hospitalized smokers. This practice is often at the discretion of the physician.

Nicotine replacement therapy (NRT) utilization in hospitalized smokers is a practice that decreases acute nicotine withdrawal symptoms, promotes smoking abstinence after discharge, and influences a positive recovery (Rigotti et al., 2008; Fiore et al., 2008). However, effects of NRT on the development of withdrawal symptoms have not been adequately explored in smokers admitted to intensive care settings. NRT in this population has the potential to decrease nicotine withdrawal symptoms, decrease the risk of delirium associated with nicotine withdrawal, and result in a comparatively shorter length of hospital stay. The lack of reported research on this topic contributes to a significant gap in the literature on appropriate management of nicotine withdrawal in intensive care settings.

Review of the Literature

Smokers admitted to intensive care settings are forced into “cold turkey” abstinence from cigarette smoking and subsequent nicotine intake. Nicotine, a constituent of tobacco products yields a variety of psychological, behavioral, and physiological symptoms that promote addictive behaviors leading to dependence (Henningfield, 1995). Nicotine dependence is associated with the need to maintain nicotine use and prevent potential withdrawal symptoms, or negative reinforcement. Sudden termination of nicotine intake in critical care patients increases the risk of developing withdrawal symptoms that may progress to delirium and ultimately increase hospital length of stay.
The use of NRT in smokers admitted to intensive care has the potential to mitigate this chain of events by decreasing or eliminating the effects of nicotine withdrawal.

**Theory of Unpleasant Symptoms**

The Theory of Unpleasant Symptoms (TOUS) is a middle-range nursing theory that examines the patient’s symptom experience, factors influencing the symptom experience, and patient outcome. As a middle-range theory, the TOUS is abstract in that it may be utilized across time, place, and discipline; in addition, it may guide specific research questions and subsequent interventions (Lenz, Suppe, Gift, Pugh, & Milligan, 1995; Lenz, Gift, Pugh, & Milligan, 2013). No examples were found of the TOUS having been utilized in critical care research; however, it has guided research on symptoms across a variety of patient populations including dyspnea and fatigue in patients with pulmonary disease (Gift, 1991; Gift & McCrone, 1993; Oh, Kim, Lee, & Kim, 2004; Kapella, Larson, Patel, Covey, & Berry, 2006; Reishstein, 2005) and cardiovascular disease (Parshall et al., 2001; Crane, 2005), fatigue of mothers during the post-partum period (Milligan, Flenniken, & Pugh, 1996; Pugh & Milligan, 1995; Pugh & Milligan, 1998; Corwin, Brownstead, Barton, Heckard, & Morin, 2005; Parks, Lenz, Milligan, & Han, 1999; Rychnovsky, 2007), physical symptoms in lung and heart-lung transplant patients (De Vito Dabbs et al., 2003), fatigue in end-stage renal patients receiving hemodialysis (Liu, 2006; (McCann & Boore, 2000) as well as a variety of symptoms in the oncology patient population (Carpenter et al., 2004, Redeker, Lev, & Ruggiero, 2000; Gift, Jablonski, Stommel, & Given, 2004; Gift, Stommel, & Given, 2003). The ability of the TOUS to guide research on unpleasant symptoms across diverse patient populations...
supports its use in exploring nicotine withdrawal symptoms and utilization of NRT in critically ill smokers.

The TOUS forms the basis of a conceptual framework regarding nicotine withdrawal symptoms and use of NRT in smokers admitted to the intensive care setting (see Figure 2.1) as the theory’s components are readily adaptable to this area of inquiry. It is proposed that admission to an intensive care unit and subsequent forced abstinence from cigarette smoking, in combination with the patient’s physiological nicotine dependence, will contribute to the development of nicotine withdrawal symptoms (anxiety, agitation, and cigarette craving). This symptom experience, if not treated appropriately, may predispose the patient to the development of delirium, a primary outcome (cognitive outcome). Delirium may then increase hospital length of stay, a secondary outcome. The administration of NRT upon admission to the intensive care setting has the potential to reduce nicotine withdrawal symptoms, prevent delirium, and result in a comparatively shorter hospital length of stay. Research supporting the model’s components is now presented.

Influencing Factors

Nicotine Dependence. Nicotine dependence, as depicted in Figure 2.1, is considered a physiological influencing factor associated with the development of unpleasant symptoms in nicotine withdrawal. Tobacco dependence is exhibited by a relapsing and remitting series of quit attempts followed by re-initiation of tobacco use. There are at least 45 million smokers in the United States; 70 percent who want to quit and approximately 44 percent who have attempted to quit smoking each year (Fiore et al.,
Nicotine is a chemical compound, or drug, found in tobacco products, that influences the development of cognitive, behavioral, and physiological symptoms over time that are associated with dependence and addiction (Henningfield, 1995; USDHHS, 2001). Nicotine enters the blood stream through the lungs (Balfour, 2002) and is rapidly distributed throughout the body. Nicotine affects brain chemistry, specifically the areas associated with reward mechanisms and pleasure. The psychopharmacological properties of nicotine are highly addictive and are implicated in the maintenance of cigarette smoking behaviors due to positive reinforcement mechanisms (Watkins et al., 2000; Bergen & Caporaso, 1999). Experiencing the effects of pleasure, arousal, decreased stress and anxiety, mild euphoria, appetite suppression, and relaxation (Watkins et al., 2000; Thompson & Hunter, 1998) associated with nicotine use yields a self-perpetuating cycle. The need to maintain these positive feelings and prevent withdrawal symptoms, or negative feedback mechanisms, promotes repeated use of nicotine containing products. With repeat dosing of nicotine, nicotine withdrawal symptoms are prevented. A smoker admitted to an intensive care unit where smoking is prohibited is unable to continue this cycle. Since many intensive care units do not offer NRT to critically ill smokers, these patients are predisposed to nicotine withdrawal and related sequelae.

**Smoking Abstinence.** Abstinence from smoking, a situational influencing factor leading to nicotine withdrawal (see Figure 2.1), is the duration of time from the last cigarette smoked until re-initiation of smoking behavior. This occurs when an individual has made a decision to quit smoking and makes a conscious effort to refrain from the behavior or is forced to abstain due to no-smoking policies. The longer an individual
abstains from smoking, the more likely he or she will undergo nicotine withdrawal. Typically, symptoms of nicotine withdrawal have a rapid onset within 24 to 36 hours after the last cigarette (Padula & Willey, 1993); however, symptoms may present up to 10 weeks after smoking cessation (Kenny & Markou, 2001). There are some hospital settings where a smoker may be permitted to leave a general medical/surgical floor to go to a designated area to smoke or who go outside to smoke despite tobacco-free policies; however, smokers admitted to intensive care units must abstain from smoking due to intensive care unit policies or medical conditions/treatments that prevent them from leaving the unit. A patient who is physiologically dependent on nicotine will begin to develop nicotine withdrawal symptoms if nicotine replacement is not initiated.

Standardized protocols exist to prevent alcohol withdrawal syndromes in critical care patients (Dissanaike, Halldorsson, Frezza, & Griswold, 2006; Eggers et al., 2002; Phillips, Haycock, & Boyle, 2006); however, scientific reports of similar protocols for nicotine withdrawal have not been found.

Unpleasant Symptoms: Nicotine Withdrawal

Nicotine Withdrawal. Nicotine withdrawal is used to describe a number of unpleasant symptoms that occur due to nicotine dependence and associated smoking abstinence (see Figure 2.1). The most commonly reported symptoms of nicotine withdrawal include anxiety, insomnia, irritability, restlessness/agitation, increased hunger, depressed mood, difficulty concentrating, and tobacco craving; these occur in association with termination or reduction of nicotine use after several weeks of daily use of nicotine containing products (Benowitz, 2008; American Psychiatric Association,
(1994). Padula and Willey (1993) examined the effects of tobacco withdrawal in patients admitted to a coronary care unit. They tested the hypothesis that smokers undergoing forced abstinence would exhibit more anxiety and other symptoms of withdrawal than non-smoking patients. The sample consisted of 16 smokers and 17 non-smokers, anxiety and nicotine withdrawal symptoms were measured in each group, and no interventions were used to prevent nicotine withdrawal. Findings were that smokers exhibited significantly more intense nicotine withdrawal symptoms, as would be expected when comparing smokers to non-smokers.

The prevalence of smokers admitted to hospitals and specifically to intensive care units is unknown due to inconsistent assessment of smoking status in patients and due to patients not reporting their smoking status during the hospital stay. This insufficient reporting of smoking status makes it difficult to determine the number of smokers who develop withdrawal symptoms during a hospital admission; however, approximately 70% to 85% of unaided quitters in the general population report withdrawal symptoms when attempting to quit smoking (Teneggi et al., 2002). This is important for smokers admitted to the hospital as nicotine withdrawal may begin early in the treatment course, adversely affect therapeutic outcomes, and increase hospital length of stay (Zack, 2001).

**Anxiety.** Nicotine withdrawal includes the unpleasant symptoms of anxiety, agitation, and cigarette craving (see Figure 2.1). Anxiety is an emotional state characterized by subjective and consciously perceived feelings of tension and apprehension or dread and foreboding (Zack, 2001; Dejong, Moser, An, & Chung, 2004). Patients admitted to intensive care settings often develop anxiety as a result of their
health status, the physical and emotional stress related to the environment, and fear of death itself (Pochard et al., 1995; Rincon et al., 2001). Anxiety is estimated to occur in approximately 70% to 87% of patients who are admitted to intensive care environments (Bone et al., 1995). Patients who express signs and/or symptoms of anxiety may exacerbate their initial medical or surgical problem that required intensive care admission, increase their risk of developing other physiological or psychological sequelae, and may compromise their therapeutic regimen. As a symptom that often accompanies the nicotine withdrawal syndrome, anxiety contributes to the psychological and physiological dependence associated with cigarette smoking behavior. Smokers admitted to high acuity areas have an increased risk of developing anxiety due to forced abstinence from cigarette smoking and nicotine withdrawal, in addition to their altered environment and health status. As these patients enter and progress through withdrawal, anxiety levels may increase due to craving for nicotine and patients may become more agitated due to their inability to alleviate withdrawal.

