

NEUROLEPTIC MALIGNANT SYNDROME:
AN ONLINE RESOURCE FOR
HEALTHCARE PROVIDERS

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ABSTRACT

Neuroleptic Malignant Syndrome (NMS) is a rare and potentially life threatening emergency. The etiology of NMS is unknown. The dopamine hypothesis is the most widely accepted explanation. NMS is thought to occur from a dopamine deficiency within the brain. This hypodopaminergic condition may be caused by exposure to dopamine blocking or depleting medications. It can present mildly with one or two signs and symptoms, or as a storm of clinical phenomena and autonomic dysfunction. NMS mirrors other medical and toxic syndromes. The diagnosis of NMS is one of exclusion.

Healthcare providers may lack the knowledge to accurately diagnose and treat NMS. The purpose of this project is to develop an online resource for healthcare professionals in an effort to educate the learner regarding the potentially fatal disorder of NMS. An online method for course delivery was selected because of convenience and low cost to the learner.

CHAPTER I

Introduction

The advent of neuroleptic medications in the 1950s led to great relief of symptoms for patients afflicted with psychiatric disorders (Mann, Caroff, Keck, and Lazarus, 2003). Undesirable side effects, as with any medication, began to surface. The earliest documentation of neuroleptic malignant syndrome (NMS) was first reported by the French in 1960. The neuroleptic malignant syndrome is an adverse reaction and potentially life threatening condition resulting from the use of neuroleptic medications, dopamine blocking or depleting agents and rapid withdrawal of dopamine agonists. The activating mechanism of NMS remains unknown. Current hypotheses implicate dopamine blockade at the dopamine two (D₂) receptor site to be the causative factor (Addonizio and Susman, 1991; Bottoni, 2002; Mann et al., 2003; Susman, 2001; and Waldorf, 2003).

NMS presents as a myriad of signs and symptoms with varying degrees of severity. Symptoms of neuroleptic malignant syndrome mirror other medical and toxic disorders, making diagnosis a challenge. The most common signs and symptoms include: hyperthermia, “lead-pipe” rigidity, altered level of consciousness, and autonomic dysfunction (hypertension, tachycardia, diaphoresis, and incontinence). NMS is a life threatening disorder; its diagnosis warrants immediate attention (Susman, 2001; and Waldorf, 2003). Treatment consists of rapid discontinuation of the offending agent and clinical management of the patient that will be presented in this manuscript.

Problem Statement

Many healthcare providers lack sufficient preparation to diagnose NMS. The syndrome presents inconsistently from patient to patient, making diagnosis difficult even for more experienced professionals. The clinical problem is compounded by the infrequency of presentation, the variety of symptoms of NMS, and the lack of healthcare provider educational preparation to accurately diagnose the disorder.

Purpose Statement

The purpose of this paper is to provide an overview of NMS and to present plans for the development of an online resource to increase healthcare providers' competencies for the accurate diagnosis and treatment of NMS. A web-based format was selected because of convenience and low cost to the learner. Robinson and Kish (2001) find that contemporary healthcare providers are aware that knowledge and technology required for practice are continually expanding. Therefore, healthcare providers must participate in continued learning to remain clinically competent.

Significance

The National Institute of Mental Health website reports that schizophrenia exists in approximately 2.4 million persons over the age of 18, roughly 1.1% of the U.S. population (<http://www.nimh.nih.gov/publicat/numbers.cfm#Intro>). The occurrence rate of NMS is relatively low. The disorder affects 0.5% to 3% of patients taking neuroleptic medication with a mortality rate of 4% to 30% (Arnath, Parameswaran, Gunatilake, Burgoyne, and Sidhom, 2004; Bottoni, 2002; Susman, 2001; Waldorf, 2003). Mann et al. (2003) found similar occurrence rates and a mortality rate of 11%. NMS has been found

equally in both genders and reported in patients ranging from age 3 to 80 years old with the greatest occurrence in young and middle-aged adults (Addonizio and Susman, 1991; Bottoni, 2002). NMS has been documented worldwide with no meaningful data related to race, ethnicity, age, sex, or geography (Mann et al., 2003).

Operational Definitions

The following section contains definitions of terminology used in contemporary psychiatry and throughout the manuscript. It is included to assist the reader in understanding the language of the project. Operational definitions were formulated using a variety of sources: the author, The American Psychiatric Glossary (1994), Sadock and Sadock's Synopsis of Psychiatry(2003), and the DSM-IV-TR (2000).

Operational Definitions

Agonist:	Having affinity towards. A substance that stimulates a receptor-mediated biological response by occupying cell receptors.
Antagonist:	Opposing or resisting the action of another. A substance that opposes, blocks, or neutralizes a receptor-mediated biologic response.
Antipsychotic medication:	Denoting the actions of such an agent (e.g. chlorpromazine), a neuroleptic. Used in the treatment of schizophrenia and psychosis.
	Atypical Antipsychotic agent: Medications (also neuroleptics) used in the treatment of schizophrenia and psychosis. Referred to as second-generation anti-psychotics (SGA) or serotonin-dopamine antagonists (SDA). First appeared in 1986. Tend to have a lower incidence of tardive dyskinesia and extrapyramidal symptoms (EPS). Improves both positive (hallucinations, delusions) and negative symptoms (flat affect, decreased cognition) of psychosis (e.g. olanzapine, risperidone).
Benzodiazepine (BZD):	A class of compounds with anti-anxiety, hypnotic, anticonvulsant, and skeletal muscle relaxant properties (e.g. diazepam).
Bradykinesia:	A decrease in spontaneity and movement. One of the features of extrapyramidal disorders, such as Parkinson's disease.
Catecholamine:	A group of biogenic amines derived from tyrosine and containing the catechol(3,4-dihydroxyphenyl) moiety (e.g. dopamine, epinephrine). Exerts an importance influence on peripheral and central nervous system activity.

Operational Definitions-*Continued*

Chorea:	Irregular, spasmodic, involuntary movements of the limbs or facial muscles, often accompanied by hypotonia.
Creatine Phosphokinase (CPK):	An enzyme catalyzing the reversible transfer of phosphate from phosphocreatine to ADP, of importance in muscle contraction. Elevated isoenzyme in plasma following myocardial infarctions, and muscle damage.
Dopamine (D or DA):	A central nervous system catecholamine that is the precursor of epinephrine and norepinephrine. Dopamine has five known receptor types and has three major neuronal pathways in the brain, mesocorticolimic- originating in the ventral tegmental area (VTA), nigrostriatal, and the arcuate nucleus (tuberoinfundibular). Excess dopamine is believed to cause psychosis.
Dyskinesia:	Difficulty in performing voluntary movements. Term usually used in relation to various extrapyramidal disorders.
Extra Pyramidal Symptoms (EPS):	Abnormal, involuntary movements attributed to pathologic states of one or more parts of the striate body and characterized by insuppressible, stereotyped, automatic movements (e.g. rigidity, tremors, shuffling gait, or posturing)that cease only during sleep. May occur as a reversible side effect of certain psychotropic drugs.
Hyperpyrexia:	An extremely high fever.

