PHARMACOLOGIC DELIRIUM MANAGEMENT IN THE ICU

SUMMARY

Delirium is an acute, fluctuating disturbance in attention occurring 20-80% of ICU patients. It is associated with increased hospital length of stay, duration of mechanical ventilation, and mortality. Benzodiazepine use has been shown to be a risk factor for the development of delirium in adult ICU patients. Atypical antipsychotics, such as quetiapine, may reduce the duration of delirium.

RECOMMENDATIONS

- **Level 1**
  - **The Intensive Care Delirium Screening Checklist (ICDSC) is a valid and reliable tool to detect delirium in ICU patients**
  - **The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) may be utilized to detect delirium in patients in the absence of neurologic injuries or history of psychosis**
- **Level 2**
  - **Routine monitoring of delirium should be performed in all adult ICU patients**
  - **In patients without contraindications, quetiapine 50 mg po q 8-12 hours may be initiated to reduce the duration of delirium**
  - **Quetiapine doses may be increased by 25 mg q 8-12 hours every 24 hours as needed for persistent delirium or need for PRN rescue medications**
  - **Dexmedetomidine may be considered in mechanically ventilated patients when extubation is inappropriate due to the severity of agitation and hyperactive delirium**
- **Level 3**
  - **Benzodiazepine use should be limited in all ICU patients in the absence of alcohol or benzodiazepine withdrawal**
  - **Valproic acid may be considered as a treatment option for hyperactive delirium**
  - **A loading dose of valproic acid 1500-2000 mg can be given to individuals in whom rapid control of agitation is required, followed by a maintenance dose of 500 mg q 8-12 hours (increase by 250 mg q 8-12 hours every 24 hours as needed)**
  - **Discontinue dexmedetomidine if extubation is unsuccessful after 24 hours**
  - **Reassess the need for quetiapine and valproic acid daily (especially for therapy lasting > 2 weeks)**
  - **Monitoring for common side effects associated with both antipsychotics and valproic acid is recommended (see Table II)**

INTRODUCTION

Delirium is characterized by changes in mental status, inattention, disorganized thinking, and altered consciousness that may be accompanied by agitation. The prevalence of delirium in medical and surgical ICU cohorts has varied from 20-80% depending on the severity of illness. Despite its high prevalence,

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

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delirium is often under-recognized by clinicians due to the difficulty in diagnosis and lack of an easy to use screening tool. Several studies demonstrate that delirium is associated with increased mechanical ventilation days, hospital length of stay, and mortality, all of which lead to increased health care costs (1-3). There are two different subtypes of delirium: hyperactive and hypoactive. Hyperactive delirium is usually associated with agitation and hallucinations while hypoactive delirium is associated with lethargy, confusion, and sedation. Several risk factors have been identified that significantly increase the risk of delirium including preexisting dementia (31,33,34), history of hypertension and/or alcoholism (3,33) and a high severity of illness at admission. Exposure to benzodiazepines may be a risk factor for the development of delirium leading to the current Society of Critical Care Medicine (SCCM) guideline recommendation to use other sedatives to minimize the risk. Previously, advanced age was recognized as a risk factor for development of delirium, however, four recent studies have reported this risk to be insignificant (2,31-33).

Previously, haloperidol was recommended as the drug of choice for the treatment of ICU delirium by the SCCM. Haloperidol is a typical antipsychotic that blocks D2 dopamine receptors resulting in amelioration of hallucinations, delusions, and unstructured thought patterns. However, safety is a major concern associated with haloperidol use. Haloperidol can cause extrapyramidal symptoms (EPS) and high doses (>35 mg per day) may result in QT prolongation. Atypical antipsychotics appear to be an effective pharmacologic treatment option for the treatment of delirium with a better safety profile as compared to haloperidol. Dexmedetomidine has received increasing support as a treatment option to reduce ICU delirium. Another promising agent, valproic acid (VPA), has recently been studied in the treatment of ICU delirium. This agent is thought to benefit patients with hyperactive or mixed delirium. VPA is beneficial in the ICU setting due to its multiple dosage forms including tablets, oral solutions, and intravenous formulations.

