C

Dexmedetomidine in the Intensive Care Unit and Challenging uses

DR.Adel Alaa El-Din Habib,MD

- Delirium is derived from the Latin word Lira meaning ‘track’ or ‘trail’, and therefore, ‘de-lirium’ can be best translated in termsof‘derailment’or‘getting off track’.

- Acute disorder of attention and awareness with disturbances in cognition and consciousness, but the level of arousal is not severely compromised as in coma. Delirium is the manifestation of an acute encephalopathy

- Delirium is not solely caused by a pre-existing neurocognitive disorder, but is caused by another medical condition.

- Aetiology of delirium is very heterogeneous, although the presentation is rather homogeneous.

- Delirium affects many patients who have been exposed to a variety of both predisposing and precipitating risk factors.

- Usually it is impossible to assign one specific cause for delirium.

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Incidence and duration of delirium

- Incidence rate of 29% during an ICU stay.
- Half of these cases become apparent within the first 2 days after admission to the ICU.
- The duration of delirium varies strongly between patients with a median duration of 2 to 3 days .

- Risk factors of delirium Multiple factors increase the risk of delirium.
- Pre-existing factors that increase a patient's vulnerability are termed predisposing risk factors.
- Factors that trigger the onset of delirium are classified as precipitating risk factors.
- Both predisposing and precipitating risk factors interact the more or the stronger predisposing factors are present, the fewer or weaker precipitating factors are required to develop delirium, and vice versa.

