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DELIRIUM MANAGEMENT IN THE ICU

Evidence Based Medicine Guideline

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SUMMARY

Delirium is a common but frequently unrecognized occurrence in admitted patients, especially those older than 65 years of age. Delirium is associated with multiple adverse consequences such as increased hospital length of stay (LOS), 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. Improved recognition and treatment of delirium is recommended to reduce LOS and physiologic impact among older patients with 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.**
  - **Non-pharmacologic interventions should be utilized for delirium prevention and initial management.**
  - **In patients without contraindications, quetiapine 50 mg po q 8-12 hours may be initiated to reduce the duration of delirium. Quetiapine 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).**

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** 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.

INTRODUCTION

Delirium is a common neurocognitive disorder seen in hospitalized adults, particularly those greater than 65 years of age, and can have devastating consequences. Delirium is defined as an acute state of confusion that is characterized by a sudden onset, fluctuating course of inattention and either hyperactive or hypoactive levels of consciousness (1). The prevalence of delirium in medical and surgical ICU cohorts has varied from 20-80% depending on the severity of illness. The cause of delirium is thought to be multifactorial, including predisposing characteristics such as older age, sensory impairment, and cognitive impairment, and precipitating characteristics such as infection, medications, and hospitalization (2). Delirium prolongs hospitalization, increases healthcare costs, increases the risk of post-discharge institutionalization, and is a predictor of mortality in hospitalized older adults.

There are two 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. Modifiable risk factors for delirium include benzodiazepine use and blood transfusions. Nonmodifiable risk factors for delirium include greater age, dementia, prior coma, pre-ICU emergency surgery or trauma, and increasing Acute Physiology and Chronic Health Evaluation and American Society of Anesthesiology scores (3).

Delirium is often preventable, and many institutions have implemented delirium protocols and/or guidelines to aid in the prevention of delirium in vulnerable patients. Screening patients for delirium with methods such as the Confusion Assessment Method for the ICU (CAM-ICU) or Intensive Care Delirium Screening Checklist (ICDSC) has allowed for earlier interventions and decreased morbidity (2). The average LOS in patients diagnosed with delirium can be decreased with the implementation of delirium protocols, delirium guidelines, or Delirium Teams, which ultimately is associated with cost savings (4).

The following guidelines outline an evidence-based medicine approach to the recognition of patients at risk for delirium and the management of patients with delirium based on the current medical literature and published consensus statements. The importance of frequent and open communication between nurses caring for the patient and the intensive care providers cannot be overemphasized.

LITERATURE REVIEW

Delirium Assessment

Due to severity of illness, frequent use of sedation and analgesia, and lack of verbal communication, it can be difficult to assess delirium in the critically ill population. Under-recognition can lead to a lack of prompt treatment in ICU patients. Unfortunately, delirium goes undetected in at least 75% of patients who are not routinely monitored for it (1). The ideal delirium assessment scale would incorporate important delirium diagnostic criteria and be quickly and easily administered at the bedside. Assessment methods such as the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) have been developed to help improve delirium recognition among the critically ill. The Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption (PADIS Guidelines) state that critically ill adults should be regularly assessed for delirium using a valid tool (3).

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 (5). 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 (6,7). 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 (6). 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 (8). The scale was validated by assessing 93 medical and surgical ICU patients daily during the first 5 days of ICU stay (8). 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) 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.

Delirium Prevention

The goal for patients who do not have delirium at the time of hospital admission is to prevent delirium from developing. Positive delirium screening in critical ill adults is strongly associated with cognitive impairment at 3 and 12 months after ICU discharge (3). Risk factors for delirium need to be identified and avoided whenever possible. Delirium prevention guidelines should emphasize the use of non-pharmacologic multicomponent interventions to minimize delirium risk. These interventions focus on meeting basic human needs while hospitalized, including hydration, sleep, comfort, accurate sensory perception, and orientation to time and place while allowing patients to safely mobilize and maintain their independence, avoiding physical and chemical restraints whenever possible. Non-pharmacologic interventions should be started on hospital admission for older adults at high risk for delirium. Delirium preventions should be implemented consistently to be effective. Along with nursing and medical staff, patients' family, friends, and hospital volunteers can aid with certain delirium prevention techniques such as reorientation, range-of-motion exercises, and oral fluid encouragement (1).

