Brigham and Women's Hospital
Founding Member, Mass General Brigham

New Sedation Strategies

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- Professor of Pharmacy, Northeastern University
- Clinical Focus: Critical care pharmacy
- Research Focus:
  - Recognition, Prevention, and Treatment of Delirium in the ICU
  - Sedative Choice, Cost and Safety
  - Recognition, Prevention and Treatment of Disrupted Sleep in the ICU
  - Pharmacoepidemiology of Delirium in Critical Illness.

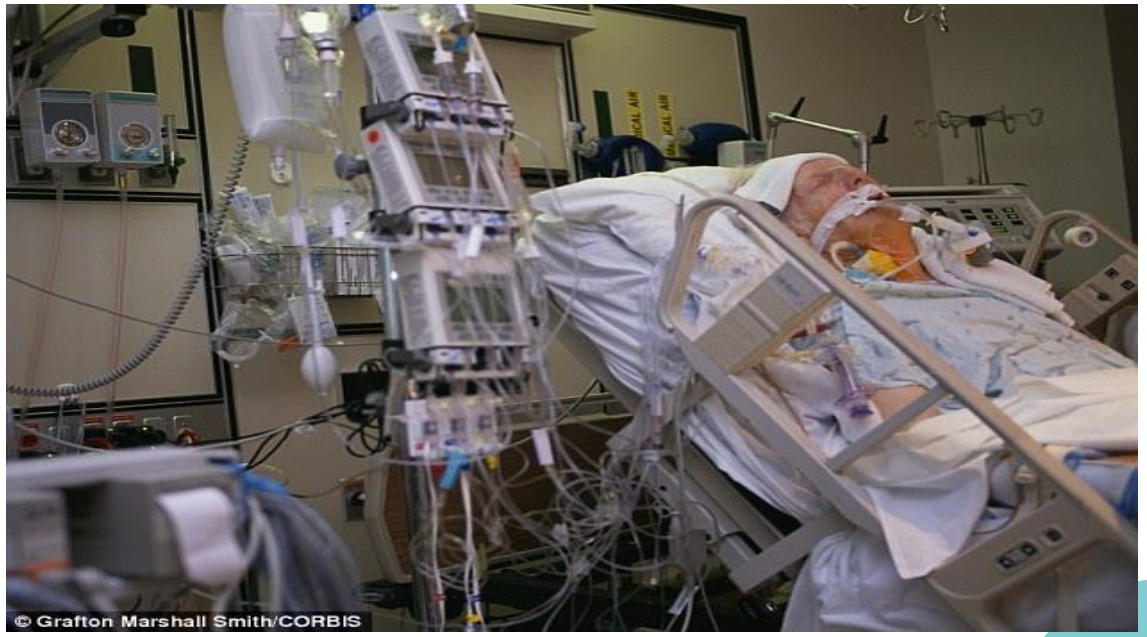
Disclosures

Research Funding:
National Institute of Aging
Canadian Institute of Health Research
Agency for Healthcare Research and Quality
Sedana Medical

Consultant:
Ceribell Inc
BioExcel Pharma

Important Daily ICU Goal:

Optimize patient comfort and safety & facilitate mechanical ventilation



Sedative Choice and Exposure

→

Sleep

Coma

↑Sedatives

Delirium

→

Post Intensive Care Syndrome

Agitation

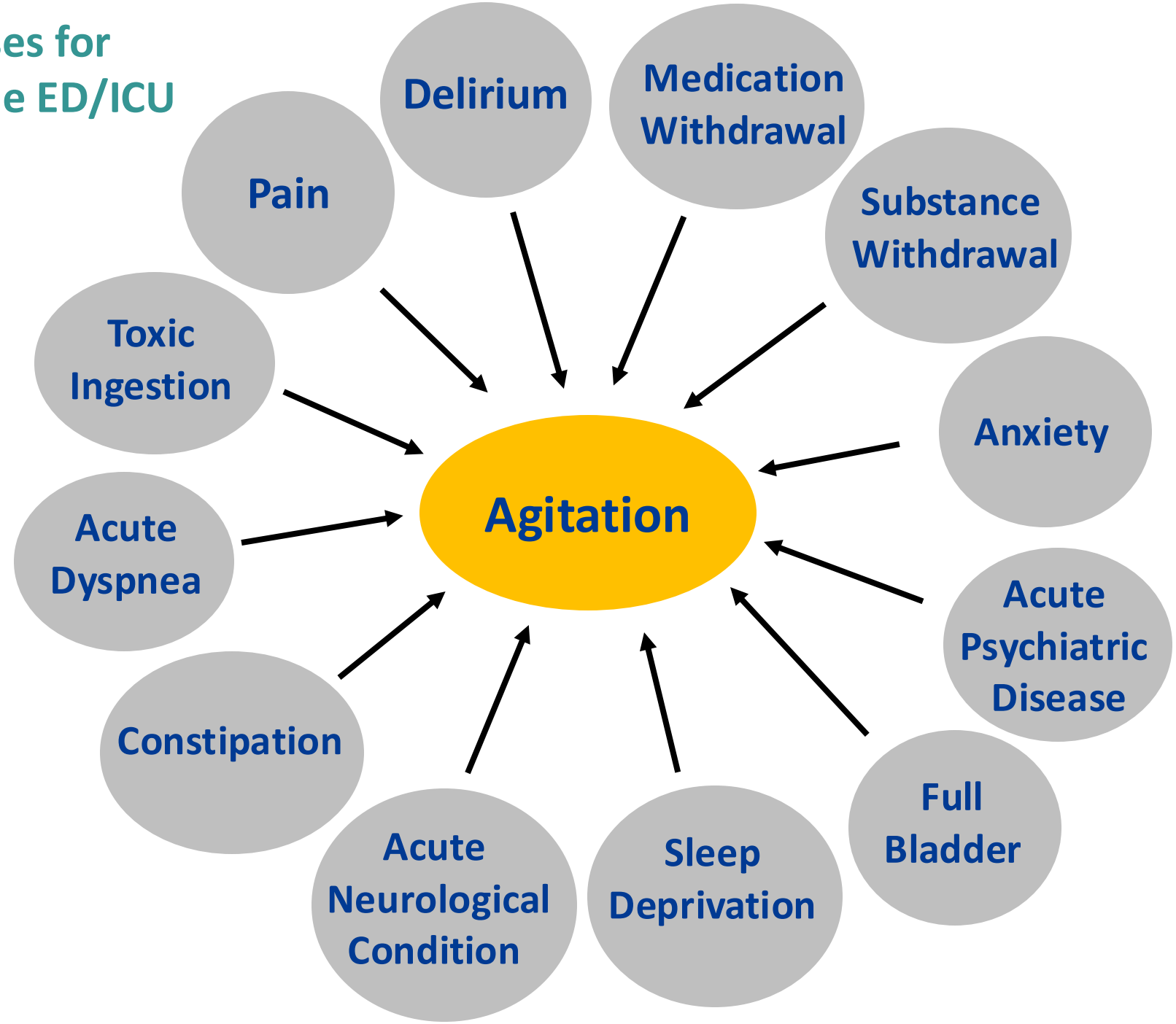
Definition: a state where patients cannot remain still or calm, characterized by internal features such as hyperresponsiveness, racing thoughts, and emotional tension; and external ones, mainly motor and verbal hyperactivity, and communication impairment.

Martínez-Raga J, et al. 1st International Experts' Meeting on Agitation: Front Psychiatry. 2018;9:54

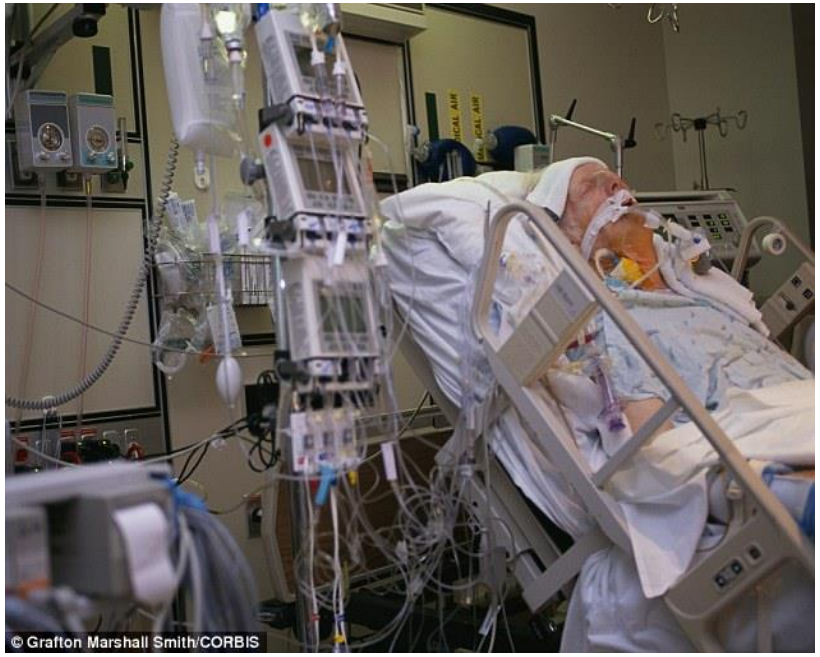
Richmond Agitation Sedation Scale

+4	Combative; overtly violent; immediate danger to staff
+3	Very agitated; pulls or removes tubes/catheters; aggressive
+2	Agitated; frequent non-purposeful movements; fights ventilator
+1	Restless; anxious but not aggressive/vigorous
0	Alert and calm
-1	Drowsy; not fully alert but sustained awakening; eye contact to voice >10 secs
-2	Light sedation; briefly awakens to voice with eye contact <10 secs
-3	Moderate sedation; movement or eye opening to voice but no eye contact
-4	Deep sedation; no response to voice; movement or eye opening to physical stimulation
-5	Unrousable; no response to voice or physical stimulation