LITERATURE REVIEW

Delirium Assessment

Due to severity of illness, frequent use of sedation and analgesia, and lack of verbal communication, it may be difficult to assess delirium in the critically ill population. Under-recognition may lead to lack of prompt treatment in ICU patients. The ideal delirium assessment scale would incorporate important delirium diagnostic criteria and be quickly and easily administered at the patient bedside. Assessment methods such as the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) and Intensive Care Delirium Screening Checklist (ICDSC) have been developed to help improve delirium recognition among the critically ill. The 2013 SCCM guidelines recommend that both the CAM-ICU and ICDSC screening methods have the highest quality of evidence in their identification of delirium.

Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) (Appendix 1)

The CAM was developed in 1990 by Inouye et al. to aide in delirium assessment by non-psychiatric personnel (6). It was modified to the CAM-ICU by Ely et al. in 2001 for use in mechanically ventilated ICU patients who are not able to verbalize (7,8). The scale utilizes four key criteria to assess delirium including 1) acute mental status change, 2) inattention, 3) disorganized thinking and 4) altered level of consciousness. The CAM-ICU was prospectively tested in 96 mechanically ventilated patients with a sensitivity of 93% and a specificity of 98% for predicting the presence of delirium (7). Patients with a history of psychosis or neurologic disease and patients who were comatose throughout admission were excluded raising concern that CAM-ICU may not be applicable in patients with neurologic injuries. (Class II)

Intensive Care Delirium Screening Checklist (ICDSC) (Appendix 2)

The ICDSC was developed in 2001 by Bergeron et al. to assess critically ill ICU patients for delirium based on DSM criteria (5). The scale was validated by assessing 93 medical and surgical ICU patients daily during the first 5 days of ICU stay (5). A score of 4 or higher was considered positive for the diagnosis of delirium with a sensitivity of 99% and a specificity of 64%. The incidence of delirium was 16% in this study as compared to 80% in previous CAM-ICU studies. Unlike the CAM-ICU studies, this study included patients with neurological injuries, dementia, or history of psychiatric disorders. (Class II)

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Devlin et al. performed a validation study of ICDSC in a medical ICU for detection of delirium before and after implementation of the screening tool (9). Physicians and nurses had greater ability to detect delirium after implementation of the ICDSC. There was also greater correlation between physician and nurse assessment after screening tool implementation. (Class II)

CAM-ICU vs. ICDSC

In a prospective observational study, both assessment tools (CAM-ICU and ICDSC) were compared in a medical and surgical ICU population for up to 7 days after ICU admission (10). Delirium was found in 41% of patients as determined by a positive result from either test. Agreement between tests was high, with a kappa coefficient for agreement of 0.8. There was an 8% discrepancy rate in delirium-negative patients and 11% discrepancy in delirium-positive patients. The study concluded that results of either assessment method are comparable. (Class II)

While it may appear that the CAM-ICU had higher specificity than the ICDSC in clinical trials, the studies validating CAM-ICU excluded patients with neurological abnormalities whereas the ICDSC trials did not. The CAM-ICU questionnaire is more involved than that of ICDSC. Thus, based on available evidence, the scales have similar reliability, but the ICDSC may be a quicker and easier tool to use.

Pharmacologic Management of Delirium: Clinical Trials

Haloperidol and Atypical Antipsychotics

Current data supporting the use of haloperidol for ICU delirium is largely based on one retrospective review of a mixed ICU population (11). Over 900 patients (83 received haloperidol; 906 no haloperidol) who remained mechanically ventilated for greater than 48 hours were evaluated for mortality, duration of mechanical ventilation, and ICU length of stay. The average dose and duration of haloperidol was 11.5 mg/day for 3.5 days. While there were no differences in the duration of mechanical ventilation and ICU length of stay, haloperidol use was associated with a significant decrease in hospital mortality compared to the non-haloperidol group (adjusted relative risk 15.6%). (Class II) Due to the retrospective nature of this trial, there was no formal assessment of delirium nor discussion of other confounding factors for delirium. The MIND trial prospectively evaluated the efficacy of haloperidol for ICU delirium management in comparison to placebo (12). The use of haloperidol was not found to improve delirium days, ventilator-free days, or mortality. Authors concluded that the small sample size may contribute to the negative findings and a large multi-center placebo trial is warranted.