Risk factors present at baseline that place patients at increased risk for developing delirium include but are not limited to dementia, severe illness, multiple comorbidities, depression, vision or hearing impairment, poor nutritional status, functional impairment, history of stroke or TIA, history of alcohol use disorder, history of delirium, and age >70 years. Risk factors that can trigger delirium include but are not limited to medications, anesthesia or sedation, toxins, acute intoxication, tethers, indwelling urinary catheters, physical restraints, IV infusions, dehydration, glucose imbalance, electrolyte abnormalities, infection, acute hypoxia, uncontrolled pain, major surgical procedures, acute kidney or liver failure, trauma, and seizures or post-ictal state (1).

Medications that can precipitate delirium include pain medications, anticholinergics, sedatives and hypnotics, anti-epileptics, antidepressants, lithium, cholinesterase inhibitors, dopamine agonists, muscle relaxants, cardiovascular medications, corticosteroids, gastrointestinal agents, diabetes agents, and herbal medications (1). Pain medications that can precipitate delirium include opioids and Nonsteroidal Anti-Inflammatory Drugs (NSAIDs). Anticholinergics that can precipitate delirium include diphenhydramine, scopolamine, and Atropine. Sedatives and hypnotics that can precipitate delirium include benzodiazepines, non-benzodiazepine "Z-drugs" (such as Zolpidem), and barbiturates. Antiepileptics that can precipitate delirium include carbamazepine, levetiracetam, phenytoin, and valproate. Antidepressants that can precipitate delirium include mirtazapine, tricyclic antidepressants (TCA), and selective serotonin reuptake inhibitors (SSRIs) when combined with other deliriogenic medications (11). Dopamine agents that can precipitate delirium include levodopa, pramipexole, ropinirole, and amantadine. Muscle relaxants that can precipitate delirium include baclofen and cyclobenzaprine. Cardiovascular medications that can precipitate delirium include antiarrhythmics, clonidine, digoxin, beta-blockers, and diuretics. Gastrointestinal agents that can precipitate delirium include metoclopramide, chlorpromazine, promethazine, dicyclomine, loperamide, and H_2-receptor blockers. Diabetes agents that can precipitate delirium include sulfonylureas and insulin. Herbal medications that can precipitate delirium include St. John's wort, valerian, and jimsonweed.

Non-Pharmacologic Management of Delirium

The most effective interventions for the management of delirium include modifying the patient's environment, cognitive stimulation, using behavioral de-escalation techniques, and enhancing comfort and sleep. Consistent care, such as the same staff caring for the patient or having a sitter, help to manage delirium. Patients first need to

be identified as high risk and prevention strategies previously discussed should be started on admission. Medications should be reviewed and deliriogenic medications should be held. Treatment teams should avoid prescribing deliriogenic medications while hospitalized, although this is not always possible.

Melatonin or ramelteon should be given approximately 2 hours before bedtime to promote a normal sleep/wake cycle (1). Stimulation should be decreased at night; any interruptions should be decreased between the hours of 10 pm and 7 am, and televisions and lights in the patient's room should be turned off to promote sleep and noise in the unit should be limited. If possible, infusions pumps and monitors that alarm at the nursing station rather than in the patient's room should be utilized to avoid sleep interruption. In the morning, blinds should be opened to allow for natural light and room and unit lights should be turned on to promote a normal sleep/wake cycle. Caffeine should be withheld after noon (12).

Physical activity should be encouraged during the day and patients should be encouraged to eat meals in a chair instead of in bed when appropriate and safe. Family visitations should be encouraged to reorient patient and promotion of usual patient routines should be encouraged; the team should communicate the routine frequently to the patient. Patient family photos can also help to promote usual patient routines and reorientation. The patient should be encouraged to perform regular personal care routines such as brushing hair, brushing teeth, etc. Patients' glasses, dentures, and hearing aids should be easily accessible to them. Use medical interpreters and translators when needed. Continues IV fluids, urinary catheters, physical restraints, and other tethering devices should be avoided whenever possible. Early mobility with daily physical therapy or rehab should be encouraged. Pain should be attempted to be managed with Tylenol or non-pharmacologic interventions; if severe pain is present, the lowest possible dose of opioids should be used. Comfort rounds should be utilized which help to ensure the patient is toileting, repositioned, has a snack/drink if appropriate, pain is well controlled, they are warm enough, and the bed alarm is within reach. A working clock and up-to-date calendar should be visible in the patient's room (13). Room changes should be avoided, particularly at night. Continuity of care should be attempted with the same nurses, patient care technicians, and physicians whenever possible (12).

