A Comparison of the Theory of Unpleasant Symptoms and the Conceptual Model of Chemotherapy-Related Changes in Cognitive Function

Jamie S. Myers, RN, MN, AOCN®

Retrospective and prospective clinical trials have substantiated the incidence of mild to moderate cognitive impairment resulting from chemotherapy to treat cancer (Ahles & Saykin, 2001; Jansen, Miaskowski, Dodd, Dowling, & Kramer, 2005). Patients with cancer report that cognitive impairment has a significant effect on their quality of life (QOL) (Ahles & Saykin, 2001). Associated factors may include age, anemia, fatigue, depression, anxiety, hormone levels, cytokine release, and genetic makeup (Jansen et al.). Establishing the appropriateness of a working model to describe the relationships would provide additional structure and focus for empirical research. The purpose of this article is two-fold: (a) to explore the use of the Theory of Unpleasant Symptoms (TUS) (Lenz, Suppe, Gift, Pugh, & Milligan, 1995) as a model for describing the symptom experience related to cognitive impairment associated with standard-dose chemotherapy, and (b) to compare and contrast that use of the TUS with the Conceptual Model of Chemotherapy-Related Changes in Cognitive Function (Hess & Insel, 2007).

Purpose/Objectives: To explore the use of the Theory of Unpleasant Symptoms (TUS) as a model for describing the symptom experience related to the cognitive impairment associated with standard-dose chemotherapy and compare and contrast that use of the TUS with the Conceptual Model of Chemotherapy-Related Changes in Cognitive Function.

Data Sources: PubMed database.

Data Synthesis: Retrospective and prospective clinical trials have substantiated the incidence of mild to moderate cognitive impairment. Patients have reported a significant effect on quality of life. Associated factors may include age, anemia, fatigue, depression, anxiety, hormone levels, cytokine release, and genetic makeup. Establishing the appropriateness of a working model to describe the relationships would provide additional structure and focus for empirical research.

Conclusions: Both models have utility for describing the relationships of factors associated with chemotherapy-related cognitive impairment.

Implications for Nursing: Blending of the TUS and the Conceptual Model of Chemotherapy-Related Changes in Cognitive Function may provide an enhanced framework for further research about the physiologic and psychological aspects of chemotherapy-related cognitive impairment.

Cognitive Impairment Secondary to Chemotherapy

An increasing body of literature supports the existence of cognitive impairment associated with standard-dose chemotherapy (Ahles & Saykin, 2001). The lay term for this treatment-related effect is "chemo brain" (Jansen et al., 2005). Retrospective trials estimate an incidence ranging from 17%–75% (Wefel, Lenzi, Theriault, Davis, & Meyers, 2004). Wefel et al. conducted the first longitudinal, prospective trial and evaluated the effects of standard-dose adjuvant chemotherapy in a small sample of women with breast cancer (N = 18). Neurocognitive testing was performed at baseline, six months (approximately three weeks from completion of therapy), and one year following the completion of chemotherapy. More than 60% of participants exhibited a decline in cognitive performance from baseline at the six-month evaluation. Nearly 50% of those subjects demonstrated cognitive improvement at the one-year evaluation.

Cognitive impairment has been demonstrated in patients receiving standard-dose chemotherapy for lymphoma. Ahles et al. (2002) compared survivors of Hodgkin disease (n = 31) and non-Hodgkin lymphoma (n = 27) with survivors of breast cancer (n = 35). Similar incidence

of cognitive impairment was seen, regardless of diagnosis, as long as 10 years after completion of therapy.

The cognitive impairment associated with standard-dose chemotherapy appears to be more subtle than that seen with acute neurologic impairment, such as toxic leukoencephalopathy (Jansen et al., 2005). The subtlety is reflected by the lack of correlation between patients' self-reports of cognitive dysfunction and subsequent performance on neurocognitive tests in some studies (Wefel et al., 2004). Ahles stated that many available neurocognitive tests were designed to assess patients with head trauma and dementia (T.A. Ahles, personal communication, June 3, 2007). The tools were not designed to pick up the more subtle changes exhibited by patients who started out with high cognitive performance at baseline (O'Shaughnessy, 2003). Imaging techniques, such as structural and functional magnetic resonance imaging (MRI), have been used months after the completion of chemotherapy to demonstrate reduction in brain structure volume, changes in the integrity of white-matter tracks between brain structures, and patterns of reduced frontal area activation during working memory tasks (Ahles & Saykin, 2007).

The exact etiology of cognitive impairment associated with standard-dose chemotherapy is not known. A variety of etiologies have been proposed: direct injury to cerebral gray and white matter (Wefel et al., 2004), DNA damage and oxidative stress (Ahles & Saykin, 2007; Chen, Jungsuwadee, Vore, Butterfield, & St. Clair, 2007), cytokine-induced inflammatory response (Ahles & Saykin, 2007), chemotherapy-induced anemia (Mancuso, Migliorino, De Santis, Saponiero, & De Marinis, 2006; Massa, Madeddu, Lusso, Gramignano, & Mantovani, 2006), and chemotherapy-induced menopause (Jansen et al., 2005). The presence of the apolipoprotein E5 allele may predispose patients to cognitive impairment (Ahles et al., 2002). It is associated with Alzheimer disease, the aging adult, and long-lasting injury following head trauma (Ahles & Saykin, 2007; Jansen et al.). A subset of patients (17%–30%) appears to sustain long-term cognitive damage following chemotherapy (Ahles & Saykin, 2002). Some prospective trials to evaluate chemotherapy-related cognitive impairment now include genetic measurements to assess the existence of a genetic predisposition to more significant and longer-lasting injury from chemotherapy (Ahles & Saykin, 2007). The prospective trials may help to answer the question of whether patients are genetically predisposed to long-term damage, and the results could have a significant effect on consideration of therapy options.

