

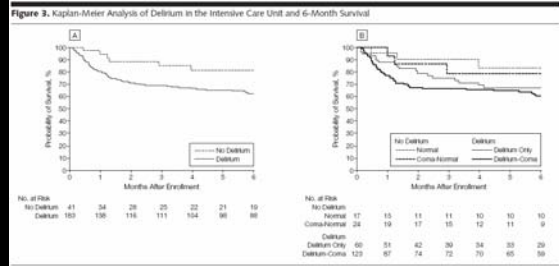
OCCP Top Papers: Critical Care 2009

Dexmedetomidine Vs Midazolam for Sedation of Critically Ill Patients: A Randomized Trial

Riker RR, Shehabi Y, Bokesch PM, et al. JAMA 2009; 301: 489-499.

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Delirium 6-Month Survival



Ely EW, Shintani A, Truman B, et al. JAMA 2004; 291: 1753-1762.

Delirium.....

A disturbance of consciousness with inattention accompanied by a change in cognition or perceptual disturbance that develops over a short period (hours to days) and fluctuates over time.

Pun B, Ely EW. Chest 2007; 132: 624-636.

Cost associated with delirium

- 39% higher ICU cost and 31% higher hospital cost

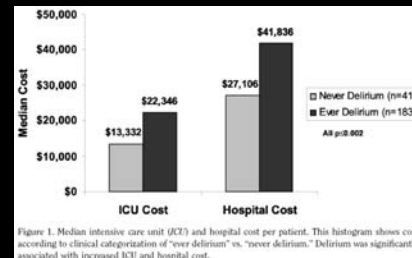


Figure 1. Median intensive care unit (ICU) and hospital cost per patient according to clinical categorization of "never delirium" vs. "ever delirium." Delirium was significantly associated with increased ICU and hospital cost.

Milbrandt EB, Deppen S, Harrison P, et al. Crit Care Med 2004; 32: 955 - 962.

ICU Delirium: Prevalence and Consequences

- Up to 80% of mechanically ventilated medical ICU patients
- Overall patient time spent in the ICU
 - 21% "normal"
 - 43% delirious
 - 35% comatose
- 3 times higher risk of mortality within 6 months of ICU admission (34% vs. 15%)
- ↑Length of hospital stay (median 10 days)
- 2 fold higher incidence of cognitive impairment at discharge (55% vs. 27%)

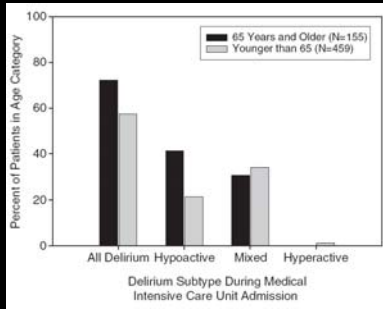
Ely EW, Shintani A, Truman B, et al. JAMA 2004; 291: 1753-1762.

Subtypes of Delirium

- **Hyperactive - paranoid, agitated**
 - Readily recognized, best prognosis
 - Purely hyperactive: 1.6% of delirium episodes
- **Hypoactive - withdrawn, quiet, paranoid**
 - "Quiet delirium"
 - Often not well recognized, misdiagnosed
 - Purely hypoactive episodes 43.5%
- **Mixed - combination**
 - Most common in ICU patients 54.9%
 - Worst prognosis

Peterson JF, Pun BT, Ditrus RS, et al. J Am Geriatr Soc 54: 479-484, 2006.

Subtypes of Delirium Based on Age

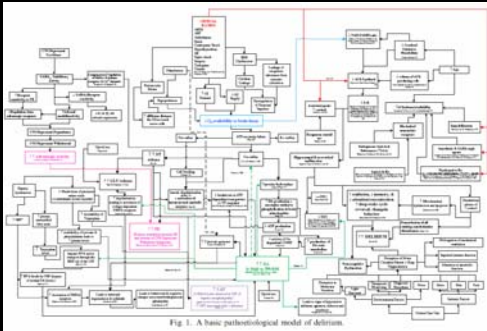


Peterson JF, Pun BT, Ditus RS, et al. *J Am Geriatr Soc* 54: 479-484, 2006

Prevention of Delirium

- Optimize ICU environment as much as possible for comfort and sleep pattern
- Remove or limit contributory medications
- Manage pain first
- Sedative strategy to minimize use of GABA agonists
- Monitor sedation and delirium using validated assessment scales (RASS, CAM-ICU)
- Use α_2 agonists??