**Agitation.** Agitation is an overt expression of an organic or psychological illness or physical and/or emotional discomfort that is characterized by excessive motor or verbal behavior (Haskell, Frankel, & Rotondo, 1997). Agitation in patients admitted to intensive care settings may be caused by multiple factors; however, the most common contributors to agitation include stress associated with the hospital and intensive care admission, alcohol/drug intoxication or withdrawal, pain, anxiety, and delirium/dementia (Haskell et al., 1997; Jabir et al., 2005). Agitation is estimated to occur in approximately 52% to 71% of patients admitted to medical-surgical intensive care units (Jabir et al.,
and patients often exhibit anxiety, restlessness, irritability, and confusion prior to or along with agitation (Haskell et al., 1997). Agitation is another symptom that accompanies the nicotine withdrawal syndrome and may occur separately or in combination with anxiety and craving. Forced nicotine withdrawal increases the risk for agitation (Lucidarme et al., 2010). Agitation is associated with higher morbidity and mortality and ultimately contributes to a longer hospital length of stay (Fraser et al., 2000). Treatment of craving associated with nicotine dependence hypothetically would help alleviate agitation and associated sequelae.

**Cigarette Craving.** Tobacco craving or urge to smoke is a function of psychological and physiological nicotine dependence and is the smoker’s desire or sense of compulsion to use tobacco to produce a desired effect that was previously experienced (Etter, Houezec, & Perneger, 2003; Miyata & Yanagita, 2001). Craving is a symptom that is experienced early in the nicotine withdrawal syndrome and may even be experienced by regular smokers while actively smoking a cigarette (Tiffany & Drobes, 1991). The intensity of tobacco craving increases during the first hour of abstinence and peaks within 6 to 24 hours after smoking the last cigarette; however, craving may still be present up to 6 months after smoking cessation (Teneggi et al., 2002). Craving prevalence has not been examined in the critical care population and only one study was found that examined craving prevalence in hospitalized smokers (Rigotti et al., 2000). The sample consisted of 650 patients admitted to medical or surgical floors who reported smoking at least one cigarette within the month prior to admission. Nicotine withdrawal symptoms, smoking frequency while hospitalized, compliance with hospital no-smoking policy, and smoking
cessation after discharge were measured. Findings were that 89% of subjects reported at least one symptom of nicotine withdrawal, over half reported three symptoms (craving, restlessness/agitation, difficulty sleeping), 49% reported anxiety, and 55% reported craving for a cigarette since hospital admission (Rigotti et al., 2000). These findings suggest that craving occurs alone or in combination with other nicotine withdrawal symptoms and is a symptom that should be considered with patients experiencing anxiety or agitation. Utilization of NRT has the potential to mitigate withdrawal symptoms associated with tobacco craving and decrease craving as well.

**Performance Outcomes**

**Cognitive Outcome-Delirium.** For the purposes of this study, delirium is considered to be a cognitive outcome influenced by the nicotine withdrawal syndrome (see Figure 2.1). It has also been included among the symptoms in the nicotine withdrawal syndrome. It is a condition that is often precipitated by anxiety and confusion, and is an acute disorder of attention and cognition (Mayer et al., 2001). It is also described as a disturbance in conscious behavior characterized by fluctuations of impaired cognitive functioning over a period of time (Ely et al., 2001). Patients admitted to intensive care environments often experience an abrupt decline in physiological and cognitive functioning related to their medical condition, withdrawal from a substance, or from other factors. The incidence of delirium in these settings varies greatly and has been reported as low as 8% up to 92% (Guenther et al., 2012). It is usually related to patient co-morbidities and risk factors, characteristics of the unit providing care (neurological vs. surgical vs. medical critical care), and the type of measurement tool used to assess
delirium. Several investigators have cited factors that predispose patients to the development of delirium (Roberts, 2004; Aldemir, Ozen, Kara, Sir, & Bac, 2001; Pandharipande et al., 2008; Ely et al., 2001; Webb, Carlton, & Geehan, 2000; Pisani, Murphy, Van Ness, Araujo, & Inouye, 2007; Axell, Malmros, Bergbom, & Lundberg, 2002; Ouimet, Kavanagh, Gottfried, & Skrobik, 2007; McCusker et al., 2001; McNicoll et al., 2003; Ely et al., 2004) and three studies have identified smoking abstinence as an independent risk factor (Dubois, Bergeron, Dumont, Dial, & Skrobik, 2001; Ouimet et al., 2007; Van Rompaey et al., 2009). The prevalence of nicotine withdrawal in the general population and the prevalence of anxiety, agitation, and delirium in patients admitted to intensive care environments (Teneggi et al., 2002; Bone et al., 1995; Fraser, Prato, Riker, Berthiaume, & Wilkins, 2000; Aldemir et al., 2001) indicates that reducing nicotine withdrawal symptoms may decrease the development of delirium as well as length of hospital stay.

**Secondary Outcome- Hospital Length of Stay.** Hospital length of stay (LOS), for the purposes of this study, is considered to be a secondary outcome influenced by the nicotine withdrawal syndrome’s effect on delirium (see Figure 2.1). LOS is the time during which a patient is admitted to and receiving care in an acute care facility and extends from admission to discharge or death. LOS may be influenced by physiological as well as psychological factors. Symptoms of withdrawal, such as anxiety and agitation, contribute to the development of delirium and prolong LOS (Ely et al., 2001; Ouimet et al., 2007; Marshall & Soucy, 2003). Thomason et al. (2005) evaluated delirium as an independent predictor of LOS and found that 48% (125 subjects) experienced delirium
that was associated with one extra day in the ICU and two extra days in the hospital. Treatment of nicotine withdrawal symptoms has the potential to decrease or eliminate the development of delirium and shorten hospital LOS.

**Nicotine Replacement Therapy**

NRT is a pharmacologic intervention used to reduce or eliminate cigarette smoking behaviors. The goal of NRT is to maintain nicotine in the bloodstream at levels that reduce withdrawal symptoms. There have been reports that smoking cessation treatments (NRT, counseling, or other psychosocial interventions) are effective in hospitalized smokers (Fiore et al., 2008); however, these studies were conducted in cardiac or general medical/surgical patients and have not included intensive care patients. Two case reports identified that NRT was effective in intensive care patients exhibiting signs and symptoms of nicotine withdrawal after multiple futile attempts with anxiolytics and antipsychotics (Honisett, 2001; Mayer et al., 2001). Two retrospective case-control studies identified that NRT was associated with increased hospital mortality (Lee & Afessa, 2007; Paciullo, Short, Steinke, & Jennings, 2009). Due to study design flaws, a cause-effect relationship could not be established by Lee and Afessa (2007) nor could the findings of Paciullo et al. (2009) be generalized from post-operative coronary artery bypass graft patients to all smokers admitted to intensive care environments. Two additional retrospective studies in neuro-ICU patients revealed that NRT appeared safe in patients with acute subarachnoid hemorrhage, that mortality was lower in patients receiving NRT when compared to patients not receiving NRT (Seder et al., 2011), and there was no difference in unfavorable discharge disposition among smokers treated with
NRT, smokers not treated with NRT, and non-smokers (Panos, Tesoro, Kim, & Mucksavage, 2010).

A prospective observational study by Cartin-Ceba, Warner, Hays, & Afessa (2011) assessed the impact of NRT on outcomes in active cigarette smokers admitted to a medical intensive care unit. Findings indicated that NRT was not associated with increased hospital mortality or hospital length of stay; however, there was a significant increase in frequency of delirium, agitation, and psychoactive drug requirements in patients receiving NRT when compared to patients not receiving NRT. This was not considered clinically significant due to a lack of data about potential confounders (alcohol withdrawal and/or psychoactive substance withdrawal), possible ineffective NRT dose for treatment of nicotine withdrawal symptoms, and possible effects of mechanical ventilation on delirium and agitation development (Cartin-Ceba et al., 2011).

Of note, no report was found of a prospective study comparing effects of smokers with NRT to a group of smokers without NRT admitted to intensive care.

Purpose

The purpose of this investigation was to describe smokers admitted to an intensive care setting and explore possible relationships among nicotine withdrawal symptoms (anxiety, agitation, craving) and the outcomes of delirium and length of hospital stay. Use of NRT and its relationship to symptoms was described as well.
Methods

Design

A prospective observational design was used in this study. Measures were collected within 24 hours of hospital admission, twice daily up to 3 days while in intensive care, and within 12 hours after discharge from the ICU to a step-down unit or regular floor care. Measures included the Faces Anxiety Scale, Richmond Agitation Sedation Scale, Craving Visual Analog Scale (VAS), a salivary cortisol response (physiologic measure of anxiety associated with nicotine withdrawal) and the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) to measure delirium.

Sample and Setting

A non-probability convenience sample of patients \( n = 8 \) was studied after approval by the Biomedical Institutional Review Board (IRB) of The Ohio State University. The investigation was conducted at The Ohio State University, University Hospitals East, Columbus, Ohio, in the intensive care unit (ICU), a 19-bed unit that admits approximately 100 patients per month or 1200 patients per year. Based on a conservative estimate of 30% smoking prevalence of smokers admitted to critical care units, it was estimated that a potential 360 patients admitted to the ICU would be smokers.

Screening of potential subjects was accomplished by verbal report of new ICU admissions from IRB-approved ICU key personnel and/or the medical center clinical nurse scientist up to twice daily. Eligibility was confirmed by medical record review and consent for study participation was obtained. Deception was used during the informed consent.
consent process per IRB request. Potential subjects were informed that the study purpose was to evaluate the effect of the ICU setting on smokers’ responses to stress and nicotine craving. This was done to prevent over-reporting of nicotine withdrawal symptoms in patients not receiving NRT and under-reporting of nicotine withdrawal symptoms in patients receiving NRT. Inclusion criteria were 18 years of age or older, male or female gender, English speaking, smoking status $\geq 5$ cigarettes per day up to the day of admission, admission to the ICU from the emergency department or any hospital floor/unit within 24 hours of hospital admission or as a transfer from another facility within 24 hours of admission to that facility, cognitively aware with the ability to verbally or non-verbally respond (nod head appropriately or ability to point to answers/selections on instruments), may or may not be intubated and mechanically ventilated. Exclusion criteria were diagnosis of acute myocardial infarction, antipsychotic, anxiolytic, or narcotic therapy preventing the ability to communicate, pregnancy, and history of dementia. Additional data extracted from the medical record included the following: patient medications including NRT, antidepressant, narcotic, anxiolytic, and antipsychotic medications and their dosages; history of alcohol use and amount; history of illicit drug use and amount, and psychiatric diagnoses. To maintain adequate representation of the types of diagnoses managed in the ICU, all patients who met inclusion and exclusion criteria were considered for study participation. Patients’ receipt of NRT was at the discretion of the physician.
Measures

Three of the unpleasant symptoms associated with nicotine withdrawal, anxiety, agitation, and cigarette craving, were the primary focus of this study. The primary outcome of delirium (cognitive outcome) and the secondary outcome of hospital length of stay were also evaluated. A review of study measures and data collection time points is presented in Table 2.1.