The age of a patient may be a relevant physiologic factor. Evidence of cognitive decline begins as individuals reach their early 60s (Barnes et al., 2007). The deficits have been associated with changes in brain structure and function (Hillman et al., 2006). White matter hyperintensities (WMH) are areas of increased signal intensity in the periventricular and deep white matter.

WMH are seen in older adults and can be observed by MRI techniques (Raz & Rodrigue, 2006). Comorbidities, particularly those that affect oxygenation (such as hypertension, diabetes, and cardiovascular disease), are more common among older adults. All of the conditions have been associated with impaired cognition (Barnes et al.; Brady, Spiro, & Gaziano, 2005; Schretlen et al., 2007; Singh-Manoux, Britton, & Marmot, 2003).

Decreases in endogenous sex hormones can occur with aging and with treatment for cancer. Sex hormones have been shown to play a role in cognitive function (Grady et al., 2002; Shumaker et al., 2004). Low serum levels have been associated with decline in global cognitive function and verbal memory (Yaffe et al., 2007). A small study recently was conducted to evaluate changes in QOL and cognitive function in premenopausal women receiving adjuvant chemotherapy for breast cancer (Klemp, Stanton, Kimler, & Fabian, 2006). Serum hormone and hemoglobin levels were compared to patients' measurements of cognitive function, perception of cognitive impairment, and depression. Although patients did not score significantly lower on the cognitive tests, they did perceive changes in cognitive function and reported an increase in symptoms associated with QOL and depression. Estradiol levels were shown to decrease significantly from baseline levels.

Dietary factors such as deficiencies in vitamin D and iron also are of interest to researchers evaluating changes in cognitive function (Brown et al., 2001; Lezak, Howieson, & Loring, 2004; Meyers, 2000; Wilkins, Sheline, Roe, Birge, & Morris, 2006). Vitamin D deficiency has been associated with declines in cognitive performance in older adults (Wilkins et al.).

Some evidence shows that intelligence quotient (IQ) and level of education may be related to the degree of cognitive impairment experienced. Ahles and Saykin (2001) cited research that demonstrated a neuroprotective effect from high IQ and education levels. They discussed the concept of "cognitive reserve," which has been examined in patients with Alzheimer disease. Ahles and Saykin (2001) recommended prospective trials to control for IQ and education level when evaluating the association of chemotherapy and cognitive impairment.

Cognitive impairment may be partially induced or exacerbated by factors such as fatigue, anxiety, and depression (Brown et al., 2001; Lezak et al., 2004; Meyers, 2000). Several trials have controlled for those variables without elimination of the effects of cognitive impairment attributable to the chemotherapy (Ahles & Saykin, 2001, 2007; Ahles et al., 2002; Wefel et al., 2004). Prospective trials are recommended to control for those variables as well as the potential contributing factor of hormonal status (Ahles & Saykin, 2001).

Chronic pain has been associated with cognitive impairment. Hart, Wade, and Martelli (2003) stated that "the concomitants of chronic pain, such as mood change,

sleep disturbance, fatigue, and other aspects of suffering (e.g., lifestyle influence secondary to disability), seem to be closely related to cognitive impairment" (p. 116). Chronic pain has been associated with neuropsychological impairment such as attentional capacity, processing and psychomotor speed, and memory (Hart et al.). The anterior cingulate cortex (ACC) is one area of the brain involved with cognitive processes. Neuroimaging studies conducted with patients in pain consistently have shown changes in the ACC. The ACC cognitive subdivision has been implicated in executive control of attention and information processing. Increased ACC activity can be measured during actual and anticipated processing of novel stimuli (Peyron, Laurent, & Garcia-Larrea, 2000).

> The importance of patient and family education about the potential for chemotherapy-related cognitive impairment cannot be overstated.

The distress associated with impairment in cognitive function may have a significant effect on patients' QOL (Ahles & Saykin, 2001; Tannock, Ahles, Ganz, & van Dam, 2004). The importance of patient and family education about the potential for chemotherapy-related cognitive impairment cannot be overstated; however, a great deal more must be learned about the incidence and causes of cognitive impairment. Subsequent knowledge from clinical research will be instrumental in designing appropriate interventions to prevent, reverse, and manage this significant side effect.