Potential Causes for Agitation in the ED/ICU



RASS = +2



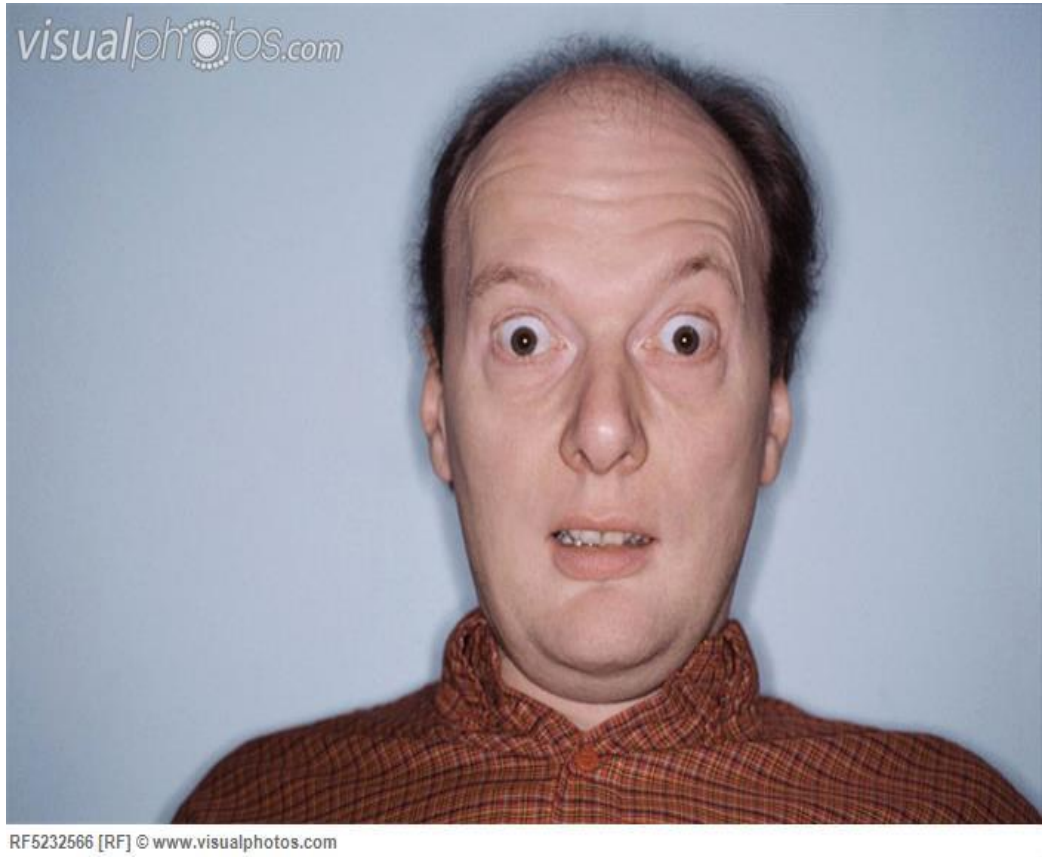
- Administer IVP bolus of appropriate sedative
- Identify agitation cause (s)
- Optimize non-pharmacologic interventions known to reduce causes of agitation

OR

- Increase continuous IV sedative infusion dose
- Apply restraints
- Causes of agitation not rigorously explored
- Non-pharmacologic interventions not optimized

Patient Wakefulness is Important!

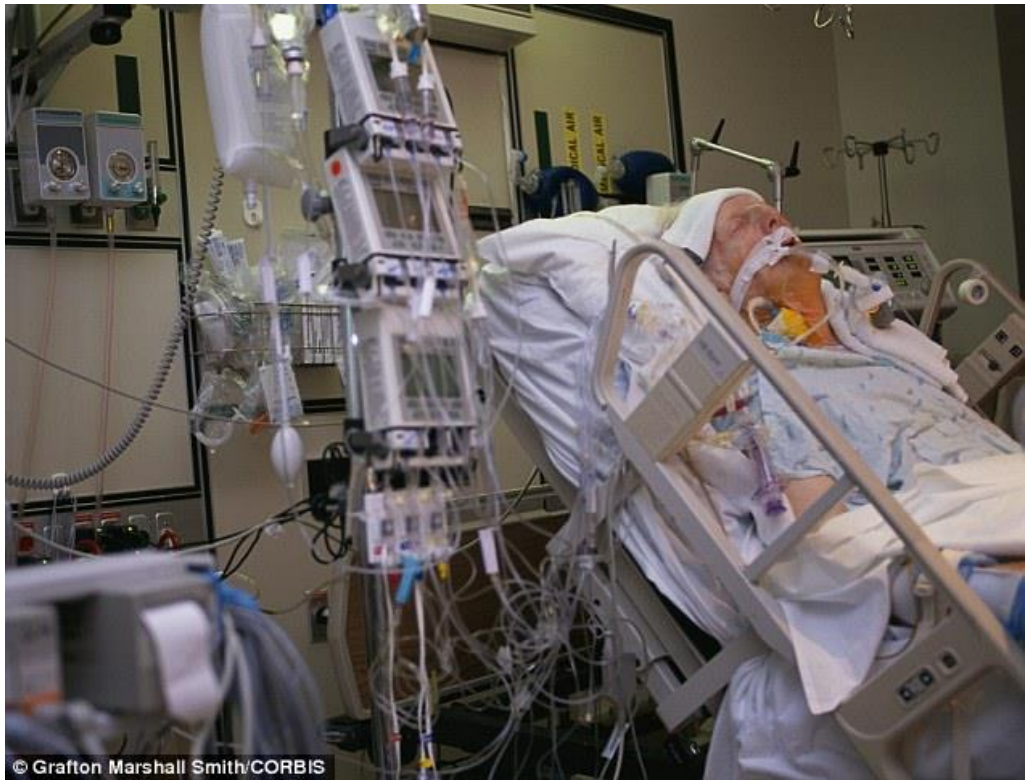
We suggest using light (RASS=-2 to 0) (vs. deep RASS=-3 or lower) sedation in critically ill, mechanically ventilated adults (conditional recommendation, low quality of evidence).



↑ Patient communication
↓ Delirium
↑ Spontaneous breathing trials
↑ Early mobilization
↓ PTSD
↓ Risk for sedative ADEs

Devlin JW, et al. Crit Care Med 2018; 46 (9); e825-873

Do all Mechanically Ventilated Adults Require Continuous Sedation?



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nonsedation or Light Sedation in Critically Ill, Mechanically Ventilated Patients

	Non-sedation group No sedation; IVP opioid prn for pain/agitation Goal RASS=0 + ABCDE bundle N=354	Sedation group Cont.sedation to RASS=-3 to -2 0-48hrs = propofol; ≥ 48 hrs midazolam + ABCDE bundle N=356	Difference
APACHE-II, median [IQR]	26 [22, 30]	25 [21, 30]	NS
Medical, %	70	67	NS
90 day mortality, %	42	37	NS
Days free from coma/delirium within 28 days, median [IQR]	27 [21-28]	26 [22-28]	NS
Days free from mechanical ventilation within 28 days, median [IQR]	20 [0-26]	19 [0-25]	NS
Self-extubation requiring reintubation within 1 hour, %	1.1	0.3	NS

Olsen HT, Nedergaard HK, Strom T, et al N Engl J Med 2020; 382:1103

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nonsedation or Light Sedation in Critically Ill,

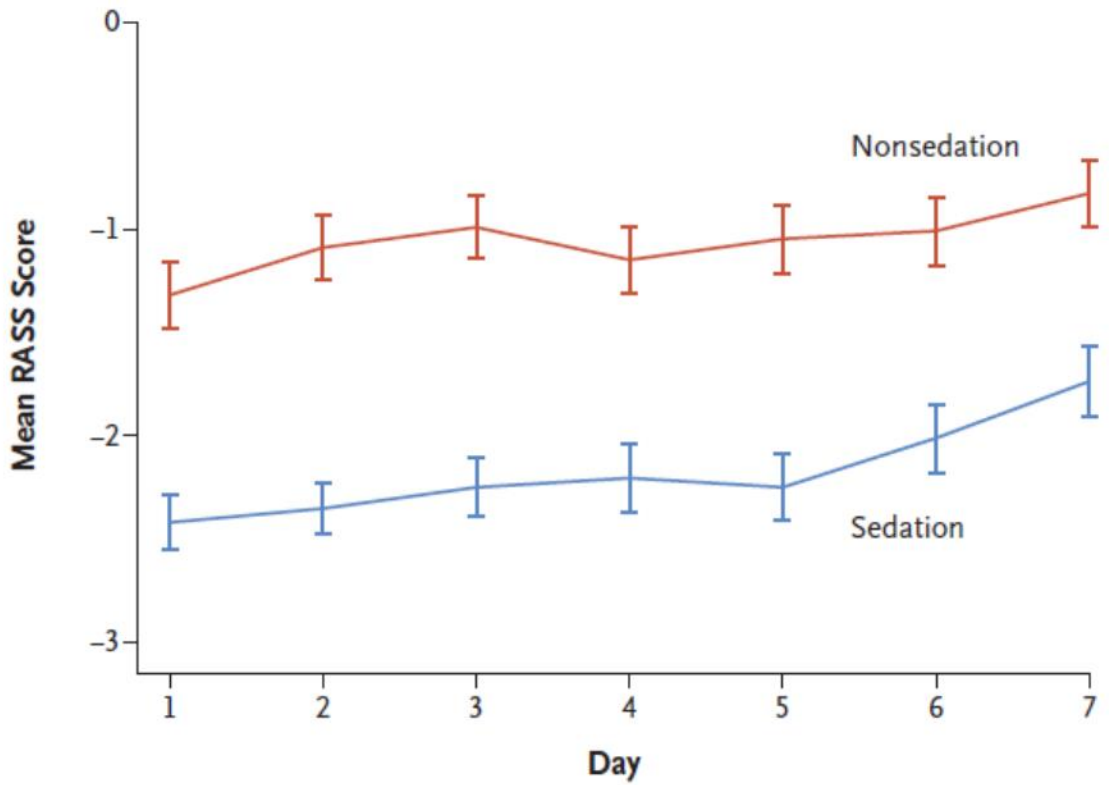


Figure 2. RASS Score during the First 7 Days of the Trial.
RASS denotes Richmond Agitation and Sedation Scale, on which scores range from −5 (unresponsive) to +4 (combative).