Several studies have examined the role of atypical antipsychotics for delirium management in various populations (Table I) (13-17). One study prospectively evaluated the use of olanzapine vs. haloperidol in medical-surgical ICU patients (16). The duration of the study was 5 days and the ICDSC screening tool was used for delirium assessment. Both olanzapine and haloperidol were found to reduce delirium symptoms. (Class II) Patients who received haloperidol experienced more extrapyramidal side effects, and no adverse events were reported in the olanzapine group. Devlin et al. conducted a prospective, randomized, placebo-controlled trial evaluating the efficacy and safety of quetiapine (17). More than 70% of the study population were medical ICU patients. Quetiapine resulted in a faster resolution of delirium compared to placebo, but no significant differences in duration of mechanical ventilation, ICU and hospital length of stay, or mortality. (Class II) The incidence of adverse drug events was similar between the two groups. Results from this study suggest that quetiapine is a safe choice for delirium management and can be considered as an add-on therapy to haloperidol.

Valproic Acid

Recent evidence has surfaced regarding the use of valproic acid (VPA) for hyperactive or mixed delirium. Due to its mechanism of action, VPA is theoretically beneficial, and a recent retrospective cohort evaluated the use of VPA for agitation in 53 critically ill patients (26). Patients were initiated on a median maintenance dose of 1500 mg/day (1000 - 2275mg). Loading doses were provided in 42% of patients at a median of 1800 mg (1000-2275 mg). Incidence of agitation on day 3 decreased significantly from 96% to 61% (p<0.0001) and incidence of delirium decreased significantly from 68% to 49% (p=0.012). The proportion of patients receiving opioids, quetiapine, and dexmedetomidine also significantly decreased by day three along with median fentanyl requirements. The most common side effects included hyperammonemia

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(19%), and thrombocytopenia (13%). This data supports the findings from a few case series. One series including 15 patients with hyperactive delirium (defined according the Liptzin criteria) demonstrated that VPA in a range of 1133 – 1258 mg in 2 to 3 divided doses resulted in resolution in 13 out of 16 patients within 6.2 days (35). In most cases, the primary team had tried multiple medications to control agitation associated with hyperactive delirium including various antipsychotics and benzodiazepine agents, opiates, dexmedetomidine, and propofol prior to starting VPA as a combination therapy. Only one patient in the case series received monotherapy with VPA due to a prolonged baseline QTc (27). A second case series reported resolution of agitation and delirium within 24 hours in two patients after administration of valproate 500 mg in two divided doses (28). These studies conclude that valproate may be a reasonable treatment option in ICU delirium, although randomized controlled studies are needed to confirm the benefits.

Dexmedetomidine

The MENDS trial, published in 2007, was a double-blind, randomized controlled study comparing dexmedetomidine and lorazepam on acute brain dysfunction in mechanically ventilated patients (36). Patients were included if either agent was used for up to 120 hours. Delirium scores were assessed twice daily utilizing the CAM-ICU scale. As a result, dexmedetomidine use in mechanically ventilated patients resulted in more days alive without delirium or coma (median days, 7 vs 3; p=0.01). The 2009 SEDCOM Trial was a prospective, double blinded, randomized control trial. Patients were included if they were expected to be mechanical ventilated for greater than 24 hours. The objective of this trial was to compare the efficacy and safety of sedation with dexmedetomidine vs midazolam. Patients treated with dexmedetomidine had comparable sedation levels, a shorter duration of mechanical ventilation, and had significantly less delirium measured via the CAM-ICU scale (37).

