The Impact of Clinical Practice Guidelines on Sedation Practices in the Trauma ICU

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Safe and effective sedation is an integral part of patient-centered care of the critically ill (Shehabi, Bellomo, Mehta, Riker, & Takala, 2013). Sedation practices should be focused on the use of medications which provide anxiolysis, tolerance for daily procedures (e.g., bathing, dressing changes), relief from the discomfort associated with essential lines and tubes, ventilator synchrony and an optimal safety profile while remaining economically feasible. Goal-directed sedation therapy has been identified as an essential strategy for improving outcomes in patients admitted to an intensive care unit (ICU) (Shehabi et al., 2013; Mansouri et al., 2013; Anger et al., 2010).

Until recently, the most commonly used intravenously (IV) administered sedatives in American ICUs were Diprivan, a short-acting sedative-hypnotic agent and Midazolam, a benzodiazepine (Jarman, Duke, Reade, & Casamento, 2013). Due to prevailing evidence that benzodiazepine use is linked to delirium, the 2013 American College of Critical Care Medicine's clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the ICU suggest that non-benzodiazepine based sedation strategies may improve outcomes in mechanically ventilated, critically ill adults (Barr et al., 2013). Following dissemination of these guidelines, a newer, costlier sedating agent, Dexmedetomidine, a selective α2-adrenergic receptor agonist, has gained popularity. (Pandharipande et al., 2008; Anger et al., 2010). Several studies compared Diprivan and Dexmedetomidine with regard to clinical outcomes in mixed medical and surgical ICU patients, however no clear superiority of one agent over the other has been identified (Xia et al., 2013).
Practice Problem

In the targeted trauma ICU in a large urban medical center, $1.4 million was spent in the year 2014 on Dexmedetomidine while a similar agent, Diprivan is available for nearly one fifth the cost per patient (personal communication with pharmaceutical buyer, September 21, 2015). No guidelines exist to provide evidence-based recommendations regarding the usage of these drugs in adult, mechanically ventilated, trauma ICU patients.

In an era of increased attention to cost containment in healthcare, the development of goal-directed, patient centered guidelines for the management of ICU sedation that are based on the best available evidence is essential. Clinical practice guidelines have become a fundamental tool in the improvement of patient outcomes, reduction of unnecessary health care costs, advancement of quality assurance initiatives, and promotion of medical education (Woolf, S.H., 1992). The purpose of this project is to develop collaborative, evidence-based, clinical practice guidelines for sedation practices in the critically ill, mechanically ventilated trauma patient. The guidelines will then be compared with current practices in the targeted trauma ICU and opportunities for improvement in care will be identified.

Theoretical Framework

An important component of this quality improvement project is the use of the Knowledge to Action framework as a tool to guide and organize the translation of current scientific evidence into clinical practice. The Knowledge to Action framework was designed to incorporate the development of knowledge and action into the concept of knowledge translation (Graham & Tetroe, 2010). The knowledge creation aspect of the framework consists of three phases, which
correspond to the steps used in this quality improvement project. The first phase is knowledge inquiry, a literature search and development of the scientifically based body of knowledge necessary for this project. The second phase, knowledge synthesis, guided the creation of clinical practice guidelines and the evaluation of content validity. Once the guidelines were validated, the third aspect of the framework, the creation of products or the translation of knowledge into practice, will govern the use of the guidelines to determine their impact on the sedation practices of mechanically ventilated patients in the trauma ICU (Graham et al., 2006). Within this final stage, barriers to implementation will also be assessed and tools created to overcome any impediment to successful implementation and application of the guidelines.

The action phases of the Knowledge to Action framework allow for the refinement of the acquired knowledge to fit with the setting in which it is intended. Furthermore, this framework guides the user through evaluation of knowledge use and outcomes (Field, Booth, Ilott, and Gerrish, 2014). It is a practical, versatile tool that has been substantiated in a variety of healthcare settings (Field et al., 2014). This is an invaluable instrument for the development and implementation of guidelines for use with a population as unique as critically ill adults who have sustained serious injury.

**Literature Review**

This literature review is a summary of an extensive search of available data on sedation practices in the ICU, with an emphasis on Dexmedetomidine and/or Diprivan. While there is a paucity of literature centering on trauma patients specifically, there is sufficient evidence focusing on surgical ICU patients to make recommendations that should be appropriate for critically ill patients who have sustained serious injury requiring ICU care.
In 2010, a systematic review analyzed the influence of implementing a sedation protocol on the outcomes of ICU patients (Jackson, Proudfoot, Cann, & Walsh, 2010). The authors compared the duration of mechanical ventilation and weaning time, ICU and hospital length of stay (LOS), duration of sedation and/or sedation costs, mortality, and incidence of ventilator associated pneumonia. In 15 of the 23 included studies, the implementation of a sedation protocol resulted in a decreased duration of mechanical ventilation of between 10% and 70%. The majority of these studies also demonstrated lower ICU LOS, hospital LOS, mortality and incidence of ventilator associated pneumonia. All 23 of the studies included a review of duration of sedation, sedation dosage and cost of sedation. Six studies concentrated primarily on duration of sedation and demonstrated a post-protocol decrease in the use of sedation (with associated reduction in cost). Twelve studies investigated associated costs by measuring length of sedation and the dosage administered. The required sedation dosage was lower after implementation of a structured sedation strategy, resulting in decreased pharmaceutical costs by 22% to 94%.

While the authors of this systematic review suggest that protocolized sedation regimens lead to fewer adverse patient outcomes, the strengths and weaknesses of each of the included studies must be considered (Jackson et al., 2010). All of the studies compared outcomes of mechanically ventilated ICU patients before and after (or concurrently with) the implementation of sedation guidelines. However, the investigations varied with regard to patient population, the type of sedative administered and protocol design. Not all studies compared the same outcomes or defined the outcomes in the same manner. This limits the generalizability of the studies (threat to external validity) and makes comparisons difficult (Steckler & McLeroy, 2008). However, the comparisons made within each study are conclusive given the intra-study validity. The majority of the studies utilized a before/after design. In fact, only four of the 23 included
studies were randomized controlled trials, which introduces the potential for bias, as patient conditions can change over the duration of study. All of the studies included small numbers of patients, thus they were not powered to show many statistical differences. Despite these limitations, this review supported the use of an evidence-based sedation protocol to increase patient safety and decrease associated costs.

Few studies directly compare Diprivan and Dexmedetomidine use in the ICU, and the majority of those studies were conducted in cardiothoracic or mixed medical and surgical ICUs (Wanat, Fitousis, Boston, & Masud, 2014; Devabhakthuni et al., 2011). Cardiothoracic ICU patients are generally extubated within 24 hours of surgery, making this population vastly different from the trauma ICU population (Reardon, Anger, Adams, & Szumita, 2013). The role of Diprivan and Dexmedetomidine in critically ill trauma patients has primarily been studied in patients with isolated traumatic brain injury (Devabhakthuni et al., 2011). The targeted ICU in my project is dedicated to the care of critically ill patients following either blunt or penetrating injury, but does not routinely care for patients with brain or spinal cord injury. Therefore, patients with traumatic brain or spinal cord injuries were excluded in this quality improvement project.

In a meta-analysis of randomized controlled trials (RCT) published in 2013, Xia et al. reviewed 10 clinical trials which included 1202 mixed medical and surgical ICU patients. They found that there was no difference in duration of mechanical ventilation, ICU length of stay or mortality among patients treated with Diprivan versus Dexmedetomidine. The largest RCT included in this study was carried out in 31 centers in 6 European countries (Jakob et al., 2012). The results of this trial were similar to those seen in the aforementioned meta-analysis, however these authors found that the patients in the Dexmedetomidine arm of the study had significantly
more adverse events (i.e., 1st degree AV block [p=0.04], higher RASS scores [p<.001]) than those treated with Diprivan, and Dexmedetomidine was discontinued in 9% of the patients due to lack of efficacy. Despite the large sample size in both investigations, a lack of standardized weaning protocols and criteria for extubation must be considered a limitation (Jakob et al., 2012). The meta-analysis included a large number of patients, but a relatively small number of trials. Tests for heterogeneity showed no significant differences, however the patients studied were quite varied with regard to diagnosis and type of ICU (medical, surgical, cardiothoracic) (Xia et al., 2013). This makes generalization of these results difficult.

