

# Emergence Delirium Subsequent to General Anesthesia in Service Members Who Served During the Global War on Terrorism

by

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The primary aims of this study were to investigate, through active duty Army anesthesia provider's perceptions, the following: 1) the extent and seriousness of emergence delirium (ED) in service members; 2) effects of ED on the safety of service members and OR/PACU personnel and 3) behaviors relevant to ED in service members. In addition to these primary aims, the study also focused on identifying through provider's perceptions, the following potential factors which may lead to the development of ED or to the alleviation of ED: 1) type of anesthetic agents; 2) physiological factors; 3) psychological factors; and 4) interventions used for alleviating the symptoms of ED. A final aim was to investigate from provider's perceptions, the relationship between perceived seriousness of ED and reported case experience, behaviors and consequences relevant to ED, and physiological and psychological factors related to the development or alleviation of ED symptoms.

This research utilized a descriptive correlational study design with a questionnaire survey and a convenience sampling technique totaling 89 active duty Army anesthesia providers. This study found that over 78% of active duty Army anesthesia providers have witnessed ED in their particular practice. Approximately 38% of the respondents felt that ED was a moderate problem. There was a statistically significant association between perceived severity of ED and ED case experience.

The behaviors which were often seen or always seen included hyperactive motor behavior, pulling at the monitoring equipment, and making disruptive movements. The current study found that the majority of anesthesia providers with ED case experience believed ED could be related to the anesthetic used. The anesthetic identified most strongly as potentially related to ED were potent inhalation agents (PIA's). Most of the providers with ED case experience believed physiological factors and psychological factors were related to ED. Over ninety percent of the providers with ED case experience reported that they intervened when their patients showed behaviors related to ED with the majority of the providers stating they talked to the patient during the ED episode.



EMERGENCE DELIRIUM SUBSEQUENT TO GENERAL ANESTHESIA IN SERVICE  
MEMBERS WHO SERVED DURING THE GLOBAL WAR ON TERRORISM

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This dissertation is dedicated to my wife April, who has endured listening to the woes of being a doctoral student and the late nights writing, I love you. I am grateful to have you in my life and appreciate the unwavering support you have provided not only me, but also my children. I certainly could not have made it through this difficult time without you by my side and for that and many more reasons, I say: Thank you April!

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## **CHAPTER 1: INTRODUCTION**

Since September 11, 2001 the United States has waged war on those responsible for harboring or producing terrorists. This Global War on Terror (GWOT)/Overseas Contingency Operation (for purposes of this study, the acronym GWOT will be used) has lasted for more than ten years with over 3 million members of our armed forces serving in areas such as Iraq or Afghanistan. The United States health care system is only now starting to recognize both the severity and extent of the traumatic psychological and physiological effects resulting from battlefield stress on service members (Quinlan, Gauron, Deschere & Stephens, 2010; Wilk, Riviere, McGurk, Castro & Hoge, 2010).

Since late 2001 through October 20<sup>th</sup> 2011, a total of 46,747 American service members have been wounded in these conflicts (n. d. Department of Defense, 2011). This number is expected to rise and consequently, a steady increase in service members requiring care. The Army in particular is now bracing for a surge in mental health cases, notably traumatic brain injury (TBI) and post traumatic stress disorder (PTSD) (Carlson et al., 2010; Vasterling et al., 2010; Cavallaro, 2007; Gallagher & Polomano, 2006; Hoge et al., 2004). These traumatic effects seen from the battlefield are now being carried over rapidly into the healthcare environment (Shea, Vujanovic, Mansfield, Sevin & Liu, 2010; Quinlan, Guaron, Deschere, & Stephens, 2010).

### **Background to the Problem**

#### **TBI and PTSD**

From May 2005 through December 2005 over 800 patients with combat related injuries were treated surgically in the operating room from the 228<sup>th</sup> Combat Support Hospital (CSH) in

Mosul, Iraq. Personal experience from the battlefield revealed that of the 800 trauma resuscitations, an estimated 25% of those treated were involved in some form of explosion (typically from roadside improvised explosive devices) that caused various forms of TBI. The 541<sup>st</sup> Forward Surgical Team (FST) from January 2007 through June 2007 in Orgun-E, Afghanistan surgically treated over 100 combat related injuries. During this time period, all the required anesthetics were provided by the researcher (Wilson, unpublished data, 2011). Of those 100 plus soldiers, one eighth involved explosions that either caused loss of consciousness or a concussion syndrome typically seen with TBI (Wilson, unpublished data, 2011). Okie (2005) estimates that 10% to 20% of those requiring care during the GWOT were due to some form of TBI. Quinlan, Gauron, Deschere, & Stephens (2010) report 10% to 20% of those who have served during the GWOT and evacuated had at least one concussion.

Concussion is classified as a mild form of TBI. For those requiring surgical intervention in the two theaters of operation (Mosul, Iraq and Orgun-E, Afghanistan), none were pre-screened for PTSD nor was data available about their pre-surgical mental health conditions. According to Hoge, et al. (2004), 15.6% to 17.1% of veterans returning from combat in Iraq and 11.2% of veterans from Afghanistan experience some form of mental disorder to include PTSD. A more recent study by Wilk et al. (2010) found from their research that 11% of the studies respondents (N = 18,305) met the most stringent criteria for PTSD and depression which required the involvement of functional impairment. Twenty five percent of service members returning from combat duty in Iraq met criteria for PTSD or depression with some associated functional impairment (Wilk et al., 2010).

## **Emergence Delirium**

For the purpose of this study, emergence delirium (ED) is defined as: Upon emerging from general anesthesia, the service member is seen thrashing around in a violent manner (to include pulling at monitoring equipment, IV catheters, ETT's, drains, Foley catheter, etc), screaming, incoherent speech, hitting, biting, or attempts to leave the operating room (fall off narrow bed) encompassing any time period from end of surgery to discharge from PACU. Any one of these displayed behaviors or a combination can constitute ED. This definition is not to be confused with the Diagnostic and Statistical Manual of Mental Disorders definition of delirium.

The Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> edition, text revision (DSM , IV, TR) published by the American Psychiatric Association (2004) defines delirium according to its presumed etiology. There are a total of four etiology categories provided by the DSM, IV, TR (2000) which include; substance-abuse delirium, delirium due to multiple etiologies, delirium not otherwise specified and delirium due to a general medical condition. Delirium associated with medical conditions includes; brain tumors, hypoxia, hypercarbia, congestive heart failure, septicemia and a multitude of other conditions further described in the DSM, IV, TR (2000).

Regardless of etiology, the DSM, IV, TR (2000) defines delirium as a disturbance of consciousness (which includes the inability to focus) and a change in cognition (including language disturbance and memory deficits) which can develop rapidly and tends to fluctuate (The American Psychiatric Association, 2000). The definition provided by the DSM, IV, TR (2000) lacks many specific behaviors which might have been done purposefully for any number of reasons to include billing purposes. One of the main features associated with ED is that it



does not fluctuate. The ED seen following general anesthesia begins upon emergence and ends prior to discharge from the PACU (Radtke et al., 2010).

Of the greater than 900 total patients requiring surgical intervention, the researcher found that upwards of 10% emerged from general anesthesia in a state of delirium while an anesthesia provider was present. Furthermore, military service personnel who had recently returned from combat and requiring surgery stateside, showed that one in ten (10%) who required general anesthesia had delirium upon emergence (Wilson, unpublished data, 2005 and 2007). Historical information obtained when the patients were lucid revealed that upwards of 70% had horrific past experiences involving explosions, gun battles, vehicle crashes, helicopter crashes, intense fear, seeing fellow service members dying, and a feeling of helplessness (all potential causes of PTSD) (Quinlan et al., 2010). This information was experienced by the researcher during the time period from 2005 through 2008 (Wilson, unpublished data, 2011).

Many soldiers who sustained a TBI showed signs and symptoms of PTSD, and were more prone to emerging from anesthesia in a state of delirium. Some anesthesia providers believe that these soldiers had anxiety preoperatively as compared to those without TBI or PTSD (Wilson, unpublished data, 2005 and 2007). These soldiers showed the following signs and symptoms: 1) they were often extremely anxious prior to surgery and required much more anesthetic to go to sleep or become sleepy than the average soldier. 2) they took much longer to become lucid following anesthesia. 3) they often awakened in a violent or thrashing way with attempts at self extubation, breath holding, intravenous line displacement, pulling off both invasive and/or non-invasive monitoring equipment, assault on the operating room staff and the potential to fall off the narrow operating room table. Any one or a combination of these deleterious outcomes can be catastrophic for the service member/patient. This violent behavior

puts all involved in caring for the patient at risk for injury, especially the operating room and PACU staffs.

### **Statement of the Problem**

The dearth of literature found relating ED and service personnel is distressing. Research on the signature wounds of the GWOT (TBI and PTSD) documents incidence and clinical characteristics but have not gone as far as relating these wounds to anesthesia outcomes to include emerging from general anesthesia. Observed behaviors in service members who have served during the GWOT while emerging from general anesthesia have not been studied nor have the observed behaviors been examined as they relate to safety for both the patient and OR/PACU personnel. Furthermore, a grossly understudied area is how TBI, PTSD, and general anesthesia affect emergence delirium within the military patient population. This study will address this crucial gap in the literature.

### **Purpose of the Study**

The primary aims of this study were to investigate, through active duty Army anesthesia provider's perceptions, the following: 1) extent and seriousness of ED in service members; 2) effects of ED on the safety of service members and OR/PACU personnel and 3) behaviors relevant to ED in service members. In addition to these primary aims, the study also focused on identifying through provider's perceptions, the following potential factors which may lead to the development of ED or to the alleviation of ED: 1) type of anesthetic agents; 2) physiological factors; 3) psychological factors; and 4) interventions used for alleviating the symptoms of ED. A final aim was to investigate through provider's perceptions, the relationship between perceived seriousness of ED and reported case experience, behaviors and consequences relevant to ED, and

physiological and psychological factors related to the development or alleviation of ED symptoms.

The significance of this research addresses four areas: 1) Recognition of the extent, seriousness, and safety risk of ED in service members. 2) Identification of behaviors associated with ED (to include the severity) and the consequences related to ED in service members. 3) Improved management potential for this adverse effect by the military health team. 4) Characteristics of a relationship between perceived physiologic (TBI), psychological (PTSD), and anesthetics with ED (if evident) in a manner that will guide further research into physiologic or psychogenic causes and mechanisms of action studies. Corollary significance includes: Lower hospital costs by decreasing the number of operating room and PACU staff required to care for those with ED and a decrease in patient suffering associated with ED. The most important need for this study is to help find a way to increase the safety margin for not only the patient but also the staff caring for the patient. The delivery of safe anesthesia in military medicine requires formal studies to substantiate (or not) the role of TBI and PTSD as potential risk factors for ED following general anesthesia. The complexities of this potential role between ED, general anesthesia and TBI and/or PTSD are reviewed by examining theoretical aspects of a pharmaco-physiological nature.

### **Theoretical Perspective (Pharmaco-physiological theory)**

Considerable pediatric research illustrated that utilizing potent inhalational agents increases the propensity for children to wake from anesthesia in a state of delirium (Nakayama, Furukawa, & Yanai, 2006; Uezono et al., 2000). This finding has led many anesthesia practitioners to change their practice to total intravenous anesthesia utilizing propofol. What is not known is why this change in type of anesthetic delivered produces such a change in wake up

behaviors. There are several theories into the exact mechanism of action of inhalational agents such as Sevoflourane and Isoflourane (two of the most commonly used inhalational anesthetics in today's O.R.) but ultimately, they are simply theories and no one fully knows the exact mechanism of action. It is thought that the gamma amino buturic acid (GABA) receptor in the brain is involved, but this is one of many theories that has yet to be proven. However, the mechanism of 2-6 diisopropylphenol (diprivan or propofol) is known. Propofol exhibits its effect on the inhibitory neurotransmitter GABA. Propofol at low doses produces profound amnesia while at higher dosing produces anesthesia to include apnea. Benzodiazepines such as midazolam or versed also exhibit their effect via the GABA receptor and are extensively utilized in the preoperative holding area (Stoelting, 1999). What is not known is if military personnel (with TBI and/or PTSD) who are administered benzodiazepines preoperatively show modified effects on ED following general anesthesia?

Crosby, Mashour, Grodin, Jiang, and Osterman (2007) described a case report where a patient with PTSD was given versed following anesthesia which resulted in a worsening ED. The case report described a patient who clearly had PTSD and emerged from general anesthesia with severe flashbacks typical of ED. The patient was a refugee from Africa, who had been beaten, raped, shackled and experienced numerous other atrocities. The patient underwent a 44 minute procedure with general anesthesia. The patient received 1 milligram (mg) of midazolam pre induction followed by a standard pharmacologic induction, maintenance and emergence. Upon arrival to the PACU, the patient experienced an agitated, anxious and disoriented state. One mg of midazolam was given intravenously (IV) in the PACU for this behavior which became noticeably worse after the administration of the benzodiazepine. Thirty mg of propofol was then given IV and the agitated state of the patient worsened and the patient began to scream

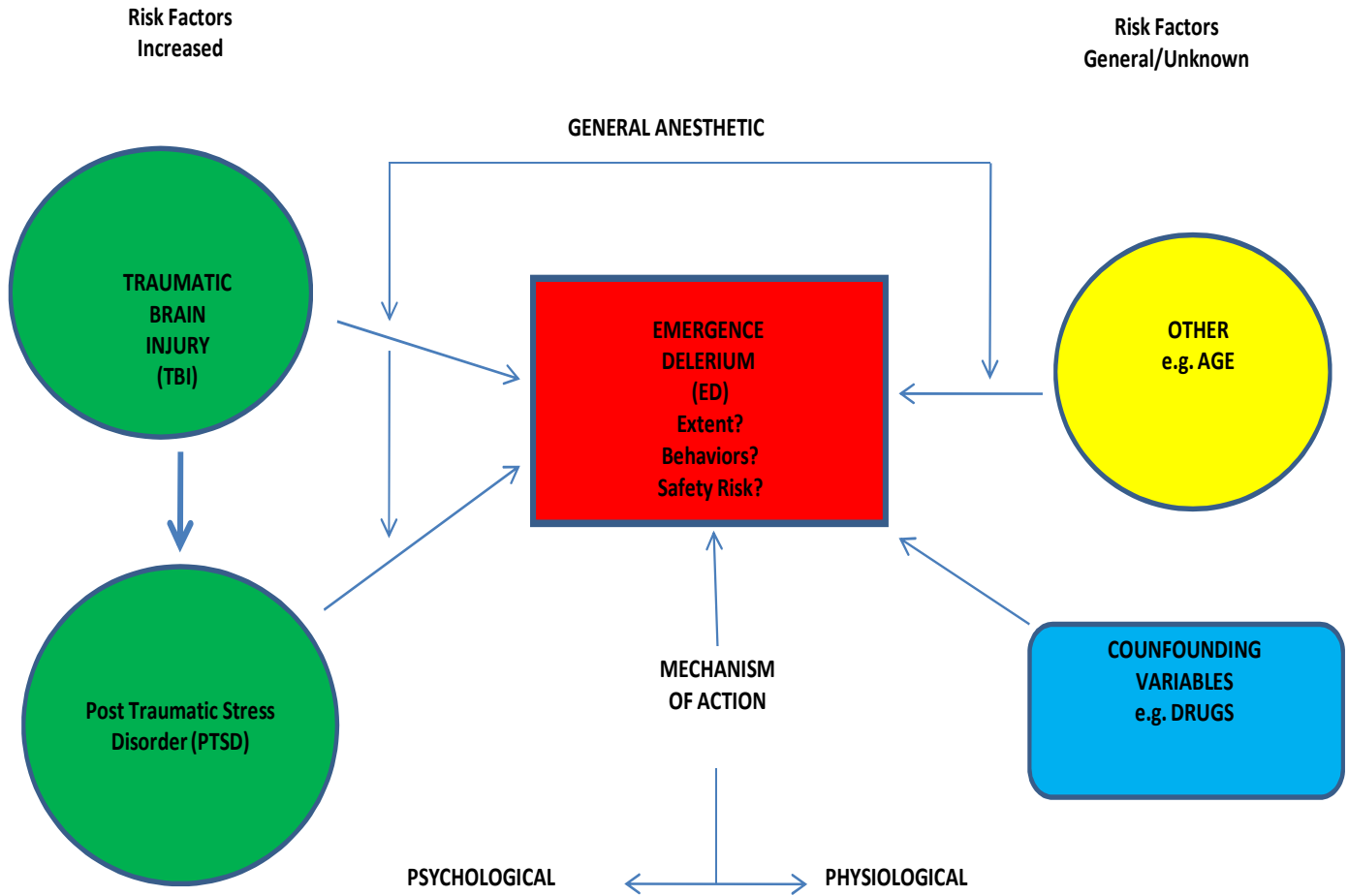
as if she were reliving the experiences of Africa. The episode lasted for an hour. This case report is important because it supports aspects of the pharmacophysiological theory where using versed in someone who has PTSD can potentially exacerbate ED following general anesthesia.

It may be possible that the combination of both the psychological (example being PTSD), the physiological (a possible example would be the benzodiazepine receptor and GABA receptor) with general anesthesia can produce ED. This pharmacophysiological theory is indicated in the clinical model depicted (See figure 1). This model incorporates confounding variables such as drugs that may offer clues to mechanism of action of general anesthetics in combination with TBI and PTSD to produce ED. The theory states that there is the possibility of combining drugs such as versed in someone who has TBI or PTSD can lead to ED following the administration of a general anesthetic.

The clinical model (figure 1) captures the salient features from the proposed theoretical perspectives. Emphasis is given to events on the left side of the diagram because of their importance to military personnel. Those shown on the right side are presumed to have less of a role in these personnel. The model proposes ED, following general anesthesia, as the central outcome found more frequently in those with TBI and/or PTSD. The relationship of PTSD resulting from TBI is shown by the heavy shaded arrow. The relationship may be altered by confounding variables, notably drugs. Clinical data are expected to help guide psychological and physiological approaches to design mechanism of action studies by using the proposed model as a guide.

Figure 1: Wilson's Proposed Clinical Model for Emergence Delirium

## A CLINICAL MODEL FOR EMERGENCE DELIRIUM (ED) The Pharmaco-Physiological Theory



ED or agitation, as it is often referred to in the pediatric population, (Scott & Gold, 2006) and postoperative delirium, cited extensively with the geriatric population and occurring sometime within the first 24 to 48 hours post anesthesia, (McGuire & Burkard, 2010) have been studied in both the pediatric and geriatric populations (See Figure 1: Other e.g. age). However, ED in military personnel with TBI and/or PTSD serving during the GWOT has received little attention (See Figure 1: Risk factors increased).