Dexmedetomidine has also recently been examined in ICU patients with agitated delirium in two control trials. The DahLIA study was a randomized, double-blind, placebo-controlled, parallel-group trial involving 74 adult patients in whom the barrier to extubation was the severity of agitation and delirium (29). Dexmedetomidine was titrated between 0 and 1.5 mcg/kg/h to achieve physician-prescribed sedation goals. As a result, dexmedetomidine increased ventilator-free hours at 7 days compared to placebo (median difference between groups: 17.0 hours; p=0.01), decreased time to extubation (median difference: 19,5 hours; p<0.007), and accelerated the resolution in delirium (median difference; 16.0 hours; p=0.01). A hierarchical Cox modeling showed that dexmedetomidine was significantly associated with earlier extubation. In a nonrandomized, controlled trial, dexmedetomidine was also studied in non-intubated ICU patients refractory to haloperidol after an initial haloperidol titration (2.5-5 mg q 10-30 minutes up to 30 mg) (30). In patients that did not achieve a RASS of 0 to -2, dexmedetomidine was started at 0.2 mcg/kg/hr (max of 0.7 mcg/kg/min) to attain a RASS score of 0. Time to attain a RASS score of 0 was similar in both groups, but more patients in the dexmedetomidine group achieved a higher percentage of time in satisfactory RASS scores than did haloperidol (92.7% vs 59.3%; p=0.0001). The study also demonstrated that haldol was associated with more adverse effects including 10 cases of oversedation and 2 episodes of QT prolongation.

TABLE I

Study	Design	Methods	Conclusions
Haloperidol			
Milbrandt EB 2005	• Retrospective cohort • >48 hr MV • Mixed MICU, SICU, CVICU, TICU	• N=989 pt: Haloperidol 83; Nonhaloperidol 906 • Mean daily dose 11.5 ± 11.6 mg x 3.5 days	• Haloperidol use was associated with decreased hospital mortality and increased survival compared to non-haloperidol group • No difference in the duration of MV or ICU LOS between 2 groups
Girard T 2010	• Prospective, R,D,P (MIND Trial) • Mechanical ventilated Medical	• N=101: Haloperidol N=35; Ziprasidone N=30; Placebo N=36 • Dose: H 15 mg/day; Ziprasidone 113.3	• No difference in the duration of delirium or coma among study groups • No significant adverse events were reported

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	and surgical ICU patients	mg/day; all given orally • CAM-ICU used for screening	
Atypical Antipsychotics			
Sipahimalani A 1998	• Prospective nonrandomized • Patients with primary psychiatric disorders (non-ICU pt) • Co-morbidity include TBI; hypoxia, infection, MI	• N=22 pts: olanzapine N=11; haloperidol N=11 • Dose: olanzapine 5-15 mg PO/day; haloperidol 1.5-10 mg PO/day • Delirium Rating Scale (DRS) was used	• Peak response achieved at Olanzapine 6.8 ± 3.5 days Haloperidol 7.2 ± 4.9 days • Duration of treatment Olanzapine 23.6 ± 28.3 days Haloperidol 14.6 ± 12.8 days
Schwartz TL 2000	• Retrospective chart review • Patients with primary psychiatric disorders (non-ICU pt) • Co-morbidity include TBI; hypoxia, infection, CA	• N=22 pts: quetiapine N=11; haloperidol N=11 • Dose: quetiapine 211.4 mg/day; haloperidol 3.4 mg/day • Delirium Rating Scale (DRS) was used	• Peak response achieved at Quetiapine 6.5 days Haloperidol 7.6 days • Duration of treatment Quetiapine 13 days Haloperidol 10.4 days
Han CS 2004	• Prospective R,DB • Mixed floor, ICU, oncology pt • Duration 7 days	• N=24 pts: risperidone N=12; haloperidol N=12 • Dose: risperidone 0.5 mg BID titrated (1.02 mg/day); haloperidol 0.75 mg BID titrated (1.71 mg/day) • The Memorial Delirium Assessment scale used	• No difference in efficacy or response rate between 2 treatments
Skrobik YK 2004	• Prospective randomized • Med-surg ICU • >24 hr ICU LOS • Duration 5 days	• N=73 pts: olanzapine N=28; haloperidol N=45 • Dose: olanzapine 5 mg PO/day titrated; haloperidol 2.5-5 mg PO Q8h • ICDSC used TID for delirium screening	• Both agents reduced delirium symptoms – no significant difference • 6 pt in haloperidol developed EPS; no ADR reported in olanzapine
Devlin J 2010	• Prospective, D,P, RCT • MICU and SICU • Duration up to 10 days	• N=36 pt (Quetiapine 18 pts; Placebo 18 pts) • Quetiapine 50mg Q12h upto 200mg Q12h • All received PRN Haloperidol	• Shorter time to first resolution of delirium with quetiapine than placebo (1 vs. 4.5 days; p=0.001) • Less time spent in delirium with quetiapine than placebo (36 vs. 120 hrs; p=0.006) • No difference in duration of mechanical ventilation, ICU and hospital LOS, and mortality