In 2001, the Institute of Medicine stimulated healthcare reform, recommending changing from the traditional "disease-centered" model to a focus on patient-centered care in which the patient participates in and helps to define the acceptable quality of care. Thus, patient satisfaction became an important outcome measure (Benedict et al., 2014). Because the primary goal of IV sedation in the ICU setting is patient comfort (Hughes, McGrane, & Pandharipande, 2012), patient-reported level of satisfaction must be considered a key element in the selection of sedation agents. Three studies over the last 10 years included self-reported patient comfort as one outcome measure when comparing Diprivan to Dexmedetomidine use in an ICU setting (Okawa, Ichinohe, & Kaneko, 2010; Benedict et al., 2014; Corbett et al., 2005). In all three studies, the patients preferred Diprivan. For instance, Corbett et al. (2005) found that the patients in the Diprivan arm experienced a more comfortable ICU stay and fewer sleep disruptions. There were several limitations to these analyses however. One (Okawa, et al., 2010) was a very small study of healthy volunteers. Benedict et al. (2014) also conducted a very small (prospective) study in which mechanically ventilated ICU patients (mixed medical/surgical/trauma) were given a sedation questionnaire approximately 24 hours after the cessation of sedation. Neither study was
powered to show a significant difference. The Corbett et al. (2005) study was a prospective, randomized trial of 89 post-operative cardiac surgery patients who were given a validated sedation questionnaire at least 24 hours after extubation, but often after discharge from the ICU. None of these studies is generalizable to the trauma ICU population (threat to external validity), although the results seem compelling.

There are no published studies that directly compare Diprivan and Dexmedetomidine in non-neurologically injured trauma ICU patients. One study done at the R Adams Cowley Shock Trauma Center at the University of Maryland does compare these two agents in a trauma population that includes brain and spinal cord injury (Devabhakthuni et al., 2011). The authors concluded that, compared to Diprivan, standard doses of Dexmedetomidine resulted in longer hospital LOS. When higher doses of Dexmedetomidine were used, patients had more hypotension, longer ICU and hospital LOS, and an increased need for supplemental analgesia, sedation and antipsychotic medications when compared to Diprivan. Further exploration is necessary to elucidate the role of these two IV sedatives in trauma patients without neurological/neurosurgical injury.

In this era of healthcare cost containment, there should be compelling evidence of superiority with regard to outcome, safety, and patient satisfaction before any provider chooses a more expensive medication when there is a less expensive alternative. There is surprisingly little data which directly compares the two most widely used sedating agents in this country's ICUs, Diprivan and Dexmedetomidine, particularly in the trauma population. The research that does exist however, leads the reader to believe that they are at least equivalent (Corbett et al., 2005; Xia et al., 2013). Given that Diprivan costs one fifth as much as Dexmedetomidine (personal communication with pharmaceutical buyer, September 21, 2015) and has a similar (if not
superior) safety profile, patient satisfaction rating and outcome pattern, it would seem to be the preferred agent for sedation in most ICU patients.

There are some instances in which Dexmedetomidine is the preferred agent. Because Diprivan is lipophilic, its use in patients with a triglyceride levels of >400 mg/dl is occasionally associated with hypertriglyceridemia-associated pancreatitis (Devlin, Lau, & Tanios, 2005). Additionally, there is some evidence that, in selected mechanically ventilated cardiothoracic ICU patients, Dexmedetomidine initiated within 24 hours of extubation may decrease time to extubation (Curtis, Hollinger, & Jain, 2013).

Methods

Guideline Development

The large discrepancy in the cost of Diprivan and Dexmedetomidine in the targeted ICU prompted the need for an evidence-based protocol regarding their use in the critically ill trauma patient without neurologic injury. Following an extensive literature search, a draft set of guidelines based on best evidence and including the purpose, scope, key elements and economic considerations of Diprivan and Dexmedetomidine use were developed. These guidelines were disseminated along with a summary of the available evidence (Table 1), to a group of content experts which included a critical care attending physician, nurse practitioner and pharmacist. This group of experts were chosen based on their knowledge of and personal experience with Diprivan and Dexmedetomidine as well as their facilitation skills. Their availability and willingness to meet bi-weekly for a period of 6 weeks, to review documents prior to meetings and to complete the appraisal form (AGREE instrument) following guideline creation was crucial to success of this project. The role of the group was defined relative to guideline creation
and review. The group discussed the target patient population and setting for the guidelines, the expected outcomes following implementation, and the providers for whom the guidelines are written. The draft guidelines were then refined.

In addition to the drafted guidelines, access to the reviewed literature was provided via RefWorks, and a copy of the AGREE II short appraisal form (Appendix A) was disseminated after the 3rd meeting to facilitate revisions. Each AGREE form was completed independently after the meeting and returned prior to the next session. The AGREE II tool is a validated instrument used in the assessment of the quality of created clinical practice guidelines. It aids in the appraisal of the internal and external validity of the recommendations as well as any potential bias (Maymone, Gan, & Bigby, 2014). The AGREE II instrument consists of 23 items within six domains assessing the scope and purpose, stakeholder involvement, methodology, clarity of presentation, editorial independence and applicability of the recommendations. A 4-point Likert scoring system was used to evaluate the items in each domain (Appraisal of Guidelines Research & Evaluation, 2010). An international consortium of researchers and guideline developers went on to validate a more concise version of the AGREE II tool. The ADAPTE Collaboration simplified the AGREE instrument (calling it a short appraisal form), keeping the 23 item/six domain format. They chose, however, to use a 4-point Likert scoring system (ADAPTE Collaboration, 2009). Polit & Beck (2006) reported that a 4-point Likert scale is preferable to an odd number of scoring alternatives because it eliminates an impartial midpoint.

The scores from the completed AGREE II short appraisal form were used to evaluate content validity. The scores on the items in each domain were totaled for each appraiser. A maximum score (4 [highest score possible] x the number of items scored at a 4 x 3 [number of appraisers]) was calculated. A minimum score (1 [lowest possible score] x the number of items...
scored at a 1 x 3 (appraisers) was also determined. The obtained score minus the minimum possible score divided by the maximum possible score minus the minimum possible score yielded the domain score. No minimum domain score or pattern of scores across domains has been identified to recommend guideline acceptance (Appraisal of Guidelines Research & Evaluation, 2010).

Only one iteration of the draft guidelines was necessary to obtain stakeholder agreement. Following the 2nd meeting (week 4) and the final meeting (week 6), the AGREE II tool was distributed to each member of the work group. The results were blinded and disseminated. Two respondents did not complete question #5 on the initial distribution of the AGREE II instrument. Question #5 relates to the views and preferences of the patient. With the degree of illness severity seen in the Multi-Trauma ICU, it would be difficult, if not impossible, to ascertain the preferred sedation practices of the patient population prior to instituting a sedation plan of care. The group agreed that using the available data on patient satisfaction with regard to sedation practices in the ICU was the only feasible surrogate to use when developing the guidelines.

After the final iteration of the guidelines, the Agree II tool was again distributed. The results are summarized in tables 2 and 3. Once the guidelines were developed and approved by all members of the panel, they were submitted for approval to the Physician-in-Chief at the Shock Trauma Center. He was asked for comments and/or modifications, which were forwarded to the committee for review and modification. At the 3rd meeting (week 6), the group unanimously recommended the final draft of the guidelines without further modification.
Data Analysis

After receiving approval from my scholarly project committee at the University of Maryland School of Nursing and the University of Maryland Institutional Review Board (IRB), a request was made to the R A Cowley Shock Trauma Center data registry for blinded patient information. The requested data included patient demographics for all patients in the Multi-Trauma ICU between the dates of May 01, 2015 and October 31, 2015 who received IV sedation. Patients were excluded if they sustained a head or spinal cord injury or were in the ICU for less than 24 hours.

The outcome variables requested were hospital length of stay, ventilator days, mortality and disposition. Due to bed constraints, patients often remain in the Multi-Trauma ICU after they are appropriate for IMC level care. Therefore, I did not feel that ICU length of stay would be a valid outcome measure. The registry also provided the name of the IV sedative/analgesia and the infusion start and stop times.