Operational Definitions-*Continued*

Lethal Catatonia:	Gradual onset of intense agitated or psychotic behavior and hyperpyrexia. Can present with markedly slowed motor activity, muscular rigidity, or bizarre posturing for long periods of time.
Malignant Hyperthermia:	Rapid onset of an extremely high fever with muscle rigidity, precipitated by exogenous agents, especially halothane or succinylcholine.
Monoamine Oxidase Inhibitor (MAOI):	Antidepressant and anxiolytic agents (e.g. phenelzine, tranylcypromine) not commonly used due to numerous dietary restrictions. Strong potential for hypertensive crisis with the consumption of tyramine containing foods (e.g. cheeses, smoked meats, fish, and beers, wines and ales).
Myoglobinuria:	Excretion of myoglobin in the urine; results from muscle degeneration which releases myoglobin in the blood. Can occur from trauma or advanced protracted ischemia of muscle.
Myonecrosis:	Necrosis of muscle.
Neuroleptic:	Any of a class of psychotropic drugs used to treat psychosis, particularly schizophrenia.
Neuroleptic Malignant Syndrome (NMS):	Life threatening complication of antipsychotic treatment marked by muscular rigidity, change in mental status, and autonomic nervous system dysfunction or instability.

Operational Definitions-Continued

Neurotransmitter:	Any specific chemical agent released by a pre-synaptic cell, upon excitation, that crosses the synapse to stimulate or inhibit the postsynaptic cell. More than one may be released at any given synapse.
Psychosis:	A mental state characterized by one or more of the following: hallucinations, delusions, paranoia, disorganized speech, thought processes, behavior, psychomotor agitation, or aggression. May be caused by drug intoxication, toxic syndromes, metabolic disorders, mental illness, brain injury or medical conditions.
Psychotropic:	Capable of affecting the mind, emotions, behavior; denoting drugs used in the treatment of mental illness.
Receptor:	A structural protein molecule on the cell surface or within the cytoplasm that binds to a specific factor, such as a drug, hormone, antigen or neurotransmitter.
Rhabdomyolysis	An acute, fulminating, potentially fatal disease of skeletal muscle that entails destruction of muscle, as evidenced by myoglobinemia and myoglobinuria.
Schizophrenia:	A chronic mental disorder characterized by both positive (hallucinations, delusions, disorganized speech and behavior, ideas of reference, paranoia) and negative symptoms (flat affect, avolition, lack of socialization, and anhedonia) resulting in impairments of insight, judgment, interpersonal relationships, self-care and daily functioning.

Operational Definitions-*Continued*

Selective Serotonin Receptor Inhibitor: (SSRI)	Class of medication used to treat depression, anxiety, obsessive-compulsive disorders (OCD), and panic disorders. Considered a first line agent. Acts by inhibiting the reuptake of serotonin at the terminal synapse (e.g. fluoxetine, sertraline).
Serotonin:	A neurotransmitter or catecholamine that is found in the GI tract and central nervous system. Serotonin imbalance may explain affective disorders. Too little serotonin is thought to cause depression, and mania is associated with too much serotonin.
Tardive Dyskinesia:	Involuntary movements of the facial muscles and tongue, often persistent, that develops as a late complication of some neuroleptic therapy, more likely with typical antipsychotics.
Tricyclic Antidepressant (TCA):	Class of medication characterized by its three ring structure. Used in the management of depression, panic disorder, generalized anxiety disorder, obsessive-compulsive disorder and pain syndromes (e.g. doxepin, clomipramine).
Typical Antipsychotic Agent:	First medications developed (1950s) in the treatment of schizophrenia and psychosis. Referred to as dopamine antagonists, blockers, or neuroleptics (e.g. haloperidol, chlorpromazine). Associated with a higher risk for movement disorders and anti-cholinergic side effects.

Summary

This chapter provided an overview of NMS and introduced terminology used in current psychiatry. The most likely etiology of NMS stems from a medication induced hypodopaminergic state. The clinical triad of NMS consists of autonomic dysfunction, altered mental status and hyperthermia. NMS is rare in occurrence, affecting 0.5% to 3% of patients taking an antipsychotic medication, and presents inconsistently from patient to patient, making diagnosis a challenge. NMS is a true psychiatric emergency. Healthcare providers must be knowledgeable about its diagnosis and treatment.

CHAPTER II

Introduction

The first section of Chapter II will review Roy's Model of Adaptation and illustrate how it is applied to NMS. The second section contains a review of the literature including a history of NMS, associated risk factors, onset, and etiology and pathophysiology. This chapter also will explore the clinical presentation, expected laboratory values, and complications. Lastly, a description of the most likely differential diagnoses will be compared and/or contrasted.

Conceptual Framework

The conceptual framework of this project is based on Roy's Adaptation Model (1960). This theory is reliant on the concepts of *Person*, *Environment* and *Adaptation*. Roy defines *Person* as a holistic system in constant interaction with the *Environment* (Andrews and Roy, 1991). The *Person* possesses regulator and cognator functions to maintain adaptation. Regulator functions are automatic responses through physiological channels: neural, chemical, and endocrine. Cognator responses are "the emotional and cognitive channels that include perceptual, information processing, learning, judgment, and emotion" (p. 159). Within the regulator and cognator domains, four coping mechanisms exist to maintain adaptation, *physiologic function*, *self-concept*, *role function*, and *interdependence*. Roy's model suggests that relationships exist among the four modes: internal and external stimuli may affect more than one mode simultaneously, one behavior may be a manifestation of disruption in more than one

mode, and each adaptive mode may act as a stimulus for each of the other modes (p. 159). The person of interest in this project is the patient experiencing NMS.

Roy defines *Environment* as, “all conditions, circumstances and influences that surround and affect the development and behavior of the person” (p.156). The model introduces the concept of *stimuli* or *inputs*. Stimuli are forces or stressors that impact the person. They are classified as internal, external, focal, contextual or residual. Internal stimuli come from within the self and external from the environment. Focal stimuli are derived from the focus of the person’s immediate attention. Contextual stimuli are peripheral inputs and exert influence on the coping of focal stimuli. Residual stimuli are referred to as general knowledge and intuitive impressions. In this paper, medication is considered a stimulus.

Stimuli are processed by the regulator and cognator functions using the four coping mechanisms. Once processed, a response occurs. The response may be adaptive or ineffective. An adaptive response progresses the person toward integrity that encompasses survival, growth, reproduction and mastery, which promote health and healing. An ineffective response serves as a stimulus and is looped back through the coping mechanisms.