The theoretical framework and clinical model serve as a guide to a possible mechanism of action linking TBI and/or PTSD with ED. The last likely question that requires consideration following knowledge about prevalence rate and the involvement of TBI and/or PTSD for ED is, “What are the likely clinical manifestations or predictors (besides TBI and PTSD) of ED within the military personnel and can anesthesia providers use these to implement a plan to ameliorate this phenomenon?” This and other questions will need to be answered with future mechanism of action type studies. For example, one theme that emerged from the pilot qualitative study by Wilson and Pokorny (2011) was, “talking to all those suspected of having a TBI and/ or PTSD prior to surgery and on emergence was vital in a smooth wake up (vocal local).” Thus, talking to those thought to be at high risk for ED are talked to both before and after an anesthetic alleviated anxiety/fears and led to better emergence from general anesthesia. This study highlighted the theme that some military members (who have served during the GWOT and who appeared nervous or anxious prior to surgery) were more likely to display ED following general anesthesia (this study will be critically reviewed in its entirety in the review of literature section). The theme of talking to all those suspected of having a TBI and/or PTSD prior to surgery and on emergence was vital in a smooth wake up from the Wilson and Pokorny (2011) study is also supported by the Eckenoff , Kneal and Dripps (1961) study which showed that the incidence of

ED was higher with operations that had the potential to cause disfigurement such as breast surgery or surgery which may cause the feeling of suffocation such as thyroid surgeries.

According to the authors, these fears could certainly lead to excitation upon emergence from anesthesia. Talking to these identified patients both prior to induction and on emergence, could have led to a decrease in excitation on emergence. Other more recent studies performed decades later examined the possibility that preoperative anxiety was a component that led to emergence delirium (Kain et al., 2004; Scott & Gold, 2006). The theme of, “talking to those at risk” from the study by Wilson and Pokorny (2011) along with other research from the past (Lepouse, Lautner, Liu, Gomi & Leon, 2006) show that perhaps preoperative anxiety/fear can potentiate ED which leads directly to a middle range theory and theorist.

Historically in nursing there have been studies on how to reduce post operative preoperative anxiety. One such nursing researcher was Dr. Jean Johnson whose focus was on preoperative preparation. Johnson’s theory became known as the sensation theory which showed a discrepancy between what a patient expected and what that same patient actually experienced during a threatening experience will result in distress. For example, one of her early experiments involved 20 college students who were divided into two groups. One group was provided information on what to expect when a tourniquet was placed on the upper arm for a period of time. The sensation of tingling, pressure, numbness and the color blue were all examples given to the first group. The second group was given a description of only the procedure and not of the different sensations one would feel. The results showed no difference in the intensity ratings but did however show a difference in the amount of distress reported (Johnson, 1973). Another study performed by Johnson (1973) involved 99 endoscopy patients. The patients were divided into three groups. One group saw photos of the procedure and was given sensory type



information on what to expect. This information was very explicit and involved every aspect of the procedure from the starting of the intravenously immediately followed by a feeling of drowsiness to the fullness in the stomach. The second group was given a step by step explanation of the events in the endoscopy suite but no sensory information. The last group received the standard or routine basic information which was given to everyone. Results after the procedure showed significantly reduced distress in the sensation group than did the other two groups (Johnson, Morrissey, & Leventhal, 1973). This type of study providing sensation teaching to patients was repeated over and over in various age groups and procedures with the same types of results, all of which lowered the amount of distress seen. Of particular interest to the current research question is a study performed by Johnson (1978) on surgical patients. The patients in this study were divided into six different groups with sensory teaching combined with post-operative exercise regimens providing evidence for the greatest benefit. This benefit also showed that those with the highest degree of fear pre-operatively benefited the most (Johnson, Rice, Fuller, & Endress, 1978). This is an interesting and important finding because those seen with PTSD with or without a TBI diagnosis have also been shown to display a great deal of pre-operative fear (Wilson & Pokorny, 2011). Perhaps, if future research can demonstrate a correlation with service members who have PTSD with or without a TBI diagnosis and pre-operative fear and anxiety, then there is the potential to abolish ED following general anesthesia by merely providing more, “vocal local” and sensation information to this target audience. In other words, if mere talking to and providing vivid accounts of what is going to occur (from entering the operating room to waking up and exactly what they should anticipate) decreases the amount of ED seen, then those service members thought to be at increased risk will now have an intervention to potentially ameliorate ED following general anesthesia. The potential link

between preoperative anxiety and postoperative ED is an important area of study that will require further examination and can potentially be guided by the middle range theory from Jean Johnson for future research studies.

## CHAPTER 2: REVIEW OF THE LITERATURE

The literature review includes a time period from 1948 to 2011. The original intent of the review of the literature on ED was to cover only a ten to eleven year time period beginning in 2001 and ending in 2011. This time period was chosen due to the current length of the GWOT. Because of the dearth of citations produced during this time span, the search was expanded to include a time period from 1950 to 2011. The search included use of six electronic bibliographic databases, CINAHL, MEDLINE via OVID, MEDLINE via PUBMED, PsychInfo, CRISP (Computer Retrieval of Information on Scientific Projects) and Micromedex (this search from the Lampus library was similar with the results from MEDLINE via PUBMED). Three key words included in the original search were: Delirium, anesthesia and emergence. Delirium in CINAHL produced 5,263 titles, 5 citations were found with the addition of anesthesia and zero after the addition of emergence. Medline via ovid produced 3,392 citations with delirium as the key word, 10,450 with the addition of anesthesia, and 2,521 with a combination of all three key words. Post traumatic stress disorder and TBI were added to the original three key words resulting in 187 citations. Military and adult were added to the search terms resulting in ten total citations with five studies being applicable to the current research questions. The first by Lepouse et al. (2006), the second study recently published by Radtke et al. (2010) and the third by Yu, Chai, Sun, & Yao (2010). The McGuire and Burkard (2010) study and the Wilson and Pokorny (2011) study were the only published studies which included ED, risk factors and the military. Medline via Pubmed produced 15,826 results for delirium alone. The key words delirium and anesthesia produced 381 research articles and combining delirium, anesthesia and emergence produced 73 results and the addition of military produced one case report. A search of PsychInfo produced 3,641 citations on delirium, 24 with the addition of emergence and one

article with a combination of all three. Lastly, a search of CRISP produced 31 abstracts associated with “delirium” but most of the research was related to the intensive care unit. Three abstracts were found by adding “anesthesia” as a key word that examined pharmacologic interventions with the elderly. Besides the recently published research study by McGuire and Burkard (2010), there were no results combining three categories, “emergence delirium”, “military” and “anesthesia”. The reference list from all eligible publications were examined and reviewed to identify studies that the electronic search failed to recognize. A total of 45 articles were retrieved for future examination including six case reports on emergence delirium.

The foregoing literature search strategy revealed individual studies of TBI or PTSD alone, while others describe clinical characteristics of emergence from anesthesia, including that of delirium without TBI or PTSD. The Lepouse et al. (2006) study, the by Radtke et al. (2010) and the third by Yu et al. (2010) were the only recent studies involving adults. Most of the published data on ED is in the pediatric literature and is usually referred to as emergence agitation. The McGuire and Burkard (2010) and the Wilson and Pokorny (2011) studies were the only two found which examined the occurrence of ED in service members with diagnosed or suspected TBI or PTSD as a result of battlefield conditions. There were no studies found that examined the extent of ED in service members, actual behavior relevant to ED in service members and the effect ED has on safety. This lack of data exposes a compelling need for this research.

This literature review will give an overview of delirium as seen in the critical care setting without general anesthesia, the physiology of anesthesia, describe characteristics of ED and tools that have been used to measure ED. The literature review will also attempt to expose what is known about ED in the average adult population minus extremes of age (pediatric and geriatric

populations). A total of five seminal studies will be critically analyzed: A study by Yu et al. (2010) which examines ED in the adult population, the Radtke et al. (2010) study which examines risk factors for ED in the adult population and a study by Lepouse et al. (2006) which quantitatively examines delirium in the post-anesthesia care unit. The other two important research studies, the McGuire and Burkard (2010) study and the Wilson and Pokorny (2011) study, will be described in full later in the review of literature section. Pharmacologic interventional studies are examined specifically a study by which found a physiological link between PTSD and the benzodiazepine receptor (Bremner et al., 2000). TBI, PTSD and a combination of both as potential risk factors for ED is then described evaluating the McGuire and Burkard (2010) study and the Wilson and Pokorny (2011) qualitative study. These studies illustrate that the phenomena of ED is more widespread than the authors past anecdotal battlefield experiences. Their study provides data into the phenomenon of ED and how ketamine may play a factor into the role of ED. Because of this finding potentially relating ED and ketamine, the literature on the pharmacologic agent Ketamine is reviewed in detail. The literature review will conclude by summarizing the research that has been done and thus serve to support the proposed research study.

### **Delirium in the Critical Care Setting without General Anesthesia**

A discussion of delirium without general anesthesia offers a contrasting perspective on ED. Signs and symptoms of delirium include incoherent speech, uncoordinated movements, the inability to rationalize and often develops into a violent and combative behavior (anecdotal evidence). A study by Patel, et al. (2009) examined delirium in the intensive care unit. The authors described the risk factors for delirium in the ICU such as excess sedation, psychoactive medications and preexisting cognitive impairment (p. 826). The study cites a follow up to a

survey by the same authors (Patel et al.) published in 2001 which showed that only 16% of health care providers utilized a specific tool for diagnosing delirium. Five years later another survey was sent by Patel, et al. to 41 North American Hospitals with a total of 1,384 respondents. The researchers distributed the survey to health care professionals at various society meetings and conferences from October 2006 through May 2007. This is a potential limitation to the study because the authors handed out the surveys which could have influenced the results of the survey if those participants knew the authors. The survey consisted of demographic data, attitudes and behaviors regarding both delirium screening and management and then behaviors of those surveyed about the management of sedation. The respondents included nurses, physicians, pharmacists and other allied health professionals. The results showed that 59% (766 of 1300) of those surveyed estimated that one quarter of all ventilated patients experience delirium. Thirty three percent (258 of 744) of the medical staff utilized a specific screening tool to diagnose those intensive care unit patients suspected of having delirium. This study is important for many reasons. First, it provides some insight into risk factors (excess sedation, psychoactive medications and preexisting cognitive impairment) for delirium in adult intensive care unit patients. These same risk factors (or confounding variables) may be similar to those experienced by military personnel with ED following general anesthesia. Second, it shows how prevalent delirium is in ICU's throughout the United States. And lastly, it provides some background information on the importance of tools to properly diagnose delirium (Patel et al., 2009).

### **Physiology of General Anesthesia**

An understanding of the normal or expected behaviors found with general anesthesia is required to appreciate the complexity of its underlying physiology. Knowing the physiologic

basis of the plains or stages of anesthesia is essential to the practice of safe and effective anesthesia. Each of the four stages is markedly different. Stage one begins with amnesia and continues to unconsciousness. Stage two is characterized by a plethora of deleterious potential complications such as: Delirium, excitation, laryngeal spasm, hypertension, tachycardia, uncontrolled movements and divergent pupils (Burns, 2003). The provider must move the patient rapidly through this stage and progress into stage three, surgical anesthesia. The last stage is characterized by excessive anesthesia and signs and symptoms of this level may be life threatening. All patients experience the first three stages of anesthesia and many do well following surgery and anesthesia. However, for some, the emergence from general anesthesia can be difficult. Characteristics of emergence have been studied for some time as illustrated by a by Smessaert, Schehr and Artusio (1960). The authors state, “The events taking place as a patient emerges from anaesthesia are not well understood and several theories have been advanced to explain the phenomena that occur during this period” (p. 181). Individual differences in physiological and psychogenic factors in response to anesthetic agents are likely explanations for observed difficulties such as ED.

### **Tools to Measure Emergence Delirium**

Finding an appropriate tool to diagnose ED postoperatively and a tool to determine one’s anxiety level preoperatively are both important to answer the current research questions. This would be an important first step in determining the incidence of ED in military personnel with either TBI or PTSD. Sadhasivam et al. (2009) stated the following regarding assessment of perioperative behaviors, “At present, there are arguably only two scales available to easily monitor and communicate perioperative behavioral conditions, the Induction Compliance Checklist (ICC) and the modified Yale Preoperative Anxiety Scale (mYpas)” (p. 822). Kain et

al. (2004) utilized the mYPAS to see if preoperative anxiety, emergence delirium, and postoperative maladaptive behavioral changes were related. The study recruited children who received oxygen, nitrous oxide, sevoflurane as their anesthetic and did not receive midazolam preoperatively. The studies data base examined 791 patients. The study found through repeated analysis of variance that how the patient emerged was associated with the level of preoperative anxiety. Their study is important because it shows how preoperative anxiety (as measured with the mYPAS ) has a direct correlation to emergence delirium. Unfortunately, the research was limited to the pediatric population.

There were three studies examining delirium utilizing the Confusion Assessment Method (CAM). Rolfson, McElhaney, Jhangri and Rockwood (1999) interviewed 71 elderly cardiac surgery patients both pre and postoperatively using the CAM. Both physicians and nurses participated in the study. Nurses were found to recognize delirium far better than the physicians did. The researchers stated that this was partially due to the training background of the operator. Rolfson et al. (1999) stated, “We conclude that the sensitivity of markers for delirium, such as the CAM and health record documentation, is dependent on the training background of the operator (p. 431). Sharma (2004) also utilized the CAM to assess recovery room/ PACU delirium one hour post discontinuation of isoflurane. Friedman, Qin, Berkenstadt, and Katznelson (2008) stated the following regarding the CAM, “The use of this tool required little training, and only 2 minutes per patient. It detected more patients with delirium than did the standard nursing assessments or other patient-clinician interactions (p. 413). To date there has not been a gold standard to determine/evaluate/diagnose ED which is problematic at best. Scott and Gold (2006) point out that there is one tool developed by Sikich and Lerman (2004) which has been shown to have good psychometric properties for evaluating ED. Sikich and Lerman



(2004) sought out to investigate a tool to evaluate ED with children that was both reliable and valid among various providers. The pediatric anesthesia emergence delirium (PAED) scale was developed using statements describing the behavior of pediatric patients following anesthesia. The questions were evaluated for both statistical significance and content validity. Seven experts comprised of four pediatric PACU nurses, a pediatric psychiatrist and two pediatric anesthesiologist were used to validate the questions. Twenty one questions were deemed to be valid. The 21 questions were then pretested with 5 being deemed to have a sufficient statistical profile. The five questions comprised the scale with an internal consistency being 0.89. The pediatric anesthesia emergence delirium scale (PAED) was shown to be both reliable and valid to determining ED (Sikich & Lerman, 2004). The scale was developed for the pediatric population but according to both email and telephone contact with the author, the PAED scale can be modified for the adult population and in this case, service personnel.

Future research questions will likely need a well validated tool to assess both anxiety levels preoperatively and ED following general anesthesia. The data generated from these tools will be analyzed statistically for a relationship between ED and military personnel suspected of having or being diagnosed with PTSD and/or TBI following general anesthesia.

### **Emergence Delirium Studies: A Critical Analysis**

An extensive search of the various electronic databases revealed articles on delirium in psychiatric and geriatric literature. There was little found when combining “delirium” with “emergence from anesthesia”. Actual ED can be seen potentially in all patient categories, but it has been documented primarily with both geriatric and pediatric patients. In the proposed Wilson clinical model, there are “right side” risk factors with a presumed minor role in military

subjects, the primary focus of this review. However, some insight into the occurrence of ED, and identification of confounding variables, is offered from work on delirium seen in young and old subjects undergoing general anesthesia (in contrast to the critical care setting).

Studies show as many as 10-15% of all cases involving the elderly experience delirium at some point postoperatively (Parikh, & Chung, 1995). Another study by Levenson (2007) showed that upwards of 40% of the elderly undergoing specific types of surgery such as orthopedic surgery, experience some form of delirium. Smessaert, Schehr, and Artusio (1960) demonstrated that children experienced postanesthesia delirium at a rate of 12%-13% versus 5.3% in adults. These studies are important because they demonstrate that delirium following anesthesia is not an unknown phenomenon in various age groups such as the elderly and very young patient populations. What needs further clarification or more understanding is when it occurs in the average adult population and whether or not ED is more likely to occur following TBI and/or PTSD within service members? It is also vitally important to understand that postoperative delirium is different than ED by virtue of time. Postoperative delirium usually occurs sometime after discharge from the (PACU) while ED is seen upon emerging from general anesthesia can continue into the PACU setting.

A study by Rose (1996) briefly describes that ED is at 3% for the general adult population and those who are highly anxious, fear the unknown, or those who have a history of psychiatric disorders that include depression and drug dependency are at greatest risk. Three percent for the adult population is also cited by Mason, (2004) in her presentation titled, *Pitfalls of Pediatric Anesthesia*.

Yu et al. (2010) found that 21.3% of the 2000 adult patients entering their PACU had some form of agitation. This study is important to the current research in that it provides recent data depicting ED in the adult population. The study emphasizes the need for more adult studies due to the potential deleterious effects ED can have such as, self-extubation, removal of catheters and hemorrhage.

The study included all patients entering the PACU aged 16 – 70 years of age. The studies methods also included a standardized anesthetic for all 2000 participants and pain was assessed every 10 minutes. The only subjects excluded from this study were 16 where the surgeon's cancelled the case. Agitation from the patient was graded as mild, moderate and severe. The definition of agitation for this study was thrashing, combative behavior and hyperactive motor movements. Mild agitation was categorized in response to a powerful stimulus such as suctioning in the PACU but the agitation stops when the stimulus stops. Moderate was classified if the observed behavior occurred without stimulation but less than 5 minutes and severe if the agitation lasted greater than 5 min and required drugs or restraint. Four hundred and twenty six or 21.3% developed agitation of which 212 experienced mild agitation, 178 of the 426 developed moderate agitation and 36 (8.4%) severe agitation. Of note, 22 of the 36 attempted self-extubation while in the PACU.

Again, this study is an important one because it is one of only a handful that is both recent and examines ED in the adult population. The researchers from the Yu et al. (2010) study state that their 8.4% severe agitation is similar to other studies such as the Rose (1996) study which had ED in the adult population at 3%. What is also interesting with this study is that 159 of the 2000 patients still had their endotracheal tube (ETT) in place while entering the PACU. This is a high number of patients entering the PACU with such a stimulus and obviously sedated.

Having an ETT in place could be due to a variety of factors especially since the study was performed in China where standards of practice vary. Of those who entered the PACU with an ETT, 71.7% had various degrees of agitation. This is certainly a disadvantage to this study because it is expected that those with such a stimulus (ETT) would have varying degrees of agitation. The study also pointed out that 80.2% of those who were agitated also reported pain. The study concluded with the knowledge that postoperative agitation is not clear and requires more study (Yu, Chai, Sun & Yao, 2010).