	Difference
Age, median [IQR]	NS
APACHE-II, median [IQR]	NS
Medical, %	NS
90 day mortality, %	NS
Days free from coma/delirium within 28 days, median [IQR]	NS
Days free from mechanical ventilation within 28 days, median [IQR]	NS

N Engl J Med 2020; 382:1103

ICU liberation strategy for ARDS

home

A ssess, prevent and manage pain
B oth awakening & spontaneous breathing trial
C hoice of drugs
D elirium monitoring & management
E arly mobility & exercice
F amily engagement & empowerment
- R espiratory Drive Control

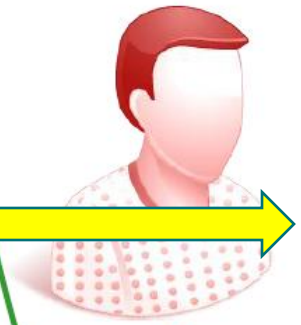
①TOP PRIORITY
Assess, prevent and manage
increased respiratory drive related factors
- ☑ stress related symptoms (e.g. pain, discomfort, anxiety, dyspnea)
- ☑ physiological factors (e.g. hyperthermia, acidosis, hypercabnia)

Patient's factors

Ventilator's factors

① TOP PRIORITY
Control Respiratory Drive
- ☑ Assess, prevent and manage Patient related factors

Set the ventilator first in case of patient/ventilator asynchrony
- ☑ adapt the ventilator to the patient and not the patient to the ventilator
- ☑ Spontaneous breathing mode as soon as possible



1. First, favor non pharmacological interventions (e.g. relaxation, ventilator setting), multimodal analgesia with non opioids
2. In last step only: Use or increase opioids ± sedatives/ psycho-active agents ± NMBA
3. Consider intermittent ordering before continuous infusion

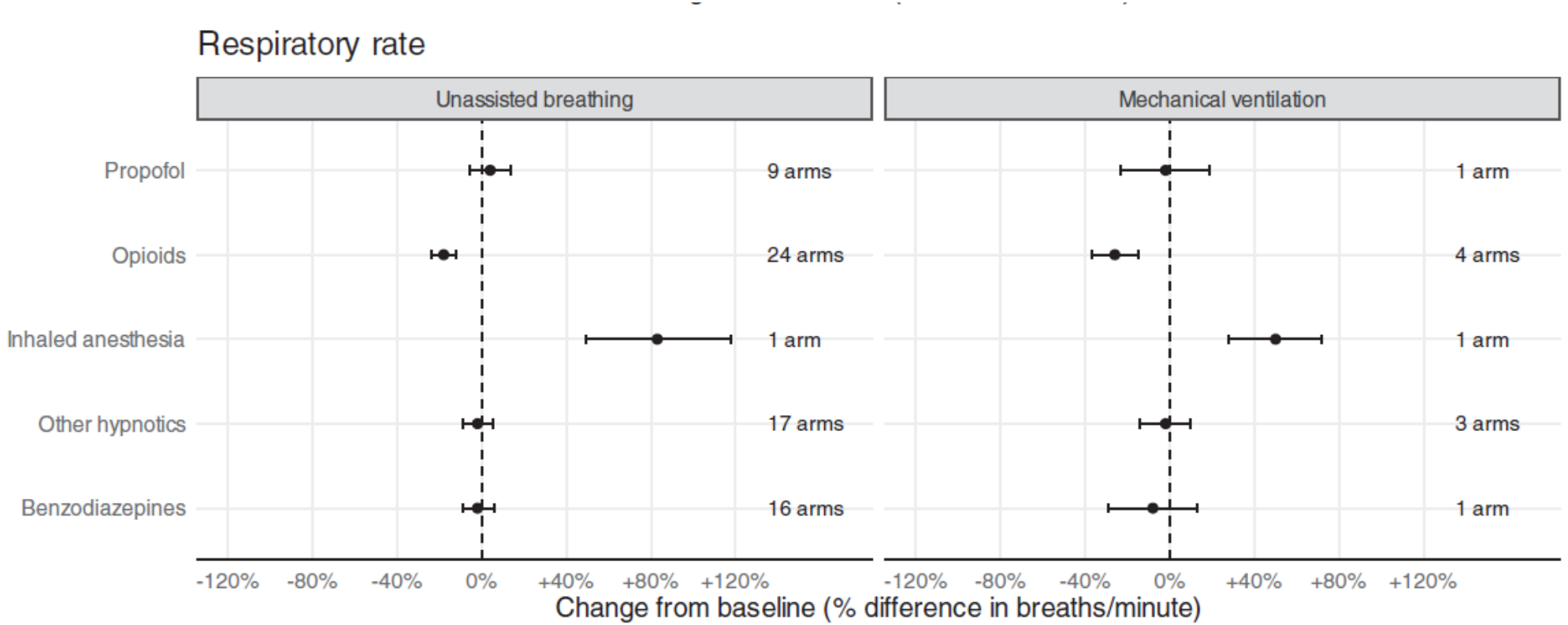
②

②

Changes G, Constatin JM, Devlin JW, et al. Intensive Care Med 2020; 46: 2342-2356

The influence of drugs used for sedation during mechanical ventilation on respiratory pattern during unassisted breathing and assisted mechanical ventilation: a physiological systematic review and meta-analysis

Danica Quickfall,[a] Michael C. Sklar,[b,c] George Tomlinson,[d] Ani Orchanian-Cheff,[e] and Ewan C. Goligher[c,d,f,g,]*



EclinicalMedicine 2024

The influence of drugs used for sedation during mechanical ventilation on respiratory pattern during unassisted breathing and assisted mechanical ventilation: a physiological systematic review and meta-analysis

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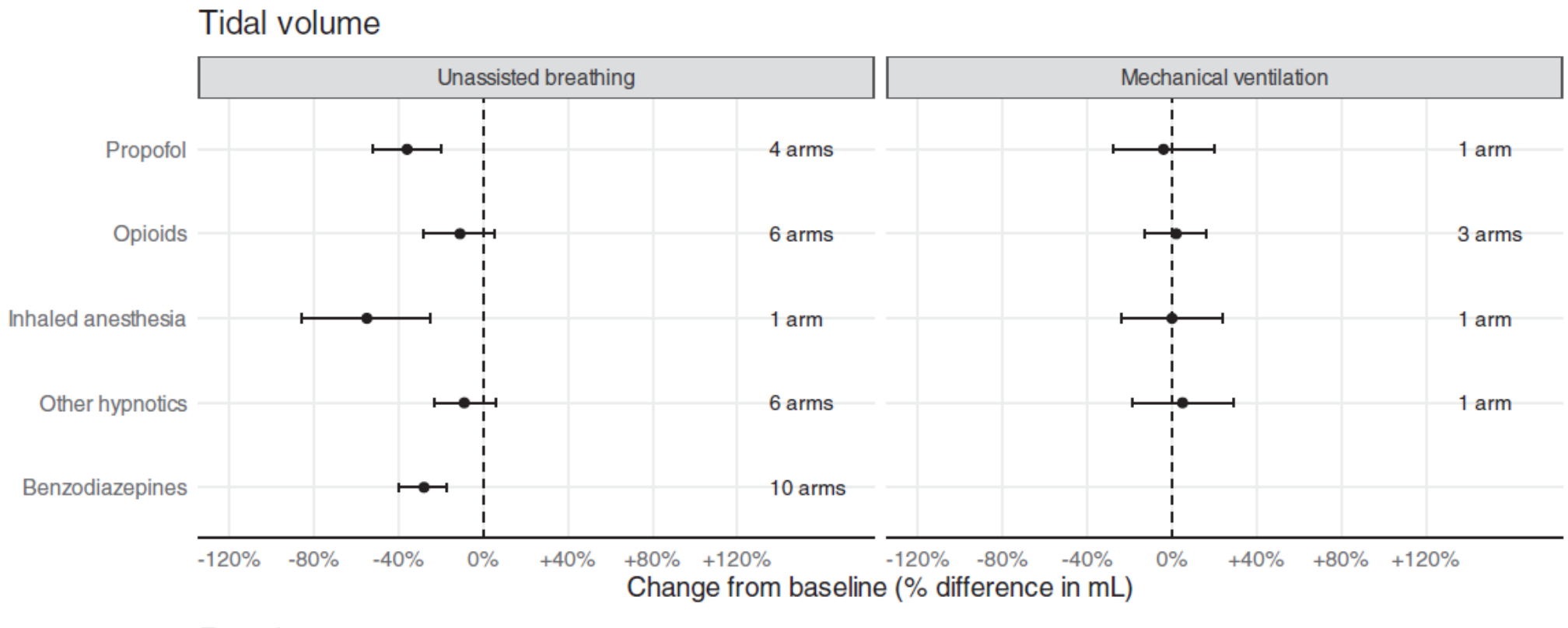


Dexmedetomidine vs. Propofol: Pharmacologic Comparison

Potential Benefits:

- Lighter sedation
- No effect on respiratory drive
- Reduced delirium
- Sleep improvement
- Analgesic activity

Potential Limitations:

- Slower onset
- Hypotension/bradycardia
- Withdrawal
- Heterogenous sedative-dose effect

Potential Benefits:

- Fast onset
- Can induce deep sedation
- Decreases respiratory drive
- Low acquisition cost
- Decrease ICP/cerebral metabolic rate

Potential Limitations:

- Slow wakeup after prolonged use
- Hypotension/bradycardia
- PRIS
- Hypertrigliridemia
- Immunosuppression
- Sleep disrupting