Delirium Pathophysiology



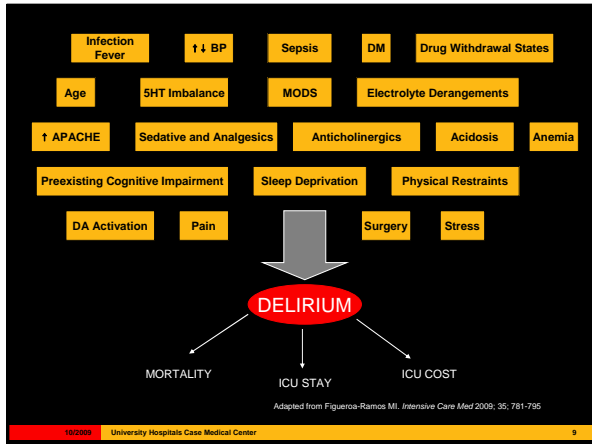
Maldonado JR. *Crit Care Clin* 2008; 24: 789-856.

Pain Assessment



Item	Description	Score
Facial expression	Relaxed	1
	Partially tightened (for example, brow lowering)	2
	Fully tightened (for example, eyelid closing)	3
Upper limbs	Grimacing	4
	No movement	1
	Partially bent	2
Compliance with ventilation	Fully bent with finger flexion	3
	Permanently retracted	4
	Tolerating movement	1
	Coughing but tolerating ventilation for most of the time	2
Fighting ventilator	Fighting ventilator	3
	Unable to control ventilation	4

Scores from each of the three domains are summed, with a total score of 3 to 12 [15].
Seasker et al. *Critical Care* 2008 12(Suppl 3):S2. doi:10.1186/cc1148



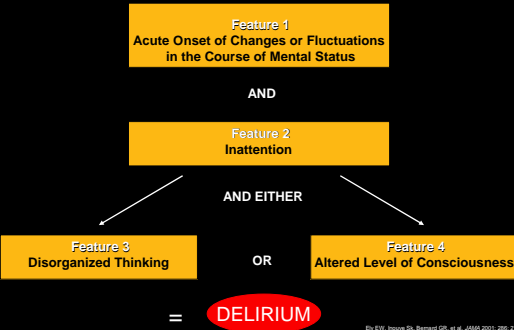
RASS

Score	Term	Description
+4	Combative	Overly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent non-purposeful movement, fights ventilator
+1	Restless	Anxious but movements not aggressive/vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained awakening (eye-opening/eye contact) to voice (≥10 seconds)
-2	Light sedation	Briefly awakens with eye contact to voice (<10 seconds)
-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

* Verbal Stimulation: +1 to +4
* Physical Stimulation: -1 to -5

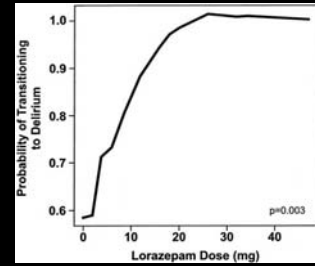
By EW, Tunari B, Sheward A, et al. *JAMA* 2002; 288: 2983-2991.

Confusion Assessment Method for the ICU (CAM-ICU)



© E.W. Hoyle, St. Bernard OR, et al., JAMA 2001; 286: 2703-2710.

Lorazepam and the probability of transitioning to delirium



The probability of transitioning to delirium increased with the dose of lorazepam administered in the previous 24 h. This incremental risk was large at low doses and plateaued at around 20 mg/day.

Pandharipande P, Girton A, Peterson J, et al. Anesthesiology 2006; 104: 21-26.