Data analytics were performed using SAS® 9.4 software (SAS Institute, Inc., Cary, NC). Because the assumption of normality cannot be met, the inferential statistics were performed using a Wilcoxon Rank Sum analysis. Mean, median or inter-quartile ranges were reported as appropriate.

Results

A total of 209 patients met the inclusion criteria and were included in this retrospective review. Patients were divided into three groups, those receiving Diprivan only, Dexmedetomidine only or those receiving both sedatives. Patient characteristics are summarized in Table 4. Mean age was 46.5 years and 79% of the study population was male. The Diprivan
only group was slightly older, with a mean age of 48 years, however there was no statistical
difference among the groups with regard to age ($p = 0.111$). Mechanism of injury is described in
Table 5. In all three groups, motor vehicle crash was the most common reason for admission,
followed by falls in the Diprivan only group and gunshot wounds in the patients that received
both Diprivan and Dexmedetomidine. The median Injury Severity Score (ISS) was 17 indicating
this was a severely injured group of patients. ISS was not significantly different among the study
groups ($p = 0.132$)

Despite collecting data over a six-month period, the Dexmedetomidine only group
contained just three patients. This may represent an institutional initiative to defray costs by
minimizing the use of Dexmedetomidine as a first line agent or perhaps it is the bias of the
Multi-Trauma ICU faculty to use Diprivan as the sedation of choice. Whatever the reason, this
makes any direct comparison between Diprivan and Dexmedetomidine impossible.

When the patients receiving Diprivan only were compared with those receiving
Dexmedetomidine in addition to Diprivan, some stark differences emerge. Mean ventilator days
are significantly lower in the Diprivan only group when compared with those who had
Dexmedetomidine added to their sedation regimen (4.08 vs. 8.47 days, $p = 0.001$) and the
patients therefore spent less time under sedation (4914 vs. 7214 minutes, $p < 0.05$). Hospital
length of stay was also statistically significantly shorter for the patients in the Diprivan only
group (12.83 vs. 17.96 days, $p = 0.001$). Mortality was not significantly different between the
two groups ($p = 0.396$).

Twelve patients (5.7%) were given or continued on IV sedation with either
Dexmedetomidine (67%) or Diprivan (33%) as the sole agent to prevent alcohol withdrawal.
Additionally, 5.3% of the patients were not given adjuvant analgesia. Thirty (14.3%) had
Ketamine (a dissociative anesthetic) added to their sedation regimen. Those patients experienced longer mean ventilator days (5.46 vs. 9.47, \( p < 0.001 \)) and significantly longer median hospital length of stay (11.7 vs. 15.95 days, \( p < 0.001 \)) than those on Diprivan alone. Dexmedetomidine was started approximately 24 hours prior to extubation in only 29 (30.2\%) of the patients who received Dexmedetomidine. In five of those patients, however, it was started due to the development of hypertriglyceridemia with Diprivan use.

**Discussion**

Sedation practices are an integral part of the care of the critically-ill trauma patient. In the past, sedation regimens consisted primarily of benzodiazepines. Diprivan was approved for use (in its current form) by the FDA in 2008. It was initially distributed for use in the operating room but gained popularity in 2013 after the American College of Critical Care Medicine's clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit suggested that non-benzodiazepine based sedation strategies may improve outcomes in mechanically ventilated, critically ill adults (Barr et al., 2013). Following dissemination of these guidelines, Dexmedetomidine also gained popularity but it’s use was limited by the prohibitive cost (Pandharipande et al., 2008; Anger et al., 2010).

Evidence-based sedation practice guidelines were created for use in the Multi-Trauma ICU (Appendix B) following an extensive literature review (Table 1) which suggests that Diprivan should be the sedation agent of choice in the ICU. Prospective, randomized studies show that Diprivan is associated with shorter hospital LOS and time to extubation with fewer side effects. While there is some evidence (all in the post-operative cardiothoracic population) that initiating Dexmedetomidine within 24 hours of extubation may shorten time to extubation,
all studies in these patients compared Diprivan and Dexmedetomidine with regard to patient comfort/satisfaction and concluded that Diprivan use was associated with improved patient comfort.

Additionally, the existing data suggests that neither Diprivan nor Dexmedetomidine should be used in alcohol withdrawal syndrome as the sole preventative agent (Sarff & Gold, 2010). Benzodiazepines remain the drug of choice in these patients to decrease the severity of withdrawal and prevent seizure activity (Perry, 2014). Finally, neither Diprivan nor Dexmedetomidine have sufficient analgesic properties. An opioid analgesic should always be given concomitantly in those experiencing pain (Barr et al., 2013).

When comparing the created guidelines with actual practice in the Multi-Trauma ICU during the six-month study period, several discrepancies were noted. Both Diprivan and Dexmedetomidine were used to treat alcohol withdrawal and analgesics were not always used in patients where it seemed appropriate. Ketamine was used with both agents and resulted in increased ventilator days and hospital LOS. Only one-third of the study patients had Dexmedetomidine limited to the 24 hours preceding extubation as recommended. Each of these practices would add expense and did not result in better patient outcomes.

Cost Analysis

Due to the low number of patients in the Dexmedetomidine only group and the inability to obtain drug dosages, a direct cost comparison between Diprivan and Dexmedetomidine cannot be made. There are several comparisons that can be made, however. During the six-month study period, it is clear that sedation practices in the Multi-Trauma ICU were not evidence-based. Only 54 percent of the reviewed patients received Diprivan alone during their ICU
course. If Dexmedetomidine was limited to use within 24 hours of extubation in the remaining 97 patients as the evidence suggests, a significant cost savings could have been achieved (Curtis, Hollinger, & Jain, 2013).

There was no significant difference in the number of hours/minutes of Diprivan use (9179.35 hours) vs. Dexmedetomidine (10,220.12 hours). Additionally, use of sedating agents without analgesia or for the sole purpose of alcohol withdrawal prevention is not evidence-based and discontinuation of this practice would likely result in lower sedation requirements and cost (Sarff & Gold, 2010).

Currently, in the targeted ICU, Diprivan and Dexmedetomidine are commonly used for sedation in the mechanically-ventilated, critically-ill trauma patient and are prescribed at the discretion of the provider. In 2014 $1.4 million was spent on the drug Dexmedetomidine while a similar IV sedation agent, Diprivan is available for nearly one fifth the cost per patient (personal communication with pharmaceutical buyer, September 21, 2015). Utilizing these drugs in an evidence-based manner would improve patient outcomes and may cut unnecessary pharmaceutical expenditures.

**Strengths and Limitations**

The principle strength of this project lies in its direct applicability to the Multi-Trauma ICU. The guidelines were developed using data limited to trauma patients (when possible) or surgical ICU patients, making them as applicable as possible to the target population. The developed guidelines are clear and concise, while leaving room for clinical judgment. The data utilized in the retrospective analysis was extracted from the population of the unit for which the
guidelines are intended. While this is only a snapshot in time, it is representative of the patient mix and provider preferences in the target unit. The enthusiasm with which the project was received is a definite strength with regard to implementation of the created guidelines.

The limitations of this project include the retrospective nature of the data, the small number of patients in the Dexmedetomidine only group which restricted the ability to directly compare the use of Diprivan only to Dexmedetomidine only, and the lack of data on administered drug dosages. However, this project is a good first step in the evaluation of current sedation practices in any ICU. The three groups that were compared did not differ with regard to patient characteristics with the exception of mortality which did not vary significantly among groups, and the lack of male patients in the Dexmedetomidine only group. However, the study would have been far more robust if the three groups had a similar number of included patients. A matched cohort would have been ideal. Additionally, performing a comprehensive logistic regression utilizing all conceived variables which potentially influence patient outcome would have added to the rigor of this project.

The AGREE II tool was invaluable to this project. The tool provided focus points for the working group and added cohesion to the discussions. It also presented some challenges. Several of the questions did not pertain directly to this project. This resulted in some confusion about the completeness of the guidelines. Questions that pertain to patient preference are difficult to assess in an ICU, particularly in one with the acuity of the Multi-Trauma ICU. While patient comfort is the primary goal of sedation, post hoc assessment of this parameter is challenging given the amnestic property of frequently used sedating agents. If sedation is done well, the majority of patients will not recall their ICU stay.
Areas for Future Research

The creation of clinical practice guidelines is just the beginning of a larger quality initiative to improve sedation practices in the Multi-Trauma ICU. Implementation of the guidelines should be the next area of focus. Barriers to implementation were assessed during this project and will require continual reassessment during the implementation process. One resource beyond the scope of this project is the creation of a dashboard as part of the electronic medical record. This dashboard would provide prescribers with current recommendations in real time. Beyond implementation, it will be important to review the degree of compliance and key outcome markers to assess the efficacy of this project. This initiative should improve patient outcomes, lower ICU costs and provide patients with a more comfortable ICU experience.