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		• ICDSC ≥4 for delirium	
Valproic Acid (VPA)			
Gagnon D 2016	• Retrospective cohort • ICU patients • Treated with VPA > 2 days	• N=53 pts • VPA median 1500 mg/day in 1-4 doses • Loading dose median of 1800 mg used in 42% of patients • CAM-ICU utilized	• Less incidence of agitation on day 3 with VPA than placebo (96% vs. 61% p<0.0001) • Less incidence of Delirium on day 3 with VPA than placebo (68% vs. 49% p=0.012) • VPA significantly decreased proportion of pts receiving opioids, dexmedetomidine, and median fentanyl requirements
Dexmedetomidine (DEX)			
Pandharipande PP 2007	• Prospective, DB, RCT • MICU, SICU patients • Mechanically ventilated	• N=106 • DEX initated at 0.15 mcg/kg/hr (max 1.5 mcg/kg/hr) • Lorazepam initiated at 1 mg/hr (max 10 mg/hr) • CAM-ICU utilized	• DEX sedation resulted in more days alive without delirium or coma (7 vs. 3 days p=0.01) • DEX patients spent more time in goal sedation • No difference in cost or 28-day mortality
Riker RR 2009	• Prospective, DB, RCT • MICU, SICU patients • Expected mechanical ventilation > 24 hours	• N=375 (DEX 244 pts, midazolam 122 pts) • DEX 0.2-1.4 mcg/kg/hr • Midazolam 0.02-0.1 mg/kg/hr • Both groups titrated to RASS -2 to +1 • CAM-ICU utilized	• Prevalence of delirium: DEX 54% vs. midazolam 76.6% (p<0.001) • Median time to extubation was 1.9 days shorter in DEX group (p=0.01) • No difference in ICU length of stay • DEX treated patients were more likely to develop bradycardia but were less likely to develop hypertension requiring treatment
Reade M 2016	• DB, PC, PG RCT • MICU, SICU, CICU patients • Agitated delirium barrier to extubation • Ventilated patients	• N=71 (DEX 39 pts, placebo 32 pts) • DEX 0.5 mcg/kg/hr titrated to rates between 0 and 1.5 mcg/kg/hr to achieve sedation goals • CAM-ICU utilized	• Increased ventilator-free hours at 7 days compared to placebo (144.8 hrs vs. 127.5 hrs p=0.01) • Reduced time to extubation (21.9 hrs vs. 44.3 hrs p<0.001) • Accelerated resolution of delirium compared to placebo (23.3 vs. 40.0 hrs p=0.01)
Carrasco G 2016	• MICU/SICU patients • RASS +1 to +4 • CAM-ICU + or ICDSC + • Non-ventilated patients	• N=132 (DEX 46 pts, haloperidol 86 pts) • Haloperidol 2.5 mg to 5 mg q10-30 min until RASS 0 to -2 or maximum 30 mg. • Nonresponders (max 30 mg haldol), started on DEX 0.2 mcg/kg/hr to max 0.7 mcg/kg/hr • CAM-ICU utilized	• DEX achieved a higher percentage of time in satisfactory sedation level compared to haldol (92.7% vs. 59.3% p=0.0001) • Haldol associated with 10 cases of oversedation and 2 cases of prolonged QT interval • Decrease in total cost compared to haldol due to decrease in ICU LOS (3.1 vs. 6.4 days p<0.0001)