Radtke et al. (2010) study included 1,868 patients and had a 5.0% ED rate in the adult population. The study immediately sets the tone by contrasting ED with the term delirium. The authors state the fundamental difference is ED does not last very long and doesn't fluctuate. The authors also echo the tone that ED has not been well studied in the adult population as it has with the pediatric population with only a few articles examining ED in adults with most of those being a few decades old. Inclusion criteria for this study included the following: All participants had to speak German (German study) and be over 18 years of age and not intubated on arrival to the PACU. Exclusion criteria included a past medical history of neurologic or psychiatric illness, a history of drug abuse, cerebral injury or intracranial surgery. Anesthesia for all participants was maintained by PIA or TIVA. Non-opioid pain medicine was given by the PACU nurses only if a numeric pain score was greater than 5. All of the patients were assessed 10 minutes after entering the PACU. ED was established utilizing the Richmond agitation and sedation scale (RASS). The RASS is a 10 point scale that measures both sedation and agitation/anxiety. The authors defined ED as any score greater than or equal to 1 point. Medical students, nurses and physicians performed the RASS on the patients but never intervened in their care. Both pain assessment and RASS levels were taken at the same time and categorized. Ninety three of the

1868 adult patients or 5% were classified as having ED. Characteristics about the sample that were statistically significant included, premedication with benzodiazepines, younger and older subsets of the adult population, using etomidate versus other induction agents and musculoskeletal surgery. Type of anesthetic used did not have an effect on ED. What is concerning about this article from Germany is the dose of midazolam used was 0.1mg/kg. Thus, an averaged adult male weighing 80 kg would receive 8 mg of midazolam preoperatively. This is a very high dose of midazolam and may have accounted for the ED seen within this subset of the population studied. This relationship between ED and benzodiazepine administration is further emphasized in the third seminal article by Lepouse et al. (2006).

The most widely referenced work when performing a literature review on ED is the study by Lepouse et al. (2006). This study found that the rate for ED in adults is 4.7%. The study also found that patients at increased risk for ED included: Preoperative administration of benzodiazepines, breast surgery, abdominal surgery, and long surgeries. Whether these are risk factors per se, or confounders of an underlying risk, remains to be studied. The study examined 1,359 adult patients (range 15-99 years) emerging from general anesthesia in the PACU. Their study documented the background information which highlighted the fact that ED is a poorly understood topic, especially within the target audience (adults). The goal of the study was to examine how many patients would experience ED and possible causative factors leading up to ED. The study was conducted in a 12 bed PACU and every patient during a three month time span was enrolled in the study (study was conducted in France). All patient variables such as height, weight, past medical and surgical history and medication profiles were recorded and an anesthesia protocol was utilized. A standard induction using propofol, maintenance via either a propofol drip or potent inhalational agent and neuromuscular blocking agent was utilized. What

was unclear in this study was whether a potent opioid was administered and if so, what type and what was the dose range. This is important information to gather and greatly influences anesthesia in regard to level of consciousness. Use of an opioid may be an important confounding variable for occurrence or severity of ED. A Riker sedation-agitation scale was used to assess patients with ED (Lepouse et al., 2006) The scale consists of numbers 1-7 with 1 being unarousable, 2 being very sedated, 3 sedated, 4 calm and cooperative, 5 agitated, 6 very agitated and lastly 7, which is dangerous agitation. The results of the study showed that the average length of the delirium to be 15 minutes and the total number that had ED was 64 or 4.7%. Seventeen were dangerously agitated, 20 were considered very agitated, and 27 agitated. There were multiple attempts at self extubation, catheters removal, bruising and injuries to staff members. The cases that showed ED usually required at least 2 to 3 staff members from the PACU to calm and or restrain the patients for safety. This study is particularly vital to the current research study in five ways. First, it shows that emergence delirium does exist in the adult population and the etiology of ED is poorly understood. More studies of adults are needed to better understand the physiological and psychological determinants of ED. Second, the study provided the anesthesia community with a sample size of over one thousand with a mean age of 51 and almost equally divided into males (55%) and females (45%). Characteristics of the sample (in table 2) are provided and allow application of study findings to the everyday adult patient population. Third, the study provides the anesthesia provider community with recent statistical information that highlights the percentage of adult patients experiencing ED from anesthesia (4.7% of the total sample size). Fourth, the study utilized and described the Riker sedation-agitation scale and its importance in accurately diagnosing ED in the PACU. This is important because it adds validity to the tool and could possibly be utilized for the current

research. The fifth and final useful information provided in the results section dealt with the type of anesthetic used. The researchers found that those patients who received potent inhalation agents were more often found agitated than those who received total intravenous anesthesia via propofol infusion ( $p = 0.006$ ). Ultimately, the study concluded that preoperative use of benzodiazepines ( $p = 0.021$ ), surgery of long duration ( $p = 0.001$ ), breast or abdominal surgery ( $p = 0.013/ p = 0.0014$ ) and preoperative severe anxiety (which was noted in the patients chart and had a  $p = 0.012$ ) all corresponded with ED. This association with benzodiazepines and ED is not clear but one study by Bremner et al. (2000) examined the physiological relationship between combat-related PTSD and the benzodiazepine receptor. In this regard, benzodiazepines may be a significant confounding variable for expression of ED.

### **Pharmacologic Interventions and Emergence Delirium**

Bremner et al. (2000) reported that those suffering from PTSD have higher levels of anxiety that are responsive to benzodiazepine medication. Multiple animal models have shown that continuous stress has led to a 20-30% decrease in the benzodiazepine receptor binding in the frontal cortex. This study also points out research that supports that giving a benzodiazepine receptor antagonist both induces and produces both panic attacks and severe anxiety in normal/healthy subjects (not diagnosed with PTSD). This particular study examined 13 patients from the Vietnam War who had combat-related PTSD and 13 healthy subjects. Neuroimaging (SPECT) was used to determine benzodiazepine receptor binding in the frontal cortex and nowhere else in the brain (pons, thalamus, cerebellum, or midbrain). It is important to note that the PTSD patients had no history of benzodiazepine usage within the 6 months prior to the study and were not taking psychotropic medication. The results from the study showed a 41% decrease in the benzodiazepine receptor binding in the prefrontal cortex as compared to the

healthy subjects with no differences in the other areas of the brain. The authors suggest that the findings could be related to down-regulation of the benzodiazepine receptor binding as a result of the stresses of war. The authors also postulate that stress-related alterations in GABAergic transmission may affect the benzodiazepine binding or changes with the endogenous benzodiazepine ligand. Most of the induction agents and those agents which produce anesthesia work on the GABA receptor in the brain. This may offer a physiological explanation for ED seen in certain patient populations. The prefrontal cortex has been shown to control both emotional and social behavior and inhibition of cognition (memories in PTSD). This is an important study for the current research because it shows a direct physiologic link between an area of the brain for anesthetic medication effects and PTSD. And, as noted earlier, there is evidence to support that both mild and moderate TBI have similar signs and symptoms as seen with PTSD. This linkage could provide the answer as to why those patients with PTSD and/or TBI show signs and symptoms of ED. This suggested linkage warrants further study.

Numerous studies have tried to identify a causative agent for ED (Uezono et al., 2000; Nakayama, Furukawa & Yanai, 2006). Anesthesia providers have noted under battlefield conditions that utilizing a propofol drip in combination with potent opioids (also called total intravenous anesthesia or TIVA) avoids many of the deleterious effects seen with PIA's alone. Provider's have stated that the awakenings are often, "smoother" and "less dramatic" (Wilson & Pokorny, 2011). Anecdotal evidence has shown promise with total intravenous anesthesia as opposed to using PIA's in decreasing the number of soldiers experiencing ED. However, most of the studies focused on the pediatric population and described which potent inhalation agents (PIA) are responsible for emergence delirium (called emergence agitation in the pediatric literature) (Uezono et al., 2000; Nakayama, Furukawa & Yanai, 2006).



Uezono et al. (2000) examined the difference between TIVA and PIA in a total of 16 pediatric patients undergoing general anesthesia. All subjects were American Society of Anesthesiologist (ASA) or physical status I or II and between the ages of 1-5 years. All subjects received 0.5 mg/kg oral versed prior to induction. No opioids were given intraoperatively. A blinded anesthesiologist evaluated the speed of recovery with the following variables: Time from the end of surgery to tracheal extubation, spontaneous eye opening, duration of the PACU stay and first oral intake. The same anesthesiologist also assessed the quality of recovery in the PACU by observing the presence or absence of emergence agitation. The criterion for emergence agitation was combative behavior, inconsolable crying, and thrashing in any combination. The duration of the behavior was also recorded. The results from this pediatric study found that 38% of those who received the PIA had emergence agitation whereas zero had agitation with TIVA.

Another pediatric study examined this same relationship but with a much higher number of patients. Nakayama, Furukawa and Yanai (2006), examined 96 children aged 2-5 years and 90 children aged 6-11 years undergoing general anesthesia. The children were randomly assigned into either the propofol group or the PIA group. The results were similar with the previously described study of only 16 with propofol in comparison to a PIA (Sevoflurane) resulting in a lower incidence of emergence agitation. There are two important differences worth noting with the current study. Both atropine and opioids were administered to all patients in the later study. Atropine is an anticholinergic which has been known to cause confusion due to its ability to cross the blood-brain barrier. Since all patients received 0.01 mg/kg of atropine and the TIVA groups still had no emergence agitation, then both the opioids and atropine likely had very little effect on the overall outcome of the study.

Only a few recent studies were found with the same or similar age range as described in the proposed research study (adults 18-45 years of age typically seen in the military). Those studies include the Yu et al. (2010) research, the Radtke et al. (2010) research, and the Lepouse et al. (2006) research. A research study by Levnen, Makela, and Scheinin (1995) had examined ketamine and dexmedetomidine and found a measure to decrease what they described as postanesthetic delirium. The Levnen, Makela & Scheinin (1995) study's goal was to examine dexmedetomidine usage to attenuate ketamine-induced cardiostimulatory effects and found that this drug also decreased postanesthetic delirium. The study examined 40 subjects aged 18-24 years and found that intramuscular injection of dexmedetomidine preoperatively not only attenuated the cardiostimulatory effect of ketamine but also attenuated postoperative delirium. This study is beneficial in that it examines an age group similar to those serving in the military but ketamine and dexmedetomidine are not drugs given routinely (certainly not IM) in the theatre of operation and military medical treatment facilities. It has been extremely difficult, as the description of search methods indicated, to find research articles on emergence delirium (ED) under conditions of PTSD/TBI in military personnel who require general anesthesia. The role of pharmacologic interventions as confounding variables or as risk factors awaits evaluation of data from future studies under these conditions.

## **TBI**

The United States Veterans Administration recently produced data regarding the health of service personnel returning from the Iraq and Afghanistan wars notably the overwhelming amount of those being diagnosed with either PTSD or TBI is seen in a much greater proportion of casualties than in other wars TBI ("The National Center for Posttraumatic Stress Disorder", n.d; National Alliance on Mental Illness, 2011). An example of this was shown from January

2003 to February 2005 when over 400 patients were treated at Walter Reed Army Medical Center (WRAMC) for TBI. While 13% of combat casualties in Vietnam were diagnosed as having a brain injury whereas upwards of 20% have been diagnosed thus far in the current conflicts (Okie, 2005). This growing number of TBI's is reportedly due to the advances of body armor used in today's conflicts as well as a more rapid and successful surgical treatment on the battlefield (Grathwohl et al., 2008). Gallagher and Polomano (2006) allude to the fact that not only the advances in protective gear and battlefield surgical interventions, but also the improved air transport of these patients from theatre of operation and the tracking systems have all aided in saving more lives from the battlefields. These "saved lives" are returning with TBI and PTSD.

TBI's can be classified into three broad categories. The first is a mild TBI which is not associated with visible abnormalities on central nervous system imaging. Mild TBI is manifested by a loss of consciousness lasting less than one hour and amnesia lasting less than 24 hours. A moderate TBI is seen with a loss of consciousness lasting between 1 and 24 hours and amnesia lasting up to seven days. Severe TBI's are seen with a loss of consciousness greater than 24 hours and amnesia lasting greater than seven days (Okie, 2005). Hoge et al. (2008) surveyed 2,525 U.S. Army Infantry soldiers three to four months after returning from Iraq and found that 124 (4.9%) reported injuries with loss of consciousness and 260 (10.3%) had injuries associated with altered mental status. A soldier's signs and symptoms usually include one or a combination of the following: Headaches, sensitivity to light and/or noise, and sleep disturbances. Behavioral changes are also apparent and may include anxiety, impulsiveness, outbursts, depression, and mood changes. Most adults with mild TBI can recover within one year while those with moderate to severe TBI's requiring longer recoveries (Okie, 2005). It is crucial to examine the association between TBI and PTSD which is described most accurately by

Warden (2006) stated, “A number of the recent studies have investigated the development of PTSD following TBI. The studies suggest that those with mild TBI have a greater risk of developing PTSD than those with severe brain injuries and longer periods of unconsciousness” (p. 400). Carlson et al. (2010) supported the claim made by Warden (2006) which showed a strong relationship between those diagnosed with TBI and PTSD. Service members diagnosed with TBI were more likely to also be diagnosed with PTSD, adjustment disorders and anxiety. These findings by Warden (2006) and Carlson et al. (2010) are supportive of the proposed research because it will explore the potential linkages between physiological factors (TBI) and psychological factors (PTSD) to ED.

## **PTSD**

Schneiderman, Braver and Kang (2008) showed that out of 2,235 respondents from military personnel who served in either Iraq or Afghanistan, 12% reported a history of TBI and 11% also screened positive for PTSD. The numbers for the past twelve months ending the 30<sup>th</sup> of June 2007 showed that those diagnosed with PTSD rose to over 20,000 or an increase of over 70%. Since the current conflict beginning in 2001 (GWOT), the Department of Veterans Affairs has seen 1 in 7 (over 100,000 soldiers) for some form of mental illness (2007). Of the 124 who reported loss of consciousness with TBI, almost half (43.9%) met inclusion criteria for PTSD (Hoge et al., 2008). As clearly indicated, TBI and PTSD rates are on the rise due to the current armed conflicts.

According to Baxter (2004) there are six criteria that must be addressed in order to make a diagnosis of PTSD. The first is exposure to the precipitating event followed by a persistent re-experiencing of the event, avoidance of the event-related stimuli, persistent

symptoms of increased arousal, duration of symptoms and lastly, significant levels of distress. Mashour, Jiang, and Osterman (2006) proposed the following symptoms for PTSD as characterized by nightmares or flashbacks, hyper vigilance, irritability, insomnia, depression and avoidance of the initial stimulus related to the trauma. There are clearly evident overlaps in the two clinical diagnoses for TBI and PTSD. The physical signs and symptoms are similar with both PTSD and TBI. Sleep difficulties, increased startle response, hypervigilance and increased irritability are a few of the examples seen with both TBI and PTSD.

### **TBI and PTSD risk factors for ED**

There were two literature reports found regarding military personnel and the effect of TBI and/or PTSD in relation to occurrence of ED following general anesthesia. The first published study by McGuire and Burkard (2010) illustrates the potential risk factors for ED in U.S. military service members. The study is more of a review of what is or more often, what is not known about ED but does cite specific details regarding unpublished data from the primary author. This unpublished data was from the primary author's dissertation work and specifically targets service members who have deployed and later require anesthesia. The study details what is known about ED within the pediatric population and then divides up the risk factors for ED into subcategories. The subcategories include: Environmental, social, biological and psychological risk factors make up the subcategories which is very similar to the Scott and Gold (2006) study. The study then identifies potential risk factors applicable to military service members. The authors describe how certain medications such as mefloquin may be a causative factor for ED, how physical trauma and the stress response could lead to ED following anesthesia and how pain could potentially be a risk factor. The authors then attempt to correlate

TBI and psychological trauma to ED and cite how further study is necessary to substantiate this association (McGuire & Burkard, 2010).

A qualitative study performed by Wilson and Pokorny (2011) found that other anesthesia providers have witnessed ED with military personnel and also believe this phenomenon is much higher in those who have TBI and/or PTSD. This study offers insight into the experiences of seasoned CRNA's who have both deployed to either Iraq or Afghanistan and/or taken care of military personnel in military treatment facilities (MTF's) since 11 September 2001. This study is reviewed in detail because of its relevance and significance to the current research questions.

The study defined what ED looked like and offered a precise time period for the behavior, "ED (seen with military personnel with TBI and/or PTSD) is defined as any behavior where the patient awakens in a violent or thrashing way with attempts at self extubation, breath holding, intravenous line displacement, assault on the operating room staff and the want to flee or fall from the narrow operating room table. This violent behavior can encompass any time period from the end of surgery to discharge from the PACU" (Wilson & Pokorny, 2011).

The study utilized a Hermeneutic (interpretive paradigm) phenomenology to gain a better understanding from nurse anesthetists regarding their lived experiences of the phenomenon ED. Interpretive phenomenology was chosen to first see if a particular phenomena exist (ED) and if so, attempt to gain a better understanding of the phenomena through focused questions and later interpretation of the lived experiences into themes. The study's primary lead questions asked, "Out of all the anesthesia cases both abroad and stateside (post 9/11/2001), have you noticed service members wake from general anesthesia (not utilizing TIVA), in a state of delirium?" If

so, can you elaborate on your experiences and thought processes as to why it was occurring?" (Wilson & Pokorny, 2011).

Purposeful sampling was utilized for the study. Three CRNA participants were selected for the study based on their varied backgrounds in deployments and time in service.

Data collection was achieved by an audiotape recording of the interviews. The results of the study identified five themes. They included the following: 1. ED exists and to a much higher degree in the military than with the general population. 2. ED was much more prevalent in the younger military population. 3. Total intravenous anesthesia (TIVA) was a superior anesthetic for those thought to have TBI and or PTSD. 4. Talking to all those suspected of having a TBI and/ or PTSD prior to surgery and on emergence was vital in a smooth wake up (vocal local). 5. There is something profound happening in regards to ketamine and PTSD /TBI. (Wilson & Pokorny, 2011).

The study noted the dearth of information on ED as it relates to TBI and/or PTSD in military personnel. The study also illustrated that ED within the military population is perhaps a much more complex issue that warrants further investigation. The qualitative study suggested that ketamine may influence ED and this finding warranted review of the literature on using this drug for anesthesia.

### **Ketamine: Review of the Current Literature**

Prior to beginning the literature review on what was currently being investigated and recently published in regards to ketamine, a thorough understanding of ketamine's pharmacodynamics and pharmacokinetics is required. Ketamine is a phencyclidine derivative and produces what is known throughout the anesthesia community as dissociative anesthesia.