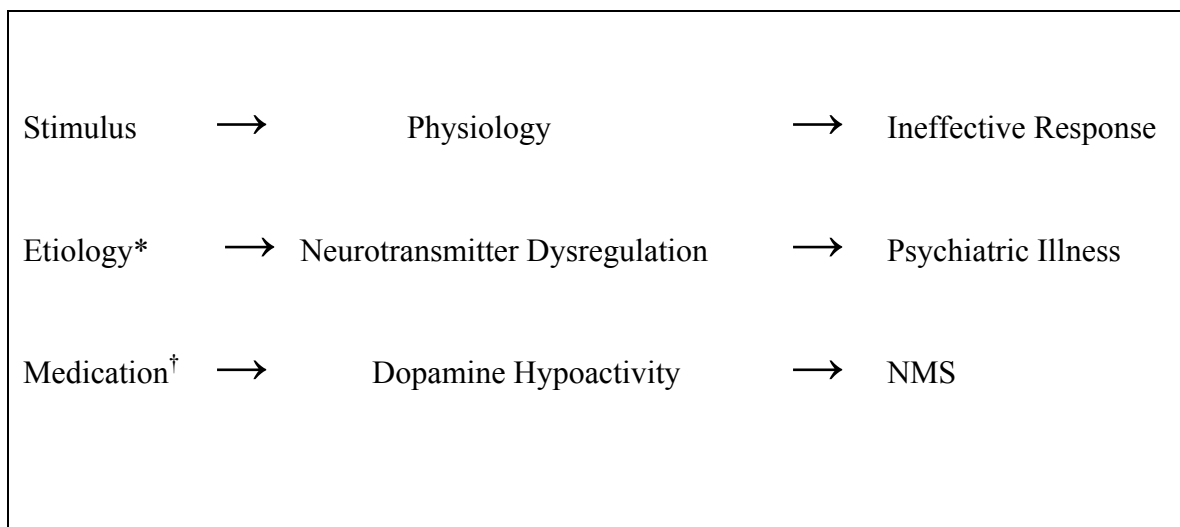
Roy’s goals of nursing are to promote positive adaptive responses, and enhance health and healing. Roy advocates the utilization of the nursing process: assessment, diagnosis, goal setting, intervention, and evaluation in achieving positive adaptation. Thus, accurate assessment and diagnosis are crucial in planning appropriate interventions.

Nursing intervention is aimed at the management or manipulation of stimuli; increasing, decreasing, altering, maintaining, or removing the stimuli (p. 162).

Figure 2.1 represents Roy's Model of Adaptation applied to NMS. Again, stimuli affect the physiological mode producing an ineffective response. The etiology of psychiatric illness remains unknown. It is hypothesized that neurotransmitter dysregulation produces psychiatric illness (ineffective response). Consistent with the current dopamine hypothesis, some medications (stimuli) may cause neurotransmitter dysfunction or dysregulation (physiological) that lead to the activation of NMS (ineffective response).

Roy's Model of Adaptation Applied to NMS

Figure 2.1.



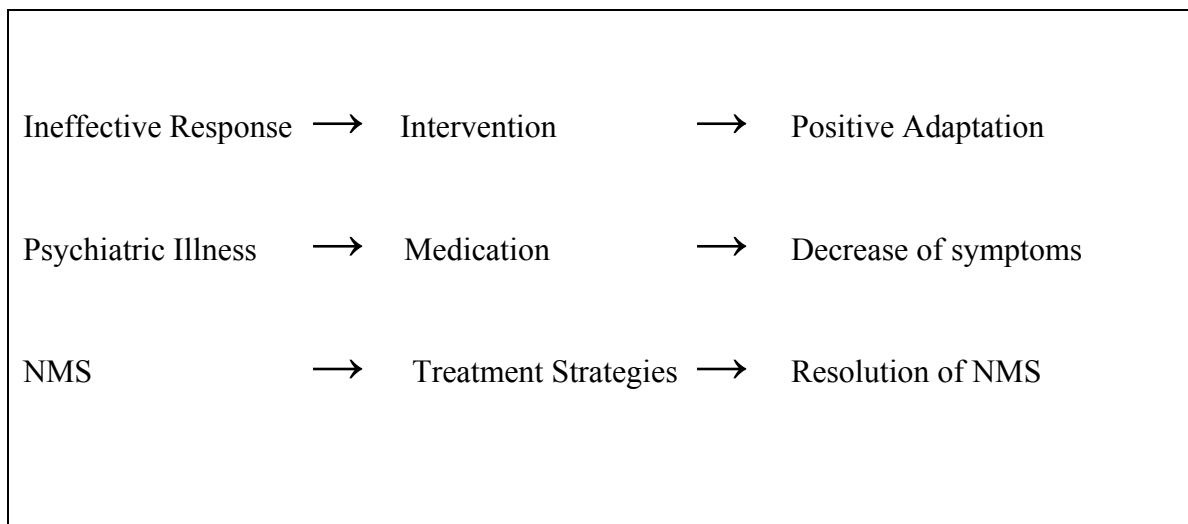
*Possible etiologies may include: neurotransmitter dysfunction or imbalances, drug intoxication, brain trauma, toxic states, sleep deprivation, and metabolic or electrolyte disturbances.

[†] Appendix B lists the medications that may cause NMS.

In Figure 2.2 the framework of Roy's Adaptation Model also can be applied to the treatment of NMS. Ineffective responses are met with intervention(s) to promote positive adaptation. Psychiatric illness (ineffective response) is managed with medication (intervention) to decrease symptoms (positive adaptation). NMS (ineffective response) is treated with recommended strategies (intervention) to promote resolution (positive adaptation). Treatment strategies are discussed in Chapter III.

Roy's Model of Adaptation Applied to the Treatment NMS

Figure 2.2.



Review of the Literature

History of Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome was first described by Delay and Deniker in 1960 (Mann et al., 2003). The French psychiatrists observed fever, altered mental status, and psychomotor changes in patients taking neuroleptic medications. They named this cluster of symptoms, “*syndrome malin des neuroleptiques*”.

NMS was largely ignored by American psychiatrists for many years (Addonizio and Susman, 1991). Cases began to surface over a decade later. In 1973, Meltzer described a myriad of symptoms in a schizophrenic patient taking fluphenazine. The patient displayed altered level of consciousness, muscular rigidity, hyperthermia, hypertension, and tremors. He also found that CPK levels were dramatically increased (Mann et al., 2003). In 1974, Cohen and Cohen published a report describing similar symptomatology in patients taking high doses of haloperidol with lithium (Addonizio and Susman, 1991). Gelenberg and Mandel (1977) found catatonic conditions in patients receiving high potency neuroleptic medications. Caroff (1980) reviewed 60 cases presenting with the clinical features described by Delay and Deniker in 1968. He found that NMS had been under diagnosed and under recognized (Mann et al., 2003).

Today, NMS has been well documented among psychiatric professionals, though under diagnosis continues to be a problem. It is believed to occur from dopamine D₂ receptor blockade. Dopamine antagonistic agents and rapid withdrawal from anti-Parkinson agents are the most likely cause (Addonizio and Susman, 1991; Bottoni, 2002; Mann et al., 2003; Susman, 2001; and Waldorf, 2003).

Risk Factors

Both typical and atypical antipsychotic medications may induce NMS (Arnath et al., 2004; and Mann et al., 2003). In addition to the neuroleptics, dopamine blocking or depleting agents may also produce this phenomenon (Arnath et al., 2004; Bottoni, 2002; Mann et al., 2003 and Susman, 2001). Appendix B lists the medications believed to trigger NMS.

Other factors have been identified as potential risks for NMS: organic brain syndrome, bilateral frontal lesions, affective disorders, dehydration, agitation, exhaustion, and rapid or parenteral administration of antipsychotic agents (Addonizio and Susman 1991; Gurrera, 1999; Waldorf, 2003). Abrupt discontinuation of antiparkinson agents may induce the syndrome (Bottoni, 2002; and Susman 2001). Schneiderhan and Marken (1994) suggest that a prior episode of NMS increases the likelihood of recurrence. Gurrera (1999) found that mental retardation is frequent among cases of neuroleptic malignant syndrome, but offered no cause.