Sedative Hypnotics

- Benzodiazepines
 - Lorazepam
 - Midazolam
- Propofol
- Dexmedetomidine

Dexmedetomidine (Precedex®)

- MOA
 - Highly selective α_2 adrenoreceptor agonist that produces sedation, anxiolysis, and partial analgesia by centrally inhibiting NE release at locus ceruleus and spinal cord
 - At high doses or rapid IV administration the peripheral α_2 receptors are activated resulting in vasoconstriction
- Neutral effect on sleep architecture
- Does not suppress the respiratory center
- Short half-life ($t_{1/2} = 2.3$ hours)
- Patients remain sedated when undisturbed and arouse with gentle stimulus → "cooperative sedation"
- Pharmacokinetics
 - Onset of action 15 min
 - $T_{max} = 1$ hour following continuous infusion
 - Biphasic 2 Compartment Model ($t_{1/2\alpha} = 6$ min, $t_{1/2\beta} = 2$ hours)
 - High protein binding of 94%
 - Large $V_d = 1.33$ L/Kg
 - Metabolism in the liver via Phase I and II to multiple inactive metabolites (95% of parent compound inactivated)
 - Cl is approximately 39 L/hour and is extensively renal
 - Doses should be adjustment downward in patients with liver and renal impairment

Szumita PM, Baroleti SA, Anger KE, et al. Am J Health-Syst Pharm 2007; 64: 37-44.

Benzodiazepines (BZDs) lorazepam (Ativan®), midazolam (Versed®)

- MOA: bind to GABA receptors in CNS and increase receptor's affinity for GABA
- Dose dependent sedation/anterograde amnesia
- Do not provide any analgesia, although they have an opioid-sparing effect due to moderation of anticipatory pain response
- All are highly protein bound and hepatically metabolized

Dose	Mechanism of Action	Time to Onset (minutes)	Half-life (hours)	Lipophilicity	Primary Metabolic Pathway	Presence of Active Metabolites	Pharmacogenetic Implications
	GABA _A /G _A receptor agonist	2-5	20-50	+++	N-dealkylation and hydroxylation (CYP3A4, 2C19 substrate)	Yes	Yes
	GABA _A /G _A receptor agonist	5-20	10-20	++	Glucuronidation	No	Yes
	GABA _A /G _A receptor agonist	2-5	3-12	+++	Hydroxylation (CYP3A4) substrate	Yes	Yes
	GABA _A receptor agonist	1-2	1.5-12.4	+++	Hydroxylation and glucuronidation (CYP2B6 substrate)	No	Yes

Davis JW, Finkle RT. Crit Care Clin 2009; 25: 431-448.

Dexmedetomidine (Precedex®) Cont...

- Adverse Reactions: significant hypotension (esp. with boluses), bradycardia
- Use caution in patients with heart block, EF <30%, liver failure, hypovolemia, hypotension.
- **Bolus dose for ICU sedation:** 1 mcg/kg i.v. over 10 min (optional)
- **Maintenance dose for ICU sedation:** continuous i.v. infusion initiated at 0.2 mcg/kg/hour and titrate to desired level of sedation. (Dosing range: 0.2 - 0.7 mcg/kg/hour)

Szumita PM, Baroleti SA, Anger KE, et al. Am J Health-Syst Pharm 2007; 64: 37-44.

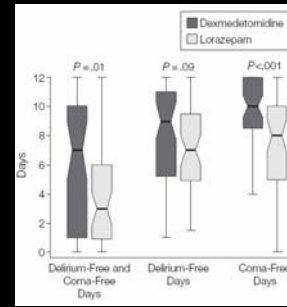
MENDS

(Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction Study)

- Prospective, double-blind, RCT of 106 MICU/SICU mechanically ventilated patients
- **Dexmedetomidine** (N = 52) via continuous i.v. infusion at 0.15 mcg/kg/hr titrated to targeted sedation or maximum (RASS) of 1.5 mcg/kg/hr or maximum of 5 days duration
- **Lorazepam** (N = 51) via continuous i.v. infusion at 1 mg/hour to targeted sedation (RASS) or maximum of 10 mg/hour
- Fentanyl allowed via intermittent doses based on behavioral pain symptomatology. CI allowed if study drug maximum threshold achieved.

Pandharipande PP, Pun BT, Herr DL, et al. JAMA 2007; 298: 2644-2653.

MENDS



Pandharipande PP, Pun BT, Herr DL, et al. JAMA 2007; 298: 2644-2653.