Devlin JW, et al. Crit Care Med 2018; 46 (9); e825-873

Early Sedation with Dexmedetomidine in Critically Ill Patients

Y. Shehabi, B.D. Howe, R. Bellomo, Y.M. Arabi, M. Bailey, F.E. Bass,
S. Bin Kadiman, C.J. McArthur, L. Murray, M.C. Reade, I.M. Seppelt, I. Takala,

Table 2. Clinical Outcomes.*

Outcome	Dexmedetomidine (N=1948)	Usual Care (N=1956)	Odds Ratio (95% CI)	Adjusted Risk Difference (95% CI)†
Death from any cause at 90 days: primary outcome — no. (%)	566 (29.1)	569 (29.1)	1.00 (0.87 to 1.15)	0.0 (–2.9 to 2.8)
Secondary outcomes				
Death at 180 days — no./total no. (%)	609/1935 (31.5)	610/1946 (31.3)	1.01 (0.88 to 1.16)	0.1 (–2.8 to 3.1)
Institutional dependency at 180 days — no./total no. (%)	89/1323 (6.7)	94/1337 (7.0)	0.96 (0.73 to 1.27)	–0.3 (–2.1 to 1.5)
Mean score on Short IQCODE at 180 days (95% CI)‡	3.14 (3.11 to 3.17)	3.08 (3.05 to 3.11)		0.06 (0.02 to 0.11)
Mean score on the EQ-5D-3L questionnaire (95% CI)§	69.8 (68.5 to 71.1)	70.2 (69.0 to 71.5)		–0.4 (–2.2 to 1.3)
Median no. of days free from coma or delirium (IQR)¶	24.0 (11.0 to 26.0)	23.0 (10.0 to 26.0)		1.0 (0.5 to 1.5)
Median no. of ventilator-free days (IQR)¶	23.0 (0.0 to 26.0)	22.0 (0.0 to 25.0)		1.0 (0.4 to 1.6)

N Engl J Med 2019;380:2506-17.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

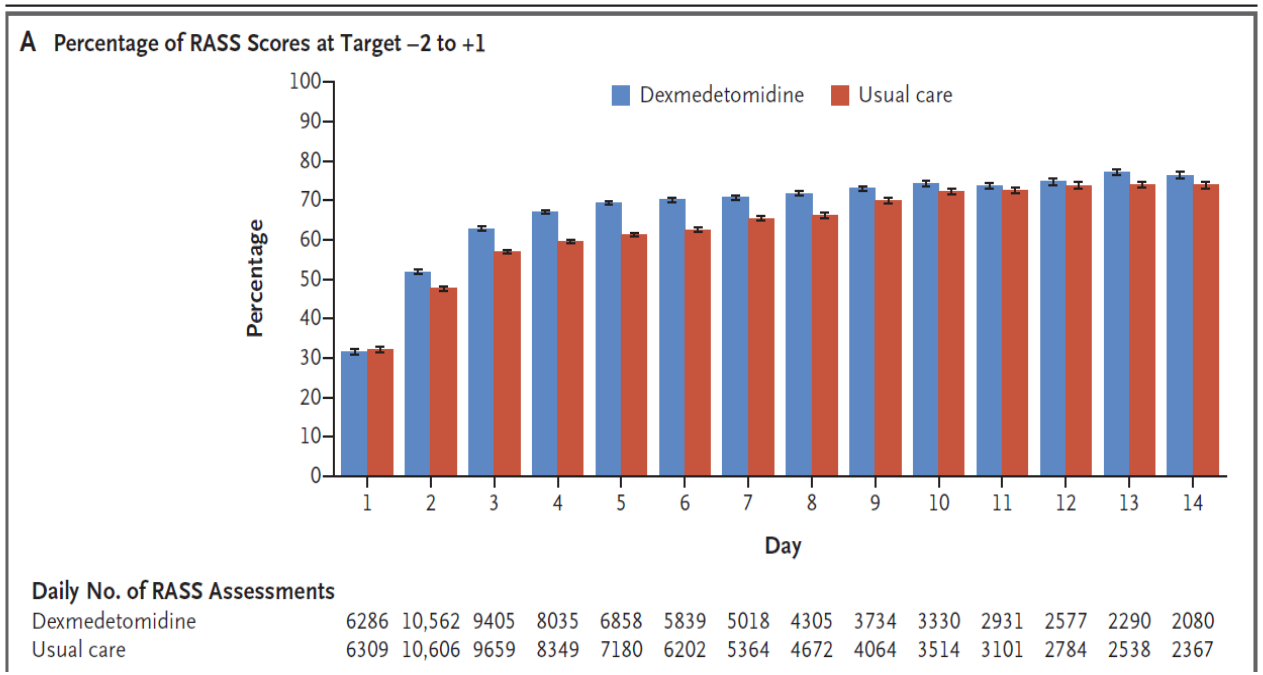
Dexmedetomidine or Propofol for Sedation in Mechanically Ventilated Adults with Sepsis

	Dexmedetomidine N=214	Propofol N=208	Difference
APACHE-II	**27 [21, 32]**	**27 [22, 32]**	
Medical	**64%**	**65%**	
Moderate-Severe ARDS	**26%**	**29%**	
Outcomes			
Days without delirium or coma at 14 d* median [95% CI]	**10.7 [8.5, 12.5]**	**10.8 [8.7, 12.6]**	**NS**
Ventilator-free days at 28 days* median [95% CI]	**23.7 [20.5, 25.4]**	**24.0 [20.9, 25.4]**	**NS**
Mortality at 90 days*	**38%**	**39%**	**NS**
Telephone Interview for Cognitive Status (TICS) at 6 mo.	**40.9 [33.6, 47.1]**	**41.4 [34.0, 47.3]**	**NS**
RASS score while receiving study sedation	**-2 [-3 to -1]**	**- 1.9 [-3 to -0.9]**	**NS**
Daily adherence to all ABCDE bundle elements	**86%**	**85%**	**NS**

*Multivariable adjustment for n=16 variables; % age-adjusted

Hughes CG, Mailloux PT, Devlin JW, et al. New Engl J Med (Feb 2 2021)

Even in RCTs with Light Sedation Goal: Patients are Frequently Not Maintained at Light Sedation



SPICE III Trial
Shehabi Y, et al. NEJM 2019

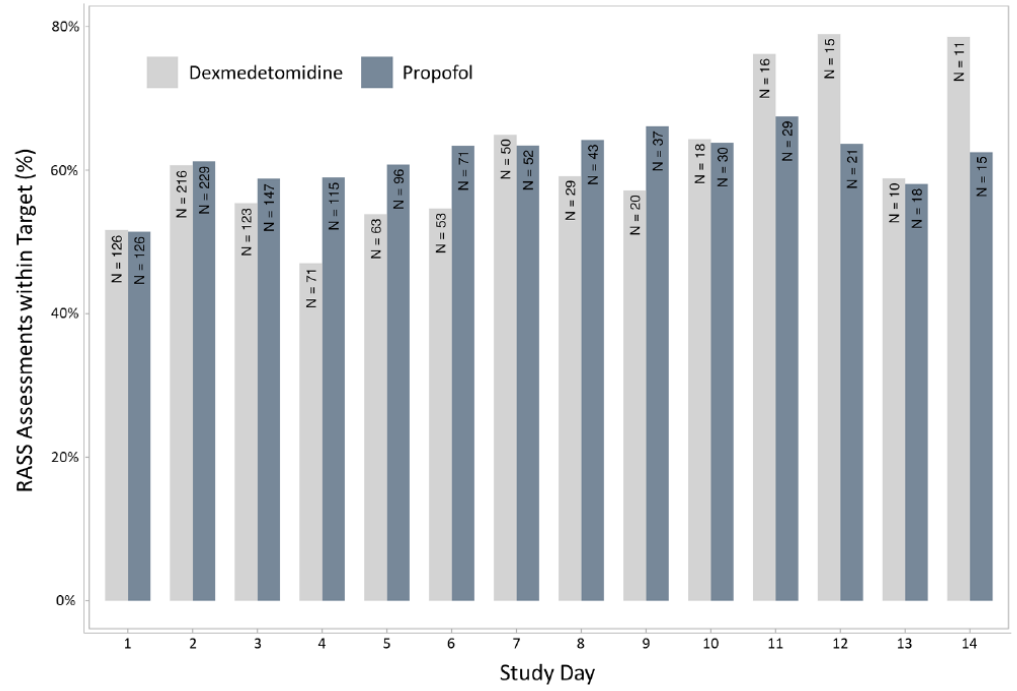
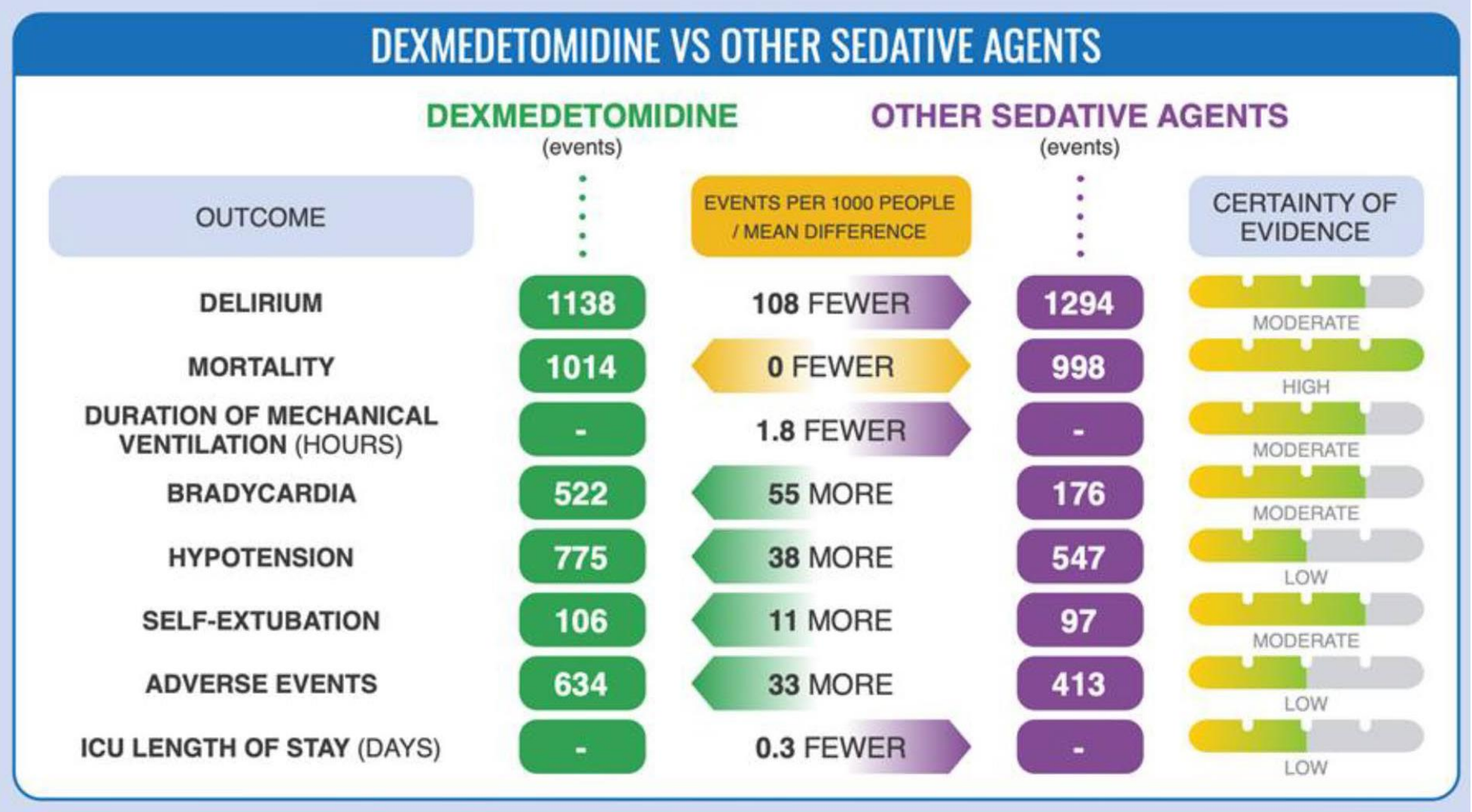