Cohen and Cohen (1974) reported cases of NMS in patients taking lithium and neuroleptics concomitantly (Addonizio and Susman, 1991). Lithium alone may produce symptoms in patients with histories of NMS (Schneiderhan and Marken, 1994). Addonizio and Susman (1991) found the combination of lithium with an antipsychotic medication produced neurotoxic and irreversible effects, neurological impairments, coma and even death. They state:

Lithium may enhance neuroleptic drug induced EPS in some patients.

There have been reports of patients developing neurotoxicity on the lithium- neuroleptic combination. One study found EPS in 73.3% of the cases in their review of lithium-neuroleptic toxicity. Most of these patients had serum lithium levels within the therapeutic range.

This report provides further evidence for a potential lithium-neuroleptic drug synergism in inducing EPS (p. 22).

The effect of lithium in NMS remains unclear. It is purely speculative and remains controversial at this time.

Onset

The onset of NMS may occur as soon as within 24 hours of the first dose of antipsychotic medication (Addonizio and Susman, 1991; and Bottoni, 2002). The average onset appears to be between 48 to 72 hours (Mann et al., 2003; Susman, 2001). Arnath et al., (2004) report an average onset of 7 days. Waldorf (2003) reports a similar onset but found that NMS could occur at any time during the course of treatment.

Etiology and Pathophysiology

Dopamine, as described by Katzung (1998) is an endogenous catecholamine that produces a variety of biologic effects, such as motor acts and gating. It is also a precursor of epinephrine and norepinephrine. Currently, there are five known types of dopamine receptors; D₁, D₂, D₃, D₄, and D₅. The three major dopamine pathways within the brain are the nigrostriatal, mesocorticalimbic (originating in the ventral tegmental area), and the tuberoinfundibular. These pathways are associated with motor activities,

the brain reward circuit, and prolactin regulation respectively. Appendix A illustrates dopamine pathways within the brain.

Psychosis is believed to exist as a result of increased dopamine levels (Addonizio and Susman, 1991; Bottoni, 2002; Mann et al., 2003; Susman, 2001; and Waldorf, 2003). Neuroleptic agents may provide relief from psychotic symptoms by blocking or limiting dopamine transmission. Neuroleptic medications specifically may target or indirectly affect the dopamine D₂ receptor sites, as well as other dopamine receptors.

Hypodopaminergic activity may explain the clinical presentation and is the current popular hypothesis for the production of NMS. Mann et al. (2003) support this hypothesis stating, “The most compelling evidence supports the occurrence of central dopamine hypoactivity as the principal factor in the development of NMS” (p. 38). The authors found that all neuroleptics implicated in causing NMS share the property of D₂ dopamine receptor antagonism. In 2000, Spivak et al. reported a decrease in dopamine concentration in plasma of NMS patients (Mann et al., 2003). Appendix B lists medications that may cause NMS.

Additional hypotheses have surfaced regarding the cause of NMS. Waldorf (2003) proposed: (1) a relative imbalance of norepinephrine to dopamine in the CNS, (2) serotonergic imbalances, and (3) excessive catecholamine secretion. Susman (2001) noted that previous studies suggest altered calcium and iron metabolism. Gurrera (1999) implicated norepinephrine dysregulation of the sympathetic nervous system. Chandran, Mikler, and Keegan (2003) cited increased serotonin levels.

Clinical Presentation

Accurately diagnosing NMS is challenging due to inconsistency in the clinical presentation. Patients may display a single symptom, a constellation of signs, or the full range of symptomatology. The severity of presentation varies among patients (Addonizio and Susman, 1991; Bottoni, 2002; Susman, 2001; and Waldorf, 2003).

Hyperpyrexia is a hallmark sign of NMS. Temperatures as high as 107.6°F with a mean of 103°F have been displayed in patients with NMS (Arnath et al., 2004; and Bottoni, 2002). Arnath et al., (2004) and Caroff and Mann (1988) report hyperpyrexia in over 95% of NMS cases. Thermoregulation in mammals is housed within the hypothalamus and the contractile apparatus of skeletal muscle (Gurrera, 1999). Hyperthermia, is not the sole the result of dopamine deficiency, but is enhanced by other mechanisms of the sympathetic nervous system within the posterior hypothalamus, including dysregulation of heat and cold receptors, and excess catecholamines (Gurrera, 1999).

Caroff and Mann (1988) and Arnath et al., (2004) found mental status changes in 97% of patients diagnosed with NMS. Patients may present: agitated, stuporous, delirious or even comatose. Mann et al., (2003) found that most patients present alert, but dazed and mute, representing catatonia or akinetic mutism.

Another cardinal sign of NMS is “lead-pipe” rigidity. Caroff and Mann (1998) found that 97% of cases diagnosed with NMS had muscular rigidity. Gurrera (1999) found the depletion of dopamine and activation of norepinephrine and epinephrine in NMS perpetuate disturbances within the sympathetic nervous system and nigrostriatal

pathways. He reports that these disturbances or imbalances cause a massive efflux of intracellular calcium ions. The calcium shifts then produce skeletal muscle contractions, which present as “lead-pipe” rigidity or catatonia and contribute to increased hyperthermia. Bottoni (2002) found that dopaminergic blockade causes muscle contraction and rigidity, which generate heat and produce pyrexia. Waldorf (2003) added that patients can present with tremors, bradykinesias, dyskinesias, and chorea.

The peripheral signs and symptoms seen in NMS, labile blood pressure, tachycardia, and diaphoresis, are due to autonomic dysfunction (Gurrera, 1999). He suggests this is not a result of excess circulating catecholamines, but rather sympathetic nervous system stimulation (p. 175). Gurrera (1999) also lists urinary incontinence as a common occurrence seen in NMS.

The clinical presentation of NMS, based on research criteria from the DSM-IV-TR (2000) is listed in Appendix C. The presence of symptoms, after the exclusion of other neuropsychiatric, systemic, and drug-induced hypermetabolic conditions, suggests a diagnosis of NMS (Mann et al., 2003). It is important to remember that NMS may appear as a single symptom, cluster of symptoms or all of the symptoms (Mann et al. 2003; and Susman 2001). The severity of symptomatology may vary (Bottoni, 2002; and Susman, 2001).

Laboratory Findings

Laboratory findings are important in making an accurate diagnosis of NMS. Creatine kinase (CK) will be elevated as a result of rhabdomyolysis from muscle contraction. Susman, (2001) found that CK levels can reach 100,000 IU/L. Arnath et al.,

(2004) and Caroff and Mann (1998) report CK elevations in over 95% of NMS cases reviewed.