Researchers have known for decades that ketamine produces dissociation between the thalamo-cortical and limbic systems (Reich & Silvey, 1989). Ketamine can produce both amnesia (anesthetic dosing) and profound analgesia (subanesthetic dosing). Ketamine's mechanism of action works by inhibiting/antagonism of the N-Methyl-D-Aspartate receptor. Ketamine also works on various opioid receptors as well as muscarinic receptors. Ketamine peaks in plasma at approximately one minute after injection and five minutes after intramuscular (IM) injection. Elimination half life is two to three hours. Dosing of ketamine depends on the intended goals for its use. Subanesthetic dosing of 0.2 mg/kg to 0.5 mg/kg are general guidelines for analgesia where 1-2mg/kg intravenous (IV) or 3-5 mg/kg IM for induction of anesthesia. Ketamine is contraindicated in patients with increased intracranial pressure and severe cardiac disease states where increases in the sympathetic nervous system could be detrimental. Ketamine does not cause or trigger malignant hyperthermia nor does it act on the Gamma Amino Butyric Acid neurotransmitter in the brain (common neurotransmitter involved with anesthesia). Ketamine has been widely used for patients with severe asthma for the induction agent of choice due to its profound bronchodilatory effects. In fact, successful treatment of status asthmaticus has been reported (Sarma, 1992). Unlike other induction agents commonly utilized today, ketamine does not produce depression of respiration but this effect is largely dose related and route of administration specific (rapid IV push of 3-5 mg/kg can and will cause apnea).

Stoelting's (1999) anesthesia text, *Pharmacology and Physiology in Anesthesia Practice*, dedicates a chapter to nonbarbiturate induction drugs where the notion of emergence reactions or delusions (which mimic or are very similar to findings with ED) are related to ketamine. The chapter continues by stating that a benzodiazepine (versed) is the most effective pharmacologic agent to attenuate emergence reactions associated with ketamine (White, 1982). The current



findings though premature, are in stark contrast to many of the studies cited in this particular chapter. At this juncture in the exploration of ketamine it became clear that there is a litany of information which most providers take at face value. More investigation into the literature and further research is necessary prior to this author taking that same conclusion. Thus, a review of the current literature that is most applicable to the current research questions was investigated.

The search was initially intended to cover from 2001 through 2010 which encompasses the GWOT and hence research with ketamine from 2001 forward is more likely to include some key indicators for the current research such as TBI and PTSD. All of the current search engines were utilized for this review to include CINAHL, Medline via Pubmed and Medline via Ovid. The initial responses from the key word of ketamine resulted in 5000 plus results. The search was further narrowed by subject matter to include the following: Peer reviewed articles, English, human subjects, and the addition of more key words such as TBI, PTSD, and emergence delirium. All three search engines produced roughly the same number of results with the total number being reduced between 200 and 450 citations. Most of the literature found was related to the pediatric population and emergence agitation. A few of those articles were retrieved and will be highlighted for completeness. The other major subsets of articles were related to pain and the use of ketamine to alleviate pain. Again, a sample of this pain literature was obtained and viewed as important due to the potential newer roles ketamine may be involved in. There were a total of 22 articles that were applicable in some manner to the current research questions being asked. In addition, some of the articles selected add to the general knowledge base and what is known and more importantly not known about ketamine. All of the articles references lists were examined to further the inquiry into ketamine and the various roles ketamine has played throughout the decades. This led to the requirement to broaden the research timeline and later

abolish the GWOT time requirement all together due to the importance of various articles found and there applicability to this research.

One such article written by White, Way, and Trevor (1982) in *Anesthesiology* has been deemed to be a seminal article where anesthesia text often reference from in regards to ketamine. This particular article will be formally detailed as it pertains to emergence reactions later in the review. In all, there were less than ten articles that involved TBI and/or PTSD, anesthesia and ketamine with most involving the pediatric population.

### **Ketamine, Pediatrics and Emergence Agitation**

A plethora of research articles have examined pediatric patients and how they wake from general anesthesia. Emergence agitation as it is commonly referred to in this population is extremely similar to that seen with our military personnel when they wake from general anesthesia. Much of the literature in this area has focused on both the type of anesthetic (TIVA vs PIA) and type of PIA used. Within the past decade numerous research studies have investigated this phenomenon of agitation within the pediatric population when emerging from general anesthesia. There are five research studies which have particular relevance to the proposed research because they clearly articulate new knowledge related to the use of ketamine.

Kawaraguchi et al. (2002) enrolled 55 children aged 3-9 years. The 55 children were divided up into three groups with group “P” (19 subjects) receiving pentazocine, group “F” (18 subjects) receiving flurbiprofen axetil and group “K” receiving ketamine. The study utilized the Aono’s four-point scale to assess agitation at various time points throughout the emergence from anesthesia and in recovery. The result of this study showed ketamine to have a lower agitation score than the other two groups. However, the study did show that those in the ketamine group

required supplemental oxygen upon tracheal extubation (Kawaraguchi et al., 2002). Abu-Shahwan and Chowdary (2007) involved 85 pediatric patients aged 4-7 years. The authors hypothesized that adding low dose ketamine to the anesthetic regimen (sevoflurane was utilized as the PIA) would reduce the incidence of emergence agitation. The study was double blinded and all the patients were given Tylenol and versed prior to going back into the operating room. There was a control group who received saline and an intervention group which received ketamine at 0.25 mg/kg. The Pediatric Anesthesia Emergence Delirium scale was utilized to assess the patients at two distinct time periods. The results found that 7 children were diagnosed in the intervention group where 13 were diagnosed as being agitated in the control group (Abu-Shahwan & Chowdary, 2007). Vardy et al. (2008) examined ketamine and its effectiveness for sedation in the emergency room (ED). The study utilized a two year audit of sedation practices which included an N of 210. Forty percent (85) were given ketamine for sedation, 51% (107) were given midazolam and 9% (18) were given propofol. Overall, the study found that there were approximately 16% complication rate total (with all three). Apnea and hypoxia occurred most often with propofol and midazolam. Ultimately, the authors concluded that ketamine is both safe and effective for sedation in the emergency room (Vardy et al. 2008). This study was chosen because it clearly shows how ketamine is not only safe but may at times be preferred over other agents even outside the OR. The next pediatric study investigated sedation outcomes between ketamine and a combination of fentanyl and midazolam. The authors hypothesized that the ketamine group would have a much higher incidence of adverse behaviors. The study's N was 554 children aged 7.5 +/- 4.5 years. The results after the Post Hospital Behavior Questionnaire were surprising. The odds of a higher score were higher with the midazolam and fentanyl group than the ketamine group (McQueen, Wright, Kido, Kaye, & Krauss, 2009).

Green et al. (2009) examined recovery agitation with ketamine in children. The study utilized multiple regression to investigate 32 emergency department studies to see which clinical variables produced both emesis and recovery agitation. The results from this study found that ketamine was statistically safe and much of the predictive indicators for emesis were related to high dosing. Recovery agitation was not age related. Green et al. (2009) stated, “These and other results herein challenge many widely held views about ED ketamine administration” (p. 180). The quote taken from a recently published research study clearly sums up this authors intent on including a small percentage of the pediatric literature to clearly illustrate that much of what was thought to be true concerning ketamine may in fact be myth. For further brevity, the next few sections of the literature review will be concise and to the point. (Ketamine with use in antidepressant therapy, cardiac surgery and pain studies have been intentionally left out. This was done to keep the information presented on target and not confuse the audience any more than needed).

### **TBI and/or PTSD, Anesthesia and Ketamine**

The review of the literature on ketamine shows that there are two opposing views about the use of ketamine. Some research supports the use of ketamine for those suffering from PTSD (recall TBI can lead to PTSD symptoms) and there are research findings that oppose the use of ketamine for PTSD patients. Guit, Koning, Coster, Niemeijer, and Mackie (1991) found that subanesthetic concentrations of ketamine in combination with propofol resulted in both hemodynamic stability, did not require further analgesics and postoperative behavior was normal (Guit, Koning, Coster, Niemeijer, & Mackie, 1991). This drug combination with ketamine was profiled against a commonly used propofol/fentanyl mixture and found to be superior. This is an

interesting finding almost two decades ago and is complimentary to the qualitative themes found in Wilson and Pokorny's (2011) study.

White, Way and Trevor (1982) have been cited numerous times in various text and journal articles. Much of the cited literature from this early 80's study was from work published in the 60's and 70's but still considered important and current. The seminal article published in *Anesthesiology* had an entire section on postanesthesia emergence reactions. This section on emergence reactions has been referred to as emergence delirium, but is it? The White, Way and Trevor (1982) article states the following concerning emergence from ketamine, "The psychic sensations reported during emergence from ketamine anesthesia have been characterized as alterations in mood state and body image, dissociative or extracorporeal (out-of-body) experiences, floating sensations, vivid dreams or illusions, 'weird trips,' and occasional frank delirium. The vivid dreams and visual illusions usually disappear immediately upon waking, although recurrent illusions (flashbacks) have been reported several weeks after ketamine administration in adults and children" (p. 120). Ultimately, the authors stated that talking to the patients both before and after the administration of ketamine is effective and prepares the patient for what he or she might experience. The section of emergence and ketamine also focused on the importance of age and how those aged > 16 are more likely to experience emergence reactions. Both of the above mentioned conclusions from the 1982 study were echoed again in the Wilson and Pokorny (2011) qualitative study. Two studies that were referenced or critiqued within the 1982 study were both revealing and contrasted much of what is perceived as true concerning ketamine. Garfield et al. (1972) found that postoperative anxiety was no different with ketamine administration than that seen with a standard anesthetic (which at the time consisted of

thiopental, N2O and halothane). Modvig (1972) found that children given ketamine or a halothane and N2O combination had no psychological differences postoperatively.

There were two notable studies performed by Schonenberg, Reinchwald, Domes, Badke and Hautzinger published in 2005 and 2008 respectively. Both studies report that ketamine should not be used with patients suspected of or having PTSD. Schonenberg et al. (2008) determined that ketamine can aggravate early post-traumatic stress reactions especially when given in the acute trauma phase. The authors concluded further that giving ketamine might actually lead to long lasting symptomatology. A study by Winter and Irle (2004) was performed at the Army's Institute of Surgical Research examined PTSD and its relationship to hippocampal volumes. The goal of the study was to investigate hippocampal volumes with those who had a traumatic event in their lifetime. Fifteen subjects had PTSD and 14 had trauma but no PTSD for a total of 29 subjects for the study. Three dimensional magnetic resonance imaging was utilized to measure the hippocampal volumes. The results of the study showed significant decreases in hippocampal volumes as compared to normal subjects (those without PTSD or trauma). The study also found that the use of ketamine led to increased right hippocampal volumes but also led to stronger PTSD symptoms. The study is both interesting and noteworthy because it provides a positive rationale for administering ketamine (decreased hippocampal volume changes) and a negative rationale (in regard to PTSD symptoms) for administering ketamine.

The study performed by McGhee, Maani, Garza, Gaylord and Black (2008) is to date, the most supportive to the current studies research questions and is extremely insightful. The studies goal was to see if those service members who received ketamine intraoperatively would have a higher incidence of PTSD. The author's assumptions were due to the fact that ketamine is associated with both dissociative and psychotic states and thus would lead to a higher incidence

of PTSD postoperatively. The study investigated a total of 147 Operation Enduring Freedom and Operation Iraqi Freedom military service members. These service members had undergone at least one surgery, received ketamine (28 had not) and completed the PTSD Checklist-Military (PCL-M). The results were contrary to what mainstream anesthesia providers would think concerning the use of ketamine. Thirty two of 119 or 27% met inclusion criteria for PTSD (those who received ketamine) where 13 of 28 or 46% in the group not receiving ketamine met PTSD inclusion criteria ( $p = 0.044$ ). These results were impressive because the ketamine group had more severe burns, underwent more operations and spent more time in the intensive care unit (McGhee et al., 2008).

This specific and in depth review of the literature on ketamine has been important to the proposed study for several reasons. Historically, the literature proved insight as to ketamine and its uses as well as its theoretical and physiological linkages. However, these linkages have become unclear with the increased uses of this non barbiturate medication because of its popularity within military medicine (McGhee et al., 2008). There is obvious debate within the medical community as to the relevance of ketamine especially as it relates to PTSD. This research topic is timely in consideration of the current war(s). There is a lot unknown about TBI/PTSD and ED as these relate to ketamine and the topic requires much more sound research to investigate the now multiple phenomenon's emerging from the literature.

There was only one published study found during the extensive review of literature which examined the frequency of occurrence of ED in soldiers. The study by McGuire and Burkard (2010) highlighted potential risk factors for ED and divided these risk factors into four sections. The study adapted these categories from the Scott and Gold (2006) study which focused primarily on the pediatric population. The risk factor categories included the following:

Environmental, social, biological (which included TBI) and psychological (which included PTSD). McGuire and Burkard (2010) merely added to the risk factors what they considered to be applicable with the adult, U.S. military population (hence, TBI and PTSD as added risk factors). The authors did however support the claim that more research is required to discover a link between ED and risk factors such as TBI and/or PTSD (among others). This lack of data exposes and verifies a compelling need for the current research.



## **CHAPTER 3: METHODOLOGY**

Chapter 3 presents the research design and method that was used to answer the stated research questions. The purpose of this descriptive correlational study was to determine, through active duty Army anesthesia provider's perceptions, the following: 1) extent and seriousness of ED in service members; 2) effects of ED on the safety of service members and OR/PACU personnel and 3) behaviors relevant to ED in service members. In addition to these primary aims, the study also focused on identifying through provider's perceptions, the following potential factors which may lead to the development of ED or to the alleviation of ED: 1) type of anesthetic agents; 2) physiological factors; 3) psychological factors; and 4) interventions used for alleviating the symptoms of ED. A final aim was to investigate through provider's perceptions, the relationship between perceived seriousness of ED and reported case experience, behaviors and consequences relevant to ED, and physiological and psychological factors related to the development or alleviation of ED symptoms. This chapter is divided into six sections: (1) research design, (2) setting and sample, (3) instrumentation, (4) data collection procedure, (5) data analysis, and (6) summary.

### **Research Design**

A descriptive correlational design was employed to examine the relationship between ED and service members, identify behaviors relevant to ED in service members, and better understand the effect ED has on safety to both the service member and OR/PACU personnel. Further, additional data gained was utilized as a descriptive correlational design to identify strength of an association between potential causative factors (physiological, psychological and anesthetic agents) and ED.

## Setting and Sample

The setting for this study was online due to the ability to reach the maximum number of participants as possible via electronic means. Two distinct advantages for utilizing online surveys is the enormous reduction in costs associated with the survey and the ease to reach a large sample size. Speed of data collection is another advantage of online surveys which are typically 10 – 20 days in length (Czaja & Blair, 2005). The Department of Defense as well as the Army Medical Command has consistently utilized online means to reach the maximum number of participants. Electronic means to gather information in the military is especially beneficial as in today's environment with anesthesia providers serving not only all over the United States but also abroad in areas such as, Afghanistan and Iraq. This one advantage can also potentially be a disadvantage as those in distant countries may not have the means or ability to access the internet and thus will not be able to become a respondent.

The study utilized a convenience sample of all currently (as of August 2011) active duty Army anesthesia providers. One hundred and fifty six Certified, Registered Nurse Anesthetist (CRNA's) and 98 Anesthesiologist for a total of 254 were included in the sample. Sheehan (2001) performed a meta-analysis on email survey response rates and noted that depending on the year, the average was between 31% and 46%. Thus, it is expected to receive a response rate between 85 and 101. Inclusion criteria consisted of only active duty personnel due to the inability to effectively obtain and reach members of the other Armed Services as well as the Reserve components. Thus, the exclusion criteria included anyone not on active duty or not practicing as an anesthesia provider (the exclusion criteria was self limiting in that only active duty anesthesia providers were sought out). It is also important to point out that Reservist and National Guard providers were not included in the survey due to the fact that they tend not to

work at military treatment facilities and thus do not often encounter service members who have deployed during the GWOT.

### **Instrumentation**

A tailored design method was utilized to design the instrument for this study (Dillman, 2007). The survey was developed based on the conceptual model developed by the researcher and will include variables to address specific concepts as they relate to ED. An online survey was eventually constructed and implemented for this study. The rationale behind the online survey was to reach the maximum number of participants possible in the allotted amount of time given for the study. Another advantage to sending the survey to individual email accounts was these accounts are secure through the Army portal. It is extremely difficult for someone other than the recipient to enter the Army email account. Thus, sending electronically is not only secure, it is also timely and can maximize the number of respondents across the World.

The survey was piloted in its early development for both validity and reliability. Volunteers from Womack Army Medical Center (WAMC) conducted the pilot which included an Anesthesiologist's and 3 CRNA's. This was performed in the providers off time (time away from duty). Feedback from their participation proved beneficial in a number of ways. First, it helped guide modifications to the actual question in the tool (survey). Second, the feedback gained from this pilot allowed changes to the survey to make the flow of these questions easier to read (change the order). Multiple revisions were made throughout the survey design with principle guidance coming from the study's dissertation committee members. The final version of the survey which was sent online in August 2011 consisted of 5 sections and 40 total questions.

The first section did not consist of any questions but rather operational definitions which were important to maintain the focus (service members) for all respondents. Service members was defined as, “any man or woman who has deployed in support of the Global War on Terrorism. The Global War on Terrorism was defined as, “synonymous with Overseas Contingency Operation and starts from 11 Sept 2001 to present day.” These definitions were important to ensure to the reader that the focus of the study was on a specific patient population (Service Members) and only for those who have deployed during a specific time period. It was also important for those being surveyed to not get confused with other forms of delirium seen postoperatively such as that with the geriatric population or agitation with the pediatric population.

The second section of the survey totaled 6 questions and centered on important demographic data. Demographic data is detailed below and included professional designation, gender, experience level, current practice site and amount of time deployed during the GWOT. Experience level was ascertained from questions such as, “How many months or years have you been practicing anesthesia?” and, “As of today, how many total months have you deployed during the GWOT (i. e. since 11 Sept 2011)?”

*Professional designation.* Professional designation was classified as either Anesthesiologist or Nurse Anesthetist.

*Gender.* Gender was classified as either male or female.

*Experience level.* Experience level was categorized into years practicing and years on active duty. Years practicing and on active duty were further categorized as less than 2 years, 2 to 5 years and greater than 5 years.

*Practice site.* Practice sites for anesthesia providers included medical center in the United States (U.S.), medical center abroad, community hospital in U.S., community hospital abroad, Iraq, and Afghanistan.

*Months deployed.* This question on the survey was an open ended question with respondents open to enter any numerical number to include 0. It was imperative that those surveyed understand that the number entered is in months and not years and thus, the question had, “months” all capitalized.

The third section of the survey focused on anesthesia practice characteristics and totaled 8 questions. Practice related questions honed in on many aspects of an anesthesia providers practice but especially on whether or not practitioners screen for PTSD or TBI. Pharmacologic questions were also ascertained in this section and what providers utilize on a routine basis and what they utilized pharmacologically while deployed. Below is a detailed description of what was sought during this portion of the survey.

*Routine screening.* Routine screening was categorized into whether or not the surveyed providers screen for either, PTSD, TBI, both or none.