MENDS

Primary Outcomes:

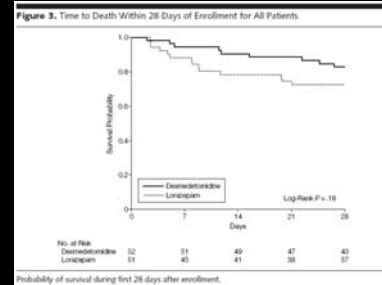
- Delirium and Coma Free Days
 - Delirium (RASS -3 or greater and CAM-ICU positive)
 - Coma (RASS -4 or -5)
- Targeted Sedation within ± 1 of RASS Goal

Secondary Outcomes:

- Length of Stay with Ventilation
- 28 Day Mortality
- 12 Month Survival
- Neuropsychological Testing after ICU Discharge

Pandharipande PP, Pun BT, Herr DL, et al. JAMA 2007; 298: 2644-2653.

MENDS



Pandharipande PP, Pun BT, Herr DL, et al. JAMA 2007; 298: 2644-2653.

MENDS

Table 2. Outcomes in Mechanically Ventilated Patients Sedated With Dexmedetomidine vs Lorazepam^a

Outcome Variable	Dexmedetomidine (n = 52)	Lorazepam (n = 51)	P Value
Duration of brain organ dysfunction, d			
Delirium-free and coma-free ^b	7 (1-10)	3 (1-6)	.01
Delirium-free ^c	9 (5-11)	7 (5-10)	.09
Coma-free ^c	10 (9-12)	8 (5-10)	<.001
Delirium	2.5 (1-5)	4 (1-6)	.71
Coma	2 (0-3)	3 (2-5)	.003
Prevalence of brain organ dysfunction, No. (%) ^d			
Delirium or coma	45 (87)	50 (98)	.03
Delirium	41 (79)	42 (82)	.65
Coma	33 (63)	47 (92)	<.001
Other clinical outcomes			
Mechanical ventilation-free, d ^e	22 (0-24)	18 (0-23)	.22
Intensive care unit length of stay, d	7.5 (5-10)	9 (6-15)	.02
28-Day mortality, No. (%) ^f	9 (17)	14 (27)	.18

^aMedian (interquartile range) unless otherwise noted.
^bIndicates the number of days alive without stated dysfunction from study days 1 to 12.
^cPrevalence is used to describe the rates of brain organ dysfunction instead of incidence because continuous care unit delirium or coma status could not be determined. Prevalence represents the occurrence of brain organ dysfunction at any time during the 12-day assessment period.
^dIndicates the number of days alive, breathing without mechanical ventilator assistance, from study day 1 to 28.

Pandharipande PP, Pun BT, Herr DL, et al. JAMA 2007; 298: 2644-2653.

MENDS

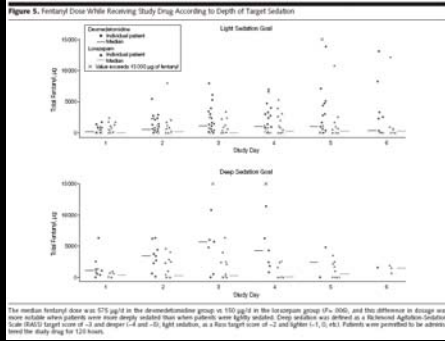
Table 3. Efficacy of Sedation With Dexmedetomidine vs Lorazepam^a

Variable	Dexmedetomidine (n = 52)	Lorazepam (n = 51)	P Value
Outcome			
Received study drug, d	5 (2-6)	4 (2-6)	.52
RASS score within 1 point of nurse goal, % (IQR) ^b	80 (58-100)	67 (48-83)	.04
RASS score within 1 point of physician goal, % (IQR) ^b	67 (50-86)	55 (8-67)	.008
Sedated deeper than nurse goal RASS score, % (IQR) ^c	15 (0-33)	33 (11-48)	.01
Overmedicated on study drug, d	1 (0-2.2)	2 (1-3.5)	.01
Other drugs received during study			
Median fentanyl, μ g/d	575 (140-2200)	150 (0-922)	.006
Any antipsychotics, No. (%)	24 (46)	18 (35)	.26
Any propofol, No. (%)	7 (13)	4 (8)	.36
Received antipsychotics, d	0 (0-5)	0 (0-3)	.32

Abbreviations: IQR, interquartile range; RASS, Richmond Agitation-Sedation Scale.
^aMedian (IQR) unless otherwise noted.
^bThe nurse and physician goal RASS score outcomes indicate the percentage of days while on study drug when patients were either at goal or within 1 RASS point of the stated goal.
^cPercentage of days the RASS score was 0 or more points deeper than the nurse goal for RASS score.