Symptom Clusters and Sickness Behavior

Patients with cancer rarely experience only a single symptom (Miaskowski et al., 2006). The nature of the disease and treatment predispose patients with cancer to a variety of concurrent symptoms. Two to three concurrent symptoms that are related to one another have been referred to as a symptom cluster (Dodd, Janson, et al., 2001; Kim, McGuire, Tulman, & Barsevick, 2005). Interesting work has been done in the area of symptom clusters. According to Dodd, Miaskowski, and Paul (2001), the strength of the relationships and the amount of time needed for all symptoms in a cluster to be present have not been specified. The symptoms do not need to have the same etiology. Symptom clusters may have a synergistic effect as a predictor of patient morbidity (Dodd, Miaskowski, et al.). Studies have been done to examine relationships among fatigue, pain, sleep disturbances, and depression. Dodd, Miaskowski, et al. reviewed a number of trials. In their summary, the authors explained that fatigue, pain, and depression were interrelated. Relationships also existed among pain, fatigue, and sleep disturbances. Recommendations have been made that symptom assessment should include fatigue, sleep disturbance (insomnia), pain, and depression because of evidence of clustering (Barsevick, 2007). Meyers (2000) noted that fatigue, pain, and anemia may contribute to cognitive deficits.

One hypothesis for a physiologic rationale behind symptom clusters is the "sickness behavior" associated with cytokine release (Barsevick, 2007). Barsevick suggested that sickness behavior is one of the underlying mechanisms that may explain symptom clusters associated with cancer and cancer therapy. Sickness behavior includes fever, fatigue, lethargy, muscle aches, decreased appetite, decreased ability to concentrate, decreased social interaction, and general behaviors consistent with the conservation of energy (Parnet, Kelley, Bluthe, & Dantzer, 2002; Pollmacher, Haack, Schuld, Reichenberg, & Yirmiya, 2002; Wilson, Finch, & Cohen, 2002). The relationship between sickness behavior and cytokines was first noted with the administration of exogenous therapeutic cytokines, such as interferon alpha and interleukin-2 (Dantzer & Kelly, 2007). Subsequent evidence has emerged to relate the endogenous release of proinflammatory cytokines to the tissue damage caused by the disease and treatment. Proinflammatory cytokines are released during the body's response to cancer cells or the tissue damage caused by cancer (Miller, 2003). Several chemotherapy agents have been associated with increased levels of proinflammatory cytokines (Ahles & Saykin, 2007).
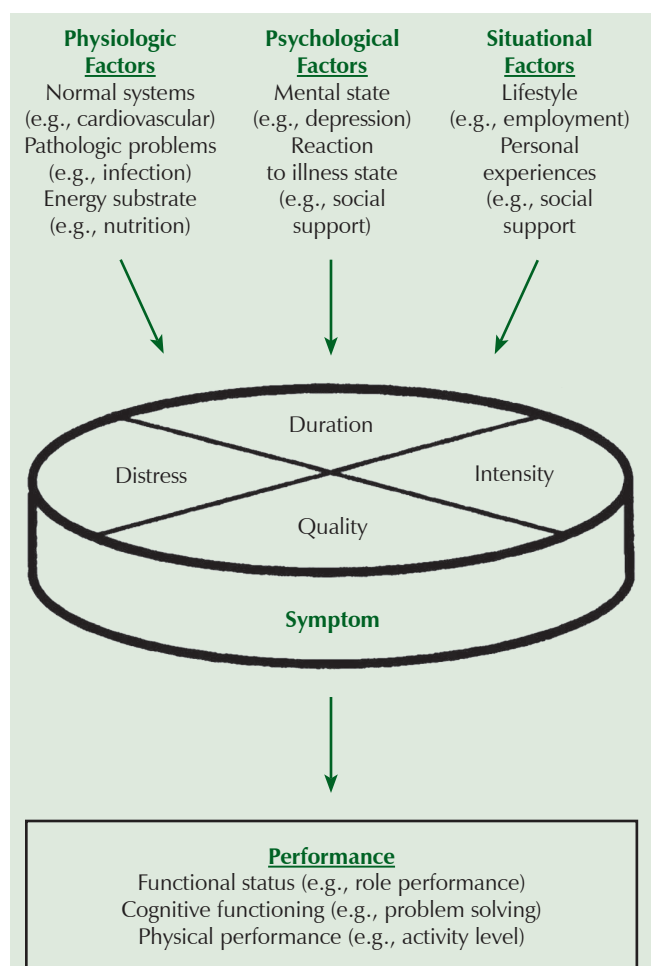
Theory of Unpleasant Symptoms
Original Theory

The TUS (Lenz et al., 1995) provides a model for the experience of, and relationships between, concurrent symptoms. The theory evolved from collaboration among three individual investigators who began work on two concepts that represent unpleasant symptoms, dyspnea and fatigue, simultaneously. The investigators noted commonalities between the two concepts and subsequently realized that a more general theoretical formulation would be appropriate for describing multiple symptoms, such as pain and other unpleasant symptoms, across different clinical populations.

The initial model was constructed to acknowledge influence from three factor categories (i.e., influencing factors): physiologic, psychological, and situational (see Figure 1). Each symptom could vary in duration, intensity, quality, and distress. The experience of the symptom ultimately produced an effect on the patient's level of performance across the three domains of functional status, cognitive functioning, and physical performance.