*Benzodiazepine administration.* The question related to benzodiazepine administration was categorized as yes or no. The next question then asked what dose of the most common benzodiazepine (midazolam) the providers administered. The answers were categorized as, less than 1 mg, 1 to 2 mg, 3 to 4 mg, greater than 4 mg and do not routinely administer Midazolam.

*Ketamine administration.* Ketamine administration was measured through Questions 10 and 11 on the survey. These questions inquired as to the frequency a provider utilizes ketamine with answer choices being: Never, rarely, occasionally and routinely and also the provider’s

routine practices. There were multiple answer choices provided which included the following:

- 1) Use ketamine to induce general anesthesia alone.
- 2) Mix ketamine with another compound such as propofol to induce general anesthesia.
- 3) Administer subanesthetic doses of ketamine during an anesthetic.
- 4) Administer ketamine orally with midazolam prior to an anesthetic.
- 5) Administer ketamine orally without midazolam prior to an anesthetic.
- 6) Administer ketamine intramuscular (IM) preoperatively with midazolam.
- 7) Administer ketamine intramuscular (IM) preoperatively without midazolam.

This question also had an, “other” space provided for providers to add any additional comments or data they deem fit.

*Analgesic administration.* Question 12 in section 3 of the survey inquired as to the providers use of analgesics. The answer choices provided included, “other” at the end and the following: 1) Morphine. 2) Fentanyl. 3) Sufentanyl. 4) Remifentanyl. 5) Demorol. 6) Dilauded.

*Anesthetics used while deployed.* Anesthetics used while deployed were measured as: 1) Never deployed. 2) PIA using Sevoflurane most often. 3) PIA using Isoflurane most often. 4) PIA using Desflurane most often. 5) TIVA. 6) Other.

*TIVA versus PIA in regards to observed differences waking up.* TIVA versus PIA is the last question in this section and was measured directly by asking the providers if they had seen a difference. Answer choices were: 1) No difference between TIVA and PIA on waking status. 2) Yes, service members receiving TIVA wake more smoothly. 3) Yes, service members receiving PIA wake more smoothly.

The fourth section of the survey sought information on the extent of ED with an emphasis on whether or not the provider has witnessed ED (question 15). The section is vital for future

studies as it seeks to find what pharmacologic regimen works and which does not in treating service personnel deployed during the GWOT. Many of the questions tailored in this section were derived from the pediatric literature which states that using or not using certain anesthetics may affect ED. The section totaled 14 questions with the second half of this section focusing on anesthetic, physiologic and psychological factors that may possibly be associated with ED. Below is a detailed listing of the various questions asked during this section title, “Emergence delirium as it pertains to service personnel”.

*Personal experience with ED with service members during the GWOT.* This question was measured as a simple yes or no. If the providers answer no to this section then they were to proceed to the end of the survey and click on the, “done” tab which will allow the survey tool to capture and code their answers for questions 1 -14.

*Number of ED cases experienced by the provider.* This question measured (by providers best possible recollection) the number of times a provider witnessed ED. The responses were grouped as: 1) Less than 5. 2) 5 – 10. 3) 11- 20. 4) 21 – 30. 5) 31 or more cases.

*ED cases decreasing, not changing or increasing.* This question measured whether or not the provider who has been providing anesthesia to service members during the GWOT to the present, can (in his or her best judgement) recall if cases are changing. The responses to this question are: 1) Decreasing. 2) Not changing. 3) Increasing.

*ED behaviors are a problem, risk for injury to themselves, and risk of injury to the provider or PACU/OR staff.* Questions 18 – 20 asked the provided whether or not he or she felt ED was a problem with answer choices being: 1) Not a problem. 2) Small problem. 3) Moderate problem. 4) Serious problem. Question 19 then proceeded to ask the provider whether

or not ED could cause injury to the service member themselves with the following as answer choices: 1) No risk. 2) Slight risk. 3) Moderate risk. 4) High risk. Question 20 stemmed from 19 in that the question asked essentially the same question but with the focus changing from service member to provider/OR/PACU personnel. In other words, could ED cause injury to others besides the service member displaying ED? The answer choices were the same as in question 19.

*ED related to the anesthetic used.* The next set of questions centered on possible causes of ED. Question 21 asked the provider if he or she believes ED could be related to the anesthetic used. The answer choices provided were either yes or no. If the provider answered no then he or she would skip the next question and proceed to question 23.

*Anesthetics used and there potential role in ED.* This question was measured by the provider selecting any number (provider could select all that applied) of answer choices that he or she thinks could cause or be related to causing ED. The answer choices included: 1) PIA's. 2) Nitrous oxide. 3) TIVA utilizing propofol. 4) Benzodiazepines. 5) Ketamine. 6) Barbiturates. 7) Potent opioids. 8) Non-depolarizing blocking agents. 9) Anticholinergics. 10) Anticholinesterases.

*Potential physiological factors related to ED.* This question sought information that could be used for future research studies. The question asked the provider if he or she believes ED could be caused by any physiological factors such as (answer choices): 1) Do not believe ED is related to any physiological factors. 2) Traumatic brain injury. 3) Type of surgery. 4) Long duration of surgery (> 3 hours). 5) Short duration of surgery (< 1 hour). 6) Pain. 7)



Young age (30 years old or less). 8) Old age (> 30 years old). 8) Medications patient is taking other than anesthetic.

*Potential psychological factors related to ED.* Information obtained by providers for this question centered on ED's potential relationship with various psychological factors. Answer choices for this question are: 1) Do not believe ED is related to any preexisting psychological factors. 2) Post traumatic stress disorder. 3) Pain. 4) Anxiety. 5) Depression. 6) Medications patient is taking other than anesthetic.

*Interventions used to treat ED.* The last 4 questions in this section focus on interventions that the providers may have utilized to treat ED. The first intervention question (number 26) was a simply yes or no question with the providers skipping question 27 if they answered no to question 26 (utilize any intervention to treat ED). Question 26 provided the respondent with a plethora of responses which included: 1) Administer Haloperidol. 2) Administer diphenhydramine. 3) Talk to the patient during episode (not preoperatively). 4) Deepen the anesthetic using induction agent such as propofol. 5) Administer analgesic. 6) Administer a benzodiazepine. 7) Nothing (allow tincture of time to alleviate signs and symptoms). Questions 27 and 28 honed in on whether or not the provider utilized any pre-operative interventions for future anesthetics. The initial question was again, a yes or no type question with those answering moving on to the next section and question 29. Those who answer yes to the then move to the next question which seeks to determine what intervention helped. This questions answers were: 1) Talking to the patient with an emphasis on explaining everything you will do from the moment the IV is started to waking up in the OR/PACU. 2) Listening to the patient with an emphasis on allowing the patient to verbalize fears of the unknown and of past experiences which may impact wake up such as bad dreams or flashbacks. 3) Giving more of your standard

dose of versed. 4) Giving less of your standard dose of versed. 5) Eliminating versed all together. 6) Administering ketamine (<1 mg/kg) IV. 6) Administering diphenhydramine. 7) Administering haloperidol. 8) Administering droperidol. 9) Other.

The 5<sup>th</sup> and final section honed in on the specific behaviors associated with ED and consisted of 12 questions. The last question was an area for the providers to write in any behavior(s) not already listed in the previous 11 questions. Providers were asked to recall from their personal experiences with service members certain behavioral characteristics seen with ED. These characteristics were derived from a previous pediatric study by Sikich & Lerman (2004) which developed an emergence delirium scale for use in the pediatric population. According to Scott & Gold (2006), this tool has good psychometric properties for identifying and evaluating ED (recall however that this scale is intended for the pediatric population). Permission was granted from Ms Sikich telephonically on 07 March 2010 to utilize aspects of her questionnaire for the current ED survey.

*ED behaviors.* To adequately measure which behavior a provider had seen and how often, the responses provided for all 11 questions were: 1) Never seen. 2) Rarely seen. 3) Occasionally seen. 4) Often seen. 5) Always seen. The 11 questions stemmed from a previous pediatric study by Sikich and Lerman, (2004). The Sikich and Lerman (2004) study developed a list of behaviors and consequences to measure emergence agitation in the pediatric population. The questions from the pediatric anesthesia emergence delirium (PAED) scale were shown to be both valid and reliable and have good psychometric properties in determining ED in pediatric patients (Sikich & Lerman, 2004; Scott & Gold, 2006). The original questions regarding behaviors/consequences for ED were modified (with written permission from Nancy Sikich on 14 March 2011) from the Sikich and Lerman (2004) pediatric study in order to make them

applicable to the adult population. Not all of the original behavior/consequence questions from the Sikich and Lerman (2004) study and incorporated into the current adult/ military member study's research tool (survey). The 11 items chosen for this survey to satisfy behavior and consequence for ED were questions numbered: 29) The service member's pull at the monitoring equipment, ETT, IV or any other invasive line connected to him/her. 30) The service member's behavior threatens his/her own safety. 31) The service member's movements are disruptive. 32) The service member's have hyperactive motor behavior. 33) The service member's behavior requires additional staff. 34) The service member's are combative towards the provider and staff. 35) The service member's behavior makes his/her CRNA/Anesthesiologist/Nurse care more difficult. 36) The service member's are vocally abusive. 37) The service member's are uncontrollable. 38) The service member's seem panic stricken. 39) The service member's behavior threatens staff and provider safety.

The entire survey was limited to 40 questions due to the fact that lengthy internet surveys tend to have a lower response rate than those with fewer questions. Those surveys which require the least amount of time usually have higher response rates than surveys that require a great deal of time (Dilman, 2007).

### **Data Collection Plan**

In order to gain access to the names of all active duty Army anesthesia providers, letters were written seeking permission from the Army's Anesthesiologist Consultant to the Surgeon General and the Army's Nurse Anesthetist Consultant to the Surgeon General. Multiple letters were sent electronically to these consultants in order to gain access to the names of all the currently serving Army Anesthesiologist's and CRNA's. In July 2011 a total of 255 names were

provided to the researcher. Each name had to be compared against a database from current active duty Army providers for verification and email address. Only those with a clearance from the Army portal can gain access to these email addresses. As previously detailed, 156 of the 255 names were Army CRNA's and 98 Army Anesthesiologist's.

Prior to the dissemination of the survey, approval had to be granted by East Carolina's University (ECU) Institutional Review Board (IRB) and the Army's Research Institute specifically, the Army Personnel Survey Program. Approval was granted in the Summer of 2011 and the first of five total letters over one month time period was sent out to all 255 participants on 01 August 2011. The initial letter was sent from the researchers ECU email in order to properly identify any mistakes in formulating/copying the email addresses from the Army online portal. The letter had no links to the actual survey. It specified the approximated time necessary for completion of the survey, which entity had approved the survey, and why the survey was being sent to them. Also included in the initial letter was the researchers contact information and information from *SurveyMonkey* which was to be used as the site from which the survey was disseminated. A total of 24 email addresses were sent back to the ECU account. Upon investigation into why the emails were sent back, it appeared that the researcher made various errors in the copying process (human error). Once the corrections were made to the 24 email addresses, each one went through successfully for a total of 255 Army email accounts.

The second letter from the internet site, *SurveyMonkey* was sent 48 hours later on 03 August 2011 and provided all 255 potential participants information on ED. The letter explained what the survey was for in detail (what information was being sought and why). This was the first letter that provided the direct link to the survey. The letter stated that their participation was voluntary and that if they wished to no longer be included in the survey or receive any further

emails then an opt out link was also provided (this opt out link was in every correspondence). . The plan to send out requests for respondents was weekly based on data from other studies which utilized online means to collect their data (Czaja & Blair, 2005). The third letter was only sent to those who had not responded yet (not taken the survey). The letter emphasized the need for more responses in order to strengthen statistical analysis. This letter was sent out on 10 August 2011. The fourth letter (only sent out to those who had not yet responded) was sent out on 17 August 2011 and emphasized that the survey would be closing in two weeks (31 August 2011). Again, there was a link to participate and a link to withdraw from the survey. Also, all the letters stated that the survey was both voluntary and confidential. The final letter sent was a repeat of the second letter sent on 03 August with a few minor adjustments. The letter emphasized the short amount of time needed to complete the survey and that the survey had only one week left to be open.

### **Data Analysis Plan**

At the completion of the online survey, all survey data were imported into the Statistical Package for Social Sciences (SPSS) version 17.0 from Survey Monkey. Prior to data analysis all the data was screened and checked for missing or inconsistent responses. For each survey question, counts were generated for the responses to each question. Associations between categorical variables were analyzed with the chi-square test statistic. Prior to any statistical testing, the level of significance was set at .05. The open ended questions which allowed the respondents to write in additional information was coded for applicability to each question and then summarized in the tables for completeness.

## Summary

This chapter described the research design, sample and setting, instrumentation, data collection plan and data analysis plan. The primary aims of this study were to investigate through active duty Army anesthesia provider's perceptions, the following: 1) the extent and seriousness of emergence delirium (ED) in service members; 2) effects of ED on the safety of service members and OR/PACU personnel and 3) behaviors relevant to ED in service members. In addition to these primary aims, the study also focused on identifying through provider's perceptions, the following potential factors which may lead to the development of ED or to the alleviation of ED: 1) type of anesthetic agents; 2) physiological factors; 3) psychological factors; and 4) interventions used for alleviating the symptoms of ED. A final aim was to investigate from the provider's perceptions, the relationship between perceived seriousness of ED and reported case experience, behaviors and consequences relevant to ED, and physiological and psychological factors related to the development or alleviation of ED symptoms.

The study utilized descriptive statistics as well as Pearson Chi-square to answer the research questions. The goal from this study is the hope that knowledge gained will foster future research studies to ultimately promote anticipatory procedures to handle ED for overall improvement of health care.

## **Chapter 4: RESULTS**

This chapter presents the findings of the study. Demographics characteristics of the study sample and an analysis of each research questions are presented. The chapter is organized by the aims of the study which include the following: The primary aims of this study were to determine, through active duty Army anesthesia provider's perceptions, the following: 1) extent and seriousness of ED in service members; 2) effects of ED on the safety of service members and OR/PACU personnel and 3) behaviors relevant to ED in service members. In addition to these primary aims, the study also focused on identifying, through provider's perceptions, the following potential factors which may lead to the development of ED or to the alleviation of ED: 1) type of anesthetic agents; 2) physiological factors; 3) psychological factors; and 4) interventions used for alleviating the symptoms of ED. A final aim was to investigate the relationship between perceived seriousness of ED and reported case experience, behaviors and consequences relevant to ED, and physiological and psychological factors related to the development or alleviation of ED symptoms.

### **Characteristics of the Sample**

A total of 254 eligible active duty Army anesthesia providers were included for this study. Eighty nine responded after four separate invitations were emailed over a one month time period. The initial response rate following the first letter (with the survey attached) was 46. After a week of collecting responses and following the second letter, 23 additional participants had completed the survey for a total of 69. The third letter was sent out one week after the second and produced an additional 12 responses for a total of 81. The final letter sent to those who had not responded was sent one week after the third letter and resulted in the fewest responses at 8 for a final total of 89. Of the 89, 87 were completed surveys. Two were discarded

because the respondents started the survey but never completed it. The overall response rate was 34% which was within the targeted 31 - 46% range as stated in the methods chapter.

### **Demographic Characteristics**

Table 1 presents the demographics characteristics of the total sample, and for the subgroups of those who had personally experienced ED in their anesthesia practice (78.2%) and those who had not personally experienced ED (21.8%). Of the 68 respondents who experienced ED in their practice, the personal experience rate was similar for both anesthesiologist (77.3%) and CRNA (78.5%). The study respondents were more likely to be Nurse Anesthetists (74.7%), have been practicing for more than five years (59.8%), been on active duty for more than five years (94.3%), been deployed for more than 6 months (58.6%), and are currently practicing in the United States (79.5%). There were no statistically significant differences between those with and without a personal experience of ED on any of the demographic variables.

### **Practice Characteristics**

Information about routine screening practices, benzodiazepine administration, midazolam dose, ketamine utilization and administration, and types of anesthetics utilized by providers while deployed are summarized in Table 2 for the total sample and for those with and without a personal experience of ED in their anesthesia practice. The majority of providers reported screening for both PTSD and TBI, and utilizing benzodiazepine with a dose of 1 – 2 milligrams in their practice. Almost half of the providers never or rarely used ketamine. When ketamine was used, it was usually administered alone at a subanesthetic dose. The anesthetic agents most often administered during deployment were Sevoflurane, Isoflurane or TIVA. There were no statistically significant differences between those with and without a personal experience of ED on any of the practice characteristic variables.