Anxiety. Many instruments used to measure anxiety in patients, for example, the Spielberger State-Trait Anxiety Scale and the Brief Symptom Inventory (McKinley et al., 2003; Derogatis & Melisaratos, 1983) are inappropriate for use with patients in intensive care settings due to response burden and patient condition. Anxiety was measured using the Faces Anxiety Scale, a single item scale consisting of a 5-point response ranging from a neutral face (score of 1) to one demonstrating extreme fear (score of 5) (McKinley et al., 2003). A study comparing the Faces Anxiety Scale to the Brief Symptom Inventory and the Visual Analog Scale-Anxiety revealed that intensive care patients were able to more easily respond to the Faces Scale versus the other two instruments suggesting decreased response burden (McKinley et al., 2003). Another study established predictive validity for the Faces Scale by using clinical judgment measures (standard interview questions and assessment of clinical signs or anxiety) and then having the patients respond to the Faces Anxiety Scale (McKinley, Stein-Parbury, Chehelnabi, & Lovas, 2004). Clinical judgment assessment and patients’ self-report on the Faces Anxiety Scale were moderately correlated with a value of 0.64.
Cortisol Production. Cortisol is a hormone released by the adrenal cortex and is a major end-product of hypothalamic-pituitary-adrenal (HPA) axis activation in humans experiencing stress and anxiety. Cortisol production increases due to circadian rhythm influences, but more importantly, to environmental or psychosocial stressors (fear, anxiety, etc.) (Kalman & Grahn, 2004; Sher, 2004). Advantages of salivary cortisol assays over plasma cortisol assays include relatively easy and painless collection procedures and samples that contain only the active unbound form of cortisol in contrast to plasma which contains protein bound and free hormone (Sher, 2004; Kirchbaum & Hellhammer, 1994; Lawrence, 2002). The normal cortisol range for the purpose of this study was .112-.812 µg/dL (Salimetrics, 2011). Saliva samples were collected via sterile plastic pipette and transferred from the subject’s mouth to the cryovial and then stored at ≤ 80° C until batch assay. Samples can be stored at room temperature for several hours without loss of hormone level (Sher, 2004; Kirchbaum & Hellhammer, 1994).

A commercial enzyme immunoassay kit (Salimetrics, LLC, State College, PA) was used to conduct cortisol assays in the Biobehavioral Lab at The Ohio State University College of Nursing. The kit included a microtiter plate coated with cortisol antibodies. Cortisol standards and samples competed for antibody binding sites with cortisol linked horseradish peroxidase enzyme provided in the kit. Adding tetramethylbenzidine (TMB) substrate allowed for detection of bound cortisol peroxidase, producing a blue color detectable by a micoplate reader at 450nm. Optical density (OD) for each sample was measured and cortisol content calculated by plotting the OD of unknown samples against a curve established by the standard samples that contained known cortisol quantities. The
amount of cortisol peroxidase detected was inversely proportional to the amount of
unbound active cortisol in the sample. Salimetrics reports a sensitivity of < 0.003 µg/dL,
an intra-assay coefficient of variation (CV) of 3.35 to 3.65%, and an inter-assay CV of
3.75 to 6.41% (Salimetrics, 2011).

**Agitation.** Agitation was measured using the observer rated Richmond Agitation-
Sedation Scale (RASS), assessing levels of agitation (+1 to +4 with +4 being combative)
or sedation (-1 to -5 with -5 being unarousable) with “0” representing a calm and alert
state (Sessler et al., 2002). The score ranged from +4 to -5. Construct validity was
determined by comparing results of the RASS with results of an attention-screening
assessment tool ($r = 0.78$), Glasgow Coma Scale ($r = 0.91$), and with bispectral analysis
($r = 0.64$) (Ely et al., 2003). Inter-rater reliability was determined by comparing
assessments by two critical care nurses, an intensivist, and a neuropsychiatrist expert
indicating a Cohen’s kappa ranging from 0.79 to 0.91. Another study established inter-
rater reliability ($k = 0.65-0.80$) between assessments by two physicians, two nurses, and a
pharmacist and concurrent validity between the RASS and a sedation-agitation VAS ($r = 0.93$) (Sessler et al., 2002).

**Cigarette Craving.** Cigarette craving was measured using the Cigarette Craving
VAS, a 100-mm, horizontal, unmarked scale ranging from 0 (no craving) to 100 (craving
as bad as can be). Subjects were asked to point to the level of craving they were
experiencing and a mark was drawn at the area indicated. One study has established inter-
rater reliability indicating a strong correlation ($0.999, p < 0.0001$) between two
independent reviewer scores and concurrent validity ($r = 0.75$) with the Shiffman-Jarvik
Craving Subscale (SJCS) (Steuer & Wewers, 1989). Another study established concurrent validity between the Craving VAS and craving items on the SJCS at two time points of 0.64 and 0.47 respectively (Wewers, Rachfal, & Ahijevych, 1990).

**Delirium.** Delirium was measured using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) (Ely & Truman, The confusion assessment method for ICU (CAM-ICU)). This instrument consists of two steps. Step one assesses level of agitation or sedation using the RASS. Step two assesses four features of delirium including: (1) acute mental status change, (2) inattention, (3) disorganized thinking, and (4) altered level of consciousness (Ely & Truman, The confusion assessment method for ICU (CAM-ICU)). Features one and two (acute mental status change and inattention) must both be present in order to proceed to the assessment of features three and four (disorganized thinking and altered level of consciousness). In the current study, the RASS score calculated from the agitation/sedation measurement was used in the CAM-ICU. If an acute fluctuation in the RASS score was present in step one, then step two feature one would be rated as “present” on the CAM-ICU worksheet. Inattention was measured using the Attention Screening Examination (ASE) which assessed patient ability to maintain focused attention. This tool consists of auditory and visual recognition components and a score of less than 8 indicates inattention. This was marked as “absent” or “present” on the CAM-ICU worksheet. Disorganized thinking (feature three) was assessed by asking the patient yes/no questions developed specifically for the CAM-ICU such as “does a stone float on water” and “do two pounds weigh more than one pound?” Disorganized thinking was marked “present” if the patient answered three out of four questions incorrectly.
Altered level of consciousness was marked “present” if the patient was anything other than alert. Delirium was considered present if features one and two and either feature three or four were present in the patient. The CAM-ICU has demonstrated high sensitivity (93%-100%) and specificity (98%-100%) in studies of delirium in intensive care unit patients (Ely et al., 2001) and inter-rater reliability has been high as evidenced by a Cohen’s kappa of 0.84 to 0.96 (Ely et al., 2001; Schuurmans, Deschamps, Markham, Shortridge-Baggett, & Duursma, 2003).

**Hospital Length of Stay.** LOS was calculated by subtracting the admission date and time, in days and hours, from the discharge date and time, in days and hours. Discharge means discharge from the hospital to home or another care facility or death.

**Cotinine.** Cotinine is a marker of nicotine dependence and was used to biochemically confirm smoking status and to determine fidelity of the intervention (subjects receiving NRT as part of care) on day 3. Cotinine is a major product of nicotine metabolism and may be measured in a number of sources including saliva, plasma, and urine to biochemically confirm self-report of smoking behavior and nicotine use (SRNT Subcommittee on Biochemical Verification, 2002) and salivary collection for cotinine analysis is non-invasive (Abrams, Follick, Biener, Carey, & Hitti, 1987). Cotinine has a long half-life of 18-20 hours that allows measurement of levels several days after last nicotine use (Benowitz, Kuyt, Jacob, Jones, & Osman, 1983). Higher levels would indicate higher exposure to nicotine in the recent past and lower levels would indicate lack of use or decreased exposure to nicotine containing products. Saliva cotinine levels utilized to classify subjects as smokers must be ≥ 15 ng/ml. The assay has a sensitivity
and specificity of 96-97% and 99-100% respectively in determining smoking status (SRNT Subcommittee on Biochemical Verification, 2002). A salivary cotinine sample was collected at baseline and the morning of study day 3 via passive drool. Saliva was collected with a sterile plastic pipette and transferred from the subject’s mouth to the cryovial. The sample was stored at The Ohio State University College of Nursing’s Biobehavioral Lab at -80° C until batch assay.

A commercial enzyme immunoassay kit (Salimetrics, LLC, State College, PA) was used to conduct cotinine assays in the Biobehavioral Lab at The Ohio State University College of Nursing. The kit contained a microtiter plate, a solution of rabbit anti-cotinine antibody, cotinine standard, and an enzyme conjugate of cotinine labeled with horseradish peroxidase. Standards and samples were added to the microtiter plate along with rabbit antibodies to cotinine and cotinine linked to horseradish peroxidase. Cotinine in the standards, samples, and conjugate competed for antibody binding sites. Samples were incubated and unbound components washed away. Bound conjugate was measured by the reaction of peroxidase enzyme to tetramethylbenzidine (TMB) substrate producing a blue color. After incubating in the dark for an additional 25 minutes a stop solution was added producing a yellow color that was detectable on a plate reader at 450nm. Optical density (OD) for each sample was measured and cotinine content calculated by plotting the OD of unknown samples against a curve established by the standard samples that contained known cotinine quantities. The amount of cotinine peroxidase detected was inversely proportional to the amount of cotinine present in the sample. Salimetrics reports a sensitivity of 0.15 ng/dL, an intra-assay coefficient of
variation (CV) of 4.5 to 8.6%, and an inter-assay CV of 4.21 to 9.04% (Salimetrics, 2011).