At the time of the initial publication, the authors acknowledged that further development of the model and theory was needed to account for the opportunity

Physiologic Factors
Normal systems
(e.g., cardiovascular)
Pathologic problems
(e.g., infection)
Energy substrate
(e.g., nutrition)

Psychological Factors
Mental state
(e.g., depression)
Reaction
to illness state
(e.g., social
support)

Situational Factors
Lifestyle
(e.g., employment)
Personal
experiences
(e.g., social
support

Duration

Distress

Intensity

Quality

Symptom

Performance
Functional status (e.g., role performance)
Cognitive functioning (e.g., problem solving)
Physical performance (e.g., activity level)

Figure 1. Middle-Range Theory of Unpleasant Symptoms

Note. From "Collaborative Development of Middle-Range Nursing Theories: Toward a Theory of Unpleasant Symptoms," by E.R. Lenz, F. Suppe, A.G. Gift, L.C. Pugh, & R.A. Milligan, 1995, *Advances in Nursing Science, 17*(3), p. 10. Copyright 1995 by Lippincott Williams and Wilkins. Reprinted with permission.

of experiencing more than one symptom at a time. They also acknowledged that further work was needed to incorporate the potential for the experience of multiple symptoms to have a multiplicative effect.

Lenz et al. (1995) postulated that because many of the same factors may be involved in the experience of multiple symptoms, similar interventions might be effective for more than one symptom simultaneously. The TUS could be used to identify preventive interventions or develop innovative treatments that could be applied across similar symptoms. Lenz et al. (1995) acknowledged that this was a middle-range theory and discussed the process of developing theory at the level of single concepts. Middle-range theory is acknowledged to be less abstract than grand theory, more appropriate for empirical testing, and more applicable to practice for explanation and implementation (Peterson & Bredow, 2004).

Revised Theory

A revision of the TUS was published in 1997 (Lenz, Pugh, Milligan, Gift, & Suppe, 1997). The revision reemphasized the three major components of the theory: the symptoms, the influencing factors that give rise to or affect the nature of the symptom experience, and the consequences of the symptom experience. The original model depicted a unidirectional influence flowing from the influencing factors to the symptom experience to the performance or consequences. The revised model is much more detailed and depicts a bidirectional flow among the three major components of the model: influence, interaction, and feedback (see Figure 2). The revised model allows for the experience of multiple symptoms at the same time. It also allows for one or more symptoms to exacerbate effects on performance as well as to provide a reciprocal influence on the physiologic, psychological, and situational factors. Interaction occurs among symptoms, allowing for the multiplicity or additive nature of the symptom experience when more than one symptom is involved.

The dimensions of the symptom experience are as follows.
- Intensity (strength or severity of the symptom)
- Timing (duration and frequency of occurrence)
- Distress (level of distress perceived, degree of discomfort or bothersomeness)
- Quality (the patient's description of what the symptom feels like).

Lenz et al. (1997) stated that the dimensions are separable but related. Each symptom can be conceptualized and measured separately or in combination with other symptoms. Quality is frequently the most difficult to discern because of individuals' varying levels of ability to describe a symptom or their ability to pinpoint or differentiate one symptom from another (Lenz et al., 1997).

The revised theory can be used to describe the potential for interaction among the influencing factors. For example, the presence of a physiologic pathology (that is causal to the symptom[s]) may trigger a psychological response (such as anxiety) that heightens the perception of the symptom experience. Similarly, psychological factors and the symptom experience may be exacerbated or mediated by situational factors (such as a strong or weak support system). Lenz et al. (1997) also pointed out that the symptom experience may have an effect on influential factors. The authors provided the example of a patient with chronic fatigue experiencing increased mood disturbance.

Use in Research

The TUS authors have continued to conduct and review studies that lend support to the model as related to fatigue during pregnancy, childbirth, and the
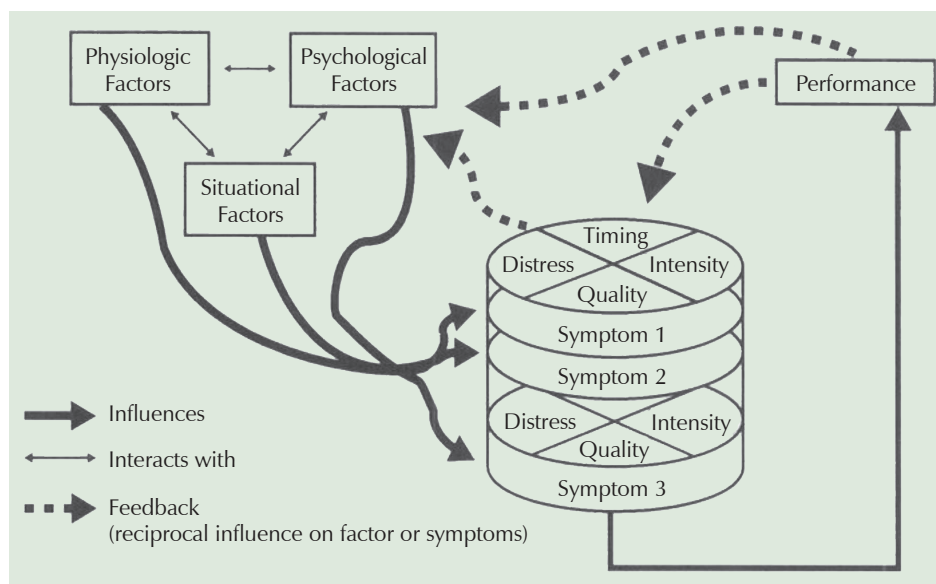
Figure 2. Updated Version of the Middle-Range Theory of Unpleasant Symptoms