THERAPEUTIC RECOMMENDATIONS

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Recent changes to the SCCM guidelines suggest atypical antipsychotics are an effective pharmacologic treatment option for delirium with a better safety profile as compared to haloperidol. Recent literature suggests agents such as VPA and dexmedetomidine, may be beneficial when used in the treatment of delirium. Therefore, the ease of administration, pharmacokinetics, potential drug interactions, and safety profile should be considered when making a therapeutic recommendation. The onset of intravenous haloperidol is approximately 3-20 minutes, and the elimination half-life is between 10-36 hours. Haloperidol is metabolized extensively through the liver and does produce an active metabolite. Major concerns with haloperidol include extrapyramidal side effects (EPS), QTc prolongation, and neuroleptic malignant syndrome (NMS). QTc prolongation is generally dose related and is more pronounced in elderly patients or those with underlying cardiac problems (19-21). Several case reports describe development of NMS associated with haloperidol use; patients with traumatic brain injury appear to be more susceptible to this complication (22).

Quetiapine is the most frequently used agent for delirium management due to its efficacy and safety profile when compared to haloperidol. Compared to other atypical antipsychotics, quetiapine has preferable pharmacokinetic properties for us in the ICU population including its relatively fast onset of action and shorter half-life which allows for rapid titration (Table II). The most common side effects among atypical antipsychotics are sedation, QTc prolongation and anti-cholinergic effects (dry mouth, tachycardia, urinary retention, and constipation).

In patients with contraindications to haloperidol or quetiapine such as a prolonged QT interval or drug-drug interactions, VPA is an alternative option for hyperactive delirium. This agent can achieve rapid agitation control and has multiple routes of administration. Limited data exists regarding utilization of a loading dose; however, this may be beneficial if rapid control of delirium is desired (Level III). The most common side effects of valproic acid include hyperammonemia, thrombocytopenia, elevated liver enzymes, pancreatitis, and somnolence. If used, physicians should monitor CBCs daily, obtain liver function tests every 3-5 days, ammonia levels (only if change in mental status), and amylase/lipase if continued for more than seven days. VPA should not be used in patients with hepatic disease, urea cycle disorders, or pregnancy.

Dexmedetomidine can be considered in situations in which profound agitation is the main barrier to extubation. This agent has no effect on respiratory drive making it an ideal agent to control hyperactive delirium if the patient is a candidate for extubation within 24 hours (Level I). Due to high cost, this agent should be reserved for patients who are refractory to or have contraindications to haloperidol, atypical antipsychotics, or valproic acid. Common adverse events of dexmedetomidine include bradycardia and hypotension.

TABLE II

	Dosage forms	**Dosing**	**Monitoring**
Risperidone	- Tablet - Orally-disintegrating tablet - Solution	- 1 mg PO Q12 hr - Increased in increments of 0.5-1 mg/day every 2-3 days - Max daily dose 6 mg - Renal and hepatic adjustment (0.5 mg Q12h)	- Obtain EKG for QTc assessment - Assess for drug-drug interactions - Monitor for EPS
Olanzapine	- Tablet - Orally-disintegrating tablet	- 2.5 mg PO QHS - Increase in increments of 5 mg/day - Max daily dose 20 mg - No renal adjustment	- Obtain EKG for QTc assessment - Liver function tests o Baseline o Every 3-5 days - Assess for drug-drug interactions - Monitor for EPS, NMS

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Quetiapine	- Tablet - Extended-release tablet	- 50 mg PO Q12 hr - Titrated in increments of 25 mg at a frequency of every 8-12 hrs - Max daily dose 600 mg - No renal adjustment	- Obtain EKG for QTc assessment o Baseline o After dose increases or addition of concomitant QT prolonging agents - Assess for drug-drug interactions - Monitor for EPS, NMS
Valproic Acid	-Tablet -Liquid oral solution -IV	- Loading dose 1500-2000 mg x 1 dose - Maintenance: 500 mg Q8-12H - Titrate by 250 mg increments - Maximum dosage: 60 mg/kg/day	- Obtain CBC daily - Liver function tests o Baseline o Every 3-5 days - Ammonia o Mental status change o Day 7 then every 3-7 days - Consider amylase/lipase after 7 days of therapy
Dexmede-tomidine	-IV	- Starting dose 0.2 mcg/kg/hr - Titrate to RASS goal - Maximum 1.5 mcg/kg/hr	- Monitor for bradycardia, hypotension