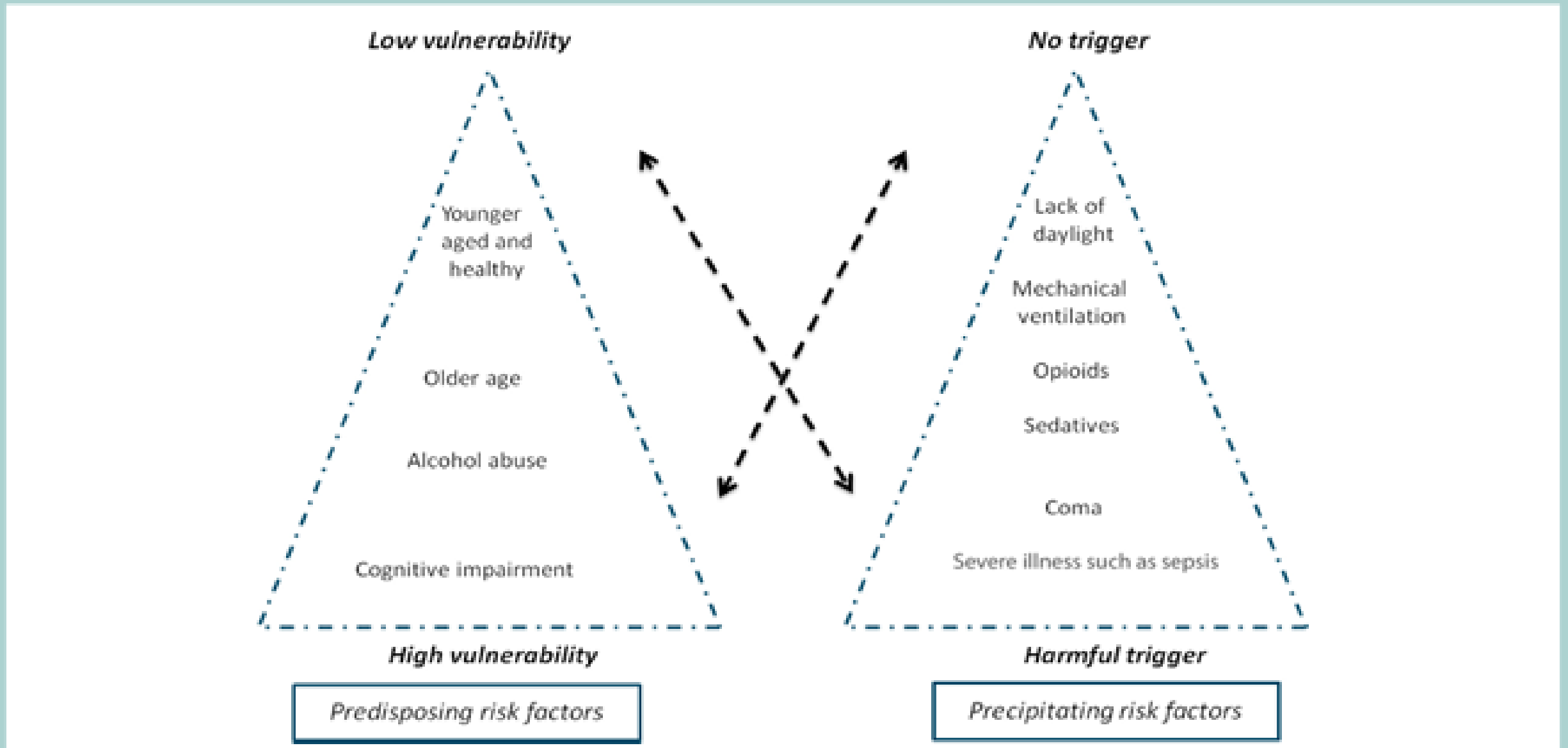

Fig 1 Association between vulnerability and triggers in relation to risk factors.

The triggering or precipitating factors can be classified in three domains:

(i) Acute illness-related factors, such as previous coma; increased severity of illness, mostly expressed in the Acute Physiology and Chronic Health Evaluation (APACHE) score; multiple trauma; sepsis; need for ventilatory support; pain; and systemic hypoperfusion with metabolic acidosis

(ii) Medication-related factors: benzodiazepines increase the risk in a dose-dependent manner; anticholinergic drugs, opioids, and corticosteroids are probably associated with the development of delirium.

(iii) Environmental factors, such as increased noise, lack of daylight, and admission to a ward (compared with a personal room) increase the risk of delirium.

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It is important to note that most triggering factors are modifiable whilst predisposing risk factors are all non modifiable.

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Pathophysiology

- .Neuroinflammation, an aberrant stress response, imbalance of neurotransmitters, and alterations in neural networks have all been considered as main underlying hypotheses for the pathophysiology of delirium.

- Critical illness is usually associated with an inflammatory response, for example, trauma, complicated surgery, or sepsis. Peripheral pro-inflammatory cytokine signals transmitted to the brain can lead to neuroinflammation that persist for months.

- The systemic inflammatory response may diminish as a result of sepsis. Many other factors play a role in delirium in sepsis, such as reduced cerebral perfusion pressure, ischaemia caused by systemic hypotension, hypoxemia and microcirculatory alterations (including endothelial dysfunction).These factors contribute to the reduction in cerebral blood flow that has been observed during delirium.

- Several stressors as surgery, systemic inflammation and pain all cause the brain to activate the limbice hypothalamice and pituitary adrenal axis with associated increased concentrations of cortisol. In healthy individuals, this response is adaptive and has adequate feedback regulation.

- Cognitive decline and ageing are associated with impaired feedback regulation of the stress response pathway, resulting in sustained high cortisol concentrations that contribute to the development of delirium.

- It is further presumed that delirium is associated with reduced activity of neurones that communicate with the neurotransmitter acetylcholine.

- Acetylcholine plays a central role in attention and consciousness particularly affected in delirium as there are interactions with other pathways such as the dopaminergic system.

- Delirium may be associated with the production of a random and loose brain network, which means that there is reduced concomitant activity of brain

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Management

- Diagnosis.
- Prediction.
- Prevention.
- Treatment

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Diagnosis

- 60 to 70% of cases are missed by ICU nurses and physicians.

- Detection of delirium, of which the Confusion Assessment Method for the ICU (CAMICU) and the Intensive Care Delirium Screening Checklist (ICDSC) are the most commonly used .Whilst the CAM-ICU is a brief assessment based on formal testing, the ICDSC is based on observations during a nursing shift.