Myonecrosis occurs from severe muscular contraction and leads to increased myoglobinuria. This may result in renal failure. Caroff and Mann (1998) found myoglobinuria in 67% of reported NMS cases. Lactic acid, transaminase, and aldolase levels can also be increased secondary to myoglobinuria. Metabolic acidosis occurs in 75% of NMS cases (Caroff and Mann, 1998). Leukocytosis (with or without a left shift) presents as a secondary response to stress or tissue damage (Susman 2001). Caroff and Mann (1998) report a leukocytosis rate of 98%. Electrolyte imbalances also often occur. Waldorf (2003) found that hypokalemia, hyponatremia, hypocalcemia, and hypomagnesaemia may present as sequelae to diaphoresis, incontinence, dehydration and renal failure.

Complications

Neuroleptic Malignant Syndrome gives rise to numerous complications. Prolonged muscle rigidity results in rhabdomyolysis, myonecrosis, myoglobinuria and possibly renal failure. Hyperthermia from skeletal muscle contractions and hypothalamic dysregulation may induce seizures. Additional complications include: myocardial infarction, aspiration pneumonia, pulmonary edema, arrhythmias, cardiac arrest, disseminated intravascular coagulation, and death. Appendix D lists the complications associated with NMS.

Differential Diagnoses

The list of differential diagnoses for NMS is extensive because the clinical presentation mirrors several medical and toxic disorders. Differential diagnoses include: serotonin syndrome, lethal catatonia, central nervous system (CNS) infection, heatstroke, encephalitis, thyrotoxicosis and drug intoxication. NMS is a *diagnosis of exclusion* (Susman, 2001). A thorough health and drug history, physical examination and laboratory investigations and lumbar puncture should be performed. Laboratory and diagnostic tests should include: electrolyte, renal function, CK, urine myoglobin, leukocyte, serum lithium, head computerized tomography (CT) (Chandran, Mikler, and Keegan, 2003). Toxicology screens are recommended to rule out drug intoxication (Addonizio and Susman, 1991; Mann et al., 2003; and Susman, 2001).

Serotonin Syndrome

Depression is hypothesized to occur from poor serotonin transmission. Early antidepressant pharmacotherapy consisted of two classes of medication: monoamine oxidase inhibitors (MAOIs) or tricyclic antidepressants (TCAs). The MAOI class has numerous drug-drug interactions (with serotonin and norepinephrine agonists) and restriction of tyramine containing foods. Combining a MAOI with a contraindicated food or medication can result in a hypertensive crisis or death (Preskorn, 1999). TCAs are sedating, which lead to safety issues and weight gain. TCAs also tend to produce undesirable anticholinergic and sexual side effects.

Selective serotonin reuptake inhibitors (SSRIs) were introduced in the 1980s.

This next generation of antidepressant therapy was welcomed because manufacturers touted a higher therapeutic efficacy and a low side effect profile. Carbone (2000) found this class of medication to enhance serotonergic transmission but stated that SSRIs also could yield a toxic state similar to NMS. Mann et al. (2003) report similar findings that state, “The serotonin syndrome (SS) appears to be mediated primarily by excessive serotonergic activity” (p. 75).

Excessive stimulation of the serotonin 5HT-_{1A} receptor has been implicated as the cause for serotonin syndrome (Boyer and Shannon, 2005; Carbone, 2000; Mann et al., 2003; Sternbach, 2003; and Westphal, 1999). Boyer and Shannon (2005) suggest the following agents may contribute to SS: antidepressants, SSRIs, OTC cough medicines, antibiotics, herbal products, cocaine, amphetamines, lithium, antiemetics, opiate analgesics, and weight reduction agents.

Clinically, the serotonin syndrome (SS) presents identical to NMS. It presents as a triad of altered mental status, autonomic hyperactivity, and neuromuscular activities (Boyer and Shannon, 2005; Carbone, 2000; and Sternbach, 2003). Carbone (2000) found altered mental status in 40% of patients with SS and reports that they may present: manic, confused, restless, stuporous, or comatose. Mann et al. (2003) report an altered mental status in 80% of patients.

Neuromotor dysfunction also is seen in SS. While the patient with NMS presents with “lead-pipe” rigidity, Carbone (2000) found that 50% of patients experiencing SS will present with hyperreflexia, myoclonus or tremor. Hyperpyrexia may occur as a

result of shivering or muscular hyperactivity. Boyer and Shannon (2005) add that some patients may display rigidity.

Westphal (1999) and Sternbach (2003) found autonomic hyperactivity in patients diagnosed with SS. The clinical manifestations include: hypertension, diaphoresis, hyperthermia, nausea, diarrhea, hyperactive bowel sounds and tachycardia. The presence of GI disturbances (diarrhea and nausea) will rule out NMS. Their presence does point to, but does not confirm the diagnosis of serotonin syndrome (Boyer and Shannon, 2005; and Mann et al., 2003). Wren, Frizzell, Keltner, and Wright (2003) offer a comparison of the syndromes in Appendix E.

There are no specific laboratory criteria for SS. Westphal (1999) suggests a thorough assessment of all agents the patient is currently taking to make an accurate diagnosis. The treatment of SS is aimed at removing the offending agent and managing the clinical presentation.

Lethal Catatonia

Lethal catatonia is virtually indistinguishable from NMS. It tends to begin with a prodromal phase; noted by mood lability and lasting about 2 weeks. NMS tends to begin with rigidity. Lethal catatonia then progresses to a hyperactive or psychotic excitement phase lasting about 7 days, then finally to exhaustion or death. Lethal catatonia can occur with or without neuroleptic exposure. Common causes include: head trauma, tumors, schizophrenia, cerebrovascular disorders, seizure disorders, metabolic disorders, toxic states (e.g. lead poisoning), and CNS infections.

Malignant Hyperthermia

Malignant Hyperthermia presents identical to NMS. The onset generally occurs minutes to hours after administration of general anesthesia. It is best to rule out a history of anesthetic exposure, specifically succinylcholine.

Heatstroke

Heatstroke presents with hot, dry skin rather than diaphoresis. Hypotension is common rather than labile blood pressure seen in NMS. Musculature tends to be of a more flaccid nature, rather than rigid.

Drug Intoxication

Drug intoxication can mirror NMS. Common causes can include: 3,4 methylenedioxymethamphetamine (MDMA, also called XTC or ecstasy), cocaine, amphetamines, phencyclidine (PCP), lysergic acid diethylamide (LSD), aspirin, carbon monoxide poisoning, lithium toxicity, anticholinergics medications, and withdrawal from alcohol, benzodiazepines, baclofen, and anti-parkinsonism agents. A drug history and toxicology screen is indicated.

Central Nervous System Disorders and Infections

Human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS), cerebral vascular accident (CVA-basilar artery, temporal lobes, and anterior cingulate gyri), viral meningitis, encephalitis, tetanus, tumors, trauma, and seizure disorders may display NMS like symptoms. Most often focal neurological and behavioral symptoms are seen. Cerebrospinal fluid examination and brain imaging are recommended.

Metabolic and System Disorders

Thyrotoxicosis (thyroid storm), Addison's disease, Cushing's disease, uremia, pheochromocytoma and systemic lupus erythematosus may present with symptoms similar to NMS.

Summary

Roy's Model of Adaptation illustrates how NMS is conceptualized in the human system. The person is considered a holistic being in constant interaction with an ever-changing environment. The person is comprised of regulator (physiological) and cognator (emotional and perceptual) domains. The person possesses four modes (physiologic, self-concept, role-function, and interdependence) to interpret internal and external stimuli. Stimuli are processed by the person and a response occurs. Responses may be ineffective or adaptive. Adaptive responses promote health, healing and growth. Nursing intervention is aimed at manipulating stimuli to produce effective adaptation.