Note. From "The Middle-Range Theory of Unpleasant Symptoms: An Update," by E.R. Lenz, L.C. Pugh, R.A. Milligan, A. Gift, & F. Suppe, 1997, *Advances in Nursing Science, 19*(3), pp. 14–27. Copyright 1997 by Lippincott Williams and Wilkins. Reprinted with permission.

However, Lenz et al. (1997) stated that the middle-range TUS was proposed as a means of integrating existing information about a variety of symptoms. As more information is learned, the model provides a structure and framework for integrating the new information. The TUS can be used to help integrate what is presently known or proposed about cognitive impairment.

Influencing Factors

Specific aspects of cognitive impairment have been outlined with the TUS framework (see Figure 3). The framework has utility in describing the experience of cognitive impairment as well as proposing some likely concurrent and synchronous symptoms (symptom clusters).

postpartum period (Lenz et al., 1997). They suggested that the TUS would have utility in development of measurements for symptom intensity, time, distress level, and quality variables. However, they stressed that unidimensional measurement of unpleasant symptoms would not be appropriate because of the overlap and multidimensional aspect of the symptoms. They suggested multifactorial and multidimensional measurement. Several examples of the use of this theory as a basis for interventions to address both influential factors and symptoms were described by the TUS authors (Lenz et al., 1997).

The TUS has been used as a framework to support a study for the identification and verification of symptom clusters in patients with cancer (Chen & Tseng, 2005). Likewise, the theory was the basis for an investigation of symptom clusters in older adult patients with lung cancer (Gift, Jablonski, Stommel, & Given, 2004). The TUS has been compared to the symptom management model published by Dodd et al. (2001). However, the symptom management model is focused more on the selection of symptom management strategies than on an explanation of the symptom experience.

The Theory of Unpleasant Symptoms as a Potential Model

The TUS has utility in describing the relationships among various aspects of cognitive impairment associated with chemotherapy. Some might argue that the research in the area of cognitive impairment is not mature enough to begin to develop a conceptual model.

A variety of physiologic factors have been postulated to be associated with chemotherapy-associated cognitive impairment. They include estimated IQ, genetic makeup, chemotherapy-induced anemia, inflammatory cytokines, decreased hormone levels, advancing age, and comorbidities (Brown et al., 2001; Jansen et al., 2005; Yaffe et al., 2007). Diagnoses of anxiety and depression may be pertinent (Brown et al.; Lezak et al., 2004) and are listed as psychological factors. Inclusion of patients' situational factors, such as employment status and type of employment, may be important, as might level of educational preparation, marital status, level of social support, and lifestyle behaviors such as diet and exercise. Such aspects of patients' lives have not yet been associated with the experience of cognitive impairment as described in the literature. However, Lenz et al. (1995) indicated in the TUS that the factors have an influential relationship on patients' symptom experiences and can increase or decrease level of symptom intensity.

Symptoms

The dimensions of duration, intensity, distress, and quality appear to be a "good fit" for evaluating patients' self-reports of cognitive impairment. Duration and intensity also could be assessed empirically with appropriate neurocognitive tests. However, self-reporting would be necessary to evaluate the level of distress and aspects of quality because they are more subjective dimensions.

As mentioned earlier, fatigue, pain, depression, and sleep disturbances have been evaluated as a symptom

Physiologic Factors
- Normal systems
  - Intelligence quotient
  - Genetic makeup
  - Age
- Pathologic problems
  - Chemotherapy-induced anemia
  - Inflammatory cytokines
  - Low serum estradiol
  - Low serum testosterone
  - Comorbidities (e.g., cardiovascular hypertension, diabetes)
  - Concomitant therapies (e.g., analgesics, antiemetics, steroids)
- Energy substrate
  - Low levels of vitamin D

Psychological Factors
- Mental state
  - Anxiety
  - Depression
- Reaction to illness state
  - Anxiety
  - Depression

Situational Factors
- Lifestyle
  - Employment status
  - Type of employment
  - Diet
  - Exercise
- Personal experiences
  - Marital status
  - Social support
  - Educational level

Symptoms

- Cognitive impairment
  - Duration
  - Intensity
  - Distress
  - Quality
- Fatigue
  - Duration
  - Intensity
  - Distress
  - Quality
- Anxiety
  - Duration
  - Intensity
  - Distress
  - Quality
- Depression
  - Duration
  - Intensity
  - Distress
  - Quality
- Pain
  - Duration
  - Intensity
  - Distress
  - Quality

Performance

- Functional status
  - Job effectiveness
  - Leadership effectiveness
- Cognitive functioning
  - Executive function
  - Information-processing speed
  - Language
  - Motor function
  - Spatial skills
  - Learning and memory
- Physical performance
  - Motor function

Figure 3. The Theory of Unpleasant Symptoms to Explain Cognitive Impairment

cluster in patients with cancer (Dodd, Miaskowski, et al., 2001; Miaskowski et al., 2006). Pain has been associated with cognitive impairment (Hart et al., 2003). Intuitively, fatigue likely would have an effect on cognitive performance (Hart et al.; Meyers, 2000). Anxiety and depression, although listed as psychological influencing factors, also have been suggested to be associated with cognitive performance (Brown et al., 2001; Lezak et al., 2004; Meyers, 2000), so they are listed as symptoms as well until more is learned about the relationships.