Dissemination

One important step in the translation of scientific evidence into practice is the dissemination of this evidence to the appropriate audience. I will present the findings of this project to the Attending Physicians, Fellows, Residents, Nurse Practitioners and Nursing staff at the targeted hospital grand rounds. Additionally, I will present at the annual Nurse Practitioner conference sponsored by the hospital.

To disseminate the results of this project to the largest possible audience, I plan to publish this data in a peer-reviewed journal such as the Journal of the American Association of Nurse Practitioners, the Journal of Trauma Nursing or the American Journal of Critical Care. Circulation of the findings of this project can lead to further research regarding the use of Diprivan and/or Dexmedetomidine in other healthcare settings or continued work in the field of trauma care.
Conclusions

No guidelines currently exist to guide the practitioner in the use of evidence-based sedation strategies in the Multi-Trauma ICU. The guidelines created during this project represent current best evidence on the use of Diprivan and Dexmedetomidine in trauma and surgical ICU patients. When these guidelines were compared to six months of retrospective patient data from the targeted ICU, it was found that current practice varied from the recommended utilization of these sedating agents. Implementation of the created clinical practice guidelines may improve patient outcomes, including ventilator days and hospital LOS, and reduce associated hospital costs.
References


withdrawal prophylaxis in the trauma ICU: Results of a randomized trial. *Journal of Trauma and Acute Care Surgery, 64*(1), 99-104. doi:10.1097/TA.0b013e31815eb12a


## Literature Review

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study objective</th>
<th>Design</th>
<th>Population</th>
<th>Outcome(s) studied</th>
<th>Results</th>
<th>Level and Quality Rating</th>
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<tbody>
<tr>
<td>Benedict, et al., 2014</td>
<td>To compare patient-reported quality of sedation to a frequently used sedation assessment scoring tool.</td>
<td>Prospective, non-randomized, single center survey</td>
<td>29 mechanically ventilated patients from mixed medical and surgical ICU's</td>
<td>Patients were given a sedation survey a mean 2.9 days after cessation of sedation and determine the correlation between patient satisfaction and their sedation score.</td>
<td>Patient perception of comfort correlated with the percent time at goal SAS. Patients spent more time at goal sedation score with Diprivan as compared with Dexmedetomidine.</td>
<td>VI C</td>
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<tr>
<td>Corbett, et al., 2005</td>
<td>To study the difference in patient satisfaction after administration of either Diprivan or Dexmedetomidine during intubation.</td>
<td>Prospective, randomized survey</td>
<td>89 adult elective CABG patients</td>
<td>Patients were randomized to either Dexmedetomidine or Diprivan prior to surgery. They were given a validated sedation questionnaire asking questions regarding comfort, recall, and level of pain, anxiety, and agitation. The survey was given at least 24 hours after extubation.</td>
<td>Diprivan resulted in a more comfortable hospital experience with fewer sleep disruptions.</td>
<td>VI B</td>
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<tr>
<td>Curtis, et al., 2013</td>
<td>To evaluate the effect of Diprivan and Dexmedetomidine on LOS, hospital cost, mortality and time of extubation.</td>
<td>Twenty-three month retrospective chart review</td>
<td>528 adult patients who were sedated after cardiac valve or CABG surgery.</td>
<td>The primary outcome measure was early extubation, defined as $&lt; 6$ hours. Secondary measures were hospital and ICU LOS, in-hospital mortality and total hospital charges.</td>
<td>Time to extubation and hospital LOS were shorter with Dexmedetomidine. There was no difference in ICU LOS or mortality. Costs were similar between groups.</td>
<td>IV A</td>
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<tr>
<td>Devabhakthuni, et al., 2011</td>
<td>To compare the safety profile and key clinical outcomes with Diprivan, standard-dose Dexmedetomidine and high-dose Dexmedetomidine.</td>
<td>Retrospective cohort chart analysis</td>
<td>127 trauma ICU patients</td>
<td>Patients were stratified into Diprivan (10-75 mcg/kg/min), low-dose Dexmedetomidine (0.2-0.7 mcg/kg/hr) or high-dose Dexmedetomidine (0.2-1.5 mcg/kg/hr) groups. Primary outcomes were blood pressure and heart rate. Secondary outcomes were hospital and ICU LOS, ventilator days and concomitant use of additional pain, sedation and antipsychotic medication required.</td>
<td>High-dose Dexmedetomidine is associated with more hypotension, longer hospital and ICU LOS and increased requirements for concomitant analgesic, sedative and antipsychotic medications than low dose Dexmedetomidine or Diprivan. Low-dose Dexmedetomidine is associated with longer hospital LOS than Diprivan.</td>
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<td>Author, year</td>
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<td>Jackson, et al., 2010</td>
<td>To understand the effect of sedation practices in the ICU on clinical outcomes.</td>
<td>Systematic Review</td>
<td>23 studies (1998-2008) were included. Most were before/after design. Four were RCTs. Studies included varying ICU populations.</td>
<td>The impact of instituting sedation protocols on mechanically ventilated ICU patients.</td>
<td>Protocolized sedation practices were associated with reduced duration of mechanical ventilation and weaning, reduced ICU LOS and hospital LOS, shorter duration of sedation and sedation costs, and a reduction in the incidence of ventilator associated pneumonia.</td>
<td>VA</td>
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<tr>
<td>Jakob, et al., 2012</td>
<td>To evaluate the efficacy of Dexmedetomidine and Diprivan in reducing ventilator days and maintaining sedation.</td>
<td>Phase III, multicenter, randomized, double-blinded, double-dummy design</td>
<td>498 patients from 31 ICU's in 6 European countries</td>
<td>Patients were randomized into Diprivan (0.3-4.0 mg/kg/hr) or Dexmedetomidine (0.2-1.4 mcg/kg/hr) groups.</td>
<td>The Dexmedetomidine group had significantly higher RASS, was discontinued due to lack of efficacy more often, had longer duration of mechanical ventilation. Hospital and ICU LOS were similar between the two groups. Adverse events were similar between the two groups with the exception of significantly more 1st degree AV block with Dexmedetomidine.</td>
<td>IA</td>
</tr>
<tr>
<td>Okawa, et al., 2010</td>
<td>To compare the effects of Diprivan and Dexmedetomidine on nervous system activity and subjective stress.</td>
<td>Prospective, randomized (not double-blinded)</td>
<td>25 healthy adult male volunteers</td>
<td>Patients were randomized to receive either Diprivan or Dexmedetomidine. Heart rate, heart rate variability, salivary amylase, and anxiety level were measured as various stressors were applied. The patients were then surveyed as to their preference of sedating agents.</td>
<td>Diprivan prevented anxiety or reduced anxiety levels, and reduced subjective stress better than Dexmedetomidine. The majority of patients surveyed indicated that they preferred Diprivan over Dexmedetomidine.</td>
<td>IC</td>
</tr>
<tr>
<td>Xia, et al., 2013</td>
<td>To assess the clinical benefits of Dexmedetomidine and Diprivan with regard to patient outcomes and adverse events.</td>
<td>Systematic review of all randomized controlled trials that review Diprivan vs. Dexmedetomidine for sedation in ICU patients.</td>
<td>10 randomized controlled trials that include 1202 patients</td>
<td>Primary outcome measures were ICU length of stay, duration of mechanical ventilation, and mortality. Secondary measures were delirium, hypotension, bradycardia and hypertension.</td>
<td>There was no difference in ICU LOS, duration of mechanical ventilation, mortality, or incidence of hypotension or bradycardia between Dexmedetomidine and Diprivan. There was more hypertension and less delirium with Dexmedetomidine.</td>
<td>IA</td>
</tr>
</tbody>
</table>
Table 2.