NMS was first described by the French in 1960. Exposure to antipsychotic or dopamine depleting agents, and rapid withdrawal from anti-Parkinson medications are considered the major risk factors for developing NMS. The onset of NMS has been documented to occur at any time during treatment.

The etiology of NMS is unknown. The most likely cause is dopamine deficiency caused by dopamine depleting medications. The clinical triad of NMS consists of autonomic instability, altered mental status, and muscular rigidity. Elevated CPK, leukocytosis and electrolyte imbalances are commonly found. Complications of NMS include, seizures, renal failure, myocardial infarction, pneumonia, disseminated

intravascular coagulation and death. NMS presents with signs and symptoms that imitate other infectious, medical and toxic states.

CHAPTER III

Introduction

As discussed in Chapter II, Roy's Model of Adaptation can be applied to the treatment of NMS. The current recommendations for treatment are outlined in this chapter. Pharmacologic, non-pharmacologic and supportive care measures are included in the discussion, as are medication re-challenge after NMS and prevention of NMS.

Clinical Management

The initial treatment strategy for NMS is immediate discontinuation of the offending agent, as this may self-limit or even resolve the course of NMS (Addonizio and Susman, 1991; Bottoni, 2002; and Mann et al., 2003; and Susman, 2001). Subsequent care should focus on the presenting symptoms. Waldorf (2003) states, "Treatment should focus on airway protection, preventing hypoxia, supporting systemic perfusion, preventing systemic organ failure and restoring the dopaminergic balance within the CNS" (p. 392). Upon diagnosis, the patient should be transferred to a critical-care unit. Bottoni (2002) provides treatment guidelines for NMS in Appendix F.

Dantrolene sodium administered intravenously remains the gold standard for treatment of muscular rigidity (Mann et al., 2003). Dantrolene inhibits excess calcium release, relaxing skeletal muscle. This relaxed state may help to reduce the hyperthermic state (Fuller and Sajatovic, 2001).

The adjunct of dopamine agonists may be warranted. Bromocriptine, levodopa, and amantadine have shown to be effective in the management of NMS and potentially shorten the course of illness (Susman, 2001; and Waldorf 2003). These medications

relieve muscular rigidity and hyperthermia by restoring the dopaminergic balance.

The use of benzodiazepines in the treatment of NMS is controversial. Mann et al. (2003) found them to be of particular use for agitation and insomnia, rather than for relaxant properties. Benzodiazepines stimulate GABA receptors and may indirectly *increase* dopaminergic activity leading to muscle relaxation (Susman, 2001; and Waldorf, 2003). Bottoni (2002) has cited benzodiazepines as a contributing agent in the development of NMS. Respiratory depression can occur with the use of benzodiazepines. If benzodiazepines are to be implemented, it is strongly recommended that respiratory function be monitored closely.

Supportive measures also are needed. Tracheal intubation may be required to establish and protect the airway. Mechanical ventilation also may become necessary. Continuous cardiac monitoring is recommended. Intravenous therapy should be implemented to correct any fluid or electrolyte imbalances. Mann et al., (2003) recommends that acid-base imbalances be corrected immediately. Oral medications should not be administered if thoracic or esophageal dystonias are present, as aspiration may occur. Medications should be administered intravenously or per nasogastric tube. Urine output may be decreased if renal function is compromised. An indwelling urinary catheter is recommended to measure output.

Bathing and cooling blankets help reduce hyperthermia. The use of antipyretics is controversial. Both Susman (2001) and Waldorf (2003) report that the use of antipyretics is not indicated in the treatment of NMS induced hyperthermia. Susman (2001) found

the heat producing mechanism in NMS is caused by hypodopaminergic muscular rigidity, and does respond to traditional pharmacological intervention.

Massage may be used to increase peripheral vasodilation. Antiembolic stockings and low dose Lovenox can help reduce the formation of deep vein thrombosis. Chest physiotherapy, range of motion exercises and frequent turning and repositioning are needed to help relieve immobility and rigidity. Bottoni (2002) provides treatment guidelines for NMS in Appendix F.

Medication Rechallenge

Patients may begin antipsychotic therapy after complete resolution of symptoms. Bottoni (2002) recommends that a 2-week “washout” period of all medications elapse after full resolution from NMS, before rechallenging. This process should be implemented under the strictest of clinical supervision to prevent relapse of NMS. A low-dose, low-potency neuroleptic from a different chemical class should be selected. Titration of the antipsychotic should be performed slowly. A benzodiazepine may be added to help decrease agitation. The patient must be monitored closely for relapse or side effects. Should NMS recur, prompt withdrawal of the offending agent and treatment for NMS must be re-instituted.

Prevention

The treatment of NMS should include prevention that may be carried out in several forms. Early recognition of extrapyramidal and catatonic symptoms should alert the prescriber for dosage reduction and clinical reassessment. Velamoor (1998) suggests reduction in agitation with the use of benzodiazepines, and avoidance frequent parenteral

injections. Adequate hydration, good nutrition and routine exercise are also recommended for prevention.

Summary

The treatment of NMS is aimed at managing the clinical presentation. Protecting the airway, supporting systemic perfusion, preventing organ failure and restoring the dopaminergic balance are the principles of treatment. Dantrolene sodium is recommended for muscular rigidity. Fluid replacement is usually needed. Supportive care measures include cooling blankets, range of motion exercises, frequent turning and positioning and massage.

Medication rechallenge may be considered after full resolution of symptoms. This must be performed under strict clinical supervision. The prevention of NMS consists of early recognition of extrapyramidal symptoms, use of benzodiazepines for agitation, and reinforcing the importance of adequate hydration, good nutrition and routine exercise.

CHAPTER IV

Introduction

Healthcare providers may not be knowledgeable about NMS. The purpose of this project is to increase healthcare provider competency in diagnosing and treating NMS. This chapter will detail the steps involved in designing, developing, and implementing a website that provides critical information regarding NMS. The evaluation process is described including the tracking of statistics, and managing customer feedback or problems.

Innovation Description

The outcome for the project is an innovative, web based teaching site about NMS that would target psychiatric mental health and acute care nurse practitioners. Nurses, physicians and other healthcare professionals also would be encouraged to participate in the web based teaching-learning program. An on-line format was chosen for cost and convenience. It is time consuming and expensive to locate a speaker, provide travel arrangements, market the presentation, and reserve a conference room. Time is another constraint for teaching-learning experiences. With an online format, participants could learn at their convenience.