Difficulty with elimination of bowels and bladder can be delirium inducing in the elderly. Assistance with toileting should be given hourly during the day, then every 2-4 hours while awake in the evening. If unable to void after 8 hours, a bladder scan should be performed. In and out catheterization should be utilized every 8 hours if post-void residual is greater than 200 mL, until volume is less than 200 mL. No oral liquids should be given after 8pm, if possible. If a Foley was inserted on admission, it should be encouraged to be removed by hospital day 3 (12). Constipation should be avoided to maintain patients' usual habits and routines; a bowel regimen should be started on hospital admission. If no bowel movement (BM) on hospital day one, a PO laxative nightly can be administered. If no BM by day 2, laxative should be increased to PO BID. If no BM by day 3, rectal intervention should be performed in the morning and the physician should be notified if no results. Warm prune juice or fruitlax can be added to the diet of patients able to take food by mouth. Lactulose 15-30 mL PO daily to BID prn is the preferred laxative through tube feeds. Magnesium hydroxide 30 mL PO daily to BID prn can be added. Senokot PO nightly or BID prn (max 8 tabs in 24h) can be added. Glycerine suppository per rectum daily PRN can be added. Bisacodyl suppository 10mg per rectum daily prn can be added (14).

Delirium Protocol

Activity	Ambulation ASAP according to orders, PT/OT
Intake and Output	Every 8 hours, including food intake
Environment and Sleep	Private room if available, no vitals between 10 pm and 6 am if possible, no non-emergent lab draws or radiological tests between 10 pm and 6 am, noise reduction (for nighttime sleep, no daylight quiet time), encourage sleep hygiene/nightly rituals
Orientation	Reorient and direct the patient as needed, validate patient experience as needed, promote day orientation (blinds and curtains open, lights on), promote night orientation (blinds and curtains closed, lights off), consistent staff whenever possible, avoid changing rooms and procedures after 9pm if possible
Bladder	If no urinary output, perform bladder scan and call provider if >300 mL
Toilet patient	Every 2 hours during waking hours
Bowel management	Avoid stool softeners without addition of a bowel stimulant, do not use milk of magnesia
Diet/Nutrition	Offer snacks and fluids between meals, assist with tray setup and meals, comfort foods, out of bed to chair for meals
Labs	Critically evaluate the need for all laboratory tests
Pain	Geriatric dosing, avoid deliriogenic medications

Pharmacologic Management of Delirium

Despite attempts to prevent delirium and utilize non-pharmacologic management strategies for treating delirium, a patient with hyperactive or mixed delirium may become aggressive, violent, or disoriented to their situation that they pose a danger to themselves or others. If non-pharmacologic strategies are insufficient for safety of the patient and others, use of antipsychotic medication may be necessary. It should be remembered that despite their short-term calming effect on aggressive behaviors, these medications do not actually treat the underlying delirium. Pharmacologic management of delirium should be individualized. Therefore, the ease of administration, pharmacokinetics, potential drug interactions, and safety profile should be considered when making a therapeutic recommendation. There is no evidence to support the routine use of antipsychotics for delirium treatment, and many of these medications carry risks for oversedation, QT interval prolongation, extrapyramidal symptoms, and increased mortality in older patients with dementia (1).

Haloperidol (Haldol)

Haldol can be given oral (PO), IV, or IM for delirium, agitation, and psychosis. Initial dosing should be 0.5-1 mg every day to twice daily. PRN dosing should be 0.25-2 mg every hour for serious agitation. 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 (15-17). Several case reports describe development of NMS associated with haloperidol use; patients with traumatic brain injury appear to be more susceptible to this complication (18). Haldol is contraindicated in patients with Parkinson disease and those with QTc>500 (4).