Table 1

*Demographic Characteristics as a Percentage of the Sample*

| Characteristics                    | Personal Experience of ED |                | Total<br>(N = 87) |
|------------------------------------|---------------------------|----------------|-------------------|
|                                    | Yes<br>(n = 68)           | No<br>(n = 19) |                   |
| <b>Professional designation</b>    |                           |                |                   |
| Anesthesiologist                   | 25.0                      | 26.3           | 25.3              |
| Nurse Anesthetist                  | 75.0                      | 73.7           | 74.7              |
| <b>Years Practicing Anesthesia</b> |                           |                |                   |
| < 2                                | 10.8                      | 15.8           | 12.6              |
| 2 – 5                              | 32.4                      | 10.5           | 27.6              |
| > 5                                | 55.6                      | 73.7           | 59.8              |
| <b>Years on Active Duty</b>        |                           |                |                   |
| < 2                                | 4.4                       | 0.0            | 3.4               |
| 2 – 5                              | 2.9                       | 0.0            | 2.3               |
| > 5                                | 92.6                      | 100.0          | 94.3              |
| <b>Current Practice Site</b>       |                           |                |                   |
| Medical Center U.S.                | 51.5                      | 47.4           | 50.6              |
| Medical Center Abroad              | 4.4                       | 21.4           | 8.1               |
| Community Hospital U.S.            | 32.4                      | 15.8           | 28.7              |
| Community Hospital Abroad          | 2.9                       | 15.8           | 5.7               |
| Iraq or Afghanistan                | 8.8                       | 0.0            | 6.9               |
| <b>Months Deployed during GWOT</b> |                           |                |                   |
| Never deployed                     | 20.5                      | 21.1           | 20.7              |
| < 6                                | 22.2                      | 15.9           | 20.7              |
| 7 – 12                             | 23.5                      | 26.3           | 24.1              |
| > 12                               | 33.8                      | 36.7           | 34.5              |

Table 2

*Practice Characteristics as a Percentage of the Sample*

| Characteristics                               | Personal Experience of ED |                | Total<br>(N = 87) |
|---|---------------------------|----------------|-------------------|
|   | Yes<br>(n = 68)           | No<br>(n = 19) |                   |
| <b>Routine screening<sup>a</sup></b>          |                           |                |                   |
| PTSD  | 14.7                      | 5.3            | 12.6              |
| TBI   | 4.4                       | 0.0            | 3.4               |
| Both (PTSD and TBI)                           | 69.1                      | 68.4           | 69.0              |
| None  | 11.8                      | 26.3           | 14.9              |
| <b>Benzodiazapine administration</b>          |                           |                |                   |
| Yes   | 99.5                      | 94.7           | 97.7              |
| No  | 1.5                       | 5.3            | 2.3               |
| <b>Midazolam dose (mg)</b>                    |                           |                |                   |
| 1 – 2 mg                                      | 86.6                      | 94.4           | 86.2              |
| 3 – 4 mg                                      | 7.5                       | 0.0            | 5.7               |
| Greater than 4 mg                             | 6.0                       | 5.3            | 5.7               |
| Missing                                       | 1.5                       | 5.3            | 2.3               |
| <b>Ketamine Utilization</b>                   |                           |                |                   |
| Never   | 4.4                       | 10.5           | 5.7               |
| Rarely  | 42.6                      | 42.1           | 42.5              |
| Occasionally                                  | 39.7                      | 36.8           | 39.1              |
| Routinely                                     | 13.2                      | 10.5           | 12.6              |
| <b>Ketamine administration<sup>a, b</sup></b> |                           |                |                   |
| Induce general anesthesia alone               | 1.5                       | 0.0            | 1.2               |
| Mix Ketamine with compound                    | 35.4                      | 26.3           | 34.1              |
| Administer subanesthetic dose                 | 78.5                      | 73.7           | 79.3              |
| IM with Midazolam                             | 1.5                       | 0.0            | 1.2               |

Table 2

*Practice Characteristics as a Percentage of the Sample (Continued)*

| Characteristics                             | Personal Experience of ED |                | Total<br>(N = 87) |
|---|---------------------------|----------------|-------------------|
|   | Yes<br>(n = 68)           | No<br>(n = 19) |                   |
| Anesthetics used when deployed <sup>a</sup> |                           |                |                   |
| Never deployed                              | 20.8                      | 21.1           | 20.7              |
| Deployed using PIA Sevoflurane              | 44.1                      | 47.4           | 44.8              |
| Deployed using PIA Isoflurane               | 29.4                      | 26.3           | 28.7              |
| Deployed using PIA Desflurane               | 1.5                       | 0.0            | 1.1               |
| Deployed using TIVA                         | 35.3                      | 52.6           | 39.1              |
| Other                                       | 5.9                       | 10.5           | 6.9               |
| Missing                                     | 1.5                       | 0.0            | 0.0               |

<sup>a</sup>Percentages don't add up to 100 as respondent can select all responses that apply. <sup>b</sup>Percentages based on the 82 respondents who used Ketamine.

### **Primary Aims 1 and 2: Extent, Seriousness, and Safety Risk of ED**

The following results focus on the first two primary aims of this study which were derived from active duty Army anesthesia provider's perceptions of the following: 1) the extent and seriousness of emergence delirium (ED) in service members; 2) effects of ED on the safety of service members and OR/PACU personnel (see Table 3). It has been reported that of the 87 total respondents, 68 (78.2%) had witnessed ED in their practices. Of those with personal experience of ED, the majority has seen 10 or fewer cases, have not seen any change in the frequency of cases over time, consider ED either not a problem or only a small problem, and consider the risk of injury to the service member or the OR/PACU staff as slight. However, over a third of the providers reported that ED was a moderate to serious problem, and involved a moderate to high risk of injury to both the service member and OR/PACU staff.

### **Primary Aim 3: Behaviors Relevant to ED in Service Members**

The third primary aim for this study was to identify behaviors relevant to ED in service members. Eleven different behaviors or behavioral consequences were rated based on how often they were observed. The response categories for each behavior or consequence included never, rarely, occasionally, often and always. Table 4 depicts the behaviors or consequences ranked from least often seen to most often seen. The behaviors or consequences seen most often included hyperactive motor behavior, pulling at the monitoring equipment, behavior requiring additional staff, and disruptive movements. The behaviors or consequences seen less often included the following: Uncontrollable behavior, behavior which threatened staff and provider safety, and vocally abusive behavior.

Table 3

*Extent, Seriousness, and Safety Risk of ED in Service Members (n = 68)*

| Characteristics  | n  | %    |
|--|----|------|
| ED cases personally experienced in service members             |    |      |
| < 5  | 18 | 26.5 |
| 5 – 10   | 19 | 27.9 |
| 11 – 20  | 18 | 26.6 |
| > 20   | 13 | 19.1 |
| Over time, have ED cases decreased, stayed the same, increased |    |      |
| Decreased  | 6  | 8.8  |
| Not Changed  | 41 | 60.3 |
| Increased  | 21 | 30.9 |
| How much of a problem is ED                                    |    |      |
| Not a problem  | 8  | 11.8 |
| Small problem  | 34 | 50.0 |
| Moderate problem   | 25 | 36.8 |
| Serious problem  | 1  | 1.5  |
| Risk of injury to service members exhibiting ED                |    |      |
| No risk  | 2  | 2.9  |
| Slight Risk  | 35 | 51.5 |
| Moderate Risk  | 22 | 32.5 |
| High Risk  | 9  | 13.2 |
| Risk of injury to OR or PACU staff from ED                     |    |      |
| No risk  | 3  | 4.4  |
| Slight risk  | 38 | 55.9 |
| Moderate risk  | 19 | 27.9 |
| High risk  | 8  | 11.8 |

Table 4

*Behaviors and Behavioral Consequences Related to ED in Service Members (n = 68)*

| Behavior or consequence      | How often seen? |             |                   |            |             |
|------------------------------|-----------------|-------------|-------------------|------------|-------------|
|                              | Never<br>%      | Rarely<br>% | Occasionally<br>% | Often<br>% | Always<br>% |
| Uncontrollable               | 13.2            | 41.2        | 35.3              | 8.8        | 1.5         |
| Threatens staff safety       | 8.8             | 45.6        | 35.3              | 8.8        | 1.5         |
| Vocally abusive              | 11.8            | 47.1        | 29.4              | 11.8       | 0.0         |
| Threatens own safety         | 7.4             | 35.3        | 35.3              | 20.6       | 1.5         |
| Panic stricken               | 10.3            | 22.1        | 44.1              | 19.1       | 4.4         |
| Combative towards staff      | 8.8             | 27.9        | 38.2              | 22.1       | 2.9         |
| Makes care more difficult    | 10.3            | 22.1        | 41.2              | 22.1       | 4.4         |
| Hyperactive motor behavior   | 8.8             | 20.6        | 38.2              | 26.5       | 5.9         |
| Pull at monitoring equipment | 5.9             | 25.0        | 35.3              | 29.4       | 4.4         |
| Requires additional staff    | 4.4             | 20.6        | 38.2              | 29.4       | 7.4         |
| Disruptive Movements         | 2.9             | 19.1        | 38.2              | 32.4       | 7.4         |

Note. \*Rank order from least to greatest in terms of how often seen combining often and always.

### **Secondary Aim: Anesthetics Related to ED**

Table 5 displays the results for question 22 which asked the respondent to identify any anesthetic agents they perceived could be related to the development of ED. Of the 68 respondents who have personal experience with ED, 44 (64.7%) reported their belief that ED could be related to the type of anesthetic used. The frequencies and percentages in Table 5 are based on the 44 respondents who reported that ED could be related to the type of anesthetic used. The most frequently cited anesthetics were potent inhalational agents (88.6%) and ketamine.

### **Secondary Aim: Physiologic Factors Related to ED**

Table 6 displays the results for question 23 which asked the respondent to identify any physiological factors they perceived could be related to the development of ED. Of the 68 respondents with a personal experience of ED, 59 (86.8%) reported that they believed ED could be related to a physiological factor. The frequencies and percentages in Table 6 are based on the 59 respondents who reported that ED could be related to a physiological factor. The majority of respondents identified age (<30 years), traumatic brain injury (TBI), and pain as possible physiological factors related to ED.

### **Secondary Aim: Psychological Factors Related to ED**

Table 7 displays the results for question 24 which asked the respondent to identify any preexisting psychological factors they perceived could be related to the development of ED. Of the 68 respondents with a personal experience of ED, 66 (97.1%) reported that they believed ED could be related to a psychological factor. The frequencies and percentages in Table 7 are based on the 66 respondents who reported that ED could be related to a psychological factor. Over 80% of the respondents identified PTSD and anxiety as possible psychological factors related to ED.

Table 5

*Anesthetic Agents Believed to be Related to ED (n = 44)*

| Anesthetic Agent              | n  | %    |
|-------------------------------|----|------|
| Potent inhalational agents    | 39 | 88.6 |
| Ketamine                      | 28 | 63.6 |
| Benzodiazepines               | 12 | 27.3 |
| Nitrous oxide                 | 8  | 18.1 |
| Anticholinergics              | 8  | 18.1 |
| TIVA                          | 6  | 13.6 |
| Barbiturates                  | 2  | 4.5  |
| Potent opioids                | 2  | 4.5  |
| Neuromuscular blocking agents | 1  | 2.3  |
| Anticholinesterases           | 2  | 4.5  |
| Other                         | 6  | 13.6 |

Note. \* Other responses included, “Lack of adequate narcotic use,” “Not enough narcotic and emerging too quickly,” “Sevo and Des,” “Specific PIA Desflurane,” “Specifically Sevoflurane.” Respondents could select more than one response.



Table 6

*Physiological Factors Believed to be Related to ED (n = 59)*

| Factor                                 | n  | %    |
|--|----|------|
| Age (< 30 years)                       | 34 | 57.6 |
| TBI                                    | 32 | 54.2 |
| Pain                                   | 31 | 52.5 |
| Medication other than anesthetics used | 23 | 38.9 |
| Long duration of surgery               | 17 | 28.8 |
| Type of surgery                        | 10 | 16.9 |
| Short duration of surgery              | 3  | 5.1  |
| Age (> 30 years)                       | 1  | 1.7  |
| Other                                  | 12 | 20.3 |

Note. \*Other significant responses included, “Obstructive Sleep Apnea,” “My limited experience is that ED happens more with my patients who have mod-severe PTSD and/or TBI,” “...Sleep deprivation, combat environment requiring constant vigilance.” Respondents could select more than one response.

Table 7

*Psychological Factors Believed to be Related to ED (n = 66)*

| Implication                       | n  | %    |
|-----------------------------------|----|------|
| PTSD                              | 58 | 88.0 |
| Anxiety                           | 56 | 84.8 |
| Depression                        | 33 | 50.0 |
| Pain                              | 30 | 45.0 |
| Medication other than anesthetics | 25 | 37.9 |
| Other                             | 2  | 3.0  |

Note. \*Other responses include, "I believe it could also be related to how safe they feel immediately prior to induction," "Violent and unpleasant personality." Respondents could select more than one response.

## **Secondary Aim: Interventions That May Alleviate ED Symptoms Arising During Anesthesia**

Table 8 displays the results for question 26 which asked the respondent to identify any interventions perceived to have helped reduce or prevent ED symptoms while the service member is undergoing anesthesia. Of the 68 respondents with a personal experience of ED, 61 (89.7%) identified one or more interventions. The frequencies and percentages in Table 8 are based on the 61 respondents who identified one or more such interventions. The interventions that were identified most frequently included talking to the service member during an ED episode, administration of an analgesic, or doing nothing and allowing the tincture of time to alleviate any signs and symptoms.

## **Secondary Aim: Interventions That May Reduce or Prevent ED before Anesthesia**

Table 9 displays the results for question 28 which asked the respondent to identify any interventions that helped to reduce or prevent ED symptoms before the service member undergoes anesthesia. Of the 68 respondents with a personal experience of ED, 54 (79.4%) identified one or more interventions. The frequencies and percentages in Table 9 are based on the 54 respondents who identified one or more such interventions. The interventions that were identified most frequently included talking to the service member before anesthesia about the upcoming intervention, actively listening to the patient, or increasing the dose of midazolam.

## **Final Aim: Relationship of Perceived Seriousness of ED and Reporting of Case Experience, ED Behaviors, and Physiological/Psychological Factors Related to ED**

The final secondary aim of the study investigated the relationship between perceived seriousness of ED and the reporting of ED case experience, behaviors and behavioral consequences of ED, and physiological and psychological factors related to ED. For these relationships,

Table 8

*Interventions Perceived to have Helped Alleviate ED Symptoms during Anesthesia (n = 61)*

| Intervention                                      | n  | %    |
|---|----|------|
| Administer a benzodiazepine                       | 40 | 65.0 |
| Talk to patient during episode                    | 31 | 51.0 |
| Analgesic   | 25 | 41.0 |
| Nothing, allow tincture of time to alleviate      | 21 | 34.4 |
| Induction agent to deepen PT                      | 17 | 27.9 |
| Haloperidol                                       | 4  | 6.5  |
| Diphenhydramine                                   | 4  | 6.5  |
| Deepen anesthetic utilizing PIA's                 | 0  | 0.0  |
| Other   | 19 | 31.1 |
| Precedex (Dexmedetomidine)                        | 4  | 6.5  |
| Have family or, "battle buddy"<br>present in PACU | 4  | 6.5  |
| Extubate deep if not contraindicated              | 2  | 3.3  |
| Propofol on emergence                             | 2  | 3.3  |
| Droperidol  | 2  | 3.3  |
| Use longer acting PIA (Isoflurane)                | 1  | 1.6  |

Table 9

*Preoperative Interventions Perceived to have Helped Reduce or Prevent ED (n = 54)*

| Intervention  | n  | %    |
|---|----|------|
| Talk to the service member with an emphasis on explaining everything that will occur from start of IV to waking up                    | 49 | 90.7 |
| Listening to service member with an emphasis on allowing the service member to verbalize fears of the unknown and of past experiences | 44 | 81.2 |
| Giving more midazolam   | 29 | 53.7 |
| Ketamine  | 9  | 16.7 |
| Giving less midazolam   | 5  | 9.2  |
| Eliminate midazolam completely  | 4  | 7.4  |
| Diphenhydramine   | 1  | 1.9  |
| Haloperidol   | 0  | 0.0  |
| Droperidol  | 1  | 1.9  |
| Other   | 12 | 22.2 |

Note. \* Other comments included, “Precedex seems to keep them calm and quiet,” “Using longer acting opioids upfront along with shorter acting opioids during the case.” Respondents could select more than one response.

level of seriousness (question 18) are categorized into two categories: minor (includes not a problem and small problem) and moderate (includes moderate problem and serious problem). These relationships are shown in Tables 10 – 13.

Table 10 shows a statistically significant association between perceived seriousness of ED and respondents ED case experience. Of the 42 respondents reporting that ED is a minor problem, 40.5% of them reported their personal experience with ED was limited to less than five cases. For the 26 respondents reporting that ED is a serious problem, all but one of them reported case experience of five or more.

Associations between perceived ED severity and the ED behaviors and behavioral consequences seen most often are reported in Table 11. Respondents who perceived ED as a moderate problem reported observing the listed behaviors and consequences more often than those who perceived ED as a minor problem with the exception of threatens staff safety. The behaviors reported most often by those who perceived ED a serious problem were pulling at monitoring equipment and disruptive movements. For those who considered ED a minor problem, disruptive movements and require additional staff were seen most often. Statistically significant differences occurred between ED severity groups on making care more difficult, pulls at monitoring equipment, and disruptive movements.

Associations between perceived ED severity and physiological factors reported to be associated with ED are presented in Table 12. Physiological factors reported most often by both severity groups included traumatic brain injury, pain, and younger age. There were no statistically significant differences between severity groups on any of the physiological factors.

Associations between perceived ED severity and psychological factors reported to be associated with ED are presented in Table 13. Psychological factors reported most often by both

severity groups included post traumatic stress and anxiety. There were no statistically significant differences between severity groups on any of the psychological factors.

Table 10

*Association of ED Case Experience and ED Severity (n = 68)*

| Variable    | ED Case Experience |            | Totals     | $\chi^2$ | p    |
|-------------|--------------------|------------|------------|----------|------|
|             | <5                 | $\geq 5$   |            |          |      |
| ED Severity |                    |            |            |          |      |
| Minor       | 17 (40.5%)         | 25 (59.5%) | 42 (61.8%) | 11.07    | .001 |
| Moderate    | 1 (3.8%)           | 25 (96.2%) | 26 (38.2%) |          |      |



Table 11

*Association of ED Severity and Behaviors or Consequences Seen Most Often as a Percentage (n = 68)*

| Behavior or consequence       | ED Severity      |                     |
|-------------------------------|------------------|---------------------|
|                               | Minor<br>(n =42) | Moderate<br>(n =26) |
| Disruptive Movements          | 26.2             | 61.5**              |
| Requires additional staff     | 33.3             | 42.3                |
| Pulls at monitoring equipment | 16.7             | 61.5*               |
| Hyperactive motor behavior    | 23.8             | 46.2                |
| Makes care more difficult     | 16.7             | 42.3*               |
| Panic Stricken                | 16.7             | 34.6                |
| Combative towards staff       | 23.8             | 26.9                |
| Threatens own safety          | 14.3             | 34.6                |
| Vocally abusive               | 7.1              | 19.2                |
| Threatens staff safety        | 11.9             | 7.7                 |
| Uncontrollable                | 9.5              | 11.5                |

\*p<.05. \*\*p<.01.

Table 12

*Association of ED Severity and Physiological Factors Believed Related to ED as a Percentage (n = 59)*

| Physiological Factor                  | ED Severity       |                      |
|---------------------------------------|-------------------|----------------------|
|                                       | Minor<br>(n = 36) | Moderate<br>(n = 23) |
| Age ( $\leq 30$ years)                | 50.0              | 65.2                 |
| Traumatic brain injury                | 50.0              | 60.9                 |
| Pain                                  | 50.0              | 56.5                 |
| Medication other than anesthetic used | 38.9              | 39.1                 |
| Long duration of surgery              | 27.8              | 30.4                 |
| Type of surgery                       | 13.9              | 17.4                 |
| Short duration of surgery             | 5.8               | 4.3                  |
| Age ( $> 30$ years)                   | 2.8               | 0.0                  |
| Other                                 | 19.4              | 8.7                  |

Table 13

*Association of ED Severity and Psychological Factors Believed Related to ED as a Percentage (n = 66)*

| Psychological Factor              | ED Severity       |                      |
|-----------------------------------|-------------------|----------------------|
|                                   | Minor<br>(n = 41) | Moderate<br>(n = 25) |
| Post traumatic stress             | 85.4              | 92.0                 |
| Anxiety                           | 80.5              | 92.0                 |
| Depression                        | 51.2              | 48.0                 |
| Pain                              | 39.0              | 56.0                 |
| Medications other than anesthetic | 31.7              | 48.0                 |
| Other                             | 2.1               | 4.0                  |

## Chapter 5: Discussion

Anesthesia providers are in the forefront of caring for service members with ED. Little is known regarding service members and ED following general anesthesia. To gain a better understanding of ED in this particular patient population, the study's primary aims were to determine, through active duty Army anesthesia provider's perceptions, the following: 1) extent and seriousness of ED in service members; 2) effects of ED on the safety of service members and OR/PACU personnel and 3) behaviors relevant to ED in service members. In addition to these primary aims, the study also focused on identifying through provider's perceptions, the following potential factors which may lead to the development of ED or to the alleviation of ED: 1) type of anesthetic agents; 2) physiological factors; 3) psychological factors; and 4) interventions used for alleviating the symptoms of ED. A final aim was to investigate through provider's perceptions, the relationship between perceived seriousness of ED and reported case experience, behaviors and consequences relevant to ED, and physiological and psychological factors related to the development or alleviation of ED symptoms.