Figure S2. Percent Assessments at Target Sedation by Treatment Group. We display the percentage of Richmond Agitation Sedation Scale (RASS) assessments, while on trial drug, within ±1 of the target RASS score set by the clinical team.

MENDS 2 Trial
Hughes C, et al. NEJM 2021

RECOMMENDATION

In invasively mechanically ventilated adult ICU patients, we **suggest** using dexmedetomidine over other sedative agents, if the desirable effects including a reduction in delirium are valued over the undesirable effects including an increase in hypotension and bradycardia



Moller et al. Rapid Practice Guidelines. *ICM* 2022

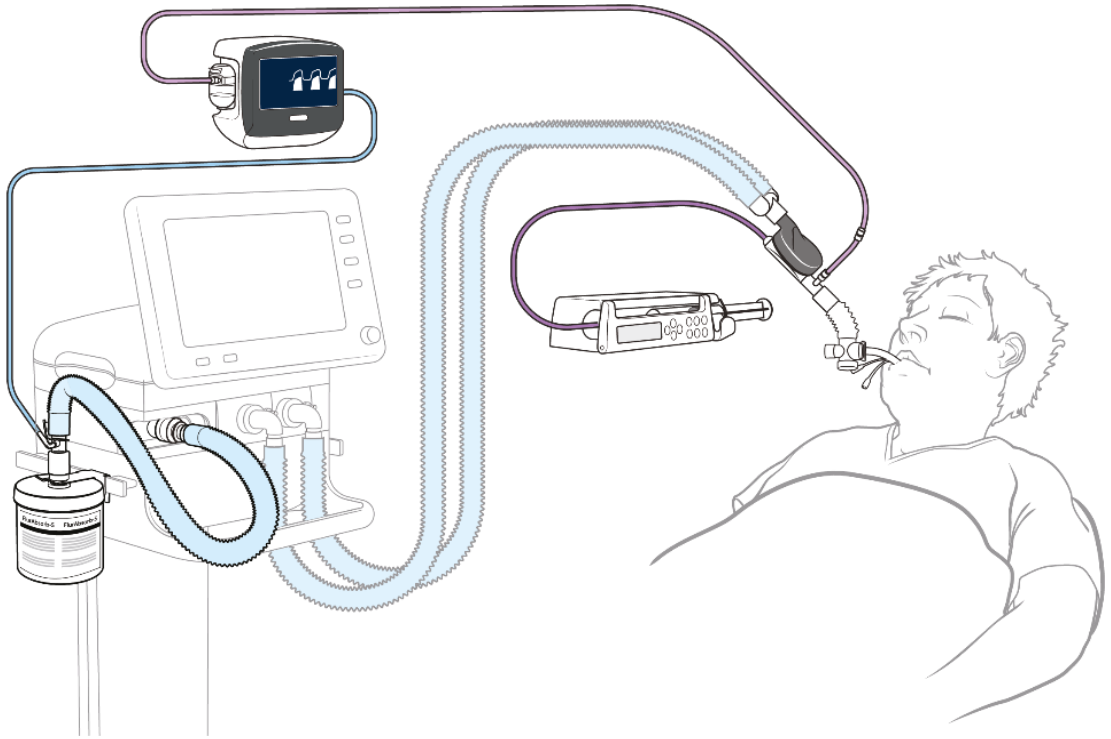
Choice of Sedative

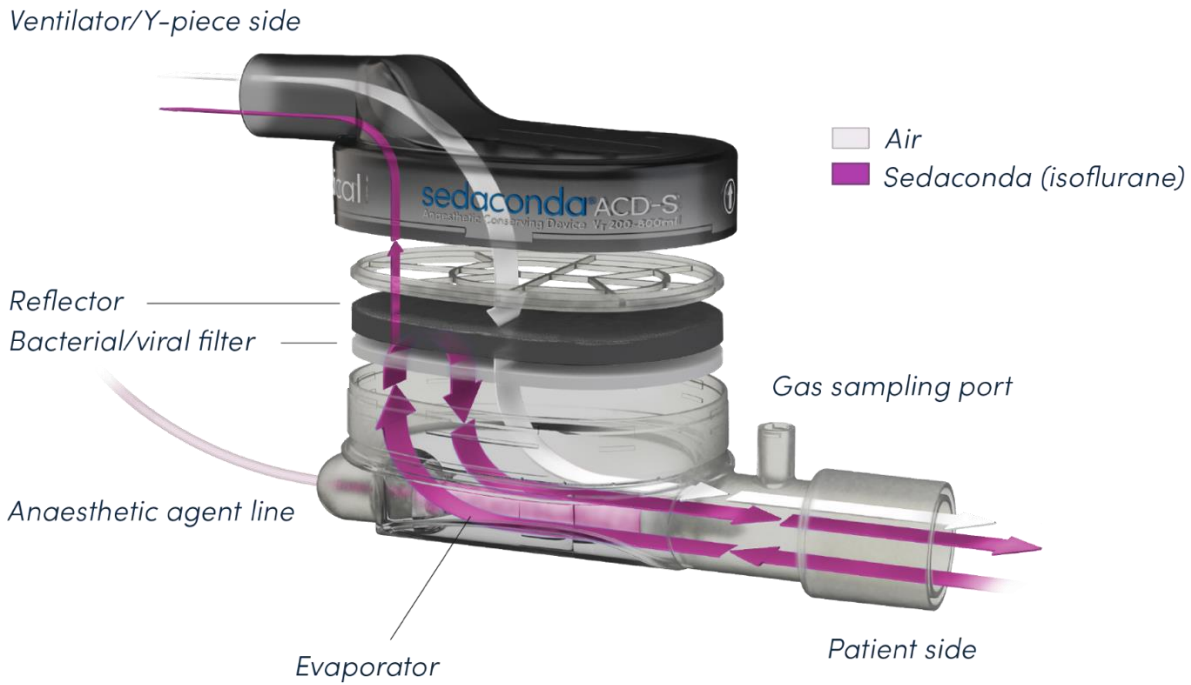
Recommendation:

We **suggest** using **either** propofol or dexmedetomidine over benzodiazepines for sedation in critically ill mechanically ventilated adults (conditional recommendation, low quality of evidence).

Devlin JW, et al. Crit Care Med 2018; 46 (9); e825-873

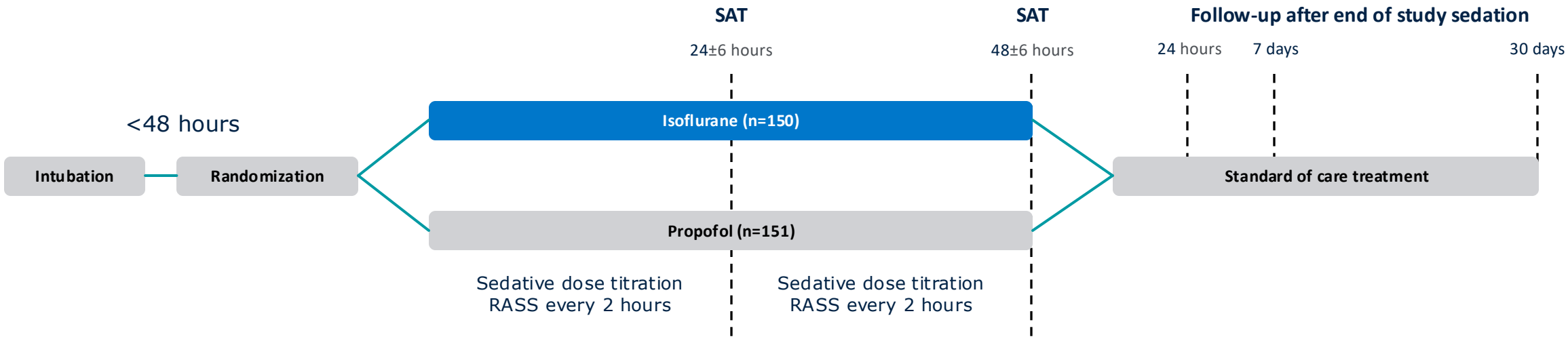
Sedaconda Anaesthesia Conserving Device (ACD-S) Delivery System