- Guidelines recommend the use of one of these instruments, and their sensitivity in research settings is adequate (80% for the CAM-ICU and 74%for the ICDSC).

Table 1 The Confusion Assessment Method for ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC). RASS; Richmond Agitation-Sedation Scale

CAM-ICU

Criteria	Positive score if
1. Acute onset or fluctuating course	One or both features present
2. Inattention *Read the following series of 10 letters and let patient squeeze on the letter 'A'* S A V E A H A A R T†	More than two errors
3. Altered level of consciousness *Based on the RASS score*	RASS score other than zero
4. Disorganized thinking *Ask the following questions:* *- Will a stone float on water?* *- Are there fish in the sea?* *- Does one pound weigh more than two pounds?* *- Can you use a hammer to pound a nail?* *Command* *Say to patient: "Hold up this many fingers" (hold two fingers in front of the patient), "Now do the same with the other hand" (without repeating the number of fingers)*	More than 1 mistake on the questions or commands

Positive CAM-ICU: Criterion 1 plus 2 and either criterion 3 or 4

The CAM-ICU can only be administered when the RASS score < -3.
† If the patient has a neuromuscular disease and squeezing is impossible, eye blinks can be used.

ICDSC

Criteria	YES	NO
1. Altered level of consciousness *YES: RASS score other than zero* *NO: RASS = 0 or recent sedative use*	1	0
2. Inattention *Difficulty in following a conversation or instructions. Easily distracted by external stimuli. Difficulty in shifting focuses. If present*	1	0
3. Disorientation *Disoriented in name, place and/or date*	1	0
4. Hallucination, delusion or psychosis *Ask if present*	1	0
5. Psychomotor agitation or retardation *Either hyperactive, requiring sedatives or restraints, or hypoactive*	1	0
6. Inappropriate speech or mood *If present*	1	0
7. Sleep-wake cycle disturbance *Either frequent awakening/ <4 hours of sleep or sleeping during most of the day*	1	0
8. Symptom fluctuation *Fluctuation of any of the above symptoms over a 24 hour period*	1	0

No delirium: 0 points
Subsyndromal delirium: 1-3 points
Delirium: 4-8 points

The Intensive Care Delirium Screening Checklist (ICDSC). It is only possible to assess the ICDSC if the RASS score < -3. The first four criteria are based on a bedside assessment, the other four on observations throughout the entire shift.
† If the patient has a neuromuscular disease and squeezing

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Prediction

- The Early Prediction of Delirium ICU(E-PRE-DELIRIC) tool predicts delirium in 68%ofcases. Consists of nine predictive factors:

- Age
- History of cognitive impairment.
- Historyof alcohol abuse.
- ICU admission category.
- Urgent admission.
- Mean arterial BP.
- Corticosteroids.
- Respiratory failure.
- Serum urea.

- The second model PRE-DELIRIC predicts delirium 24h after admission to the ICU,and consists of 10 predictors:
- Age.
- APACHE II score.
- Coma
- ICU admission category.
- Infection.
- Presence of metabolic acidosis.
- Use of morphine.
- Use of a sedative drug.
- Urea concentration.
- Urgent admission.

- PREDELIRICmodel is a better predictor, clinicians found theE-PRE-DELIRICmore feasible

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Non-pharmacological prevention and treatment

- Earlymobilisation.
- Use of earplugs
- Reductions of night-time light and noise.
- Increased exposure to daylight,
- Reorientation programme with cognitive training

Table 2 Delirium statement derived from the PADIS guideline. [15] HMG-CoA, 5-hydroxy-3-methylglutaryl-coenzyme A.