Performance and Consequences

A patient's functional status (such as the ability to perform a job or function effectively in a leadership position) can be affected by cognitive impairment (McCracken & Iverson, 2001). Cognitive functioning is particularly germane to cognitive impairment. Aspects of cognitive function that may be affected by chemotherapy include executive function, information-processing speed, language, motor function, spatial skills, learning, and memory (Jansen et al., 2005). Manifestations of physical performance may be dependent on the level of motor function affected by cognitive impairment, such as changes in fine motor control or physical tasks requiring intact cognitive function such as memory or perceptual speed (Meyers, 2000).

Using the Theory of Unpleasant Symptoms to Guide Concept Development and Research

The TUS appears to have utility in describing the concurrent symptom experience (i.e., symptom cluster) common to individuals with cancer. Use of the TUS to describe the symptom experience for those with cognitive impairment can lend structure to the pursuit of ongoing research. The TUS provides support and rationale for not examining cognitive impairment in isolation of potentially contributing factors such as anxiety, depression, fatigue, anemia, altered hormone levels, inflammatory cytokines, advancing age, and comorbidities. Lenz et al. (1997) stated, "Unidimensional measurement of unpleasant symptoms is unpromising, because these concepts are multidimensional, and the conceptualizations often overlap" (p. 22). Ahles and Saykin (2002) made strong recommendations for prospective, longitudinal trials to evaluate patients' baseline cognitive status prior to initiation of chemotherapy. The trials should be controlled carefully for evaluation of contributing and confounding factors. Nursing research related to the symptom experience also should take multiple factors into account and use multidimensional symptom assessment tools (Paice, 2004). The recommendation made in this article for

use of the TUS to describe the symptom experience of cognitive impairment is obviously in the beginning stages. Much more work is needed to build evidence to support the presence of cognitive impairment as a component of a symptom cluster, as defined by Dodd, Miaskowski, et al. (2001).

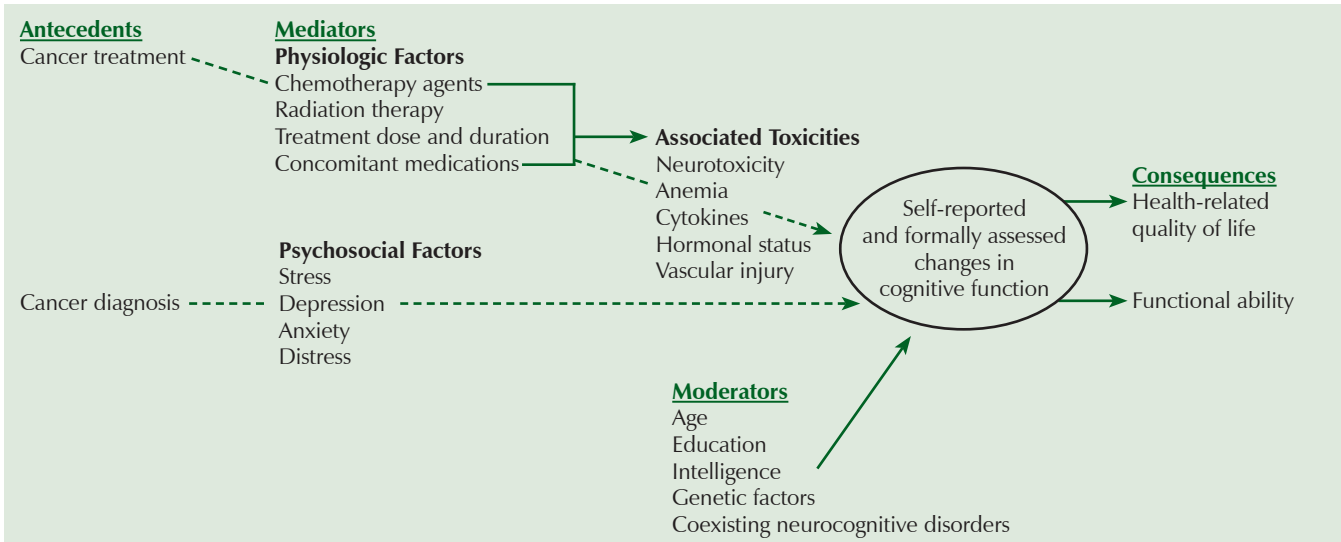## Conceptual Model of Chemotherapy-Related Changes in Cognitive Function

Hess and Insel (2007) published the Conceptual Model of Chemotherapy-Related Changes in Cognitive Function (see Figure 4). The elegant model is based on an extensive review of the literature. The authors included a comprehensive table of working definitions and measures of cognitive function and related domains (executive function, attention, concentration, intelligence, memory and recall, psychomotor ability, processing, verbal ability, vigilance, and visuospatial and visuomotor ability). Hess and Insel noted that, to date, consistency has been lacking in the instruments used to measure the effect of chemotherapy on cognitive domains, as well as the definitions of terms and concepts. The two issues have been a significant barrier to defining the precise effects of chemotherapy on cognitive function. The authors acknowledged the need to assess both the physiologic and psychosocial effect of a cancer diagnosis in addition to the effects of cancer-related treatment.