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Surgical Critical Care Evidence-Based Medicine Guidelines Committee

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Appendix 1: Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)

Feature 1: Acute Onset or Fluctuating Course Positive if you answer 'yes' to either 1A or 1B.	**Positive**	**Negative**
1A: Is the patient different than his/her baseline mental status? or **1B**: Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation scale, GCS, or previous delirium assessment?	**Yes**	**No**
Feature 2: Inattention Positive if either score for 2A or 2B is less than 8. Attempt the ASE letters first. If patient is able to perform this test and the score is clear, record this score and move to Feature 3. If the patient is unable to perform this test or the score is unclear, then perform the ASE pictures. If you perform both tests, use the ASE pictures' results to score the Feature.	**Positive**	**Negative**
2A: ASE Letters: record score (enter NT for not tested) Directions: Say to the patient, *"I am going to read you a series of 10 letters. Whenever you hear the letter 'A,' indicate by squeezing my hand."* Letters from the following letter list in a normal tone. **S A V E A H A A R T** Scoring: Errors are counted when patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A."	**Score (out of 10):** _____	
2B: ASE Pictures: record score (enter NT for not tested) Directions are included on the picture packets.	**Score (out of 10):** _____	
Feature 3: Disorganized Thinking Positive if the combined score is less than 4.	**Positive**	**Negative**
3A: Yes/No Questions (Use either Set A or Set B, alternate on consecutive days if necessary): **Set A** 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does one pound weigh more than two pounds? 4. Can you use a hammer to pound a nail? **Set B** 1. Will a leaf float on water? 2. Are there elephants in the sea? 3. Do two pounds weigh more than one pound? 4. Can you use a hammer to cut wood? **Score** _____ (patients earns 1 point for each correct answer out of 4)	**Combined Score (3A+3B):** _____ **(out of 5)**	
3B: Command Say to the patient, *"Hold up this many fingers"* (examiner holds two fingers in front of patient) *"Now do the same thing with the other hand"* (not repeating the number of fingers). *If patient is unable to move both arms, for the second part of the command as the patient to *"Add one more finger."* **Score** _____ (patients earns 1 point for each correct answer out of 4)		
Feature 4: Altered Level of Consciousness Positive if the actual RASS score is anything other than zero.	**Positive**	**Negative**
Overall CAM-ICU (Features 1 and 2 must be positive and either Feature 3 or 4 positive)	**Positive**	**Negative**

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Appendix 1: Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) (continued)

Richmond Agitation-Sedation Scale (RASS)

+4	**Combative**	Combative, violent, immediate danger to staff
+3	**Very agitated**	Pulls or removes tube(s) or catheter(s); aggressive
+2	**Agitated**	Frequent nonpurposeful movement, fights ventilator
+1	**Restless**	Anxious, apprehensive but movements are not aggressive or vigorous
0	**Alert and calm**	
-1	**Drowsy**	Not fully alert, but has sustained awakening to voice (eye opening & contact > 10 sec)
-2	**Light sedation**	Briefly awakens to voice (eye opening & contact < 10 sec)
-3	**Moderate sedation**	Movement or eye opening To voice (but no eye contact)
-4	**Deep sedation**	No response to voice, but movement or eye opening to physical stimulation
-5	**Unarousable**	No response to voice or physical stimulation

Sedation and Delirium Assessments: A Two Step Approach

Step One: Sedation Assessment *(RASS)*

If RASS is -4 or -5, then **Stop** & **Reassess** patient at later time
If RASS is above - 4 (-3 through +4) then **Proceed to Step 2**

Step Two: Delirium Assessment *(CAM-ICU)*

Feature 1: Acute onset of mental status changes or a fluctuating course

And

Feature 2: Inattention

And

Feature 3: Disorganized Thinking

Or

Feature 4: Altered Level of Consciousness

= DELIRIUM

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Ely, Crit Car Med 2001: 29,1370-1379.
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Appendix 2: Intensive Care Delirium Screening Checklist (ICDSC)