Pandharipande PP, Pun BT, Herr DL, et al. JAMA 2007; 298: 2644-2653.

MENDS



SEDCOM

(Safety and Efficacy of Dexmedetomidine COmpared with Midazolam)

- Design and Inclusion:** Prospective, double-blind, RCT involving 68 centers and 375 MICU/SICU adult patients mechanically ventilated for less than 4 days with at least 3 more days of treatment expected.
- Exclusion:**
 - Trauma or burns
 - ARF or ESRD + RRT
 - Pregnancy
 - Continuous NMB
 - Epidural
 - CNS pathology at BL
 - Severe liver disease
 - Unstable angina or recent MI
 - CHF (LVEF < 30%)
 - HR < 50 bpm
 - 2nd or 3rd degree heart block
 - SBP < 90 mm Hg despite two vasopressors

MENDS

Table 4. Safety Outcomes With Dexmedetomidine vs Lorazepam*

Safety Variable While Receiving Study Drug	Dexmedetomidine (n = 52)	Lorazepam (n = 51)	P Value
Blood pressure history			
Lowest systolic blood pressure, mm Hg	96 (86-105)	97 (88-102)	.60
Lowest diastolic blood pressure, mm Hg	48 (44-55)	49 (44-54)	.91
Ever systolic blood pressure <80 mm Hg, No. (%)	13 (25)	10 (20)	.51
Hypotensive, d	0 (0-0.2)	0 (0-0)	.51
Vascoactive drug history			
Days received	0 (0-2)	0 (0-3)	.72
Number of vascoactive drugs/d ^b	0 (0-0.6)	0 (0-1)	.55
Ever vascoactive drugs increased, No. (%)	15 (29)	18 (35)	.48
Vascoactive drugs were increased, d	0 (0-1)	0 (0-1)	.73
Heart rate/rhythm, No. (%)			
Ever sinus bradycardia, <60/min	9 (17)	2 (4)	.03
Heart rate <40/min	1 (2)	1 (2)	.99
Ever sinus tachycardia, >100/min	36 (69)	37 (73)	.71
Ever atrial fibrillation	3 (6)	0 (0)	.08
Seizures, No. (%)	2 (4)	1 (2)	.57
Self-extubations, No. (%)	4 (8)	2 (4)	.41

*Measured during 100-hour study drug protocol. Median (interquartile range) unless otherwise noted.
^bReported as the median of the average number of vascoactive drugs that the patients were administered daily in each group.

SEDCOM

Dosing Regimen

- Patients randomized 2:1 DEX (N = 224) to MDZ (N = 122)
- Sedatives discontinued and RASS had to be -2 to +1 prior to randomization
- Optional blinded i.v. LD of DEX 1 mcg/kg or MDZ 0.05mg/kg at investigators discretion
- Maintenance sedative infusions (given until extubation or total of 30 days):
 - DEX 0.8 mcg/kg/hour to targeted RASS of -2 to +1 (measured and adjusted q 4 hours) or maximum of 1.4 mcg/kg/hour
 - MDZ 0.06 mg/kg/hour to targeted RASS of -2 to +1 (measured and adjusted q 4 hours) or maximum of 0.1 mg/kg/hour
- Open label "rescue" for either arm consisted of MDZ of 0.01-0.05 mg/kg q 10-15 min (max of 4 mg in 8 hours)
- Analgesia with intermittent fentanyl bolus doses of 0.5-1.0 mcg/kg could be administered q 15 min. CI fentanyl could be administered in anticipation of noxious stimuli. No other analgesics or sedatives allowed.
- Delirium/agitation was treated with haloperidol 1-5 mg i.v. q 10-20 min prn.

MENDS Conclusion

- In this double-blind, randomized controlled trial, dexmedetomidine was more effective than lorazepam for achieving sustained sedation of mechanically ventilated medical and surgical ICU patients.
- Dexmedetomidine-treated ICU patients had 4 more days alive and without delirium or coma, significantly higher accuracy at meeting the stated sedation goals, and no added cost of care, as measured using data obtained at the largest enrolling site.