Cancer treatment and the meaning of the cancer diagnosis are listed as the antecedents in the model. Mediators are divided into physiologic factors (e.g.,

chemotherapy agents, radiation therapy, treatment dose and duration, concomitant medications) and psychosocial factors (e.g., stress, depression, anxiety, distress). Bidirectional influence is depicted between the psychosocial factor mediators and the associated toxicities (e.g., neurotoxicity, anemia, cytokines, hormonal status, vascular injury). Moderators include age, education, intelligence, genetic factors, and coexisting neurocognitive disorders. The consequences of changes in cognitive function are listed as health-related QOL and functional ability. Hess and Insel (2007) included the following descriptive-relational statement: "Cognitive function, defined as an individual's higher-order mental processes, may be altered among individuals diagnosed with cancer along two distinct and interacting pathways: (a) cancer diagnosis (the meaning of cancer), leading to anxiety, stress, distress, and depression, and (b) direct physiologic effects of cancer treatment, both of which may affect cognitive function" (p. 990).

Comparison of the Two Models

A number of similarities exist between the proposed use of the TUS model for describing patients' symptom experiences with standard-dose chemotherapy and the Conceptual Model of Chemotherapy-Related Changes in Cognitive Function. Both appear to have utility for description of the related factors for cognitive impairment. Hess and Insel's (2007) consequences for health-related QOL and functional ability mirror the performance category in the TUS. Psychological factors are congruent, with the exception of stress and distress in the Hess and Insel model.

Figure 4. The Conceptual Model of Chemotherapy-Related Changes in Cognitive Function
Note. From "Chemotherapy-Related Change in Cognitive Function: A Conceptual Model," by L.M. Hess & K.C. Insel, 2007, *Oncology Nursing Forum, 34*(5), p. 991. Copyright 2007 by the Oncology Nursing Society. Reprinted with permission.
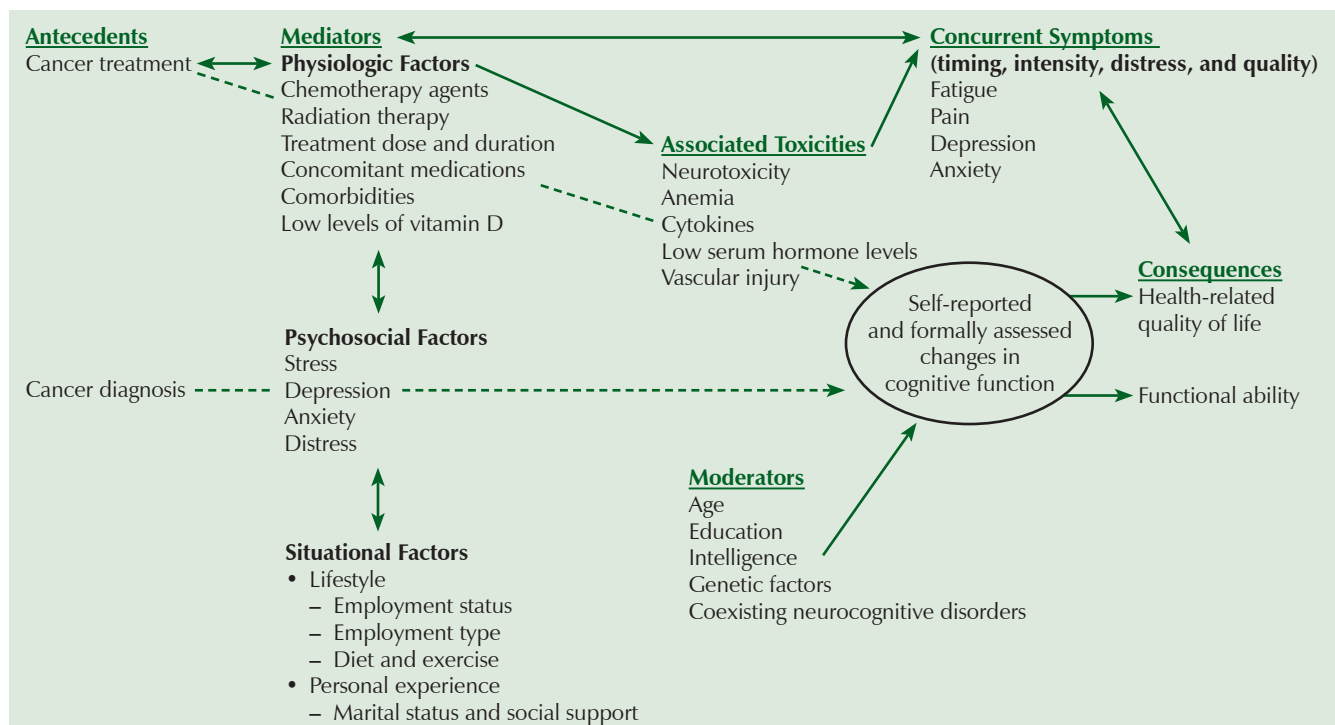
Differences