Delirium monitoring
(i) Critically ill adults should be regularly assessed for delirium using a valid tool (good practice statement).
(ii) The level of arousal may influence delirium assessments with a validated screening tool (ungraded statement).
Outcomes associated with delirium
(i) Strong association with long-term cognitive impairment and may be with a longer hospital stay
(ii) Not associated with post-traumatic stress disorder or post-ICU distress
(iii) Not associated with ICU length of stay, discharge disposition to a place other than home, depression, functionality/dependence, or mortality
Pharmacological delirium prevention
(i) It is suggested not to use haloperidol, an atypical antipsychotic, dexmedetomidine, an HMG-CoA reductase inhibitor (i.e. statin), or ketamine to prevent delirium in all critically ill adults (conditional recommendation: very low to low quality of evidence).
Delirium treatment
(i) Regarding subsyndromal delirium, it is suggested not to use haloperidol or an atypical antipsychotic (conditional recommendation: very low to low quality of evidence).
(ii) Regarding delirium, it is suggested not to routinely use haloperidol, an atypical antipsychotic, or an HMG-CoA reductase inhibitor (i.e. a statin) to treat delirium (conditional recommendation: low quality of evidence).
(iii) It is recommended to use dexmedetomidine for delirium treatment in mechanically ventilated patients, in which agitation is precluding weaning or extubation (conditional recommendation: low quality of evidence).
Non-pharmacological delirium prevention and treatment
(i) It is suggested not to use bright light therapy as single intervention to prevent delirium (conditional recommendation: moderate quality of evidence).
(ii) It is suggested to use a multicomponent, non-pharmacological intervention focusing at (but not limited to) reducing modifiable risk factors; improving cognition; and optimising sleep, mobility, hearing, and vision in critically ill adults (conditional recommendation: low quality of evidence).
Multicomponent interventions include (but are not limited to) strategies to reduce or shorten delirium (e.g. reorientation, cognitive stimulation, and use of clocks), improve sleep (e.g. minimising light and noise), improve wakefulness (i.e. reduced sedation), reduce immobility (e.g. early rehabilitation/mobilisation), and reduce hearing or visual impairment (e.g. enable the use of devices, such as hearing aids or eyeglasses).

Psychosis

- The preferred agent for treatment of psychosis in delirium is haloperidol because of its rapid effects and the possibility of i.v. administration (0.5 to 5 mg repeated three times, depending on age).

Agitation

- The first step in the management of agitated patients is to evaluate and treat underlying causes, such as pain, itching, constipation, or bladder retention.
- Reassurance and implementation of non-pharmacological measures, such as relaxing music.
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- Dexmedetomidine and clonidine may be superior to haloperidol

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Anxiety

- alpha 2agonists, such as dexmedetomidine and clonidine, have anxiolytic properties as well.

- Disturbed sleep Benzodiazepines are often prescribed to promote sleep but if started early benzodiazepines may induce delirium, and although they may promote light sleep, they suppress deep sleep and rapid-eye-movement sleep, and, therefore, recovery.

- Patients receiving antipsychotic treatment may be switched to quetiapine (25 to 50 mg at night

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Hyperadrenergic state

- A hyperadrenergic state presents with hypertension, tachycardia, spontaneous hyperventilation, and sweating, and is particularly .
- Common in patients with substance withdrawal, such as withdrawal of alcohol.
- Benzodiazepines are often prescribed in alcohol withdrawal is limited and based on older literature.
- As benzodiazepines also increase the risk of ICU delirium, it is currently unclear whether benzodiazepines are superior to other approaches in patients with a hyperadrenergic state, such as a2-agonists and anticonvulsant drugs.

Dexmedetomidine and challenges in the Intensive Care Unit

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KEY POINTS

- Dexmedetomidine is a highly selective alpha-2 adrenoceptor agonist.
- It is a safe sedative agent that has useful analgesic and anxiolytic effects.
- It has a particular role in facilitating weaning from the ventilator and extubation, especially when standard sedation strategies have proven ineffective.
- Clinical trials have demonstrated that the benefits of dexmedetomidine compared with other more traditional agents for critical care sedation include reductions in time to extubation, duration of mechanical ventilation, and length of critical care stay.
- Bradycardia is the main recognised side effect, and there are few absolute contraindications