**Summary of domain items from AGREE II tools**

<table>
<thead>
<tr>
<th>Domain</th>
<th>N</th>
<th>Minimum</th>
<th>Mean</th>
<th>Maximum</th>
<th>Std Dev</th>
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<tr>
<td>I. Scope and Purpose</td>
<td>3</td>
<td>36.0</td>
<td>36.0</td>
<td>36.0</td>
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<td>II. Stakeholder involvement</td>
<td>3</td>
<td>25.0</td>
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<td>III. Rigor of Development</td>
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<td>95.0</td>
<td>95.0</td>
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<td>36.0</td>
<td>0.000</td>
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<tr>
<td>V. Applicability</td>
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<td>40.0</td>
<td>43.5</td>
<td>47.0</td>
<td>4.950</td>
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<td>VI. Editorial Independence</td>
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<td>36.0</td>
<td>36.0</td>
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Table 3.

**AGREE II Content validity**

<table>
<thead>
<tr>
<th>Appraiser</th>
<th>1st Iteration</th>
<th>2nd Iteration</th>
<th>Agreement</th>
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<tbody>
<tr>
<td>Appraiser 1</td>
<td>0.431</td>
<td>0.383</td>
<td>0.889</td>
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<tr>
<td>Appraiser 2</td>
<td>0.333</td>
<td>0.333</td>
<td>1.000</td>
</tr>
<tr>
<td>Appraiser 3</td>
<td>0.386</td>
<td>0.344</td>
<td>0.892</td>
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Table 4.

*Patient Characteristics*

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Diprivan (only)</th>
<th>Dex (only)</th>
<th>Both</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>48.1 (20.6)</td>
<td>40.7 (19.4)</td>
<td>44.8 (19.8)</td>
<td>0.444</td>
</tr>
<tr>
<td>15-20 (%)</td>
<td>10 (8.9)</td>
<td>0 (0)</td>
<td>6 (6.4)</td>
<td></td>
</tr>
<tr>
<td>21-30 (%)</td>
<td>18 (16.7)</td>
<td>1 (33.3)</td>
<td>28 (29.8)</td>
<td></td>
</tr>
<tr>
<td>31-40 (%)</td>
<td>18 (16.7)</td>
<td>1 (33.3)</td>
<td>15 (16.0)</td>
<td></td>
</tr>
<tr>
<td>41-54 (%)</td>
<td>23 (20.5)</td>
<td>0 (0)</td>
<td>17 (18.1)</td>
<td></td>
</tr>
<tr>
<td>55+ (%)</td>
<td>43 (38.1)</td>
<td>1 (33.3)</td>
<td>28 (29.8)</td>
<td></td>
</tr>
<tr>
<td>Sex, male (%)</td>
<td>89 (42.6)</td>
<td>0 (0)</td>
<td>76 (36.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>ISS, median (IQR)</td>
<td>17 (10-22)</td>
<td>26 (22-43)</td>
<td>17 (10-26)</td>
<td>0.132</td>
</tr>
<tr>
<td>Ventilator Days, mean (SD)</td>
<td>4.1 (4.0)</td>
<td>3.0 (1.0)</td>
<td>8.5 (10.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital LOS, median (IQR)</td>
<td>10.1 (7-15)</td>
<td>14.7 (7-18)</td>
<td>14.8 (9-23)</td>
<td>0.004</td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>10 (4.8)</td>
<td>0 (0)</td>
<td>7 (3.3)</td>
<td>0.396</td>
</tr>
</tbody>
</table>

Table 5.

*Mechanism of Injury*

<table>
<thead>
<tr>
<th>Sample size, n(%)</th>
<th>Diprivan</th>
<th>Dex</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assault (blunt)</td>
<td>2 (1.8)</td>
<td>0 (0.0)</td>
<td>4 (4.2)</td>
</tr>
<tr>
<td>Assault (handgun)</td>
<td>16 (14.3)</td>
<td>1 (33.3)</td>
<td>23 (24.5)</td>
</tr>
<tr>
<td>Assault (stabbing)</td>
<td>11 (9.8)</td>
<td>0 (0.0)</td>
<td>4 (4.2)</td>
</tr>
<tr>
<td>Bicyclist Struck</td>
<td>2 (1.8)</td>
<td>0 (0.0)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>CO Poisoning</td>
<td>3 (2.7)</td>
<td>0 (0.0)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Crush Injury</td>
<td>3 (2.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Electrocution</td>
<td>1 (0.9)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Fall</td>
<td>21 (18.7)</td>
<td>0 (0.0)</td>
<td>15 (16.0)</td>
</tr>
<tr>
<td>Motor Vehicle Crash (car)</td>
<td>31 (27.6)</td>
<td>2 (66.7)</td>
<td>25 (26.6)</td>
</tr>
<tr>
<td>Motorcycle Crash</td>
<td>17 (15.2)</td>
<td>0 (0.0)</td>
<td>11 (11.7)</td>
</tr>
<tr>
<td>Pedestrian Struck</td>
<td>3 (2.7)</td>
<td>0 (0.0)</td>
<td>3 (3.2)</td>
</tr>
<tr>
<td>Self-Inflicted</td>
<td>2 (1.8)</td>
<td>0 (0.0)</td>
<td>4 (4.2)</td>
</tr>
<tr>
<td>Undetermined</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>3 (3.2)</td>
</tr>
</tbody>
</table>
Appendix A.

*Modified AGREE II tool*

### Domain 1. Scope and Purpose

1. The overall objective(s) of the guideline is (are) specifically described.

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strongly Disagree</td>
<td></td>
<td></td>
<td>Strongly Agree</td>
</tr>
</tbody>
</table>

*Comments:*

2. The question(s) covered by the guideline is (are) specifically described.

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
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<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strongly Disagree</td>
<td></td>
<td></td>
<td>Strongly Agree</td>
</tr>
</tbody>
</table>

*Comments:*

3. The population (patients) to whom the guideline is meant to apply is specifically described.

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
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<th>4</th>
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</thead>
<tbody>
<tr>
<td>Strongly Disagree</td>
<td></td>
<td></td>
<td>Strongly Agree</td>
</tr>
</tbody>
</table>

*Comments:*
### Domain 2. Stakeholder Involvement

4. The guideline development group includes individuals from all relevant professional groups.

<table>
<thead>
<tr>
<th></th>
<th>1 Strongly Disagree</th>
<th>2</th>
<th>3</th>
<th>4 Strongly Agree</th>
</tr>
</thead>
</table>

Comments:

5. The views and preferences of the target population (patients) have been sought.

<table>
<thead>
<tr>
<th></th>
<th>1 Strongly Disagree</th>
<th>2</th>
<th>3</th>
<th>4 Strongly Agree</th>
</tr>
</thead>
</table>

Comments:

6. The target users of the guideline are clearly defined.

<table>
<thead>
<tr>
<th></th>
<th>1 Strongly Disagree</th>
<th>2</th>
<th>3</th>
<th>4 Strongly Agree</th>
</tr>
</thead>
</table>

Comments:
### Domain 3. Rigour of Development

7. Systematic methods were used to search for evidence.

<table>
<thead>
<tr>
<th></th>
<th>1</th>
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<th>4</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Strongly Disagree</td>
<td></td>
<td></td>
<td>Strongly Agree</td>
</tr>
</tbody>
</table>

Comments:

8. The criteria for selecting the evidence are clearly described.

<table>
<thead>
<tr>
<th></th>
<th>1</th>
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<th>4</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Strongly Disagree</td>
<td></td>
<td></td>
<td>Strongly Agree</td>
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</tbody>
</table>

Comments:

9. The strengths and limitations of the body of evidence are clearly described.

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Strongly Disagree</td>
<td></td>
<td></td>
<td>Strongly Agree</td>
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</table>

Comments:
### Domain 3. Rigour of Development (continued)

10. The methods for formulating the recommendations are clearly described.

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
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</thead>
<tbody>
<tr>
<td><strong>Strongly Disagree</strong></td>
<td></td>
<td></td>
<td><strong>Strongly Agree</strong></td>
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</table>

**Comments:**

11. The health benefits, side effects and risks have been considered in formulating the recommendations.

<table>
<thead>
<tr>
<th>1</th>
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<tbody>
<tr>
<td><strong>Strongly Disagree</strong></td>
<td></td>
<td></td>
<td><strong>Strongly Agree</strong></td>
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</tbody>
</table>

**Comments:**

12. There is an explicit link between the recommendations and the supporting evidence.

<table>
<thead>
<tr>
<th>1</th>
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<tbody>
<tr>
<td><strong>Strongly Disagree</strong></td>
<td></td>
<td></td>
<td><strong>Strongly Agree</strong></td>
</tr>
</tbody>
</table>

**Comments:**
### Domain 3. Rigour of Development (continued)

13. The guideline has been externally reviewed by experts prior to its publication.

<table>
<thead>
<tr>
<th>1</th>
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<th>4</th>
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<tbody>
<tr>
<td>Strongly Disagree</td>
<td></td>
<td></td>
<td>Strongly Agree</td>
</tr>
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</table>

**Comments:**

14. A procedure for updating the guideline is provided.

<table>
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<tr>
<th>1</th>
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<tbody>
<tr>
<td>Strongly Disagree</td>
<td></td>
<td></td>
<td>Strongly Agree</td>
</tr>
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</table>

**Comments:**
# Domain 4. Clarity of Presentation

15. the recommendations are specific and unambiguous.