**Demographic and Clinical Variables.** Demographic and clinical information collected included age, admission diagnosis, concurrent diagnoses, severity of illness (APACHE IV), alcohol and/or drug use, medications and dosages, cigarettes smoked per day, and time of last cigarette smoked prior to admission. Information was obtained from the medical record and confirmed by subject/family interview.

**Procedure**

Patients were recruited from new admissions to the ICU who met inclusion and exclusion criteria from August 2010 to March 2012. Screening of potential subjects was accomplished by verbal report from ICU nurse key personnel who identified new ICU admissions who were smokers. After determining eligibility, an explanation of the study using IRB-recommended partial disclosure was provided (subjects were informed during the consent process that the study purpose was to evaluate smokers’ responses to stress and craving when admitted to the ICU versus the effects of NRT on nicotine withdrawal symptoms in critically ill smokers). Informed consent was obtained from the patient after study explanation. A series of instruments were then completed including the Faces Anxiety Scale, Richmond Agitation-Sedation Scale, Craving VAS, and Confusion Assessment Method-Intensive Care Unit (CAM-ICU). The instruments were completed in the patient’s room with the doors closed. Patients also provided a salivary cotinine sample to verify smoking status/nicotine dependence and a salivary cortisol sample to determine baseline cortisol levels. All measures, excluding salivary cotinine, were
collected in the morning (between 8 AM and 11 AM) and evening (between 8 PM and 11 PM) of ICU days 2, 3, and 4 and within 12 hours of discharge from the critical care unit to the step-down unit (see Table 2.1). This data collection schedule was designed to capture the diurnal variations in physiological measures. A second salivary cotinine sample was collected the morning of ICU day 3 to determine fidelity of treatment in subjects receiving NRT as part of care. Demographic and clinical information was collected at study admission. At the conclusion of the last study visit, subjects were debriefed, according to IRB approved protocol, on the true intent of the study regarding the impact of NRT on withdrawal symptoms. Subjects remained in the study during the present hospitalization until the following: they were transferred from the ICU to a step-down unit, they requested removal from the study, or death.

**Data Analysis**

Descriptive statistics were used to characterize the subjects on demographic and clinical variables. Nonparametric statistics were used to explore relationships among study variables. Subjects were grouped into those receiving NRT as part of care and those who did not receive NRT as part of care and variables were described and compared. Significance level was set *a priori* at 0.05 for all analyses. Data were analyzed using SPSS for Windows (version 19.0, Chicago, IL).

**Results**

Demographic and clinical characteristics of participants are presented in Table 2.2 with one participant receiving NRT and seven participants not receiving NRT as part of their ICU care. The sample had an equal number of males and females and the one
participant receiving NRT was female. The majority of the sample was over the age of 50 and African American with only two Caucasian participants. The most common admission diagnosis was diabetic ketoacidosis. Secondary diagnoses were variable between subjects and included chest pain, acute renal failure, abdominal pain, hypotension, tobacco dependence, possible meningitis, and hypertension. No participants received antipsychotic medications. Three (37.5%) participants received anxiolytic medications as needed, five (62.5%) participants received narcotics as needed, and two (25%) participants received scheduled antidepressant medication. Four (50%) participants received corticosteroids. Three (37.5%) participants reported regular use of alcohol and two (25%) participants reported using recreational drugs on a weekly basis. The number of cigarettes smoked per day prior to admission ranged from 6 to 20 with a mean of 10.38 ± 4.34 cigarettes smoked. The time from last cigarette smoked to admission to the ICU ranged from 3.25 hours to 17.5 hours with a mean of 11.53 ± 4.82 hours. The severity of illness of participants, as determined by the Acute Physiology and Chronic Health Evaluation (APACHE IV) score ranged from 37 to 86 with a mean of 56.13 ± 18.98 with higher scores indicating greater illness severity. The mean ICU length of stay and mean hospital length of stay were 1.62 ± .60 and 6.61 ± 3.60 days respectively. Of note, no participants required intubation with mechanical ventilation.

Confirmation of smoking status was established at baseline for five participants. Insufficient quality and/or quantity of saliva samples for the remaining three study participants precluded analysis. Salivary cotinine levels ranged from 19.30 ng/ml to 488.70 ng/ml with a mean level of 196.2 ng/ml ± 191.97 ng/ml. There were no salivary
cotinine results for ICU day 3. The only two subjects remaining in the ICU at this time point did not provide saliva samples of sufficient quality and/or quantity. In addition, salivary cortisol levels were obtained as physiologic confirmation of anxiety in three participants at study admission and morning of study day 2 and in four study participants at study discharge. Results for salivary cortisol are displayed in Table 2.3. Salivary cortisol results were also limited due to insufficient saliva quality and/or quantity for sample processing. Collected and missing data time points for cotinine and cortisol measures are displayed in Table 2.4.

Descriptive statistics for Faces Anxiety Scale and Craving VAS scores at admission, the morning of ICU day 2, and at discharge for all subjects (n = 8) are presented in Table 2.5. In addition, repeated measures analysis of Faces Anxiety Scale and Craving VAS scores at admission, the morning of ICU day 2, and at discharge were conducted for all subjects using the Friedman test. Results indicated that there were no significant differences in median anxiety levels ($\chi^2 (2) = 3.895, p = .143$) or craving levels ($\chi^2 (2) = 1.652, p = .438$) over the three time points. Collected and missing data time points for anxiety and cigarette craving are displayed in Table 2.6. There were no participants exhibiting signs of agitation or delirium at any of the study time points; therefore, agitation and delirium were not examined in these analyses.

To examine relationships between variables as indicated in the TOUS model (see Figure 2.1), a Kendall’s tau-b ($\tau_b$) correlation analysis was performed for data collected at available measurement time points. At admission, Kendall’s tau-b coefficient was used to examine the extent to which smokers’ cotinine levels were associated with anxiety and
craving levels. The results indicated a non-significant negative relationship with anxiety ($\tau_b = -.11$, two tailed $p = .801$) and a non-significant positive relationship with cigarette craving ($\tau_b = .40$, two tailed $p = .327$). Of note, there were only 5 cotinine samples available for this analysis.

Kendall’s tau-b was also used to examine relationships between anxiety and cigarette craving at admission, morning of study day 2, and at discharge. The results at admission indicated a non-significant positive relationship ($\tau_b = .432$, two tailed $p = .155$). The results for morning of study day 2 ($\tau_b = .824$, two tailed $p = .009$) and study discharge ($\tau_b = .923$, two tailed $p = .003$) were both significant indicating strong positive relationships between anxiety and cigarette craving at those two time points.

Relationships among cortisol, anxiety, and cigarette craving were examined at admission and morning of study day 2 for three subjects and at study discharge for four subjects (see Table 2.7). Cortisol and craving scores for admission and study day 2 time points had significant negative relationships indicating higher cortisol levels were associated with lower craving scores; however, there was no significant relationship between cortisol and craving at study discharge ($\tau_b = .667$, two tailed $p = .174$). In addition, there were no significant relationships between cortisol and anxiety at study admission ($\tau_b = .333$, two tailed $p = .602$), morning of study day 2 ($\tau_b = -.816$, two tailed $p = .221$), or study discharge ($\tau_b = .707$, two tailed $p = .180$).
Discussion

As a middle-range theory, the Theory of Unpleasant Symptoms (TOUS) has been utilized to guide symptom research in multiple patient populations, but has not guided research in critical care patients until the current study. Critical care patients experience a number of unpleasant symptoms. The TOUS provides a framework that allows for the evaluation of those symptoms as well as relationships among symptoms, influencing factors, and performance outcomes, and is appropriate to consider when conducting research in this patient population. This study explored characteristics of smokers admitted to an intensive care setting and relationships among nicotine withdrawal symptoms (anxiety, agitation, cigarette craving), delirium, and length of hospital stay and the TOUS, as a guiding framework (see Figure 2.1), was useful in accomplishing this goal. The results of this study lent some support to hypothesized relationships in the TOUS, specifically relationships between physiological influencing factors (nicotine dependence) and symptoms (cigarette craving) as well as relationships among symptoms (anxiety and cigarette craving) of nicotine withdrawal. The use of NRT and its relationship to symptoms was explored as well; however, only one study participant received NRT, thus no conclusions could be drawn.

Smoking status was biochemically confirmed by salivary cotinine in five study participants with levels ranging from 19.3 to 488.7 ng/ml. Cotinine was the proxy measure for nicotine dependence, thus establishing it as a physiological influencing factor, since levels were well above those required to classify participants as smokers (SRNT Subcommittee on Biochemical Verification, 2002). Samples obtained from the
remaining three study participants were unable to be processed due to insufficient saliva quantity or quality. An explanation for the reported level 488.7 ng/ml is unclear as this study participant was not receiving NRT, smoked only 10 cigarettes the day before ICU admission, and had not smoked a cigarette for 13 hours prior to saliva sample collection. Of note, the participant receiving NRT had a salivary cotinine level of 276.1 ng/ml, smoked 10 cigarettes the day before hospital admission, and had not smoked a cigarette for 17.5 hours prior to saliva sample collection.

This study supports the existence of a relationship between unpleasant symptoms of anxiety and cigarette craving as a strong significant positive relationship existed between the two symptoms indicating that patients with high levels of cigarette craving experienced high levels of anxiety. However, this relationship was only present the morning of study day 2 and at study discharge and not at study admission. This is an interesting finding as mean scores for anxiety and craving were highest at study admission (see Table 2.5) and trended down over the course of the ICU stay. The higher levels were most likely due to outlier scores for anxiety and cigarette craving present at study admission. A significant inverse relationship was present between salivary cortisol and cigarette craving at study admission and morning of study day 2 indicating that patients with higher levels of cortisol had lower levels of cigarette craving. This conflicts with findings by Cohen, al’Absi, and Collins (2004) where higher cortisol levels were associated with higher levels of cigarette craving and nicotine withdrawal in healthy smokers. These results seem counterintuitive and should be interpreted with caution as only 3 cortisol samples were sufficient for analysis at these 2 time points. Of note,
participants reporting the highest craving levels did not provide sufficient saliva samples for cortisol analysis.