- Serves as an HME that rapidly and continuously vaporizes isoflurane delivered by syringe pump
- Response of patient to isoflurane dependent on patient's tidal volume
- Isoflurane is rapidly reflected and adsorbed to the carbon filter
  - amount of isoflurane in Flurisorb scavenger < 5% of what delivered by syringe pump
- Closed system: environmental exposure of isoflurane is very low
- Scavenging filter (FlurAbsorb) collects the small amount of wasted isoflurane

The Sedaconda Study



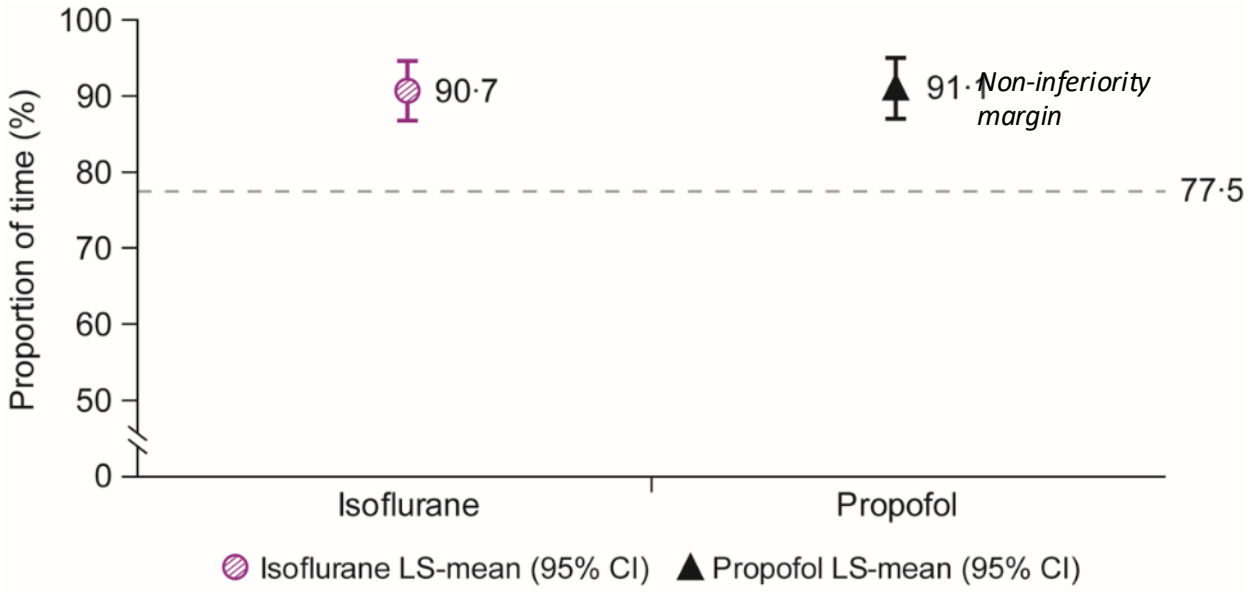
A phase 3, randomised, controlled, open-label, multicentre, parallelgroup, non-inferiority trial designed to meet the European regulatory requirements for approval

Meiser et al., Lancet Resp Med 2021.

Sedation Onset and Maintenance of Target RASS

Rapid onset: Rapid alveolar update and deliver to the brain

Proportion of time within sedation target



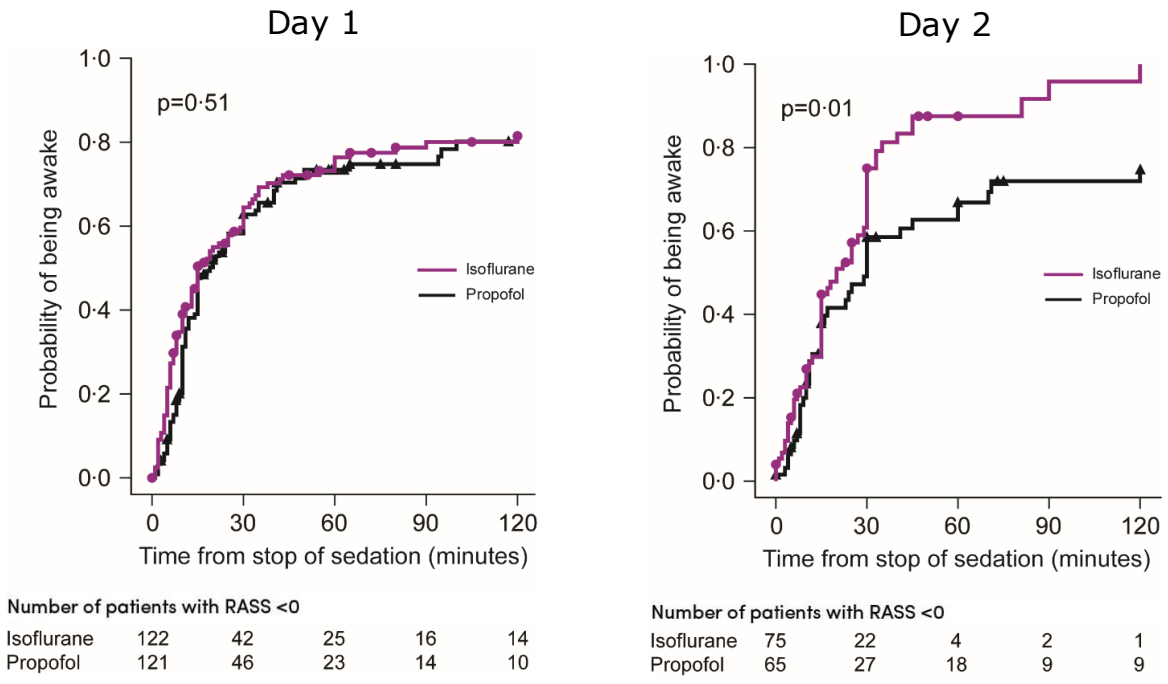
- Comparable time spent in the target RASS range without rescue sedation
- > 90% in both groups

Meiser et al., Lancet Resp Med 2021.

RASS=Richmond Agitation–Sedation Scale

Wake-up Time

Time to wake-up during SAT (sedation stopped)



Day 2

<u>Averge Isoflurane wake up time:</u>

= 20 min (IQR 10-30 min)
(< 30 min for 75% of patients to wake up)

<u>Average Propofol wake up time:</u>

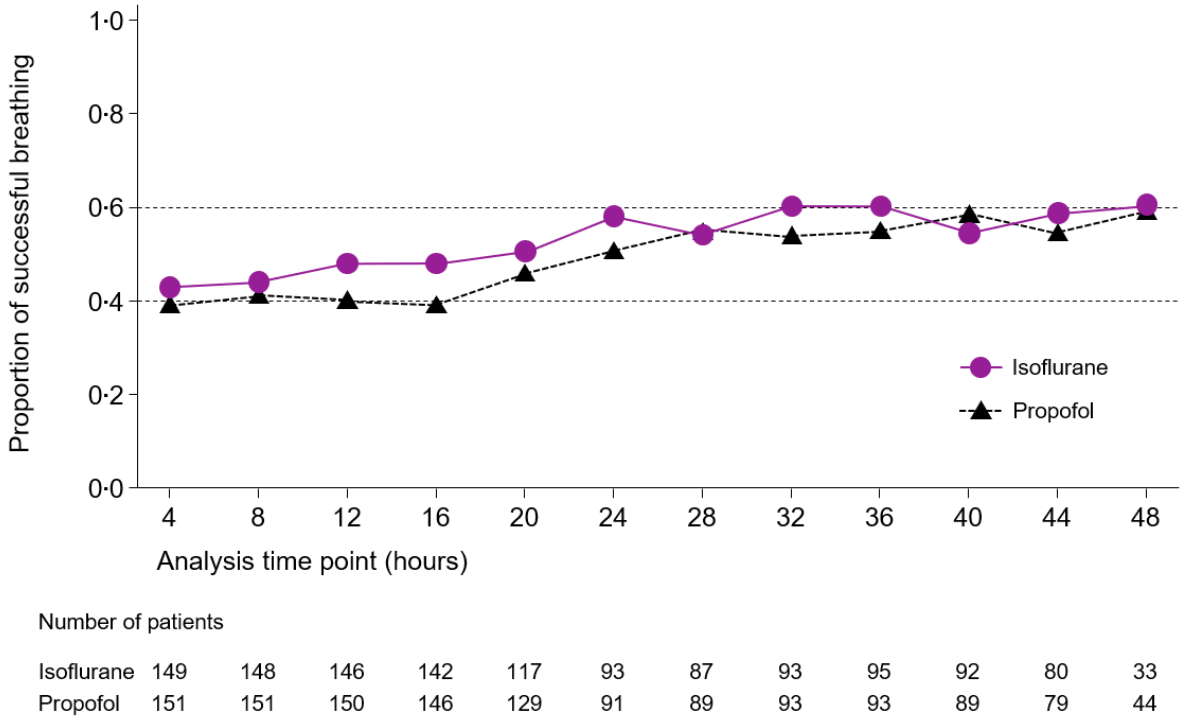
= 30 min (IQR 11-120 min)
(< 120 min for 75% of patients to wake up)

- Isoflurane > 99.5% eliminated during exhalation
  - < 0.5% metabolized: therefore elimination independent of liver or renal function
- No binding to tissue or fat

Meiser et al., Lancet Resp Med 2021.