<table>
<thead>
<tr>
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<th>4</th>
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<tr>
<td></td>
<td>Strongly Disagree</td>
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<td></td>
<td>Strongly Agree</td>
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</tbody>
</table>

**Comments:**

16. The different options for management of the condition are clearly presented.

<table>
<thead>
<tr>
<th></th>
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<th>4</th>
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<tr>
<td></td>
<td>Strongly Disagree</td>
<td></td>
<td></td>
<td>Strongly Agree</td>
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</tbody>
</table>

**Comments:**

17. Key recommendations are easily identifiable.

<table>
<thead>
<tr>
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<th>1</th>
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<th>4</th>
</tr>
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<tr>
<td></td>
<td>Strongly Disagree</td>
<td></td>
<td></td>
<td>Strongly Agree</td>
</tr>
</tbody>
</table>

**Comments:**
### Domain 5. Applicability

18. The guideline describes facilitators and barriers to its application.

<table>
<thead>
<tr>
<th></th>
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<th>4</th>
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<tr>
<td></td>
<td>Strongly Disagree</td>
<td></td>
<td></td>
<td>Strongly Agree</td>
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</tbody>
</table>

**Comments:**

19. The guideline provides advice and/or tools on how the recommendations can be put into practice.

<table>
<thead>
<tr>
<th></th>
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<th>4</th>
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<tr>
<td></td>
<td>Strongly Disagree</td>
<td></td>
<td></td>
<td>Strongly Agree</td>
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</tbody>
</table>

**Comments:**

20. The potential resource implications of applying the recommendations have been considered.

<table>
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<tr>
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<tr>
<td></td>
<td>Strongly Disagree</td>
<td></td>
<td></td>
<td>Strongly Agree</td>
</tr>
</tbody>
</table>

**Comments:**
### Domain 5. Applicability (continued)

21. The guideline presents monitoring and/or auditing criteria.

<table>
<thead>
<tr>
<th>1</th>
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<th>4</th>
</tr>
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<tbody>
<tr>
<td><strong>Strongly Disagree</strong></td>
<td></td>
<td></td>
<td><strong>Strongly Agree</strong></td>
</tr>
</tbody>
</table>

**Comments:**
## Domain 6. Editorial Independence

22. The views of the funding body have not influenced the content of the guideline.

<table>
<thead>
<tr>
<th></th>
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<th>2</th>
<th>3</th>
<th>4</th>
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<td></td>
<td>Strongly Disagree</td>
<td></td>
<td></td>
<td>Strongly Agree</td>
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</tbody>
</table>

Comments:

23. Competing interests of the guideline development group members have been recorded and addressed.

<table>
<thead>
<tr>
<th></th>
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<th>3</th>
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</tr>
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<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Strongly Agree</td>
</tr>
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</table>

Comments:
# Overall Guideline Assessment

For each question, please choose the response which best characterizes the guideline assessed:

1. Rate the overall quality of this guideline.

<table>
<thead>
<tr>
<th></th>
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<th>4</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Strongly Disagree</td>
<td></td>
<td></td>
<td>Strongly Agree</td>
</tr>
</tbody>
</table>

2. I would recommend this guideline for use:

- Yes
- Yes, with modifications
- No

NOTES:
Appendix B.

Clinical Practice Guidelines

Guideline Scope and Clinical Objectives

1. **Targeted Intervention(s):** Diprivan and Dexmedetomidine.

2. **Purpose:** To determine evidence-based usage of Diprivan and Dexmedetomidine for the sedation of mechanically ventilated, trauma intensive care unit (ICU) patients without neurologic injury.

3. **Scope:** Mechanically ventilated, trauma ICU patients without neurologic injury.

4. **Literature Inclusion Criteria:** Date range 2005 – 2015.

5. **Epidemiology:** Diprivan and Dexmedetomidine are sedating agents with similar sedating properties, and are the two most frequently prescribed sedating agents used in American ICUs. Diprivan however, is available for one-fifth the cost per patient.

6. **Intended Users:** ICU practitioners (Attending Physicians, Fellows, Residents and Nurse Practitioners).

7. **Public Health Impact:** Compliance with evidence-based practice and the potential for cost savings.

8. **Target Population:** Mechanically ventilated, trauma ICU patients without neurologic injury.

9. **Intended Use:** Quality improvement.

10. **Can Flow Diagrams be used for summation?** Yes.

11. **How Does the Guideline Impact/Improve Broad Health System Improvement Goals?** Provides cost-effective, evidence-based recommendations regarding the choice of sedating agents as is encouraged by the 2010 U.S. Affordable Care Act.

12. **Amount of Clinical Flexibility:** Moderate.
Clinical Practice Guidelines for the Infusion of Sedation in the Mechanically Ventilated, Trauma Intensive Care Unit Patient Without Neurologic Injury

Sharon A. Boswell
University of Maryland School of Nursing

Safe and effective sedation is an integral part of patient-centered care of the critically ill (Shehabi, Bellomo, Mehta, Riker, & Takala, 2013). Sedation practices should focus on the use of medications which provide anxiolysis, tolerance for daily procedures (e.g., bathing, dressing changes), relief from the discomfort from essential lines and tubes, ventilator synchrony and an optimal safety profile while remaining economically feasible. Goal-directed sedation therapy has been identified as an essential strategy for improving outcomes in patients admitted to an intensive care unit (ICU) (Shehabi et al., 2013; Mansouri et al., 2013; Anger et al., 2010).

EXECUTIVE SUMMARY.

The most commonly used intravenously (IV) administered sedatives in American ICUs are Diprivan, a short-acting sedative-hypnotic agent and Midazolam, a benzodiazepine (Jarman, Duke, Reade, & Casamento, 2013). Due to recent evidence that benzodiazepine use is linked to delirium, the 2013 American College of Critical Care Medicine’s “Clinical Practice Guidelines for the Management of Pain, Agitation and Delirium in Adult Patients in the Intensive Care Unit” (Barr et al., 2013) divulge that non-benzodiazepine based sedation strategies may improve outcomes in mechanically ventilated, critically ill adults. Following this publication, a newer, costlier sedating agent, Dexmedetomidine, a selective α2-adrenergic receptor agonist, gained popularity. (Pandharipande et al., 2006; Anger et al., 2010).

In the Multi-Trauma ICU at the R A Cowley Shock Trauma Center, $1.4 million was spent in the year 2014 on the drug Dexmedetomidine while Diprivan is available for nearly one fifth the cost per patient (personal communication with the pharmaceutical buyer, R A Cowley Shock Trauma Center, September 21, 2015). Currently, these agents are prescribed at the discretion of the ICU provider. No guidelines currently exist to provide
evidence-based recommendations regarding the utility of these drugs in adult, mechanically ventilated, trauma ICU patients. In an era of increased attention to cost containment in healthcare, further investigation is necessary to determine whether Diprivan is an acceptable sedating agent for use in this specific patient population.

**Narcotic Analgesics**

*Recommendation:* Narcotic analgesics should be added to the sedation plan of care for analgesia and anxiolysis in the critically ill trauma patient (Grade of recommendation – 2A).

Narcotics should be administered in a continuous infusion rather than on an as needed basis in mechanically ventilated ICU patients (Grade of recommendation- 2B).