Creation of a web site with interactive learning modules addresses the problems of reducing overhead costs, learner time constraints, and providing a user-friendly delivery system to increase provider knowledge. Participants can simply navigate around the site, clicking on the topic or link of interest. The following learning modules or links would be included on the site:

- I. Introduction
 - a. Learning objectives
 - b. Optional pre-test
 - c. History of NMS
- II. Etiology and Pathophysiology
 - a. Epidemiology and pathophysiology
 - b. Risk Factors and onset
- III. Diagnosis
 - a. Clinical Presentation and Laboratory Values
 - b. Differential Diagnoses
 - c. Complications
 - d. Case Studies
- IV. Treatment Strategies
- V. Post-test- optional

The interactive modules would consist of text, Power Point slides with voice-overs, tables and figures, and an optional post-test. Navigation through the entire site should take the learner approximately 90 minutes. Upon completion of the learning modules, the learner may choose to test his/her knowledge by taking the post-test. This will be a short test of 20 questions derived from the material. The learner will self-grade his/her exam. Answers with rationale will be posted on the site. The site would also provide the learner with an email address for questions or comments. The website homepage is shown in Appendix H.

Human Subjects Approval

No ethical or humans rights issues have been identified with this program. IRB approval may be sought if evaluative data are needed from participants.

Innovation Implementation

Several components are needed to implement the innovation. The following sections detail the process. These steps are also outlined in Appendix G.

Create the Learning Content

The content of the teaching-learning program is created following a thorough review of the literature and formulation of learning objectives. The key concepts are organized and presented using text, tables, figures and Power-Point slides. Pre- and post-tests are developed based upon critical content. A survey instrument is constructed to evaluate efficacy the teaching-learning program and the web site.

Design the Web Page

Consultation with a web page designer, costing approximately \$18-\$20 per hour, is helpful in designing the layout, color schemes, sounds and format of the content with consistent navigation themes (B. Washburn, personal communication, October 5, 2005 and November 16, 2005). This innovation utilized Microsoft Publisher.

Moving to the World Wide Web

Once the webpage has been created, it must be moved onto the World Wide Web. The manager must decide on a name for the website and purchase a domain name server (DNS). This names the site, so that no one else can use that name. Double Domains (www.doubledomains.com) provides this service for \$15 per year. Website hosting also is necessary and provides technical support, customer feedback, email accounts, and user tracking and statistics (which pages are viewed the most, time spent on the site and on each particular page, what site did the user come from or go to). Half Price Hosting

(www.halfpricehosting.com) charges \$200 per year. Some universities and employers provide free website hosting.

The content data must be coded to activate the site's links. Each page is considered a link. Testing with different browsers and modem speeds are needed to ensure efficient navigation. Refinements to the site, content or navigation themes may be needed.

Site Promotion

Running the web site requires promotion of it. Link sharing with other websites such as, the American Psychiatric Association, American Academy of Nurse Practitioners, American College of Nurse Practitioners, and National Alliance for the Mentally Ill (NAMI) can attract the attention of medical professionals. Further promotion could occur through the University Arizona Colleges of Nursing, Medicine-Department of Psychiatry, and Pharmacy. The site could be enlisted with any number of search engines such as, Google or Yahoo!. Sponsored pages on a search engine site generally require a fee.

Site Management and Evaluation

The site will require routine management and evaluation. The site manager is responsible for reviewing site statistics, number of hits, country of origin, which search engine was used, who visited the site, which pages were most viewed, and length of time at each page and the site. The manager is also responsible for responding to feedback and emails. Navigation, site or content refinements should be performed on a continuing basis.

Innovation Evaluation

After completion of the design and data coding, the site must be beta tested prior to release. Content or navigation refinements may be needed. With purchased web hosting, the statistical data (time spent on each page, time at website, popular pages visited, etc.) are provided. A site manager must be selected to review this data and respond to learner questions or comments. A short learner survey should be added to elicit feedback. Refinements can be made based on the findings.

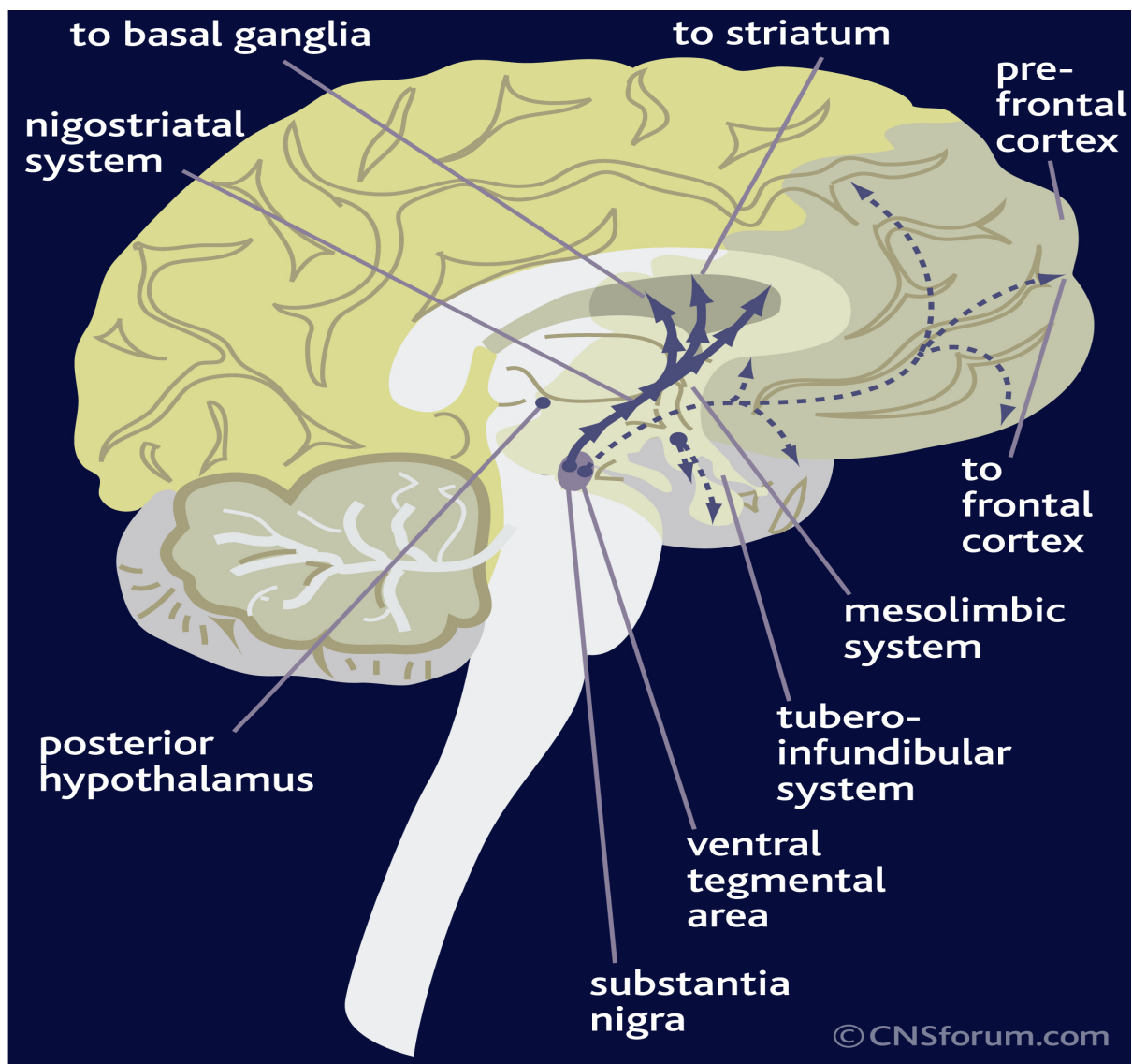
Summary and Conclusion

Neuroleptic Malignant Syndrome is a rare, complex and potentially life threatening disorder. It requires accurate diagnosis and warrants immediate treatment with supportive nursing care. Though the cause remains unknown; it is most likely attributed to the use of dopamine blocking or depleting medications, such as those used in contemporary psychiatry.