SAT = spontaneous awakening trial

Spontaneous Breathing



Proportion of time spontaneously breathing

Day 1 (all patients)

- Isoflurane 50.3%
- Propofol 37.0%

} p=0.013

Day 2 (all patients)

- Isoflurane 65%
- Propofol 51%

} p=0.13

Surgical Subgroup (both days 1+2)

- Isoflurane 82%
- Propofol 35%

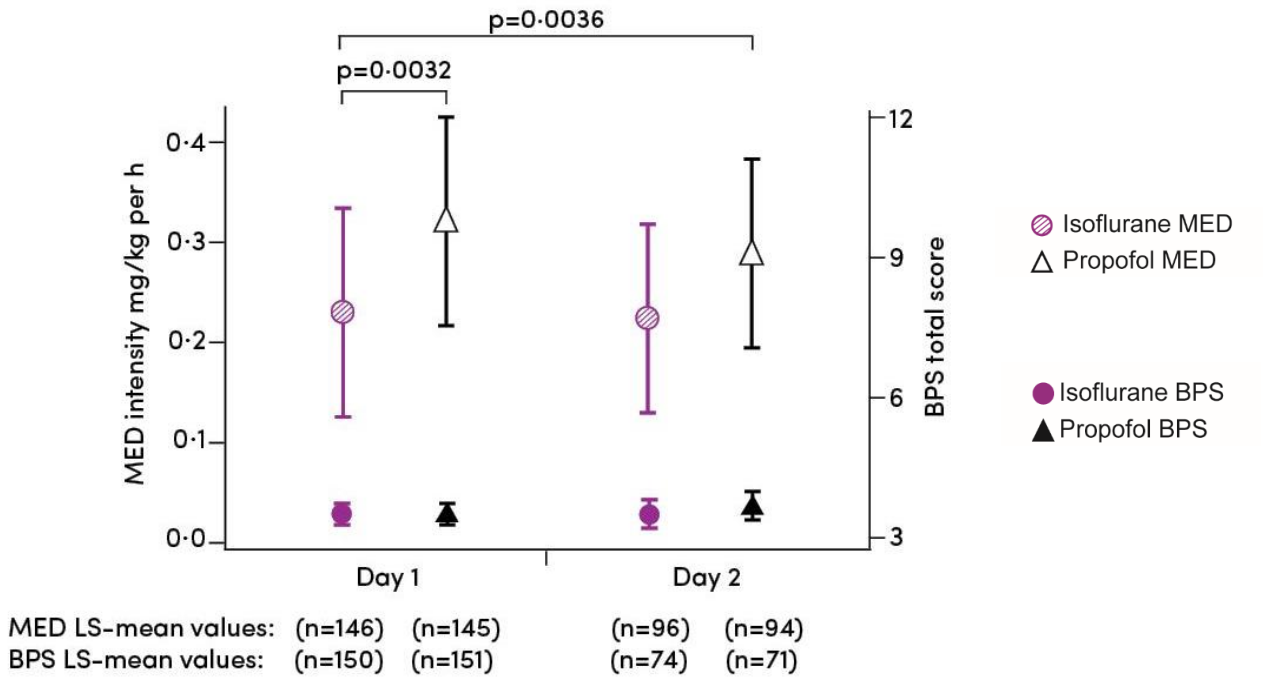
} p=<0.001

Increased spontaneous breathing appears to be a direct effect of isoflurane (and not mediated by opioid exposure or PaCO2)

Meiser et al., Lancet Resp Med 2021.
Ferrière et al., J Crit Care 2021.

Opioid requirements

Morphine equivalent dose intensity and BPS during study sedation



- **Opioid dose intensity was 29% lower in the isoflurane group.**
- **BPS scores were similar between the two groups; opioid dose reduction independent of pain.**

Why? Inhaled anaesthetics have antinociceptive effects on the spinal cord[1]

Meiser et al., Lancet Resp Med 2021.

MED=Morphine Equivalent Dose. BPS=Behavioural Pain Scale

Effect of inhaled anaesthetics on cognitive and psychiatric outcomes in critically ill adults: a systematic review and meta-analysis

Sean Cuninghame[1], Angela Jerath[2,3,4,5], Kevin Gorsky[2], Asaanth Sivajohan[6], Conall Francoeur[7], Davinia Withington[8,9], Lisa Burry[10,11], Brian H. Cuthbertson[2,5], Beverley A. Orser[2,3], Claudio Martin[1], Adrian M. Owen[12,13], Marat Slessarev[1,12,*], for the Sedating with Volatile Anesthetics Critically Ill COVID-19 Patients in ICU: Effects on Ventilatory Parameters and Survival study investigators

Delirium Prevalence

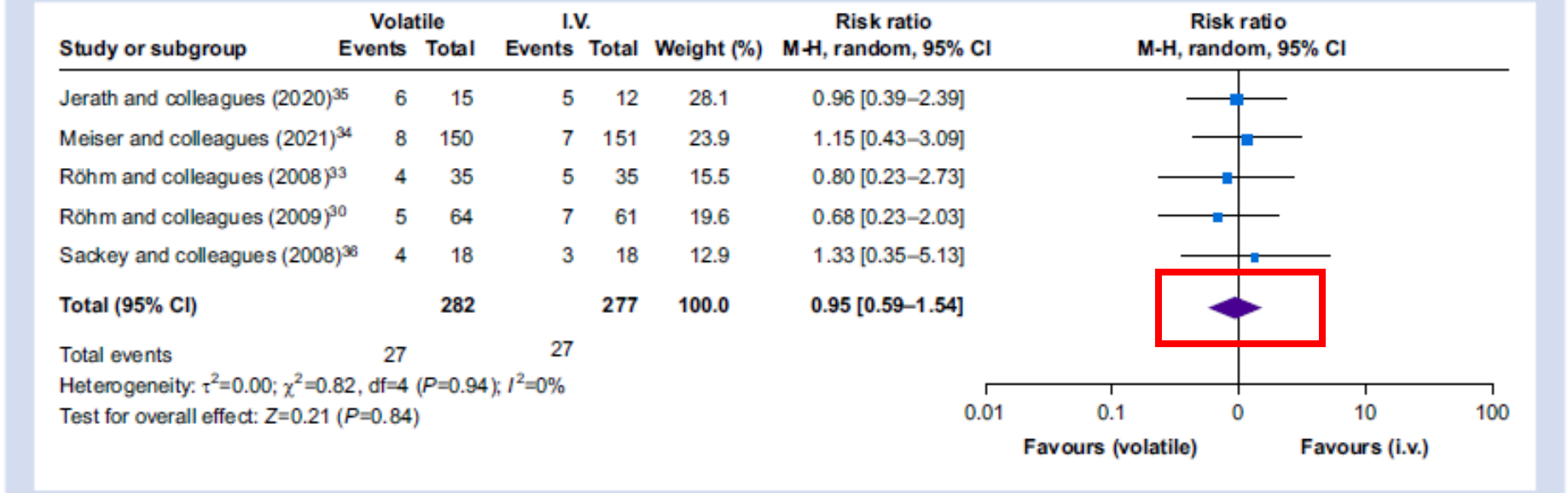


Fig 2. Effect of inhaled volatile anaesthetics on delirium incidence compared with intravenous anaesthesia in critically ill adults. CI, confidence interval.

Long term cognitive dysfunction @ 3 months (TICS ≤ 26) not different in between ISO (n=7 (78%) vs. IV sedation (n=10 (67%) (Jerath A, et al. Crit Care Explorations 2020)

Cunninghame S, et al. BJA 2023

Safety

	Inhaled Isoflurane (n=51)	Propofol (n=51)	
Hypotension	7%	1%	NS
Vasopressor Use	79%	77%	NS
Delirium	5%	5%	NS
Oliguria	5%	4%	NS
Atrial Fibrillation	3%	3%	NS

Meiser et al., Lancet Resp Med 2021.

Precautions

Malignant Hyperthermia (MH)

- Sedation with isoflurane is contraindicated in patients with known or suspected genetic susceptibility to MH.[1]
- MH is a rare genetic disorder (incidence 1/10.000–250.000[2]) where isoflurane sedation may trigger a skeletal muscle hypermetabolic state.

Intracranial Pressure (ICP)

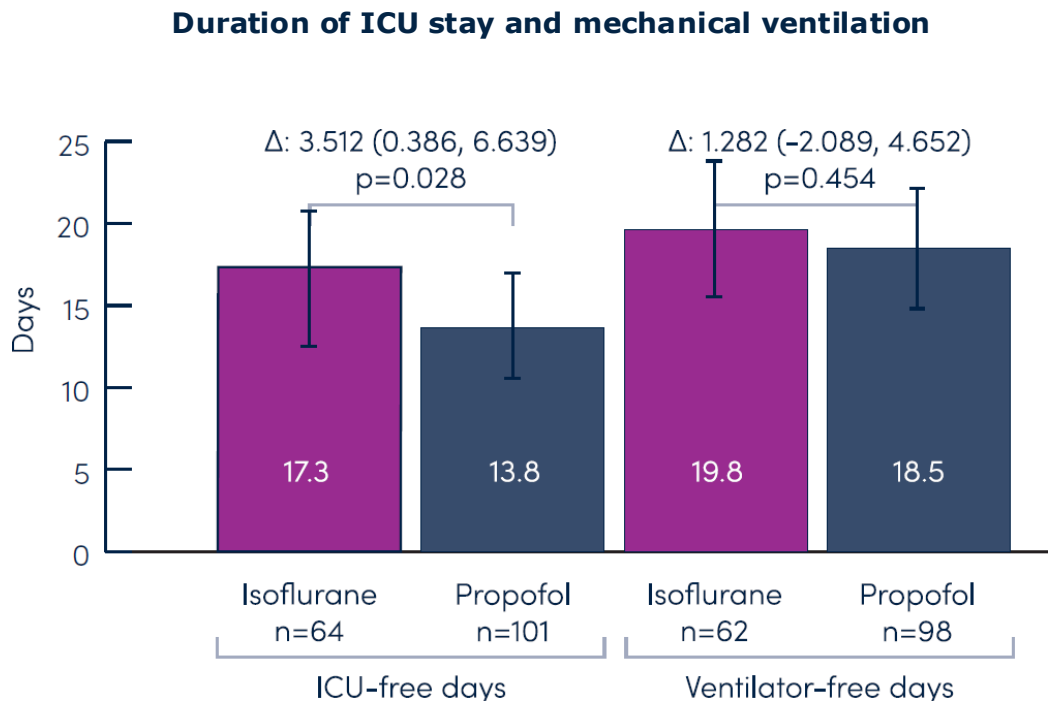
- During sedation with isoflurane, ICP may increase slightly.[1]
- Caution should be taken when administering isoflurane to patients with increased ICP, and ICP must be monitored in such patients.[1]

M/EN/PH/220001 AUG 2023

1. Sedaconda® SmPC – August 2021. 2. Rosenberg et al., Orphanet J Rare Dis 2015.

ICU Length of Stay

Post-hoc analysis[1] of the Sedaconda study (n=178)



In a *post-hoc* analysis[1] of the Sedaconda study[2]:

- **ICU stay was 3.5-days shorter** in patients who received only isoflurane as primary sedative in the 30 days from randomization* (ICU-free days: 17.3 vs 13.8, p=0.028).
- Differences in ventilator-free days favored isoflurane but were not statistically significant.