Protocolized analgesia should be the mainstay of narcotic administration in the mechanically ventilated ICU patient (Grade of recommendation – 2B).

An essential goal in the provision of care to critically-ill trauma patients is adequate analgesia, sedation and anxiolysis, without cardiovascular compromise (Wheeler, 1993). The causes of anxiety in the critically ill patient are multifactorial. Sleep deprivation, noxious stimuli and the inability to communicate effectively add to a patient’s loss of control, causing anxiety. Acute agitation may also be a manifestation of pain and/or anxiety (Jacobi et al., 2002). The administration of narcotic analgesics to ameliorate pain often has the added benefit of reducing anxiety, preventing agitation and lowering sedative requirements (Muellejans et al., 2004).

Evidence suggests that maintaining a protocolized analgesia regimen is the key factor in providing optimal pain management. The agent of choice should have a rapid onset and offset of action, be easily titratable, cost effective and have an exceptional safety profile (Gommers & Bakker, 2008). The analgesia plan of care should be patient-centered and frequently reassessed. A continuous infusion of opiates or scheduled dosing is preferred over dosing on an as needed basis (Jacobi et al., 2002).

Adverse cardiovascular, respiratory and gastrointestinal effects of opioids occur frequently in the ICU setting. Narcotic analgesics have significant respiratory depressant
properties and should be dosed with caution in the spontaneously breathing patient or those on spontaneous modes of ventilatory support. Hemodynamic instability can also occur in critically-ill patients as a result of narcotic administration, particularly in patients who are hypovolemic (Jacobi et al., 2002). Additionally, intravenous opioid use is significantly associated with development of colonic ileus. Some studies suggest that a liberal daily dose of narcotic analgesics is more significantly associated with ileus than is prolonged use (Barletta, Asgeirsson, & Senagore, 2011).

**Indications for Sedation**

*Recommendation:* Sedation should be administered in mechanically ventilated patients exhibiting symptoms of anxiety and/or agitation after attempting non-pharmacologic interventions. (Grade of recommendation – 1C).

Anxiety and agitation in critically ill patients are associated with prolonged LOS, morbidity and mortality (Chevrolet & Jolliet, 2007). Anxiety has been defined as “a feeling of dread, fear and/or lack of control” (Tate, Dabbs, Hoffman, Milbrandt, & Happ, 2012). Agitation is a psychomotor disturbance that presents as loss of motor control (generally non-purposeful) and confusion caused by excessive motor and psychological activity and associated with internal stress (Chevrolet & Jolliet, 2007; Crippen, 1999). Prompt recognition and treatment of these conditions is imperative to avoid any associated negative sequelae (Barr et al., 2013). The most commonly used treatment for anxiety and agitation in the ICU is sedation. It is important however, to consider and treat any potential underlying causes. Non-pharmacologic measures such as efforts to maintain a normal sleep cycle, patient comfort and frequent patient reorientation should be attempted before the administration of sedating agents (Barr et al., 2013).
Choice of Sedation

**Recommendation:** A structured sedation protocol should be implemented to improve patient outcomes, ensure patient comfort and reduce costs (Grade of recommendation – 1A).

In 2010, a systematic review was undertaken to analyze the influence of implementing a sedation protocol on the outcomes of ICU patients (Jackson, Proudfoot, Cann, & Walsh, 2010). The studies in this review were executed to compare the duration of mechanical ventilation and weaning time, ICU and hospital LOS, duration of sedation and/or sedation costs, mortality, and incidence of ventilator associated pneumonia. In 15 of the 23 studies reviewed, the implementation of a sedation protocol resulted in a decreased duration of mechanical ventilation of 10% to 70%. The majority of the patients in this research also experienced a decrease in ICU LOS, hospital LOS, mortality and incidence of ventilator associated pneumonia. Twelve studies in this review primarily investigated costs associated with sedation by measuring length of sedation and the dosage administered. Most exhibited a decreased duration of sedation and a lower required dosage after implementation of a structured sedation strategy, resulting in a lowering of sedation costs by 22% to 94%.

While the authors of this systematic review suggest that protocolized sedation regimens lead to fewer adverse patient outcomes, the strengths and weaknesses of each of the included studies should be considered (Jackson et al., 2010). All of the covered research compared key outcomes of mechanically ventilated ICU patients before and after (or concurrently with) the implementation of sedation guidelines. However, the investigations varied with regard to patient population, the type of sedation medication administered and protocol design. Not all studies compared the same outcomes or defined the outcomes in the same way. This limits the generalizability of the studies (threat to external validity) and makes comparisons difficult. However, the comparisons made within each study are conclusive given the intra-study validity. The majority of
this research was before/after design. In fact, only 4 of the 23 included studies were randomized controlled trials (RCT), which introduces the potential for bias as patient conditions can change over the duration of study. All of the studies included small numbers of patients, thus they were not powered to show many statistical differences. Despite these limitations, all data included in the review supported the use of an evidence-based sedation protocol to increase patient safety and decrease associated costs.

Sedation strategies using non-benzodiazepine sedatives are preferred (Grade Recommendation – 2B).

A ground-breaking study on the effects of benzodiazepine use in the ICU showed that a commonly used treatment for anxiety, agitation and delirium in the ICU, lorazepam, is associated with cognitive deficits as long as three months after discharge from the ICU (Pandharipande et al., 2006). In 2013, The Society of Critical Care Medicine in conjunction with the American College of Critical Care Medicine published “Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit” (Barr et al., 2013). Their meta-analysis concluded that benzodiazepine-based sedation strategies are associated with longer ICU LOS and an extended duration of mechanical ventilation. The guidelines recommend against the use of benzodiazepines for ICU sedation except when it is also necessary to treat alcohol or benzodiazepine dependence or seizures.

Diprivan should be the drug of choice when initiating sedation in the trauma ICU. (Grade of recommendation – 2A).

Two commonly used intravenously (IV) administered, non-benzodiazepine sedatives are Diprivan, a short-acting sedative-hypnotic agent and Dexmedetomidine, a selective α₂-
adrenergic receptor agonist (Curtis, Hollinger, & Jain, 2013). Few studies exist that directly compare Diprivan and Dexmedetomidine use in the ICU and the majority of these studies are set in the cardiothoracic or mixed medical and surgical population (Wanat, Fitousis, Boston, & Masud, 2014; Devabhakthuni et al., 2011). Cardiothoracic ICU patients are generally extubated within 24 hours of surgery, making this population vastly different from the trauma ICU population (Reardon, Anger, Adams, & Szumita, 2013).

In a meta-analysis of RCTs published in 2013, Xia et al. reviewed 10 clinical trials which included 1202 mixed medical and surgical ICU patients. They found that there was no difference in duration of mechanical ventilation, ICU LOS or mortality between Diprivan and Dexmedetomidine. The largest RCT included in this study was carried out in 31 centers in 6 European countries (Jakob et al., 2012). The results of this trial were similar to those seen in the aforementioned meta-analysis, however these authors found that the patients in the Dexmedetomidine arm of the study had significantly more adverse events (i.e., 1st degree AV block \( p=0.04 \), higher RASS scores \( p<.001 \)) than Diprivan and Dexmedetomidine was discontinued in 9% of the patients due to lack of efficacy. Despite the large sample size in both investigations, a lack of standardized weaning protocols and criteria for extubation must be considered a limitation (Jakob et al., 2012). The meta-analysis included a large number of patients, but a relatively small number of trials. Tests for heterogeneity showed no significant differences, however the patients studied were quite varied with regard to diagnosis and type of ICU (medical, surgical, cardiothoracic) (Xia et al., 2013). This makes generalization of these results unreliable.