SEDCOM

Primary and Secondary Outcomes

Primary Outcome

- Percentage of time spent in target RASS (-2 to +1)

Secondary Outcome

- Prevalence and duration of delirium
 - Assessment with daily arousal with RASS -2 to +1 and CAM-ICU administered
- Delirium free days
- Fentanyl use
- Open label MDZ use
- Duration of mechanical ventilation
- Length of stay

SEDCOM Demographics

Table 1. Baseline Demographics and Characteristics of Study Population

Characteristic	No. (%)		P Value
	Desmedetomidine (n = 244)	Midazolam (n = 122)	
Age, mean (SD), y	61.5 (14.8)	62.9 (16.8)	.26
Sex	125 (51.2)	57 (46.7)	.44
Weight, mean (SD), kg	88.1 (23.9)	87.8 (21.5)	.89
APACHE II score, mean (SD)*	19.1 (7.9)	18.3 (6.2)	.38
Medical ICU patients	212 (86.9)	103 (84.4)	.51
Surgical ICU patients	32 (13.1)	19 (14.7)	.51
Severe sepsis [†]	182 (74.6)	84 (71.1)	.79
Shock [‡]	79 (32)	45 (36.9)	.30
Pneumonia	156 (63.9)	76 (62.3)	.82
Liver dysfunction [§]	124 (51.0)	54 (44.3)	.27
Childs-Pugh B	115 (47.3)	67 (54.9)	.18
Creatinine, median (IQR), mg/dL	1.0 (0.7-1.4)	1.1 (0.8-1.4)	.20
Pre-study drug sedative			
Barbiturates	156 (70.9)	100 (82.0)	.68
Propofol	125 (51.2)	56 (45.9)	.36
Desmedetomidine	1 (0.4)	2 (1.6)	.26
Time from ICU admission to start of study drug, median (IQR), h	40.6 (22.2-64.8)	30.3 (24.5-72.8)	.78
Delirium at enrollment (CAM-ICU-positive) [¶]	138 (56.3)	70 (59.3)	.82

Rivar RR, Sheikh Y, Boksch PM et al. JAMA 2020; 323: 489-499.

SEDCOM Results

Table 2. Efficacy Outcomes in Patients Treated With Desmedetomidine vs Midazolam

Outcome	No. (%)		P Value
	Desmedetomidine (n = 244)	Midazolam (n = 122)	
Time in target sedation range (RASS score -2 to +1), mean, %* Patients completing all daily arousal assessments	77.3	75.1	.18
Patients requiring study drug interruption to maintain RASS score -2 to +1	225 (92)	103 (84.3)	.09
Duration of study drug treatment, median (IQR), d	3.5 (2.0-5.2)	4.1 (2.8-6.1)	.01
Time to extubation, median (95% CI), d [†]	3.7 (3.1-4.9)	5.6 (4.6-5.9)	.01
ICU length of stay, median (95% CI), d [‡]	5.9 (5.7-7.6)	7.6 (6.7-8.6)	.04
Delirium			
Prevalence	132 (54)	80 (76.6)	<.001
Mean delirium-free days [§]	2.5	1.7	.002
Open-label midazolam use			
No. treated	153 (63)	60 (49)	.02
Dose, median (IQR), mg/kg [¶]	0.09 (0.03-0.23)	0.11 (0.03-0.28)	.65
Extubation			
No. treated	180 (73.8)	97 (79.5)	.25
Dose, median (IQR), µg/kg [¶]	6.4 (1.8-26.3)	9.6 (2.9-28.9)	.27

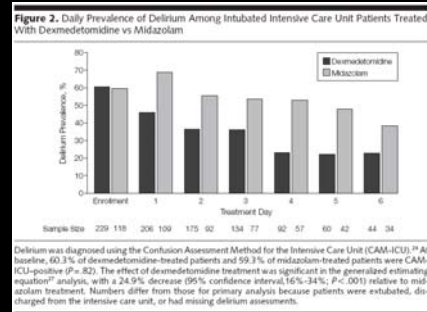
Rivar RR, Sheikh Y, Boksch PM et al. JAMA 2020; 323: 489-499.

SEDCOM Safety

- Adverse events recorded until 48 hours after study drug stopped
- Serious adverse events and mortality recorded up to 30 days after ICU admission
- Vital signs q 4 hours and with every dosage change and were considered adverse if:
 - 160 mm Hg < SBP < 80 mm Hg
 - 100 mm Hg < DBP < 50 mm Hg
 - 120 bpm < HR < 40 bpm
 - >30% change from baseline BP or HR
 - Therapeutic intervention required for hypotension
- Hyperglycemia > 150 mg/dL
- Infection (+ culture and/or empiric antibiotics started)
- 30 day mortality

Rivar RR, Sheikh Y, Boksch PM et al. JAMA 2020; 323: 489-499.