One primary difference is the utility of the TUS for description of the occurrence of concurrent and synchronous symptoms, or symptom clusters. The TUS model allows a depiction of the interrelationship of symptoms as well as influencing factors and performance (consequences). The symptom experience in the TUS model includes descriptors (i.e., timing, intensity, distress, and quality). The TUS model includes the relationship of situational factors, such as lifestyle (e.g., employment status, type of employment, diet, exercise) and personal experiences (e.g., educational level, marital status, social support). The potential for influence of performance on the symptom experience as well as the influencing factors are integral parts of the TUS. For example, one aspect of cognitive impairment that has yet to be studied is whether anxiety, depression, and fatigue contribute to the level or intensity of the cognitive impairment experience, or whether the cognitive impairment experience is causal to anxiety, depression, and fatigue. The Conceptual Model of Chemotherapy-Related Changes in Cognitive Function acknowledges the antecedent events of cancer treatment and the meaning of the cancer diagnosis and relates the consequences of cognitive impairment to health-related QOL. The TUS has a less direct inclusion of the antecedents within the psychological factors (i.e., reaction to illness state) and does not specifically address the synthesis of the consequences on QOL.

Suggestions for Consideration and Further Study

Opportunity may exist for blending of the TUS model and the Conceptual Model of Chemotherapy-Related Changes in Cognitive Function (see Figure 5). The recommendations include: (a) addition of situational factors to the mediators, (b) demonstration of bidirectional influence between situational and psychosocial factors, (c) inclusion of the relationship of concurrent symptoms with associated toxicities, (d) depiction of bidirectional influence between mediators and concurrent symptoms, and (e) depiction of bidirectional influence between concurrent symptoms and consequences. In the combined model, the normal systems physiologic factors of the TUS (e.g., IQ, genetic makeup, age) would be included as moderators. With a combination of the two models, a more complete description and representation of the symptom experience of cognitive impairment may be possible because the combination would allow for the concurrent experience of multiple symptoms (as represented in the TUS) in addition to cognitive impairment while maintaining the antecedent components of the cancer diagnosis and treatment (as represented in the Conceptual Model). The primary disadvantage of the combined model would be the loss of the more three-dimensional depiction of multiple symptoms and the descriptors of timing, distress, intensity, and quality portrayed in the TUS.

Antecedents
Cancer treatment

Mediators
Physiologic Factors
Chemotherapy agents
Radiation therapy
Treatment dose and duration
Concomitant medications
Comorbidities
Low levels of vitamin D

Associated Toxicities
Neurotoxicity
Anemia
Cytokines
Low serum hormone levels
Vascular injury

Concurrent Symptoms
(timing, intensity, distress, and quality)
Fatigue
Pain
Depression
Anxiety

Self-reported and formally assessed changes in cognitive function

Consequences
Health-related quality of life

Functional ability

Psychosocial Factors
Stress
Depression
Anxiety
Distress

Cancer diagnosis

Moderators
Age
Education
Intelligence
Genetic factors
Coexisting neurocognitive disorders

Situational Factors
• Lifestyle
   – Employment status
   – Employment type
   – Diet and exercise
• Personal experience
   – Marital status and social support

Figure 5. Revised Conceptual Model of Chemotherapy-Related Changes in Cognitive Function Based on the Theory of Unpleasant Symptoms

Note. From "Chemotherapy-Related Change in Cognitive Function: A Conceptual Model," by L.M. Hess & K.C. Insel, 2007, *Oncology Nursing Forum, 34*(5), p. 991. Copyright 2007 by the Oncology Nursing Society. Adapted with permission.

Conclusion

Cognitive impairment is an important sequela of standard-dose chemotherapy. Oncology nurses play a key role in the assessment, diagnosis, and management of treatment-related symptoms, as well as patient and family education. Conceptual models are necessary to provide a framework for ongoing research, nursing practice, and symptom management. The TUS and the Conceptual Model of Chemotherapy-Related Changes in Cognitive Function have utility for describing the cognitive impairment experienced by patients receiving standard-dose chemotherapy. A blending of the two models may enhance that utility. Further refinement likely will be needed as researchers learn more about physiologic and psychological aspects of chemotherapy-related cognitive impairment.

Jamie S. Myers, RN, MN, AOCN®, is a doctoral student in the School of Nursing at the University of Kansas Medical Center in Kansas City. No financial relationships to disclose. Mention of specific products and opinions related to those products do not indicate or imply endorsement by the *Oncology Nursing Forum* or the Oncology Nursing Society. Myers can be reached at jamyers@swbell.net, with copy to editor at ONFEditor@ons.org. (Submitted November 2007. Accepted for publication January 15, 2008.)

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