As of June 2011, all active duty Army anesthesia providers (254) were invited to participate in the study's survey. In the target population of 254 Army anesthesia providers, 98 (38.6%) were anesthesiologists and 156 (61.4%) were nurse anesthetists. Completed surveys were received from 87, which represented an overall response rate of 34%. Of the 87 respondents in the study sample, 22 were anesthesiologists and 65 were nurse anesthetists. The response rate for anesthesiologists was 22.4% and 41.7% for nurse anesthetists. The majority of those surveyed had practiced anesthesia for over 5 years in the United States, been on active duty greater than 5 years, and had deployed and seen ED at some point in their career.

## **Practice Characteristics**

Routine screening for either PTSD or TBI did not occur in the years 2005 - 2007 when the study's author was deployed as a nurse anesthetist. Over 68% of the providers in the current study reported screening for both PTSD and TBI. Of those who had experienced ED in their practice, almost all of them administer a benzodiazepine with the majority giving 1 -2 mg of midazolam preoperatively to their patients. This finding is important because two recent studies found a statistically significant relationship between the administration of a benzodiazepine and the occurrence of ED (Lepouse et al., 2006; Radtke et al., 2010). Bremner et al. (2000) found that there are alterations in the benzodiazepine receptors in those diagnosed with PTSD which further substantiates the evidence found with the Lepouse et al. (2006) and Radtke et al. (2010) studies. These findings are in sharp contrast to the White (1982) and McGuire and Burkard (2010) studies where patients emerging in a state of delirium are given a benzodiazepine. Their study does not report whether or not benzodiazepine administration is beneficial, but rather it is part of their standard operating procedure to give a benzodiazepine where ED is present in the PACU.

McGhee et al. (2008) showed that the use of ketamine lowered PTSD prevalence rates following surgery in service members. This potential linkage between ketamine and PTSD suggests that ketamine could be used to treat service members with known PTSD and ED (McGuire & Burkard, 2010; Wilson & Pokorny, 2011). However, Schonenberg et al. (2005 and 2008), and Winter and Irle (2004) reported that giving ketamine to service members with PTSD can aggravate or make worse their symptomatology. Ketamine use was assessed and for those who had experienced ED, almost half of the providers never or rarely used ketamine. Only 13% of providers who had experience with ED used it routinely.

The final practice characteristic identified was the type of anesthetic utilized while deployed. The majority of providers who had experienced ED used PIA Sevoflurane or Isoflurane (53%) or TIVA (25%) while deployed. Two studies have reported a link between PIA use and ED in pediatric cases (Uezono et al., 2000; Nakayama, Furukawa & Yanai, 2006). It is not known if this link between PIA use and ED occurs in service members.

**Primary Aim: Extent, Seriousness, and Safety Risk of ED in Service Members**

This study found that over 78% of active duty Army anesthesia providers have witnessed ED in their particular practice. Over half of the respondents experienced 10 or fewer cases of ED, and 19% experienced more than 20 ED cases. Only a few recent studies have examined ED in the adult population (Rose, 1996; Lepouse et al., 2006; Radtke, et al., 2010; Yu et al., 2010) and only two that have examined ED in a military population (McGuire & Burkard, 2010; Wilson & Pokorny, 2011). The extent of ED within the adult population is between 3% and 8.4% (Lepouse et al., 2006; Radtke et al., 2010; Yu et al., 2010). The studies pertaining to the military population did not have an estimate as to the extent of ED although it was reported in the McGuire and Burkard (2010) study that part of their unpublished data from 2009 estimated that ED was present in 29% of service members who had deployed. No other information was provided in regards to the how the 29% was determined.

Approximately 38% of the respondents felt that ED was a moderate problem. There was a statistically significant association between perceived severity of ED and ED case experience. Almost all of the providers who reported that ED was a moderate or serious problem had experience with 5 or more cases of ED, while those who reported that ED is not a problem or only a small problem, 41% of them reported experience with less than five ED cases. In terms of safety risk, approximately 47% felt that the risk of injury to the service member with ED was

moderate or serious, while 40% reported that the risk of injury to OR or PACU staff from service members with ED was moderate or high.

The evidence from this study and the few published studies that examined ED in adults suggests that ED may range from 3% to 8.4% in adults and as high as 29% in deployed service members. Over three-fourths of the anesthesia providers in this study had experienced one or more cases of ED in service members, with 46% of the providers with ED case experience reporting personal experience with 11 or more cases of ED. Over 40% of the providers with ED case experience reported that the risk of injury to the service member or to the OR/PACU staff was moderate to high in cases with ED.

### **Primary Aim: Behaviors and Behavioral Consequences Related to ED**

There have been no published studies examining the actual behaviors and consequences seen with ED in adults or service members. This study asked providers who had personal experience to indicate how frequently they had seen any of a list of possible ED behaviors or consequences of ED behavior. ED related behaviors never seen or rarely seen by a majority of the providers included the service member acting in an uncontrollable manner or being vocally abusive. The behaviors which were often seen or always seen included hyperactive motor behavior, pulling at the monitoring equipment, and making disruptive movements. The consequences of ED that was seen most often included behavior that made the patient's care more difficult and behavior that required additional staff. The two ED behavioral consequences that were never or rarely seen included behavior that threatened staff safety or the patient's safety. However, both of these consequences were still seen either occasionally, often, or always by more than 47% of the providers. The evidence from this study suggests that ED behaviors are not usually violent and do not often threaten the safety of the patient or the staff. However,

the behaviors can often be disruptive which can make the care of the patient more difficult, and often requires additional staff. The evidence from this study also suggests that more violent behavior, in the form of vocal abuse and combativeness towards the provider and staff, does occur and needs to be addressed.

### **Secondary Aim: Anesthetic Implications for ED**

The current study found that the majority of anesthesia providers with ED case experience believed ED could be related to the anesthetic used. The anesthetic identified most strongly as potentially related to ED were potent inhalation agents (PIA's). Two pediatric studies have found a similar correlation between PIA and ED (Uezono et al., 2000; Nakayama, Furukawa & Yanai, 2006). Recent studies have also shown there to be a correlation between better emergence from general anesthesia utilizing TIVA versus PIA in adults (Lepouse et al., 2006; Yu et al., 2010; Wilson & Pokorny, 2011). However, Radtke et al. (2010) found no difference between type of anesthetic used and the occurrence of ED. Ketamine use was also identified as being related to ED by a majority of the providers. Recent studies have shown that ketamine use, in pediatrics populations, lowers the incidence of ED (Kawaraguchi et al., 2002; Abu-Shahwan & Chowdary, 2007). There is evidence that the type of anesthetic used is related to ED in adults and children, but there are no studies that have looked at type of anesthetic used and ED in service members.

### **Secondary Aim: Physiological and Psychological Factors Related to ED**

Most of the providers with ED case experience believed there were physiological factors and psychological factors related to ED. Three physiological factors - TBI, pain, and younger age - were identified by a majority of providers. Two psychological factors – PTSD and anxiety



- were identified by over 80% of the providers. No studies have been found that examined risk factors for ED development in service members.

### **Secondary Aim: Interventions for Treatment and Prevention of ED**

Over ninety percent of the providers with ED case experience reported that they intervened when their patients showed behaviors related to ED. The majority of the providers said they talked to the patient during the ED episode. Administering an analgesic for pain and doing nothing were used by 41% and 34% of the providers, respectively. Almost 80% of the providers reported that they used pre-operative interventions to help prevent ED or minimize the effects of ED. The most common pre-operative intervention was talking to the patient about the details of the anesthetic procedure and answering questions about the upcoming intervention. A majority of the providers reported that they gave more midazolam to patients that they suspected were at risk for ED. No studies have been found that have evaluated interventions for the treatment or prevention of ED in service members. Two studies on adults suggested not administering benzodiazepines (Lepouse et al., 2006) or avoiding certain induction agents such as etomidate (Yu et al., 2010) may prevent ED.

### **Final Aim: Relationship of Perceived Seriousness of ED and Reporting of Case Experience, ED Behaviors, and Physiological/Psychological Factors Related to ED**

It has been shown that of those providers with ED case experience; thirty eight percent of them consider ED to be a moderate or serious problem. Of those providers who reported that ED was a moderate/serious problem, almost all of them reported personal ED experience with 5 or more cases, while those providers who consider ED to be a minor problem were more likely to have experience with fewer than 5 ED cases. This secondary aim examines whether providers who consider ED more serious report different experiences with ED – behaviors/consequences

related to ED and perceptions of risk factors for ED – than providers who consider ED less serious. When comparing observed ED behaviors and behavioral consequences, those who considered ED more serious reported seeing more incidents of pulling at the monitoring equipment and disruptive movements that resulted in making the patient’s care more difficult than those who considered ED less serious. Interestingly, when comparing judgment regarding physiological and psychological factors that could be related to ED, provider’s who considered ED more serious identified the same risk factors as those who considered ED less serious.

### **Study Strengths and Limitations**

A major strength of this study was the ability to reach a broad audience all over the World via an electronic survey. Respondents included both anesthesiologists and nurse anesthetists. Of the 89 providers who responded to the survey, only two surveys had to be discarded because of extensive missing data. The questionnaire was designed using Dillman’s tailored design methodology (Dillman, 2007), which has as its main goal the production of high quality information. Pilot testing with a sample of Army anesthetists helped to ensure that the survey questions had a common understanding among the respondents. The survey’s content carefully addressed crucial aims to provide information about prevalence and characteristics of ED; validity testing and statistical approach to the results obtained; comparison of data to that in the literature in order to substantiate and interpret; choice of a real and currently important topic that was shown to need more research.

The major limitation of the study was that the response rate was only 34% and there was no information on whether the characteristics and ED experience of the non-respondents was similar to the respondents. Even though a high proportion (78%) of the respondents had personal experience with ED, it is possible that those who did not respond were those with little or no

experience with ED. If we assume that none of the 167 non-respondents had any personal experience with ED, the proportion of providers who had experienced ED would be 27%, a very different result compared to the 78% found in the study.

Another limitation relates to the lack of a standard definition for ED in the adult population, and in particular, for those service members who served or continue to serve during the GWOT. Even though the survey provided a definition of ED, the identification of an ED case by one provider does not ensure that another provider would identify the same case as an ED case. This lack of standardization also applies to the criteria that providers used to determine the level of ED seriousness. For example: One provider's identification that certain observed ED behaviors represent a moderate problem, may elicit a response from another provider observing the same behaviors that it is only a small problem. Overall, a major limitation was the studies restriction to observational and associated events in line with the aims. This is both a limitation and strength. That is, the study was careful to focus on what was needed as a first step in the understanding of events related to ED from the Wilson's clinical model for emergence delirium.

### **Future Research Implications**

Although the evidence from this study of anesthesia providers suggests that ED may be widespread among service members that have served and continue to serve during the GWOT, data is lacking from individual cases. Another important step would be a service-wide case review of anesthetic interventions in service members to determine the extent and seriousness of ED among this population of service members. This study also suggests that anesthesia providers believe strongly that TBI and PTSD are related to the development of ED. There is a growing realization of the seriousness of TBI and PTSD in service members. To determine the

role of TBI and PTSD in ED, longitudinal cohort studies need to be implemented so that the relative risk of these factors in the development of ED can be determined.

There is a need to design and test randomized controlled interventions to determine the role of different types of anesthesia on the development of ED. A large multi-site trial could include subjects with PTSD, TBI, anxiety, pain, and normal controls and different types of anesthesia to determine any differential effects of anesthesia type and patient characteristics on the development of ED. A similar design approach could be applied to the role of confounders such as ancillary drugs and age.

There is also a need to develop a prospective clinical database involving all military anesthesia providers that could collect demographic, psychological, and physiological information on all service members undergoing anesthesia. In addition, type of anesthesia used, dose, length of anesthesia exposure, and such outcome information as occurrence of ED and type ED behaviors, length of stay, and follow-up studies of quality of life data could be collected if standard practice guidelines were defined a priori. This kind of longitudinal data would provide answers to many of the unanswered questions that we currently have regarding ED.

### **Implications for Professional Practice**

This study was not designed to make recommendations for clinical practice. The major implication from this study is that ED may be widespread, is a moderate problem, and that patients exhibiting ED behaviors may require additional staff to adequately care for them. For a sizeable minority of ED cases, the resulting ED behaviors may threaten both the patient and staff safety. The strongest implication from this study are: 1) a lack of evidence at the patient-level regarding the extent and seriousness of ED, and 2) the anesthetic, physiological, and

psychological factors that may be related to the development of ED or to the alleviation of ED in service members. In essence, this study is perhaps the first to offer a data-based approach to both the recognition of ED and to identification of factors important for its management in practice.

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# APPENDIX A: INSTITUTIONAL REVIEW BOARD APPROVAL LETTER



## EAST CAROLINA UNIVERSITY

University & Medical Center Institutional Review Board Office  
IL-09 Brody Medical Sciences Building • 600 Moye Boulevard • Greenville, NC 27834  
Office 252-744-2914 • Fax 252-744-2284 • www.ecu.edu/irb

TO: J. Tyler Wilson, Graduate Student, College of Nursing, ECU  
FROM: UMCIRB  
DATE: June 14, 2011  
RE: Expedited Category Research Study  
TITLE: "Potential Factors Influencing Emergence Delirium following General Anesthesia in Service Personnel who have served during the Global War on Terrorism"

### UMCIRB #11-0354

This research study has undergone review and approval using expedited review on 6/14/11. This research study is eligible for review under an expedited category number 7: research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. The Chairperson (or designee) deemed this **unfunded study no more than minimal risk** requiring a continuing review in **12 months**. Changes to this approved research may not be initiated without UMCIRB review except when necessary to eliminate an apparent immediate hazard to the participant. All unanticipated problems involving risks to participants and others must be promptly reported to the UMCIRB. The investigator must submit a continuing review/closure application to the UMCIRB prior to the date of study expiration. The investigator must adhere to all reporting requirements for this study.

**\*\*\*Approval to begin the study procedures will be dependent upon documentation that the Army approves the conduct of this study. A copy of this documentation from the Army should be forwarded to the UMCIRB by the PI.**

The above referenced research study has been given approval for the period of 6/14/11 to 6/13/12. The approval includes the following items:

- Internal Processing Form (received 5/26/11)
- Email invitation (received 5/26/11)
- Survey (received 5/26/11)

The Chairperson (or designee) does not have a potential for conflict of interest on this study.

**The UMCIRB applies 45 CFR 46, Subparts A-D, to all research reviewed by the UMCIRB regardless of the funding source. 21 CFR 50 and 21 CFR 56 are applied to all research studies under the Food and Drug Administration regulation. The UMCIRB follows applicable International Conference on Harmonisation Good Clinical Practice guidelines.**

IRB00000705 East Carolina U IRB #1 (Biomedical) IORG00000418  
IRB00003781 East Carolina U IRB #2 (Behavioral/SS) IORG00000418  
IRB00004973 East Carolina U IRB #4 (Behavioral/SS Summer) IORG00000418  
Version 3-5-07

UMCIRB #11-0354  
Page 1 of 1

## **APPENDIX B: COMMUNICATION FROM THE ARMY FOR APPROVAL**

Classification: UNCLASSIFIED

Caveats: NONE

LTC Loughren,

Thank you!

MAJ Wilson, you may proceed.

Morris

Morris Peterson

Chief, Army Personnel Survey Office

U.S. Army Research Institute

2530 Crystal Drive (Taylor Building, 4th Floor)

2511 Jefferson Davis Highway (U.S.P.S. mail only) Arlington, VA

22202-3926

(703) 602-7858 or (703) 545-2354

DSN 332-7858

Fax (703) 602-7706

## APPENDIX C: LETTERS WRITTEN TO ARMY ANESTHESIA PROVIDERS

01 August 2011 (Monday) @ 1326

Title: Anesthesia Emergence Delirium Survey

Dear Fellow Anesthesia Provider,

In a few days, you will receive an email invitation from a site titled, "Survey Monkey". This survey relates directly to the field of anesthesia with an emphasis on emergence delirium (ED). I hope you will take the 10 – 15 minutes necessary to complete the survey which will add to the body of knowledge regarding ED following general anesthesia.

The institutional review board at East Carolina University as well as the Army Personnel Survey Office at the U.S. Army Research Institute has approved this survey. The survey is completely voluntary and confidential. No respondent will be identified by name and results will be reported statistically.

The responses will be used for partial PhD fulfillment. A high number of responders will strengthen statistical analysis of data for my dissertation. If you do not wish to participate, there will be a link in the survey to be automatically withdrawn from receiving future emails. For general questions regarding the survey, you may email me directly at: [john.tyler.wilson@us.army.mil](mailto:john.tyler.wilson@us.army.mil) or [wilsonj08@ecu.edu](mailto:wilsonj08@ecu.edu)

Survey monkey utilizes user, physical, network, storage, organizational and software security. If you have any technical questions regarding the tool utilized for the ED survey, you may contact survey monkey directly at: [support@surveymonkey.com](mailto:support@surveymonkey.com)

I thank you in advance for taking the time to complete this worthwhile survey which will aid in the advancement of knowledge regarding ED following general anesthesia.

Sincerely,

J. Tyler Wilson, CRNA, PhD(c)

Major/AN

03 August 2011

Title: Emergence Delirium Survey

Dear Colleague,

I need your help in exploring behavior of military members following general anesthesia.

From my personal experiences and from other anesthesia providers, there seems to be an increasing incidence in military members exposed to wartime stresses, of waking from general anesthesia in an extremely agitated and oftentimes violent state of behavior. There is very little research evidence with service members on the extent and effects of this type of behavior, referred to as emergence delirium (ED).

The purpose of this survey is to explore your personal experiences with ED in service personnel, to determine the extent of ED, the effect of ED on patient and staff safety, the existence of any physical or psychological factors that may be associated with the occurrence of ED, whether you have found any interventions to moderate the symptoms of ED, and to identify the particular behaviors that you observed in personnel with ED.

This survey can be completed within ten to fifteen minutes. Your participation is voluntary but vital. The link to the survey: [SurveyLink]

Please note: If you do not wish to receive further emails from us, please click the link below, and you will be automatically removed from our mailing list; [RemoveLink]

Thank you very much,

J. Tyler Wilson, CRNA, PhD(c)

Major/AN

10 August 2011 @ 0545

Title: Emergence Delirium Survey Reminder

Dear Colleague,

My sincere appreciation to those who have completed the survey on Emergence Delirium(ED). Your prompt response emphasizes the importance of ED to our practice of anesthesia.