SEDCOM Results



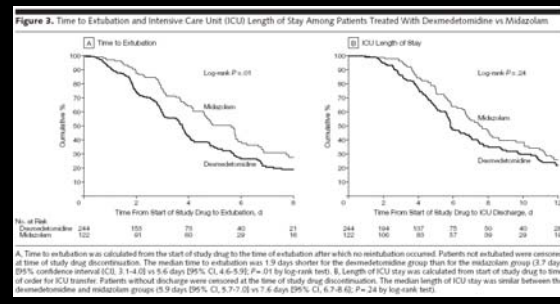
Rivar RR, Sheikh Y, Boksch PM et al. JAMA 2020; 323: 489-499.

SEDCOM Results

- Mean maintenance infusion dose
 - DEX 0.83 mcg/kg/hour
 - 0.2-0.7 mcg/kg/hour (39%)
 - 0.71-1.1 mcg/kg/hour (32%)
 - > 1.1 mcg/kg/hour (29%)
 - MDZ 0.056 mg/kg/hour
- Optional loading doses
 - DEX (8.2%)
 - MDZ (7.4%)
- Open-label "rescue" MDZ
 - First study day (43% DEX vs. 30% MDZ; p = 0.02)
 - Entire treatment period (63% DEX vs. 49%; p = 0.02)

Rivar RR, Sheikh Y, Boksch PM et al. JAMA 2020; 323: 489-499.

SEDCOM Results



Rivar RR, Sheikh Y, Boksch PM et al. JAMA 2020; 323: 489-499.

SEDCOM Results

Table 3. Safety Outcomes During Treatment With Dexmedetomidine vs Midazolam

Outcome*	No. (%)		P Value
	Dexmedetomidine (n = 244)	Midazolam (n = 122)	
Cardiovascular			
Bradycardia	103 (42.2)	23 (18.9)	<.001
Bradycardia with intervention	12 (4.9)	1 (0.8)	.07
Tachycardia	62 (25.4)	54 (44.3)	<.001
Tachycardia with intervention	24 (9.8)	12 (9.8)	>.99
Hypertension	137 (56.1)	69 (56.5)	>.99
Hypertension with intervention	69 (28.3)	33 (27)	.00
Hypotension	106 (43.4)	54 (44.3)	.91
Hypotension with intervention	46 (18.9)	36 (29.5)	.00
Myocardial Perfusion Compromise	138 (56.6)	52 (42.6)	.02
Infections	25 (10.2)	24 (19.7)	.02
30-d mortality ^b	55 (22.5)	31 (25.4)	.60

*Base "Outcome Measures and Safety End Points" for definitions and details of variables.
^bIncludes mortality rate for 30 days after ICU admission.

Riser RR, Doherty Y, Bosworth PM et al. JAMA 2009; 301: 489-499.

SEDCOM Cons

- Exclusion criteria
- No difference in primary outcome
- Delayed study "track in"
- Daily arousal vs. daily interruption
- Loading dose not evaluated
- Clinical effect of adverse hemodynamic parameters and lack of detailed description of therapeutic measures

Riser RR, Doherty Y, Bosworth PM et al. JAMA 2009; 301: 489-499.

SEDCOM Conclusion

- Target level of sedation was not significantly different between DEX and MDZ.
- Sedation with DEX reduced the prevalence of delirium when compared to MDZ.
- DEX significantly shortened duration of mechanical ventilation when compared to MDZ.
- Doses up to 1.4 mcg/kg/hour can be used safely and for a duration greater than 24 hours with no rebound phenomenon.

Riser RR, Doherty Y, Bosworth PM et al. JAMA 2009; 301: 489-499.

Questions...

SEDCOM Pros

- Revolutionary paper using a new sedation approach in critically ill patients
- Large double-blind, randomized, multi-center trial
- Patient population (MICU, SICU)
- Dosing strategy
- Sedation and delirium assessment and outcome measures
- Safety analysis

Riser RR, Doherty Y, Bosworth PM et al. JAMA 2009; 301: 489-499.