In 2001, the Institute of Medicine changed this country's healthcare paradigm from a "disease-centered" model to a focus on patient-centered care in which the patient participates in and determines the acceptable quality of care. Following this paradigm shift, patient satisfaction became an important outcome measure (Benedict et al., 2014). The primary goal of IV sedation in the ICU setting is patient comfort (Hughes, McGrane,
& Pandharipande, 2012), therefore, patient-reported level of satisfaction must be considered a key element in the selection of sedation agents. Three studies published during the last 10 years included self-reported patient comfort as one outcome measure in an analysis of Diprivan and Dexmedetomidine for use as sedating agents in an ICU setting (Okawa, Ichinohe, & Kaneko, 2010; Benedict et al., 2014; Corbett et al., 2005). In all three studies, the patients expressed a preference for Diprivan. Corbett et al. (2005) found that the patients in the Diprivan arm experienced a more comfortable ICU stay and fewer sleep disruptions. There were several limitations to these analyses. One (Okawa, et al., 2010) was a very small study of healthy volunteers. Benedict et al. (2014) also conducted a very small (prospective) study in which mechanically ventilated ICU patients (mixed medical/surgical/trauma) were given a sedation questionnaire approximately 24 hours after the cessation of sedation. Neither study was powered to show a significant difference. The research conducted by Corbett et al. (2005), was a prospective, RCT of 89 post-operative cardiac surgery patients who were given a validated sedation questionnaire at least 24 hours after extubation, and often after discharge from the ICU. None of these studies are generalizable to the trauma ICU population (threat to external validity), although the results are compelling. There are no published studies that directly compare Dexmedetomidine and Diprivan for use in non-neurologically affected trauma ICU patients.

A 2009 randomized, double-blinded Phase 4 trial compared Dexmedetomidine to Midazolam in mixed medical and surgical ICU patients (Riker et al., 2009). The authors found a significantly shorter time to extubation with the use of Dexmedetomidine (3.7 days [3.1 - 4.0] vs. 5.6 days [4.6 – 5.9]; \( p=0.1 \)). Trauma patients, however, were excluded from this study.

One study done at the R A Cowley Shock Trauma Center at the University of Maryland does compare these two agents in a trauma population that includes brain and spinal cord injury (Devabhakthuni et al., 2011). The authors concluded that, compared to
Diprivan, standard dosing of Dexmedetomidine resulted in longer hospital (13 days [9-21] vs. 21 days [13-27]; \(p<0.001\)) and ICU LOS (12 days [7-20] vs. 17 days [9-26]; \(p=0.004\)). When higher doses of Dexmedetomidine were used, patients had more hypotension (98% vs. 78%; \(p=0.02\)), longer ICU (12 days [7-20] vs. 20 days [12-35]; \(p=0.004\)) and hospital LOS (12 days [7-20] vs. 20 days [12-35]; \(p=0.004\)), and an increased need for supplemental analgesia, sedation and antipsychotic medications when compared to Diprivan. MacLaren et. al. (2013) also found that a Dexmedetomidine dose over 1.5 \(\mu\)g/kg/h offers little or no clinical benefit.

Further exploration is necessary to elucidate the role of these two IV sedatives in trauma patients without neurological/neurosurgical injury.

*Dexmedetomidine may be considered as a first line agent in mechanically ventilated patients that are within 24 hours of extubation* (Grade of Recommendation – 2A).

There is some evidence that, in selected mechanically ventilated cardiothoracic ICU patients, Dexmedetomidine initiated within 24 hours of extubation may decrease the time to extubation (Curtis, Hollinger, & Jain, 2013; Pasin et al., 2013). Another study of post-operative cardiac surgery patients, however, failed to show any reduction in duration of mechanical ventilation (Anger et al., 2010).

The United States Food and Drug Administration has limited its approval of Dexmedetomidine to use for less than 24 hours because the use of “Dexmedetomidine beyond 24 hours has been associated with tolerance and tachyphylaxis and a dose-related increase in adverse reactions.” (U.S. Food and Drug Administration, 2016). Therefore, the Dexmedetomidine product insert recommendations state it is to be used for “sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting. Administer by continuous infusion not to exceed 24 hours.” (Hospira, 2015).
Dexmedetomidine is the recommended sedation strategy for use in patient with hypertriglyceridemia (Grade of recommendation – 1C).

Because Diprivan is a lipophilic agent, its use in patients with a triglyceride level of >400 mg/dl is strongly associated with hypertriglyceridemia-associated pancreatitis (Devlin, Lau, & Tanios, 2005; Devaud et al., 2012). In a prospective, non-interventional study of 220 mechanically ventilated ICU patients, Devaud et al. (2012) discovered that hypertriglyceridemia occurred in 45% of patients receiving Propofol sedation. The most likely cause of this phenomenon is the chemical makeup of Propofol, which is suspended in a 10% lipid emulsion (Marino, 2008). In Devaud’s study, there were no incidences of hypertriglyceridemia-associated pancreatitis and no increase in mortality when patients receiving Propofol infusion were compared to those receiving a non-lipophilic agent, however, research published in 2005 found that 10% of the 29 patients who developed Propofol-related hypertriglyceridemia developed pancreatitis (Devlin et al., 2005).

A benzodiazepine-based sedation strategy should be utilized in patients with alcohol withdrawal syndrome. Diprivan or Dexmedetomidine may be considered as adjunct therapy (Grade of recommendation – 1A).

Dexmedetomidine has been investigated as a treatment for alcohol withdrawal. A randomized, double-blinded, placebo-controlled dose range study of 24 patients exhibiting alcohol withdrawal in a medical ICU concluded that Dexmedetomidine may reduce the need for benzodiazepines in the early stages of withdrawal, however, more patients who were treated with Dexmedetomidine rather than Lorazepam required intubation (Mueller et al., 2014). While those treated with Dexmedetomidine required lower doses of benzodiazepines than placebo (IQR -94.5 to -16.8 mg vs. IQR -31.3 to -76.2 mg; \( p=0.037 \)) at 24 hours, the median Lorazepam requirements after 7 days were
not statistically different. All patients in the study required Lorazepam after 72 hours. This trial is the only RCT published that reviews Dexmedetomidine use in alcohol withdrawal syndrome (AWS). Other publications are limited to 11 case reports and one retrospective comparison to a historical control group (MacLaren et.al., 2013). A systematic review completed by MacLaren et. al. (2013) warns against the use of Dexmedetomidine for AWS based on available literature. Additionally, the Dexmedetomidine product insert states that Dexmedetomidine is not indicated in the treatment of alcohol withdrawal (Hospira, 2015).

Two recent retrospective reviews of the management of alcohol withdrawal syndrome agree that benzodiazepines are the mainstay in the treatment of withdrawal from alcohol cessation (Sohraby, Attridge, & Hughes, 2014; Wong, Benedict, & Kane-Gill, 2015). Both articles consider Diprivan an attractive alternative to be used as an adjunct to benzodiazepines in refractory withdrawal. No RCTs currently exist to establish the role of Diprivan in the treatment of AWS (Sarff & Gold, 2010).

One RCT of 50 patients in a trauma ICU compared ethanol vs. benzodiazepines for alcohol withdrawal. The authors of this study maintain that benzodiazepines remain the treatment of choice for alcohol withdrawal in the trauma ICU (Weinberg et al., 2008).

**Conclusion**

In this era of healthcare cost containment, there should be compelling evidence of superiority with regard to outcome, safety, and patient satisfaction before any provider chooses a more expensive medication when there is a less expensive alternative. There is surprisingly little research which directly compares two widely used sedating agents in this country's ICUs, Diprivan and Dexmedetomidine, particularly in the trauma population. The research that does exist however, leads the reader to believe that they are at least equivalent (Corbett et al., 2005; Xia et al., 2013). Given that Diprivan is available for one-fifth the cost of Dexmedetomidine (personal communication with
pharmaceutical buyer, September 21, 2015) and has a similar (if not superior) safety profile, patient satisfaction rating and outcome pattern, it should be the preferred method of sedation in most ICU patients.
SEDATION PRACTICES IN THE TRAUMA ICU

Sedation Algorithm

- Consider Dexmedetomidine or Benzodiazepines
- Fluid Administration
- Pressors

- Increase dosage by 5 mcg/kg/min q5min to goal RASS 0 to -2 or max dose of 75 mcg/kg/min

- Was RASS 0 to -2 reached with Diprovan ≤ 75 mcg/kg/min

- Yes
  - No
  - Hypotension?
    - No
      - Continue Diprovan
    - Yes
      - Triglycerides <400 units
      - Yes
        - Stop Diprovan Consider Dexmedetomidine or Benzodiazepines
      - No
        - Consider Dexmedetomidine

- No
  - Triglycerides <400 units
    - Yes
      - Stop Diprovan Consider Dexmedetomidine or Benzodiazepines
    - No
      - Continue Diprovan

- Within 24 hours of extubation?
  - Yes
    - Consider Dexmedetomidine
  - No
    - Continue Diprovan