There were no significant relationships between salivary cortisol level and anxiety level, despite cortisol being a physiological indicator of stress and anxiety (Kalman & Grahn, 2004). Due to saliva sample quantity and quality, few samples were available for this analysis which limits the usefulness of these findings. In addition, three of the four participants who had adequate samples of saliva for cortisol analysis were receiving exogenous corticosteroids, which could interfere with the validity of these results; however, the findings in this study were similar to diurnal cortisol concentrations measured in patients with coronary heart disease (Fantidis et al., 2002). Of note, the participant receiving NRT had an admission cortisol level of 0.59 µg/dL and a discharge cortisol level of 0.12 µg/dL. The cortisol level for this participant on the morning of study day 2 was > 3.150 µg/dL and was not included in the cortisol analysis. The rationale for this finding is probably related to the fact that the participant received both oral and intravenous corticosteroids just prior to saliva sample collection.

No study participants exhibited agitation during the course of the study; therefore, the relationships between agitation, cigarette craving, and anxiety could not be assessed.

The findings of this study did not support relationships between the nicotine withdrawal symptom experience and the cognitive outcome of delirium in critically ill smokers as there were no study participants that exhibited signs of delirium. This could be related to illness severity of patients participating in the study. Study participants were
not receiving invasive therapies, such as intubation with mechanical ventilation, and were not receiving continuous or regularly scheduled psychoactive medications, both of which increase the risk of delirium in ICU patients (Truman & Ely, 2003). In addition, a relationship between the nicotine withdrawal symptom experience and the outcome of hospital length of stay could not be established based on study findings. The average hospital length of stay in this patient sample was 6.61 days; however, after removing outliers for two patients who had hospital length of stays of 12.5 and 11.9 days respectively, the average hospital length of stay was 4.75 days, which is similar to the national average of 4.6 days (Wier et al., 2011).

Limitations

There are several limitations that affect the generalizability of these study findings. The exploratory nature of this study is a major limitation in understanding how NRT influences the development of nicotine withdrawal symptoms in critical care patients; however, randomization of patients to a treatment group receiving NRT or control group without NRT was not feasible due to discretionary prescribing practices of NRT by ICU physicians. The small sample size was another limitation and is related to the number of admissions to the ICU that were smokers as well as patient characteristics. The study site ICU was estimated to have 100 admissions per month (1200/year) whereas the actual average of admissions per month was 50 (600/year). This limited the number of smokers available for study participation. In addition, the acuity level of patients admitted to the study site ICU made it difficult to enroll smokers who met study inclusion criteria as participants were required to be awake and alert at study admission. However,
participants that met this study criterion and completed the study did not exhibit signs of agitation or delirium thus contributing to biased results. The demographic composition of the sample also limits generalizability of study findings as the majority of the sample was African American.

Conclusion

In summary, the results of the present study suggest that symptoms of nicotine withdrawal, specifically anxiety and cigarette craving, occur in critically ill smokers; however, the influence of nicotine withdrawal symptoms on delirium development or hospital length of stay could not be determined. In addition, the influence of NRT on the development of nicotine withdrawal symptoms could not be effectively assessed and warrants further study. Future research is needed to explore symptoms of nicotine withdrawal in critically ill smokers, utilization of NRT in this patient population, as well as the effect of NRT on withdrawal symptoms, and the TOUS is a useful theory to facilitate this process. The use of NRT in hospitalized smokers decreases acute nicotine withdrawal symptoms and promotes a positive recovery (Rigotti et al., 2008; Fiore, et al., 2008); however, the lack of NRT use in critically ill smokers impedes knowledge development regarding this patient issue. A clearer understanding of the unpleasant symptoms of nicotine withdrawal in critically ill smokers will promote improved assessment of nicotine withdrawal and implementation of appropriate interventions.
References


research: Recent developments and applications. *Psychoneuroendocrinology, 19*, 313-333.


Figure 2.1. The Theory of Unpleasant Symptoms as a Model for the Affects of Nicotine Replacement Therapy (NRT) on Nicotine Withdrawal in Critically Ill Smokers. Adapted from “The middle-range theory of unpleasant symptoms: An update,” by E. Lenz, L. Pugh, R. Milligan, A. Gift, and F. Suppe, 1997, Advances in Nursing Science, 19, p. 17. © 1997 Aspen Publishers, Inc.
<table>
<thead>
<tr>
<th>Measure</th>
<th>Description</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>D/C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faces Anxiety Scale</td>
<td>Single item 5-point scale ranging from a neutral face (score of 1) to one demonstrating extreme fear (score of 5)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Salivary cortisol</td>
<td>Normal range -.112-.812 µg/dL</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>RASS&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Observer-rated single item scale assessing level of agitation (+1 to +4 with +4 being combative) or sedation (-1 to -5 with -5 being unarousable). “0” represents a calm and alert state. Score range: -5 to +4.</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Cigarette Craving VAS</td>
<td>Single item, 100-mm, horizontal scale ranging from 0 (no craving) to 100 (craving as bad as can be)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CAM-ICU&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Two-step observer-rated instrument assessing delirium</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Step 1: Sedation level assessed by the RASS. If RASS is -4 or -5 stop and reassess patient later. If RASS is above -4 (-3 through +4) then proceed to step 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Step 2: Delirium assessment: four features assessed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Feature 1: Acute mental status change</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Feature 2: Inattention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Feature 3: Disorganized thinking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Feature 4: Altered level of consciousness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Delirium is present if features 1 and 2 are present as well as feature 3 and/or feature 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salivary cotinine</td>
<td>Levels ≥ 15 ng/ml classify subjects as smokers. Higher levels indicate higher exposure and lower levels indicate decreased exposure to nicotine products</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Richmond Agitation-Sedation Scale; <sup>b</sup> Confusion Assessment Method for the Intensive Care Unit; <sup>c</sup> Discharge from ICU
<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Gender</th>
<th>Race/Ethnicity</th>
<th>Admission Diagnosis</th>
<th>APACHE IV Score</th>
<th>CPD</th>
<th>Received NRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject 1</td>
<td>47</td>
<td>Male</td>
<td>African-American</td>
<td>AE CHF</td>
<td>37</td>
<td>10</td>
<td>No</td>
</tr>
<tr>
<td>Subject 2</td>
<td>51</td>
<td>Female</td>
<td>African-American</td>
<td>DKA</td>
<td>41</td>
<td>11</td>
<td>No</td>
</tr>
<tr>
<td>Subject 3</td>
<td>27</td>
<td>Male</td>
<td>African-American</td>
<td>DKA</td>
<td>56</td>
<td>10</td>
<td>No</td>
</tr>
<tr>
<td>Subject 4</td>
<td>62</td>
<td>Male</td>
<td>African-American</td>
<td>Hypotension</td>
<td>79</td>
<td>20</td>
<td>No</td>
</tr>
<tr>
<td>Subject 5</td>
<td>67</td>
<td>Female</td>
<td>African-American</td>
<td>Pneumonia</td>
<td>65</td>
<td>6</td>
<td>No</td>
</tr>
<tr>
<td>Subject 6</td>
<td>61</td>
<td>Female</td>
<td>African-American</td>
<td>AE COPD</td>
<td>48</td>
<td>10</td>
<td>Yes</td>
</tr>
<tr>
<td>Subject 7</td>
<td>36</td>
<td>Female</td>
<td>Caucasian</td>
<td>Allergic reaction</td>
<td>37</td>
<td>10</td>
<td>No</td>
</tr>
<tr>
<td>Subject 8</td>
<td>63</td>
<td>Male</td>
<td>Caucasian</td>
<td>Sepsis</td>
<td>86</td>
<td>6</td>
<td>No</td>
</tr>
</tbody>
</table>

Note. AE CHF = acute exacerbation congestive heart failure; DKA = diabetic ketoacidosis; AE COPD = acute exacerbation chronic obstructive pulmonary disease; CPD = cigarettes smoked per day
Table 2.3  *Salivary cortisol mean scores in µg/dL at study admission, morning of day 2, and discharge*

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>M</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission</td>
<td>3</td>
<td>.331</td>
<td>.255</td>
</tr>
<tr>
<td>Study day 2 (AM)</td>
<td>3</td>
<td>.409</td>
<td>.285</td>
</tr>
<tr>
<td>Discharge</td>
<td>4</td>
<td>.130</td>
<td>.028</td>
</tr>
<tr>
<td>Subject</td>
<td>Cortisol</td>
<td>Cotinine</td>
<td>Day 2</td>
</tr>
<tr>
<td>----------</td>
<td>----------</td>
<td>----------</td>
<td>-------</td>
</tr>
<tr>
<td></td>
<td>Admit</td>
<td>AM</td>
<td>PM</td>
</tr>
<tr>
<td>Subject 1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Subject 2</td>
<td>-</td>
<td>X</td>
<td>-</td>
</tr>
<tr>
<td>Subject 3</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Subject 4</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Subject 5</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Subject 6</td>
<td>X</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Subject 7</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Subject 8</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Note. X = data collected; - = missing data; blank = patient not in ICU*
Table 2.5  Anxiety and cigarette craving mean scores at study admission, morning of day 2, and discharge (n = 8)

<table>
<thead>
<tr>
<th></th>
<th>Admit</th>
<th>Day 2 (AM)</th>
<th>Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
</tr>
<tr>
<td>Faces Anxiety Score</td>
<td>3</td>
<td>1.512</td>
<td>2.88</td>
</tr>
<tr>
<td>Craving VAS</td>
<td>43</td>
<td>33.709</td>
<td>36.63</td>
</tr>
</tbody>
</table>
Table 2.6 Collected and Missing Data for Anxiety, Agitation, Cigarette Craving, and Delirium Measures

<table>
<thead>
<tr>
<th></th>
<th>Day 2</th>
<th></th>
<th>Day 3</th>
<th></th>
<th>Day 4</th>
<th></th>
<th>Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Admit</td>
<td>AM</td>
<td>PM</td>
<td>AM</td>
<td>PM</td>
<td>AM</td>
<td>PM</td>
</tr>
<tr>
<td>Subject 1</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Subject 2</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Subject 3</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Subject 4</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Subject 5</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Subject 6</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Subject 7</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Subject 8</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

Note. X = data collected; blank = patient not in ICU
Table 2.7  Kendall’s tau correlation coefficients for anxiety, cigarette craving, and cortisol at 3 study time points

<table>
<thead>
<tr>
<th></th>
<th>Admit (n = 3)</th>
<th>Day 2 (AM) (n = 3)</th>
<th>Discharge (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anxiety</td>
<td>Craving</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Cortisol admit</td>
<td>.333</td>
<td>-1.000*</td>
<td>-</td>
</tr>
<tr>
<td>Cortisol day 2 (AM)</td>
<td>-</td>
<td>-</td>
<td>-.816</td>
</tr>
<tr>
<td>Cortisol discharge</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*p = 0.05
Chapter 3: Research Challenges and Strategies
to Improve Study Participation in Critically Ill Patients

Patients admitted to critical care environments are medically complex with greater morbidity and mortality when compared to other hospitalized patients. Critical care patients occupy approximately 15% of inpatient hospital beds and contribute to approximately $81.7 billion or 13.4% of overall inpatient hospital costs (Society of Critical Care Medicine, 2012; Halpern & Pastores, 2010). This dynamic patient population provides unique opportunities for research on numerous diseases, associated symptoms, and their potential interaction as well as interventions that may change the clinical course and promote positive health outcomes. As medical advances extend life expectancy and the population continues to age, demand for critical care services will rise (Society of Critical Care Medicine, 2012) and the need for critical care focused research will increase.