Diagnosing NMS is difficult because it presents with a cluster of symptoms that imitate numerous metabolic, drug-induced, and infectious disorders. The quantity and quality of the presenting symptoms may vary. Diagnosis consists of a careful health and drug history, physical examination and laboratory studies. NMS is a diagnosis of exclusion. Treatment is aimed at discontinuation of the offending agent and managing the clinical presentation. It must also be advocated that further research is needed to unmask the causative factor(s), facilitate the development of improved and safer medications and to identify “at risk” patients.

Psychiatric Mental Health Nurse Practitioners and other health care providers must be competent in the diagnostic and treatment protocols of NMS. This project provides information about NMS using an online format. This format is preferred because participants may learn at their own convenience with no cost. The goal of this innovation is to illustrate the steps implemented in designing an on-line learning experience for health care providers.

APPENDIX A
DOPAMINERGIC PATHWAYS



Kruk and Pycock (1993).

APPENDIX B
MEDICATIONS THAT MAY CAUSE NMS

Neuroleptics:

Phenothiazines:	Mellaril, Compazine, Thorazine, Phenergan, Prolixin
Butyrophenones:	Haldol, Inapsine
Thioxanthenes:	Navane
Dibenzepines:	Zyprexa, Clozaril
Benzisoxazoles:	Risperdal

Dopamine Antagonists:

Reglan
Vistaril
Reserpine

Anti-Parkinson's Agents: (NMS may occur from sudden withdrawal of these)

Amantadine
Levodopa
Lithium
Bromocriptine

APPENDIX C
RESEARCH CRITERIA FOR 333.92
NEUROLEPTIC MALIGNANT SYNDROME

- A. The development of severe muscle rigidity and elevated temperature associated with the use of neuroleptic medication.
- B. Two (or more) of the following:
 - I. Diaphoresis
 - II. Dysphagia
 - III. Tremor
 - IV. Incontinence
 - V. Changes in level of consciousness
 - VI. Mutism
 - VII. Tachycardia
 - VIII. Elevated or labile blood pressure
 - IX. Leukocytosis
 - X. Laboratory evidence of muscle injury (e.g., elevated CPK levels)
- C. The symptoms in criteria A and B are not caused by another substance or a neurological or other general medical condition. (e.g., viral encephalitis).
- D. The symptoms in criteria A and B are not better accounted for by a mental disorder. (e.g., mood disorder with catatonic features).
DSM-IV-TR (2000)

APPENDIX D
COMPLICATIONS ASSOCIATED WITH NMS

- Rhabdomyolysis- from sustained muscle contraction
- Renal Failure-secondary to myonecrosis
- Respiratory failure, pulmonary embolism, and aspiration pneumonia- from chest wall rigidity
- Seizures-from hyperthermia
- Myocardial infarction, arrhythmias, and cardiac arrest- from altered cardiac conduction
- Thromboembolism-from immobility and hyperthermia.

Chandran, Mikler, and Keegan (2003)

APPENDIX E
COMPARING NMS AND SEROTONIN SYNDROME

	<u>NMS</u>	<u>SS</u>
Drug History	usually antipsychotic	serotonin enhancing agent
Onset	days to weeks	minutes to hours
Pathophysiology	hypodopaminergic state	hyperserotonergic state
Hyperthermia	more likely (90%)	less likely (46%)
Mortality	NMS>SS	SS<NMS
Muscle tone	rigidity, more rhabdomyolysis	restlessness, myoclonus, hyperreflexia
Autonomic dysregulation	more than SS	less than NMS
Resolution	5-10 days	<24hours
Wren, Frizzell, Keltner, and Wright (2003)		

APPENDIX F
RECOMMENDED TREATMENT PROTOCOLS FOR NMS

- Discontinuation of the offending agent
- Airway management: intubation for airway protection, continuous pulse-oximetry, adequate oxygenation and ventilation.
- Transfer to critical care unit
- Circulatory support: cardiac monitoring, fluid resuscitation, hemodynamic support.
- Cooling measures: cooling blankets, bathing, fans,
- Screening for infections: head CT, lumbar puncture, blood and urine cultures.
- Toxicology screen
- Avoid anticholinergic agents
- Amantadine for hyperthermia, 100mg BID, oral or NGT
- Bromocriptine for hyperthermia, 2.5-10mg TID, oral or NGT
- Dantrolene Sodium for muscular rigidity and hyperthermia, 2-3 mg/kg IV every 6 hours (to a maximum dose of 10mg/kg per 24 hours). Bottoni (2002)

APPENDIX G
INNOVATION IMPLEMENTATION

- I. Create the Learning Content
 - a. Review of the literature.
 - b. Formulate the learning objectives.
 - c. Write and assemble content: text, tables, figures, PowerPoint slides, pre- and post-test, and survey.

- II. Design the Web Page
 - a. Locate a web page designer; Brennan Washburn from the UA College of Nursing was consulted.
 - b. Design the layout; color schemes and sounds. Microsoft Publisher was used.
 - c. Format the content with consistent navigation themes.

- III. Moving to the World Wide Web
 - a. Purchase a domain name server (DNS) or name for the site. Double Domains (www.doubledomains.com) charges \$15 per year.
 - b. Obtain web hosting; for technical support, customer feedback, email accounts, user tracking and statistics. Half Price Hosting (www.halfpricehosting.com) charges \$200 per year. Or attempt to obtain free hosting.
 - c. Data coding to make each page interactive; activating the links.
 - d. Site testing, with different browsers and modem speeds.
 - e. Navigation, site or content refinements.

- IV. Site Promotion
 - a. Enlist with search engines: Google and Yahoo.
 - b. Link sharing with other websites: National Alliance for the Mentally Ill, American Psychiatric Association. American Academy of Nurse Practitioners. American College of Nurse Practitioners.
 - c. Promote the site with UA College of Medicine, Nursing and Pharmacy Department of Psychiatry Heads and profession based web sites.

- V. Site Management and Evaluation
 - a. Navigation, site or content refinements.
 - b. Review web statistics; number of hits, which search engine was used, who visited the site, country of origin, which pages were most viewed, and length of time at the site.
 - c. Respond to learner feedback and emails.

APPENDIX H
INNOVATION HOMEPAGE



THE NEUROLEPTIC MALIGNANT SYNDROME PROVIDER RESOURCE

HISTORY

ETIOLOGY AND
PATHOPHYSIOLOGY

CLINICAL
PRESENTATION

RISK FACTORS

COMPLICATIONS

TREATMENT STRATEGIES

PREVENTION

PATIENT EDUCATION

RECOMMENDED SITES

[History](#) | [Etiology and Pathophysiology](#) | [Clinical Presentation](#) | [Risk Factors](#) | [Complications](#) | [Treatment Strategies](#) | [Prevention](#) | [Patient Education](#) | [Recommended Sites](#)

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