1. **Bracht et al. 2023.**
2. **Meiser et al. 2021**

UK National Institute for Health and Care Excellence (NICE)
Published January 27th 2022

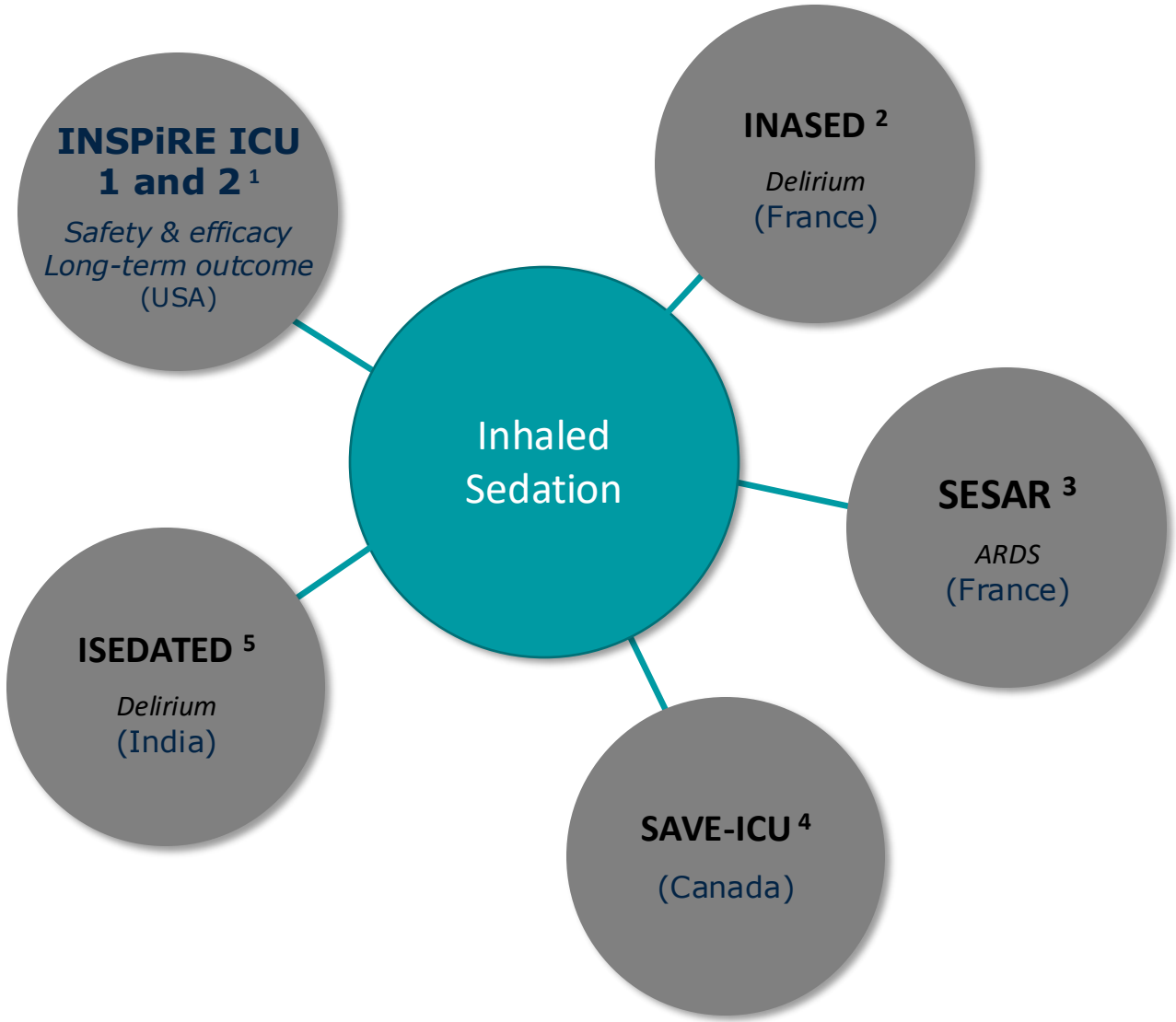
1. Recommendations
   - 1.1 Sedaconda ACD-S (Anaesthetic Conserving Device) is recommended as a cost-saving option for delivering inhaled sedation in an intensive care setting when the volatile anaesthetics isoflurane or sevoflurane are being considered.
   - 1.2 Further research is recommended to identify any health conditions or groups of patients that would benefit more from inhaled sedation with Sedaconda ACD-S than from standard care.

https://www.nice.org.uk/guidance/mtg65/

<u>The clinical experts agreed that inhaled sedation is likely to be beneficial in the following subgroups:</u>

- difficult to sedate
- acute bronchospasm
- acute respiratory distress syndrome
- patients requiring multiple sedative agents
- overdose who need a fast wake up
- neurological assessment after cardiac arrest
- older adults at high risk of delirium
- children with resistant status epilepticus
- people with difficult intravenous access

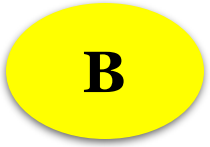
Ongoing ICU Inhaled Sedation RCTs



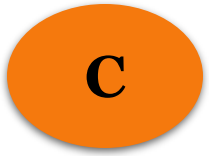
ClinicalTrials.gov Identifiers: 1. INSPiRE ICU 1 & 2, NCT05312385 & NCT05327296. 2. INASED, NCT04341350. 3. SESAR, NCT04235608. 4. SAVE-ICU, NCT04415060.

ABCDEF Bundle Elements

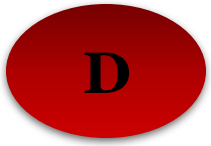
Assess, Prevent and manage Pain



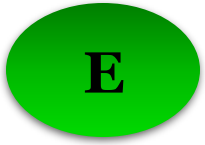
Both SAT and SBT



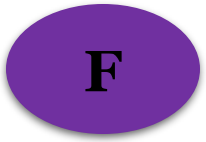
Choice of Analgesia and Sedation



Delirium: Assess, Prevent and Manage



Early Mobility and Exercise



Family Engagement and Empowerment

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Case of RS – ICU day #2 (8am)

RS is a 72 year-old female who remains in the Surgical ICU POD #2 after emergent surgical repair of a leaking 3-inch abdominal aortic aneurysm.
HR =110, BP = 98/63, RR = 20; SaO2 =99%
CPOT= 1, RASS = +1, CAM-ICU = positive
Mechanically ventilated: SIMV =14, TV 500, FiO2 = 40%, PEEP=5
Tolerating tube feeds at 20 mL/hr
Receiving fentanyl 25-50 mcg IVP q4h prn pain, propofol @ 30 mcg/kg min, and haloperidol 1mg IV q6h
She has not left the bed since she arrived in the emergency department.
Prior to admission she enjoyed bridge and golfed weekly in a women's golf league.

What is the most important intervention to make in RS's care at this time?

a. Stop haloperidol as it has not been shown in multiple RCTs to resolve ICU delirium.
b. Titrate up her propofol infusion to maintain light sedation.
c. Stop propofol and initiate inhaled isoflurane to maintain light sedation.
d. Stop propofol and initiate a dexmedetomidine infusion to maintain light sedation.

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D. is correct; RCT data suggests use of short-term dexmedetomidine infusion in a patient with agitated delirium may help facilitate SBT/extubation. A. is wrong as haloperidol may be effective in reducing delirium-associated agitation (although one could make the argument to increase IV haloperidol and put patient on an SBT). B. is wrong as patient likely close to extubation and increasing propofol will not help facilitate SBT/extubation. C. is wrong as there no evidence to suggest inhaled isoflurane facilitates SBT/extubation better than dexmedetomidine.

Summary

- There is no “one-size-fits-all” approach to sedation in intensive care
- Many important reasons to maintain patients at a light level of sedation
- Continuous benzodiazepines should be avoided (unless very deep sedation or continuous NMB therapy is required)
- Balance the risks and benefits of using dexmedetomidine vs propofol on a daily basis.
- Inhaled sedation may allow for rapid sedative onset (to deep levels) and rapid sedative offset but additional large RCTs are required

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Shehabi Y, et al. Early sedation with dexmedetomidine in critically ill patients. N Engl J Med 2019; 380: 2506-17.

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Moller MH, et al. Use of dexmedetomidine for sedation in mechanically ventilated ICU patients: a rapid practice guideline. Intensive Care Med 2022; 48: 801-810.

Meiser A, et al. Inhaled isoflurane via the anaesthetic conserving device versus propofol for sedation in invasively ventilated patients in intensive care units in Germany and Slovenia: an open-label, phase 3, randomized controlled, non-inferiority trial. Lancet Respir Med 2021.