Critical care patients are prime candidates for research studies; however, there are limitations to including this patient population in research. Chlan, Guttormson, Tracy, and Bremer (2009), in their research with patients receiving mechanical ventilation, identified several challenges impacting recruitment including the intensive care unit (ICU) environment, unit culture and routines, relationships and support from staff nurses
and key unit leaders, initial time investment to gain access to research sites, unit practice changes, as well as difficulty in sustaining awareness of the study on the participating units. More patient-specific barriers to recruitment and participation in critical care nursing studies have been identified by Grap and Munro (2003) and include the inability of patients to provide informed consent, family members’ or designated surrogate’s inability to process information during a major health crisis of a loved one, as well as the critical status of the patient in general. In addition to these critical care unit and patient specific challenges, regulations and mandates by the Health Insurance Portability and Accountability Act (HIPAA), often implemented and administered by institutional review boards (IRB) (Sullivan-Bolyai, et al., 2007; Weierbach, Glick, & Fletcher, 2010; Steinberg & Rubin, 2009), and medical centers have created further barriers to the conduct of clinical research including increased bureaucratic, administrative, and financial burdens (Marsh, McMaster, Parvizi, Katz, & Spindler, 2008) as well as decreased access to medical records and hampered recruitment of research participants to name a few (Cohen & Rubin, 2008). These barriers to clinical research have been especially challenging to the conduct of predoctoral dissertation research within an academic medical center setting as no predoctoral nursing research has been conducted within the medical center since the implementation of HIPAA. Similar barriers have not occurred with other investigator-initiated (physician, nurse, etc.) studies conducted within medical center due to the research infrastructure present for medical center employees.

Identifying potential challenges and strategies to improve participation of critical care patients in clinical research is a significant priority if we are to determine evidence-
based practices to reduce morbidity and mortality in this patient population. The primary aim of this paper is to report recruitment outcomes in a recent study evaluating nicotine withdrawal symptoms experienced by critically ill smokers and utilization of nicotine replacement therapy in these patients. Drawing from these findings, challenges to clinical research in this patient population as well as strategies to improve recruitment of critical care patients in research are considered.

Study Protocol

A lack of reported research on the management of nicotine withdrawal in critically ill smokers contributes to a significant gap in the literature on this topic. To address this issue, a prospective observational investigation was conducted to describe smokers admitted to an intensive care setting, their development of nicotine withdrawal symptoms (anxiety, agitation, and cigarette craving) and delirium, and the length of hospital stay in this patient sample. A second aim was to describe the use of nicotine replacement therapy (NRT) and its relationship to symptoms in these patients.

Participants were recruited from the intensive care unit at an urban, tertiary care, community-based medical center which is part of a large academic medical health system in the Midwest. Persons of both genders were recruited to the study if they were 18 years of age or older, English speaking, smoked 5 or more cigarettes per day up to the day of hospital admission, admitted to the ICU from the emergency department or any hospital floor or unit within 24 hours of hospital admission, admitted to the ICU as a transfer from another facility within 24 hours of admission to that facility, and cognitively aware with the ability to verbally or non-verbally respond (nod head appropriately or able to point to
answers or selections on instruments). Patients supported by mechanical ventilation were also considered if they met these inclusion criteria. Patients were excluded from participation if they were admitted to the hospital with a diagnosis of myocardial infarction, were receiving antipsychotic, anxiolytic, or narcotic therapy preventing the ability to communicate, or had a history of dementia. In addition, female patients were excluded if they were pregnant.

Potential participants were originally identified by the ICU clinical nurse specialist and/or ICU key personnel (see Table 3.1). After 14 months of recruitment efforts and no participants enrolled, the medical center’s clinical nurse scientist began assisting with screening. New ICU admissions were screened up to twice daily. If a patient met the study inclusion and exclusion criteria, then ICU key personnel would approach the patient to determine their interest in participating in the study. When a potential participant expressed interest in the study, the principal investigator reviewed the study criteria with the patient’s nurse and confirmed eligibility by medical record review, then approached the potential participant and introduced the study with an IRB approved recruitment script. If the potential participant had continued interest after study introduction, informed and HIPAA consents were obtained and baseline data collection was completed.

Baseline data were collected within 24 hours of hospital admission and included psychologic measures assessing anxiety (1-item Faces Anxiety Scale), agitation (observer-rated Richmond Agitation Sedation Scale), cigarette craving (1-item Craving Visual Analog Scale), and delirium (observer-rated Confusion Assessment Method for
the Intensive Care Unit) as well as physiologic measures assessing anxiety (salivary cortisol) and smoking status (salivary cotinine). The psychologic measures for anxiety, agitation, and delirium were selected due to their previous use in critically ill patients (McKinley, Coote, & Stein-Parbury, 2003; McKinley, Stein-Parbury, Chehelnabi, & Lovas, 2004; Sessler, et al., 2002; Ely, et al., 2003; Ely, et al., 2001; Ely, et al., 2001; Schuurmans, Deschamps, Markham, Shortridge-Baggett, & Duursma, 2003). Participants spent approximately 45 minutes with the principal investigator during the initial study visit (approximately 30-35 minutes for eligibility screening and informed consent, and approximately 10-15 minutes for baseline data collection). Subsequent measures were obtained in the morning and evening of ICU days 2, 3, and 4, and within 12 hours of discharge from the ICU to a step-down unit and included those items previously mentioned with the exclusion of salivary cotinine, which was measured at baseline and the morning of ICU day 3 only. Participants spent approximately 5-10 minutes with the principal investigator during the study follow up visits and approximately 10-15 minutes during the study discharge visit. Subjects were expected to be in the study for a total of 5 days.

The principal investigator maintained contact by email and/or phone with the medical center clinical nurse scientist and/or ICU key personnel on a daily and up to twice daily basis to encourage consistent identification of potential participants. The inclusion and exclusion criteria as originally planned (inclusion criteria of smoking status of ≥ 10 cigarettes per day up to admission, admission to the ICU from the emergency department only, and < 12 hours since admission to the ICU and exclusion criterion of
receiving corticosteroid therapy) restricted recruitment more than anticipated. As depicted in Table 3.1, after 5 months of recruitment efforts no participants were enrolled and the inclusion criteria were reduced to include patients with a smoking status of 5 (vs. 10) or more cigarettes per day up to admission and admission to the ICU from the emergency department or from another hospital floor or unit within 24 (vs. 12) hours of hospital admission. In addition, the criterion of admission to the ICU as a transfer from an outlying facility within 24 hours of admission to that facility was added to capture these ICU patients. After another 8 months of recruitment efforts and no participants enrolled, the medical center clinical nurse scientist began assisting the principal investigator and ICU key personnel with screening activities. The modification of inclusion criteria and the assistance of the medical center clinical nurse scientist with screening over the last 7 months of the study increased the number of participants to 8 by study conclusion. The exclusion criterion of corticosteroid therapy was removed; however, this information was included in data collection for future analysis as a confounding variable to cortisol measurement. The inclusion criterion of cognitively aware/alert and the exclusion criterion of communication barrier due to narcotic, antipsychotic, or anxiolytic therapy limited many patients from study participation; however, these criteria were retained due to patient status requirements needed for baseline data collection as well as for informed consent procedures.

**Enrollment Progress**

One hundred and five critically ill smokers were screened for study participation during a 20 month recruitment period and 10 critically ill smokers were determined to be
eligible. A total of 8 critically ill smokers (80% of those eligible) were enrolled into the study (see Table 3.2). An average of one critically ill smoker was enrolled in the study per month during the last 7 months of recruitment. Ages of participants ranged from 27 to 67. Admitting diagnoses of study participants were diverse with the most common reasons for critical care admission being diabetic ketoacidosis, sepsis, and pneumonia. Of note, the majority of the sample was African American with only two Caucasian participants.

Ninety-seven of the 105 critically ill smokers screened were not enrolled in the study (see Figure 3.1). Of these, 95 were determined to be ineligible for participation and 2 critically ill smokers who were eligible declined to participate in the study (see Table 3.2). The majority of critically ill smokers were determined ineligible for study participation despite the revision of the inclusion and exclusion criteria (see Table 3.3). There were no critically ill smokers who declined study participation while screening with the revised criteria and 100% of subjects completed the study after study enrollment.

Discussion

Improving the participation of critically ill patients in clinical research studies is an important step toward establishing evidence-based practices to reduce morbidity and mortality in this patient population. Critically ill smokers were recruited during their hospitalization into our recent study evaluating nicotine withdrawal symptoms experienced by these patients as well as utilization of nicotine replacement therapy in this patient sample during critical care admission. Our recruitment efforts over 20 months resulted in a 7.6% enrollment rate (8 out of 105 patients screened); however, 80% of
eligible patients were enrolled in the study (8 out of 10 eligible patients). This enrollment rate is quite low when considering the length of time that recruitment efforts took place and the number of patients that were screened. Challenges to study recruitment were multifactorial and included barriers at the patient, unit, and organizational level. Strategies to improve recruitment based on these challenges will be discussed (see Table 3.4).