For those who have not had time to complete the survey, may I request a few minutes of your time to do so. Additional responses will strengthen statistical analysis of the data. A copy of the survey is attached to this email via the following link: [SurveyLink]

My hope is that potential findings from this project will increase support for future research on the cause and treatment of ED in service members. I thank you in advance for a response to this request.

Best regards,

J. Tyler Wilson, CRNA, PhD(c)

Major/AN

To no longer be included in this survey, the link to opt out is: [RemoveLink]

17 August 2011 @ 0545

Dear Anesthesia Provider,

During the past few weeks you received emails requesting participation in a survey that I am conducting on the phenomena of emergence delirium (ED). Your responses will be used to prepare my PhD dissertation.

The survey will be closing in two weeks (31 August 2011). If you haven't had the opportunity to complete the survey, please take a moment to do so. Your responses are crucial to enhance understanding of ED and the role of general anesthesia. The direct link to the survey is: [SurveyLink]

Thank you very much for your time,

J. Tyler Wilson, CRNA, PhD(c)  
Major/AN

Please note that this survey is both voluntary and confidential. If you wish to receive no further emails regarding this study, please click on the following tab: [RemoveLink]

24 August 2011 @ 0545

Title: Last week to complete Emergence Delirium Study

Dear Colleague,

I need your help in exploring behavior of military members following general anesthesia. This survey will be closing on 31 August 2011. The direct link to the survey is: [SurveyLink]

From my personal experiences and from other anesthesia providers, there seems to be an increasing incidence in military members exposed to wartime stresses, of waking from general anesthesia in an extremely agitated and oftentimes violent state of behavior. There is very little research evidence with service members on the extent and effects of this type of behavior, referred to as emergence delirium (ED).

The purpose of this survey is to explore your personal experiences with ED in service personnel, to determine the extent of ED, the effect of ED on patient and staff safety, the existence of any physical or psychological factors that may be associated with the occurrence of ED, whether you have found any interventions to moderate the symptoms of ED, and to identify the particular behaviors that you observed in personnel with ED.

This survey can be completed within ten to fifteen minutes. Your participation is voluntary but vital. Again, the link to the survey is: [SurveyLink]

Thank you very much,

J. Tyler Wilson, CRNA, PhD(c)

Major/AN

Please note: If you do not wish to receive further emails from us, please click the link below, and you will be automatically removed from our mailing list: [RemoveLink]



## APPENDIX D: SURVEY

### 1. Emergence Delirium: A patient safety questionnaire for military anesthesia...

Service members for this study are defined as: Any man or woman who has deployed in support of the Global War on Terrorism. Global War on Terrorism is synonymous with Overseas Contingency Operation and starts from 11 Sept 2001 to present day.

## 2. Demographic information:

### 1. What is your professional designation?

- A. Anesthesiologist  
 B. Nurse Anesthetist

### 2. What is your gender?

- A. Male  
 B. Female

### 3. How many total months or years have you been practicing anesthesia?

- 0 - 11 Months  
 1 - 2 Years  
 2 - 5 Years  
 5 - 10 Years  
 10 - 20 Years  
 Greater than 20 Years

### 4. As of today, how many months or years have you been on active duty?

- 0 - 11 Months  
 1 - 2 Years  
 2 - 5 Years  
 5 - 10 Years  
 10 - 20 Years  
 Greater than 20 Years

### 5. Where are you currently practicing?

- Medical Center in United States  
 Medical Center Abroad (non war zone)  
 Community hospital in United States  
 Community hospital Abroad (non war zone)  
 Iraq  
 Afghanistan  
 Kuwait

Other (please specify)

**6. As of today, how many total MONTHS have you deployed during the GWOT (i.e. since 11 Sept 2001)? If zero, please write in the numerical "0".**

### 3. Anesthesia Practice Characteristics

**7. During your preanesthetic evaluations of service members, do you routinely screen for post-traumatic stress disorder (PTSD), traumatic brain injury (TBI), both of these, or none of these?**

- PTSD
- TBI
- Both of these
- None of these

**8. Do you routinely administer a benzodiazepine, such as midazolam, preoperatively?**

- A. Yes
- B. No (skip next question)

**9. What dose of the most commonly used benzodiazepine (midazolam) do you routinely give to the average adult preoperatively? Please estimate in milligrams.**

- Less than 1 mg
- 1 - 2 mg
- 3 - 4 mg
- > 4 mg
- Do not routinely administer Midazolam

**10. How often do you utilize ketamine when providing anesthesia to service members?**

- Never (Please move to question 12)
- Rarely
- Occasionally
- Routinely

**11. When utilizing ketamine with service members, which of the following are your routine practices? (Select all that apply.)**

- Use Ketamine to induce general anesthesia alone
- Mix Ketamine with another compound such as propofol to induce general anesthesia
- Administer subanesthetic doses of Ketamine during an anesthetic
- Administer Ketamine orally with Midazolam prior to an anesthetic
- Administer Ketamine orally without Midazolam prior to an anesthetic
- Administer Ketamine intramuscular (IM) preoperatively with Midazolam
- Administer Ketamine intramuscular (IM) preoperatively without Midazolam

Other (please specify)

**12. Which of the following analgesics do you routinely use in your practice? (Select all that apply).**

- Morphine
- Fentanyl
- Sufentanyl
- Remifentanyl
- Demerol
- Dilaudid

Other (please specify)

**13. While deployed, which of the following anesthetics did you routinely utilize? (Select all that apply).**

- Never deployed
- Potent inhalational agent (PIA) utilizing Sevoflurane most often
- PIA utilizing Isoflurane most often
- PIA utilizing Desflurane most often
- Total Intravenous Anesthesia (TIVA)
- Other (please specify)

**14. When providing anesthesia to service members, have you observed differences in waking up from those receiving Total Intravenous Anesthesia (TIVA) compared to those receiving Potent Inhalational Anesthesia (PIA)?**

- No difference between TIVA and PIA on waking status
- Yes, service members receiving TIVA wake more smoothly
- Yes, service members receiving PIA wake more smoothly

#### 4. Emergence delirium as it pertains to service personnel

For the purpose of this study, emergence delirium(ED)is defined as: Upon emerging from general anesthesia, the service member is seen thrashing around in a violent manner (to include pulling at monitoring equipment, IV catheters, ETT's, drains, Foley catheter, etc), screaming, incoherent speech, hitting, biting, or attempts to leave the operating room (fall off narrow bed) encompassing any time period from end of surgery to discharge from PACU. Any one of these displayed behaviors or a combination can constitute ED.

##### 15. Have you personally experienced Emergence Delirium (ED) in your anesthesia practice with service members who have served during the GWOT?

- Yes
- No (it is not necessary for you to complete the remainder of the questionnaire. Please proceed to the end of the survey and click on the, "done" tab to close out the survey. Thank you for your time and consideration).

##### 16. To the best of your recollection, how many ED cases in service members have you personally experienced?

- Less than 5
- 5 - 10
- 11 - 20
- 21 - 30
- 31 or more

##### 17. Over the time you began providing anesthesia to service members who have deployed during the GWOT (since 11 Sept 2001)to the present, have you observed the number of ED cases decreasing, not changing, or increasing?

- Decreasing
- Not changing
- Increasing

##### 18. To what extent do you consider the ED behaviors that you have observed in service members to a be a problem?

|                   | Not a problem         | Small problem         | Moderate problem      | Serious problem       |
|-------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Please choose one | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

##### 19. For service members exhibiting one or more ED behaviors emerging from general anesthesia, what is the risk that the service members behavior could cause injury to themselves?

|                   | No risk               | Slight risk           | Moderate risk         | High risk             |
|-------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Please choose one | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

**20. For service members exhibiting one or more ED behaviors emerging from general anesthesia, what is the risk that the service members behavior could cause injury to the OR or PACU staff?**

Please choose one

|                       |                       |                       |                       |
|-----------------------|-----------------------|-----------------------|-----------------------|
| No risk               | Slight risk           | Moderate risk         | High risk             |
| <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

**21. For the service members that you observed exhibiting one or more ED behaviors, do you believe their ED could be related to the anesthetic used?**

- Yes
- No (please move to question 23)

**22. Which of the following anesthetic agents do you believe could be related to the development of ED in service members? (Please select all that apply)**

- Potent inhalational agents (PIA)
- Nitous Oxide
- Total Intravenous anesthetic (TIVA) utilizing propofol
- Benzodiazepines
- Ketamine
- Barbiturates
- Potent opioids
- Non-depolarizing neuromuscular blocking agents
- Anticholinergics
- Anticholinesterases

Other (please specify)



**23. For the service members that you observed exhibiting one or more ED behaviors, do you believe their ED could be related to any of the following physiological factors? (Please select all that apply)**

- Do not believe that ED is related to any physiological factor
- Traumatic brain injury
- Type of surgery
- Long duration of surgery (> 3 hours)
- Short duration of surgery (< 1 hour)
- Pain
- Young age (30 years old or less)
- Old age (> 30 years old)
- Medications patient is taking other than anesthetic

Other (please specify)

**24. For those service members that you observed exhibiting one or more ED behaviors, do you believe their ED could be related to any of the following preexisting psychological factors? (Please select all that apply)**

- Do not believe that ED is related to any preexisting psychological factors
- Post traumatic stress disorder
- Pain
- Anxiety
- Depression
- Medications patient is taking other than anesthetic

Other (please specify)

**25. For the service members that you observed exhibiting one or more ED behaviors, did you utilize any interventions to help alleviate their symptoms?**

- Yes
- No (Please go to question number 27)

**26. Which of the following interventions helped to alleviate the ED symptoms that you observed in service members (after ruling out hypoxia, hypercarbia, too much anesthetic still on board, etc)? (Please select all that apply)**

- Administer Haloperidol
- Administer Diphenhydramine
- Talk to the patient during episode (not preoperatively)
- Deepen anesthetic utilizing PIA's
- Deepen anesthetic utilizing an induction agent such as propofol
- Administer analgesic
- Administer a benzodiazepine
- Nothing (allow tincture of time to alleviate signs and symptoms)
- Other (please specify)

**27. For the service members that you observed exhibiting one or more ED behaviors in prior anesthetics, did you use any pre-operative interventions for future surgeries/anesthetics that helped reduce or prevent ED symptoms?**

- Yes
- No (Please go to question 29)

**28. Which of the pre-operative interventions helped to reduce or prevent ED symptoms in known service members with ED (documented from previous anesthetics)?**

- Talking to the patient with an emphasis on explaining everything you will do from the moment the IV is started to waking up in the OR/PACU.
- Listening to the patient with an emphasis on allowing the patient to verbalize fears of the unknown and of past experiences which may impact waking up such as bad dreams or flashbacks
- Giving more than your standard dose of versed
- Giving less than your standard dose of versed
- Eliminating versed all together
- Administering ketamine (< 1 mg/kg) IV
- Administering Diphenhydramine
- Administering Haloperidol
- Administering Droperidol

Other (please specify)

## 5. The phenomena of Emergence Delirium:

There is no standard definition of ED as it exists in service members who have deployed during the GWOT. There is little known about the specific behaviors and the consequences of the behaviors seen in service members exhibiting symptoms of ED.

Based on your personal experiences with ED in service members, please indicate how often you observed the following behaviors and behavioral consequences in your ED cases.

### 29. The service member's pull at the monitoring equipment, ETT, IV or any other invasive line connected to him/her.

|             | Never Seen            | Rarely Seen           | Occasionally Seen     | Often Seen            | Always Seen           |
|-------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Please rate | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

### 30. The service member's behavior threatens his/her own safety.

|             | Never Seen            | Rarely Seen           | Occasionally Seen     | Often Seen            | Always Seen           |
|-------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Please rate | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

### 31. The service member's movements are disruptive.

|             | Never Seen            | Rarely Seen           | Occasionally Seen     | Often Seen            | Always Seen           |
|-------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Please rate | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

### 32. The service member's have hyperactive motor behavior.

|             | Never Seen            | Rarely Seen           | Occasionally seen     | Often Seen            | Always Seen           |
|-------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Please rate | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

### 33. The service member's behavior requires additional staff.

|             | Never Seen            | Rarely Seen           | Occasionally Seen     | Often Seen            | Always Seen           |
|-------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Please rate | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

### 34. The service member's are combative towards the provider and staff.

|             | Never Seen            | Rarely Seen           | Occasionally Seen     | Often Seen            | Always Seen           |
|-------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Please rate | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

### 35. The service member's behavior makes his/her CRNA/Anesthesiologist/Nurse care more difficult.

|             | Never Seen            | Rarely Seen           | Occasionally Seen     | Often Seen            | Always Seen           |
|-------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Please rate | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

### 36. The service member's are vocally abusive.

|             | Never Seen            | Rarely Seen           | Occasionally Seen     | Often Seen            | Always Seen           |
|-------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Please rate | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

### 37. The service member's are uncontrollable.

|             | Never Seen            | Rarely Seen           | Occasionally Seen     | Often Seen            | Always Seen           |
|-------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Please rate | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

**38. The service member's seem panic stricken.**

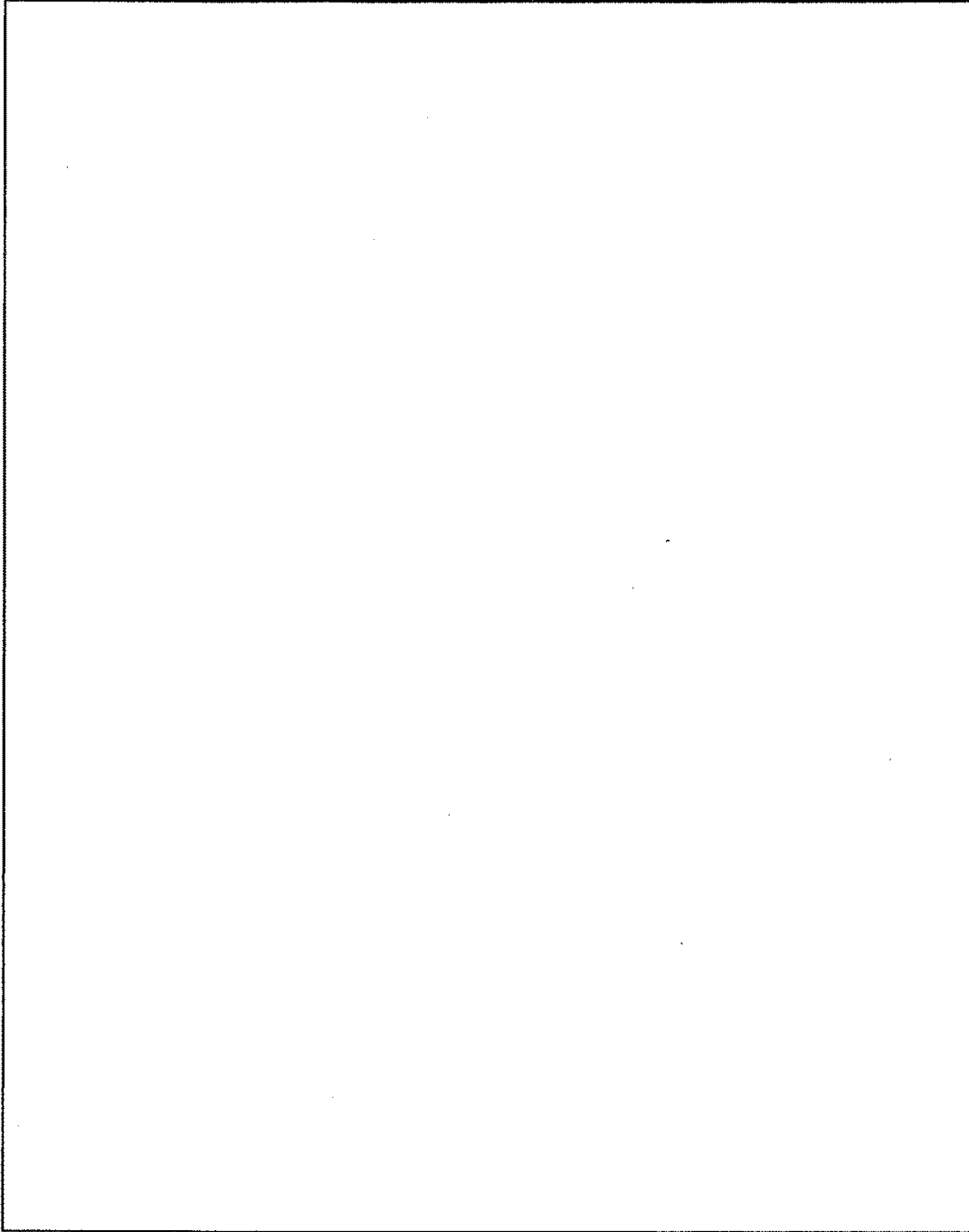
|             | Never Seen            | Rarely Seen           | Occasionally Seen     | Often Seen            | Always Seen           |
|-------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Please rate | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

**39. The service member's behavior threatens staff and provider safety**

|             | Never Seen            | Rarely Seen           | Occasionally Seen     | Often Seen            | Always Seen           |
|-------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Please rate | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

**40. Other observed behaviors that were not listed. Please describe in field provided.**

**6. Thank you very much for taking the time to participate in this worthwhile s...**



## APPENDIX E: COMMUNICATION TRASCRIPT FROM NANCY SIKICH

Re: Tyler Wilson from ECU

Page 1 of 1

**Re: Tyler Wilson from ECU**

Nancy Sikich [nancysikich@gmail.com]

**Sent:** Monday, March 14, 2011 9:40 AM

**To:** Wilson, John Tyler

**Cc:** Jerrold Lerman [jerrold.lerman@gmail.com]

Hi Tyler,

Happy to have you use the items in the PAED Scale for your survey. As always, any publication resulting out of your research which uses the PAED scale, its items or concepts should be given appropriate referencing and credit.

Good luck with your research!

Best,

Nancy Sikich

On Mon, Mar 7, 2011 at 9:21 AM, Wilson, John Tyler <WILSONJ08@students.ecu.edu> wrote:

Hi Nancy,

It was nice talking with you the other day and I appreciate your advice especially as it relates to your research tool. Too bad you are not still working in that area of research b/c I truly feel you were/are on to something vital to the study of emergence delirium.

If you don't mind, I would like something, "in writing" allowing me to utilize your research tool for my survey. As we discussed, my target population is the military so I will have to modify the questions a bit and will not use the ones you did for reliability (since you have already done that).

Thanks again!

Tyler Wilson  
East Carolina University

<https://sn2prd0102.outlook.com/owa/?ae=Item&t=IPM.Note&id=RgAAAAABpdi0B5zvfR...> 9/23/2011

## **APPENDIX F: DEPARTMENT OF DEFENSE DISCLOSURE STATEMENT**

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