<table>
<tr><th></th><th>Points</th></tr>
<tr><td>
1. Altered level of consciousness (SAS Score)
Note: May need to reassess patient if recent administration of sedation therapy
<table>
<tr><th>Behavior</th><th>Score</th></tr>
<tr><td>Unarousable: minimal or no response to noxious stimuli</td><td>1</td></tr>
<tr><td>Very sedated: arouses to physical stimuli only</td><td>2</td></tr>
<tr><td>Sedated: difficult to arouse, awakens to verbal stimuli or gentle shaking</td><td>3</td></tr>
<tr><td>Calm and cooperative: calm; awakens easily</td><td>4</td></tr>
<tr><td>Agitated: anxious or agitated but calms down to verbal instructions</td><td>5</td></tr>
<tr><td>Very agitated: Does not calm down on verbal reminder, requires physical restraints</td><td>6</td></tr>
<tr><td>Dangerous agitation: pulling at tubes/removes catheters/thrashing side to side; hits staff</td><td>7</td></tr>
</table>
➢ Exaggerated response to normal stimulation: SAS = 5, 6, or 7 → score 1 point
➢ Normal wakefulness: SAS = 4 → score 0 points
➢ Response to mild or moderate stimulation (follows commands): SAS = 3 → score 1 point
Score 0 if altered level of consciousness related to recent sedation/analgesia
➢ Response only to loud voice and pain: SAS = 2 **Stop assessment
➢ No response: SAS = 1 **Stop assessment
</td><td></td></tr>
<tr><td>
2. Inattention - Score 1 point for any of the following abnormalities:
A. Difficulty in following commands OR
B. Easily distracted by external stimuli OR
C. Difficulty in shifting focus
Does the patient follow you with their eyes?
</td><td></td></tr>
<tr><td>
3. Disorientation - Score 1 point for any one obvious abnormality:
A. Mistake in either time, place or person
Does the patient recognize ICU caregivers who have cared for him/her and not recognize those that have not? What kind of place are you in?
</td><td></td></tr>
<tr><td>
4. Hallucinations or Delusions - Score 1 point for either:
A. Equivocal evidence of hallucinations or a behavior due to hallucinations
(Hallucination = perception of something that is not there with NO stimulus) OR
B. Delusions or gross impairment of reality testing
(Delusion = false belief that is fixed/unchanging)
Any hallucinations now or over past 24 hrs? Are you afraid of the people or things around you? [fear that is inappropriate to clinical situation]
</td><td></td></tr>
<tr><td>
5. Psychomotor Agitation or Retardation - Score 1 point for either:
A. Hyperactivity requiring the use of additional sedative drugs or restraints in order to control potential danger (e.g. pulling IV lines out or hitting staff) OR
B. Hypoactive or clinically noticeable psychomotor slowing or retardation
Based on documentation and observation over shift by primary caregiver
</td><td></td></tr>
<tr><td>
6. Inappropriate Speech or Mood - Score 1 point for either:
A. Inappropriate, disorganized or incoherent speech OR
B. Inappropriate mood related to events or situation
Is the patient apathetic to current clinical situation (i.e. lack of emotion)? Any gross abnormalities in speech or mood? Is patient inappropriately demanding?
</td><td></td></tr>
<tr><td>
7. Sleep/Wake Cycle Disturbance - Score 1 point for:
A. Sleeping less than four hours at night OR
B. Waking frequently at night (do not include wakefulness initiated by medicalstaff or loud environment) OR
C. Sleep ≥ 4 hours during day Based on primary caregiver assessment
</td><td></td></tr>
<tr><td>
8. Symptom Fluctuation - Score 1 point for:
A. Fluctuation of any of the above items (i.e. 1 – 7) over 24 hours (e.g. from one shift to another)
Based on primary caregiver assessment
</td><td></td></tr>
<tr><td>TOTAL SCORE (Add 1 – 8): Delirium is defined as an ICDSC score > 4 PLUS clinical judgment</td><td></td></tr>
</table>

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