**Patient Barriers to Recruitment**

The critical nature of patients admitted to the ICU presents unique challenges when attempting to conduct research in this patient population and the complexity of critical illness and injury must be accounted for in these patients when preparing critical care focused research studies (Deutschman, Ahrens, Cairns, Sessler, & Parsons, 2012). Of the 105 critically ill smokers screened for this study, 90% were excluded due to their critical illness burden. Patients recruited for this study were expected to be cognitively aware and alert as well as verbally responsive or have the ability to non-verbally communicate (point to selections on study instruments). This was essential for the informed consent process as well as baseline data collection and subsequent data collection in order to determine changes from baseline characteristics. Though patients on mechanical ventilation were considered for study participation, they were often heavily sedated during the first 24 hours of ICU admission, thus impairing mentation and communication and excluding them from the study. The illness burden of smokers admitted to the ICU also affected their ability to smoke during the time preceding hospital admission. Early in study recruitment, there were patients screened for study
participation who did not meet the inclusion criterion of smoking 10 or more cigarettes per day up to the day of admission. This criterion was established to determine level of nicotine dependence prior to hospital admission and to allow for biochemical confirmation of smoking status. Changing this criterion to smoking 5 or more cigarettes per day was based on the number of critically ill smokers who smoked between 5 and 10 cigarettes per day up to the day of hospital admission who were excluded from study participation (n = 2). This change improved participation rates in the study. Potential participants often cited “not feeling well” and being “too sick to smoke” as their reasons for not smoking as much before coming to the hospital.

In this study, the combination of inclusion criteria including admission to the ICU from the emergency department only and less than 12 hours since admission to the ICU affected participation rates as well. Potential participants requiring transfer to the ICU who were admitted to regular floor care or from an outlying facility were originally excluded due to the origin of transfer not being the emergency department (n = 3). This criterion, in combination with the criterion of being admitted within 12 hours to the ICU from the emergency department (n = 1), excluded patients who might have been eligible under the revised study criteria. The exclusion criterion of corticosteroid therapy was also removed to allow potential participants meeting all other inclusion and exclusion criteria the opportunity to participate in the study. If a study participant received corticosteroids as part of their care, then this information was extracted from the medical record to be used in data analysis.
The criteria originally developed for this study restricted recruitment efforts more than what was originally expected. Modification of these criteria during the study through an IRB amendment helped to improve recruitment of potential participants; however, characteristics of the study site provided challenges to recruitment as well.

**Unit Barriers to Recruitment**

The characteristics of the ICU in which critical care research takes place can affect the overall success of study recruitment and the ultimate outcomes of the research. During this study, there were several unit related barriers that affected the success of study recruitment including work burden of staff nurses and key personnel, difficulty sustaining awareness of the study on the unit, patient census characteristics, as well as unexpected unit practice changes.

Early in the research planning process we involved key hospital administrators, including the ICU manager, ICU medical director, and the chief nursing officer, in order to build rapport and gain cooperation and support for obtaining access to critical care patients. Prior to data collection, two of these individuals (ICU manager and chief nursing officer) left their positions in the hospital. The departure of the ICU manager was especially critical as this was the only ICU staff member who was going to screen for potential study participants. This change in leadership resulted in further discussions regarding access to and screening of potential participants with the new chief nursing officer and the ICU clinical nurse specialist. Based on these discussions, it was decided that the ICU clinical nurse specialist would serve as study liaison between the principal investigator and the ICU staff. In addition, the ICU clinical nurse specialist helped
identify five ICU staff nurses to assist with screening and data collection activities who were added to the IRB-approved protocol as “key personnel.” These nurses completed training in research ethics and human subjects protection through the Collaborative Institutional Training Initiative (CITI) program and their assistance with the study was considered for their clinical ladder progression. The inclusion of ICU staff in nursing research also provided support for the hospital’s designation as a Magnet-recognized organization (American Nurses Credentialing Center, 2008).

As identified by Newberry and colleagues (2010) in their work with patients suffering neurological trauma, the ICU staff involved with study activities were often working in a stressful and busy environment that led to inconsistent recruitment efforts. To enhance consistency with recruitment, in month 15 the medical center clinical nurse scientist began assisting with screening and reviewed the ICU patient census daily for potential subjects. The identification of potential participants in this manner yielded the only enrolled participants and decreased the study-related work burden originally requested of the ICU key personnel and the ICU clinical nurse specialist.

Efforts were made prior to study initiation and throughout study recruitment to sustain and enforce awareness of the study on the unit. The study was initially presented to ICU nursing staff at meetings prior to study implementation and intermittently during the course of study recruitment. Meetings were scheduled at varying times throughout the day including early morning and night visits to include staff from all shifts. Study information was also uploaded to the ICU’s education website. In addition, the principal investigator visited the study site weekly to answer study questions and to
bring homemade baked goods to show appreciation for the ICU staff’s assistance. Later in the recruitment process, study update flyers and laminated pocketcards including study inclusion criteria as well as the names and contact information of the principal investigator and ICU key personnel were distributed in the ICU staff’s mailboxes. Laminated cards were also posted in documentation stations around the unit to facilitate ICU nurse assessment of their patients for possible study participation. These methods of maintaining awareness of the study by the ICU staff were not as effective as anticipated. Other recommended strategies to overcome this barrier include daily visits to the study site by the principal investigator and having the principal investigator obtain temporary hospital employment (Weierbach, Glick, & Fletcher, 2010). It is also recommended that research personnel maintain a physical presence in the unit to promote partnership with staff and to increase familiarity with the study on the unit. Due to geographic limitations of the principal investigator, daily presence in the ICU and temporary employment in the ICU were not feasible; however, these strategies will be considered when conducting future research.

This research study was developed and guided by the principal investigator’s past experiences in critical care nursing at another community hospital and not based on the ICU serving as the study site. The 19-bed study site ICU in this community hospital was selected instead of other ICUs within the hospital system due to the lower acuity of critical care patients at a community-based hospital. Despite pre-study validation by the ICU manager and chief nursing officer that the study site ICU would provide the number and type of patients required for the study, many of the patients admitted were too ill to
participate (see Table 3.3); therefore, a representative sampling of the population under study did not occur. In addition, the ICU census fluctuated, often yielding lower numbers of admissions than were expected. The expected average of admissions per month, as indicated by the ICU manager at study onset, was 100 (1,200/year); whereas the actual average of admissions per month was 50 (600/year). Despite working with the study site ICU early in the study design process, the characteristics of this ICU did not meet the expected recruitment goals of the study. Strategies to overcome this barrier and determine adequacy of the study site include requesting relevant descriptive data on the patient characteristics of interest for the year previous to study initiation including the number of admissions per month and year rather than relying on employees’ estimates. The collection of these data early in the study design and implementation processes would have allowed the principal investigator to consider the addition of a second study site. The addition of another study site may have enhanced recruitment efficiency (Cook, et al., 2008), increased the number of study participants, and provided a more representative sample of critical care patients.

The implementation of a new electronic medical record system at the study site created a final unit related barrier encountered during the last 5 months of the study. The ICU staff originally maintained paper records at the bedside for documentation purposes that allowed for easier and less time consuming data extraction. Though ICU nursing staff were agreeable to assisting the principal investigator with data extraction from the electronic medical record, the type and amount of information required for study-related documentation was burdensome to already stressed and time-challenged nurses. The
medical center’s clinical nurse scientist attempted to obtain view-only access to the electronic medical record for the principal investigator; however, due to organizational barriers (addressed below), this access was not obtained. The clinical nurse scientist then completed data extraction for the principal investigator. This barrier as well as other organizational barriers created further challenges during the study development and recruitment phases.

**Organizational Barriers to Recruitment**

The increasing requirements of the HIPPA Privacy Rule make access to personal health information a growing challenge to the researcher. The Privacy Rule does not directly regulate research activities; however, it does restrict how and to whom a health care professional can disclose patient health information for research purposes (Gunn, Fremont, Bottrell, Shugarman, Galegher, & Bikson, 2004; Nosowsky & Giordano, 2006; Steinberg & Rubin, 2009). This can be particularly problematic for researchers who are not employees of the hospital, or “covered entity,” where they wish to conduct their study (Cohen & Rubin, 2008). Health care providers, hospitals, health plans, and/or health care clearinghouses, designated as covered entities under the Privacy Rule (Cohen & Rubin, 2008), may require persons accessing patient information for research purposes to be employees under the covered entity (Wipke-Tewis & Pickett, 2008). The principal investigator for this study was not an employee of the hospital system in which the study took place; however, a strategy used to overcome this barrier was the creation of a non-salaried appointment in the hospital’s department of nursing quality and translational
research prior to study recruitment. This appointment provided the principal investigator employment under the covered entity which facilitated access to the study site.

Despite the principal investigator’s status as a hospital employee, direct access to patients remained a challenge as no treatment relationship existed between the principal investigator and potential participants, a requirement under HIPAA regulations (Wipke-Tevis & Pickett, 2008). To comply with this requirement, it was recommended by the medical center legal department that staff nurses directly involved in the care of potential participants obtain participants’ permission for the principal investigator to approach them about the study. This challenge was resolved by having the ICU clinical nurse specialist approach potential participants, briefly present the study, and ask their permission for the principal investigator to approach them. The strategies used to overcome these organizational barriers were effective, but time-consuming. Determining potential challenges associated with HIPAA regulations and IRB procedures as well as developing relationships with hospital-based clinical nurse scientists early in study development is crucial to research progress and study outcomes.

**Summary**

There were several barriers to subject recruitment that occurred during the course of this study including those at the patient, unit, and organizational levels (see Table 3.4). Barriers at the patient level included patient illness burden and strict inclusion and exclusion criteria that limited the number of patients eligible for study participation. Strategies to overcome these barriers include considering patient illness burden when
designing studies involving critically ill patients and carefully selecting inclusion and exclusion criteria during the study design process to facilitate greater study participation.