Risperidone (Risperdal)

Risperdal can be given orally, via orally disintegrating tablet (M-tab), or in depot form but no a standard IM for delirium, psychosis/agitation, and aggression. It is less sedating that Quetiapine or Olanzapine. Initial dosing should be 0.5-1 mg every day or twice daily. PRN dosing should be 0.5-1 mg every 4 hours, not exceeding 6 mg per day. Risperdal should be avoided in patients with Parkinson disease and in those with QTc>500. Risperdal causes less QTc prolongation than Haldol (1). Risperdal may cause tachycardia and hypotension (4).

Quetiapine (Seroquel)

Seroquel is given orally and is the preferred agent for delirium in patients with Parkinson disease as there is a lower risk or neuroleptic malignant syndrome. 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 I). Initial dosing is 25 mg twice daily or nightly and can increase to 50-100 mg per day. PRN dosing should be 12.5-25 mg every 4-6 hours. The most common side effects among atypical antipsychotics are sedation, QTc prolongation and anti-cholinergic effects (dry mouth, tachycardia, urinary retention, and constipation). Seroquel should be avoided in patients with QTc>500 (4).

Olanzapine (Zyprexa)

Zyprexa can be given orally, via orally disintegrating tablet (Zydis) or IM and is the second-choice medication for delirium in patients with Parkinson disease, psychosis, and agitation. Initial dosing should be 2.5-5 mg per day. PRN dosing should be 2.5-5 mg every 4 hours, not to exceed 20mg per day. Zyprexa should be avoided in patients with Parkinson disease or Lewy body dementia (1) and with QTc>500. Zyprexa causes less QTc prolongation than Haldol (1) Zyprexa may cause hypotension and sedation (4).

Lorazepam (Ativan)

Ativan can be given orally, sublingually, IM, or IV for anxiety and ethanol withdrawal. Initial dosing should be 0.5-2 mg. PRN dosing should be 0.5-1 mg every 6 hours. Ativan may cause patients to have a paradoxical reaction, and patients should be monitored for signs of withdrawal. Ativan will worsen delirium unless delirium is from alcohol or benzodiazepine withdrawal (4).

Valproic Acid (VPA)

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. 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.

Dexmedotomidine (Precedex)
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. 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.

Non-antipsychotic mediations
Medications such as trazodone, ramelteon, melatonin, and suvorexant have shown promise in managing delirium. These medications are believed to work by regulating the patient's sleep-wake cycle to allow for more restful and restorative nighttime sleep. These medications should only be used at bedtime and should not be used during the day (1).

Table I

	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
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

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 (19). 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 (20). 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) (21-25). One study prospectively evaluated the use of olanzapine vs. haloperidol in medical-surgical ICU patients (24). 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 (25). 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 – 2275 mg). 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 (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 (27). 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 (28). 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 (29). 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 (30). 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 (31).

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 (32). 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) (33). 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 II

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 and surgical ICU patients	• N=101: Haloperidol N=35; Ziprasidone N=30; Placebo N=36 • Dose: H 15 mg/day; Ziprasidone 113.3 mg/day; all given orally • CAM-ICU used for screening	• No difference in the duration of delirium or coma among study groups • No significant adverse events were reported
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 • ICDSC ≥4 for delirium	• 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
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)

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**

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

Ely, JAMA 2001; 286, 2703-2710.
Ely, Crit Car Med 2001: 29,1370-1379.
Inouye, Ann Intern Med 1990; 113:941-948.

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

Behavior	Score
Unarousable: minimal or no response to noxious stimuli	1
Very sedated: arouses to physical stimuli only	2
Sedated: difficult to arouse, awakens to verbal stimuli or gentle shaking	3
Calm and cooperative: calm; awakens easily	4
Agitated: anxious or agitated but calms down to verbal instructions	5
Very agitated: Does not calm down on verbal reminder, requires physical restraints	6
Dangerous agitation: pulling at tubes/removes catheters/thrashing side to side; hits staff	7

- 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

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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?

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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?

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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]

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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

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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?

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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**

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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

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TOTAL SCORE (Add 1 – 8): Delirium is defined as an ICDSC score > 4 PLUS clinical judgment

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</table>

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