Unit-based barriers included access to the study site ICU and access to study patients, characteristics of the study site ICU, work burden of staff nurses and ICU key personnel, difficulty sustaining awareness of the study in the ICU, and electronic medical record implementation. Involving key hospital administrators and ICU clinicians early in the study design process and identifying an ICU nurse study liaison is recommended to allow for development of collegial relationships and rapport needed for study site and patient access. Assessing characteristics of the study site ICU prior to study implementation is also essential to determine appropriateness of the site in meeting study recruitment goals. In addition, assessing study site characteristics early in the study design process allows for the consideration of other sites to increase the number of potential participants. To maintain awareness of the study at the study site ICU, it is recommended that the principal investigator visit the ICU frequently/daily and maintain a physical presence in the ICU. Temporary employment with the hospital system and study site ICU may also be a strategy to overcome this barrier. Work burden of ICU staff nurses should be considered when involving them with screening and recruitment activities and identifying a nursing research champion, such as a clinical nurse scientist, to assist with study activities can help overcome this barrier. To overcome obstacles encountered with electronic medical record access, it is recommended to work with appropriate hospital departments (ie. information technology) early in the research process so that permissions for access are obtained prior to study initiation.
Organizational barriers consisted of HIPAA, IRB, and medical center policies and procedures that restricted access to the study site ICU as well as potential study participants. Identifying policies and procedures that could be potential barriers early in the research process is imperative and identifying a nursing research champion (clinical nurse scientist) to assist with navigating these policies and procedures is critical to the timely conduct of clinical research.

Conclusion

The demand for critical care services is expected to increase as the population ages and advances in medicine contribute to extended life expectancy (Society of Critical Care Medicine, 2012). As the critical care patient population becomes more complex, costs associated with critical care admissions will increase. Therefore, representation of critically ill patients in research studies is crucial to the development of evidence-based practices that reduce morbidity and mortality in these patients. Potential challenges to participation and strategies to enhance participation of critically ill patients in research need to be considered early in the design and implementation of studies investigating critical care patient issues.
References


Nosowsky, R., & Giordano, T. (2006). The health insurance portability and
accountability act of 1996 (HIPAA) privacy rule: Implications for clinical research. *Annual Reviews in Medicine, 57*, 575-590.


Figure 3.1. Participant Recruitment and Enrollment Flow Chart
Table 3.1 *Summary of Factors Impacting Study Progression*

<table>
<thead>
<tr>
<th>Factors</th>
<th>Timeline (in months)</th>
<th>0-5</th>
<th>6-14</th>
<th>15-20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Criteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Original Inclusion:</td>
<td>Revised Inclusion:</td>
<td>No change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (18 years or older)</td>
<td>Smoking status ≥ 5 CPD up to admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>English speaking</td>
<td>Admission to ICU from ED or other hospital floor/unit within 24 hrs of hospital admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking status ≥ 10 CPD up to admission</td>
<td>Admission to ICU from an outlying facility within 24 hrs of admission to that facility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission from ED to ICU</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitively aware/alert</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbally or non-verbally responsive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 12 hrs since admission to ICU</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Original Exclusion:</td>
<td>Revised Exclusion:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current or recent (≤ 2 weeks) diagnosis of MI</td>
<td>Admission to the ICU within 24 hrs of hospital admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Communication barrier d/t narcotic, antipsychotic, or anxiolytic therapy</td>
<td>Removed corticosteroid therapy as an exclusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroid therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of dementia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personnel</td>
<td>ICU clinical nurse specialist</td>
<td>ICU clinical nurse specialist</td>
<td>ICU clinical nurse specialist</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ICU nurse key personnel</td>
<td></td>
<td>Clinical nurse scientist</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>EMR (month 15)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number Enrolled</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

*Note. CPD = cigarettes per day; EMR = electronic medical record*
Table 3.2  Demographic and Clinical Characteristics of Eligible and Enrolled Critically Ill Smokers

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Eligible</th>
<th></th>
<th>Refused</th>
<th></th>
<th>Enrolled</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 10)</td>
<td>(%)</td>
<td>(n = 2)</td>
<td>(%)</td>
<td>(n = 8)</td>
<td>(%)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-29</td>
<td>1</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>12.5</td>
</tr>
<tr>
<td>30-39</td>
<td>2</td>
<td>20</td>
<td>1</td>
<td>50</td>
<td>1</td>
<td>12.5</td>
</tr>
<tr>
<td>40-49</td>
<td>1</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>12.5</td>
</tr>
<tr>
<td>50-59</td>
<td>1</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>12.5</td>
</tr>
<tr>
<td>60-69</td>
<td>5</td>
<td>50</td>
<td>1</td>
<td>50</td>
<td>4</td>
<td>50</td>
</tr>
<tr>
<td>≥ 70</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6</td>
<td>60</td>
<td>2</td>
<td>100</td>
<td>4</td>
<td>50</td>
</tr>
<tr>
<td>Female</td>
<td>4</td>
<td>40</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>50</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>7</td>
<td>70</td>
<td>1</td>
<td>50</td>
<td>6</td>
<td>75</td>
</tr>
<tr>
<td>White (non-Hispanic)</td>
<td>3</td>
<td>30</td>
<td>1</td>
<td>50</td>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>Admission Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>2</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>Hypertensive crisis</td>
<td>1</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>12.5</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>1</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>12.5</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>2</td>
<td>20</td>
<td>2</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 3.3 *Criteria on which Critically Ill Smokers were Excluded from Study Participation*

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Ineligible Smokers (n = 91)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td><strong>Original Inclusion:</strong></td>
<td></td>
</tr>
<tr>
<td>Age (18 years or older)</td>
<td>0</td>
</tr>
<tr>
<td>English speaking</td>
<td>0</td>
</tr>
<tr>
<td>Smoking status ≥ 10 CPD up to admission</td>
<td>2</td>
</tr>
<tr>
<td>Admission from ED to ICU</td>
<td>3</td>
</tr>
<tr>
<td>Cognitively aware/alert</td>
<td>49(^a)</td>
</tr>
<tr>
<td>Verbally or non-verbally responsive</td>
<td>49(^a)</td>
</tr>
<tr>
<td>Less than 12 hrs since admission to ICU</td>
<td>1</td>
</tr>
<tr>
<td><strong>Original Exclusion:</strong></td>
<td></td>
</tr>
<tr>
<td>Current or recent (≤ 2 weeks) diagnosis of MI</td>
<td>0</td>
</tr>
<tr>
<td>Communication barrier d/t narcotic, antipsychotic, or anxiolytic therapy</td>
<td>49(^a)</td>
</tr>
<tr>
<td>Pregnant</td>
<td>0</td>
</tr>
<tr>
<td>Corticosteroid therapy</td>
<td>3</td>
</tr>
<tr>
<td>History of dementia</td>
<td>0</td>
</tr>
<tr>
<td><strong>Revised Inclusion:</strong></td>
<td></td>
</tr>
<tr>
<td>Smoking status ≥ 5 CPD up to admission</td>
<td>12</td>
</tr>
<tr>
<td>Admission to ICU from ED or other hospital floor/unit within 24 hrs of hospital admission</td>
<td>19(^b)</td>
</tr>
<tr>
<td>Admission to ICU from an outlying facility within 24 hrs of admission to that facility</td>
<td>2(^b)</td>
</tr>
<tr>
<td>Admission to the ICU within 24 hrs of hospital admission</td>
<td>21(^b)</td>
</tr>
<tr>
<td><strong>Revised Exclusion:</strong></td>
<td></td>
</tr>
<tr>
<td>Removed corticosteroid therapy as an Exclusion</td>
<td>0</td>
</tr>
</tbody>
</table>

*Note.* Four of the 95 patients determined ineligible had received transfer orders for regular floor care. \(^a,b\) Categories are not mutually exclusive.
Table 3.4 *Barriers and Strategies to Improve Recruitment of Critically Ill Patients in Clinical Research*

<table>
<thead>
<tr>
<th>Barriers</th>
<th>Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Barriers</strong></td>
<td></td>
</tr>
<tr>
<td>Patient illness burden</td>
<td>Consider patient illness burden when designing critical care based studies</td>
</tr>
<tr>
<td>Strict inclusion/exclusion Criteria</td>
<td>Select inclusion/exclusion criteria carefully and modify as necessary</td>
</tr>
<tr>
<td><strong>Unit Barriers</strong></td>
<td></td>
</tr>
<tr>
<td>Access to study site ICU</td>
<td>Involve key hospital administrators and ICU clinicians early in the research process to gain site access</td>
</tr>
<tr>
<td>Characteristics of study site ICU</td>
<td>Assess characteristics of the study site ICU prior to study implementation to ensure appropriateness of site in meeting study recruitment goals</td>
</tr>
<tr>
<td><strong>Work burden of staff nurses and key personnel</strong></td>
<td>Consider work burden of ICU staff nurses when involving them with screening and recruitment activities</td>
</tr>
<tr>
<td><strong>Difficulty sustaining awareness of study on unit</strong></td>
<td>Identify a nursing research champion (clinical nurse scientist) that may assist with screening when needed</td>
</tr>
<tr>
<td><strong>Electronic medical record Access</strong></td>
<td>Collaborate with appropriate hospital departments to obtain access to electronic medical records for conduct of the study</td>
</tr>
<tr>
<td><strong>Organizational Barriers</strong></td>
<td></td>
</tr>
<tr>
<td>HIPAA, IRB, and medical center policies</td>
<td>Identify medical center policies and procedures that could be potential barriers to research access early in the research process</td>
</tr>
<tr>
<td></td>
<td>Identify HIPAA and IRB policies that could be potential barriers to research early in the research process</td>
</tr>
<tr>
<td></td>
<td>Identify a nursing research champion (clinical nurse scientist) to help navigate medical center policies and procedures</td>
</tr>
<tr>
<td>Access to study patients</td>
<td>Identify an ICU nurse as study liaison to facilitate screening of and access to study participants</td>
</tr>
</tbody>
</table>
Bibliography


Schumacher, K., & Gortner, S. (1999). (Mis)conceptions and reconceptions about traditional science. In E. C. Polifroni, & M. Welch (Eds.), *Perspectives on philosophy of science in nursing; an historical and contemporary anthology* (pp. 61-69). Philadelphia: Lippincott.


subarachnoid hemorrhage. *Neurocritical Care, 14*, 77-83.