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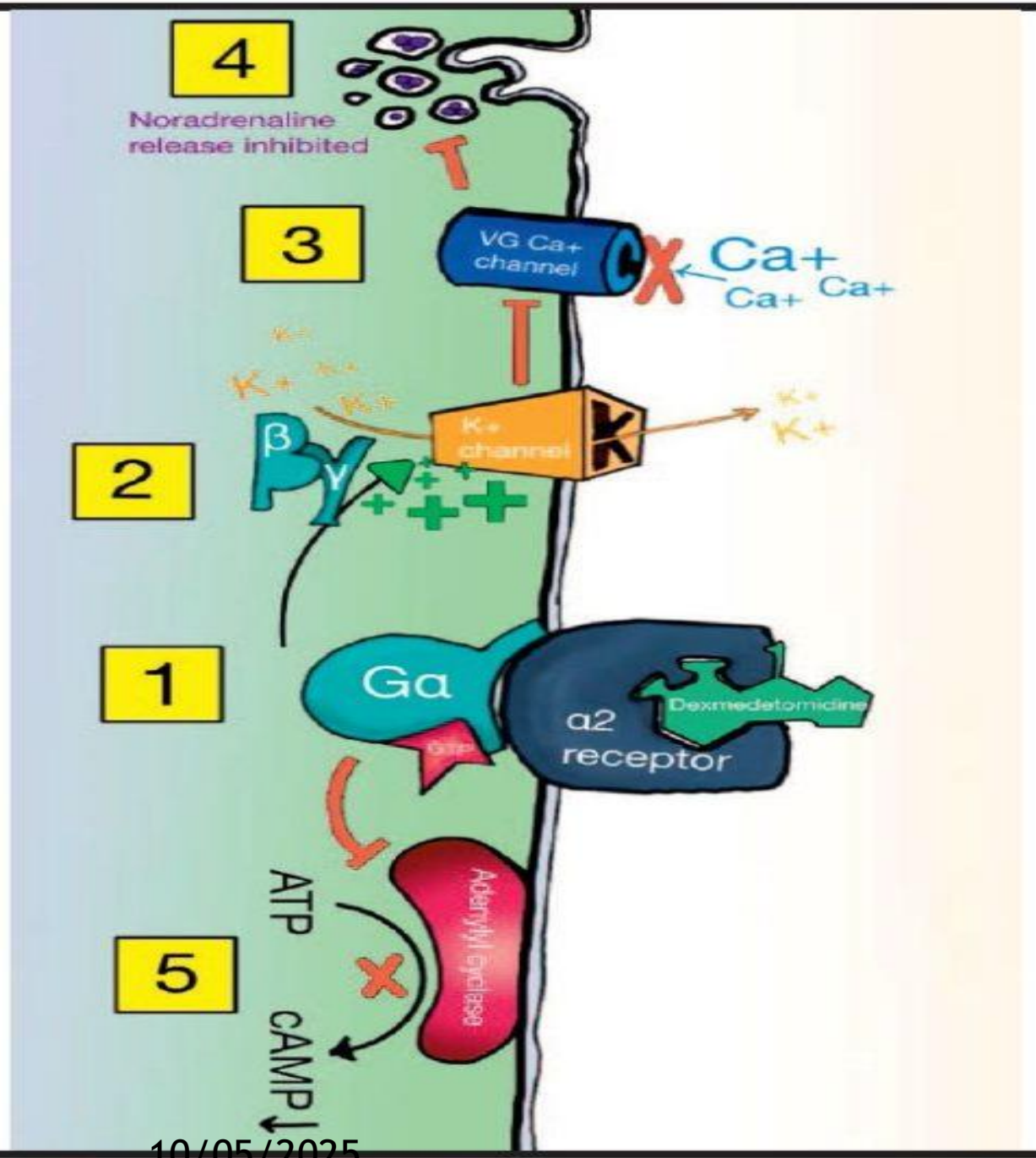
PHARMACOLOGY

- Dexmedetomidine is an imidazole-derivative drug
- Dexmedetomidine is a highly selective alpha-2 receptor agonist
- Produces spinal and supraspinal analgesia via reduced nociceptive transmission according to the gate theory
- Its major sympatholytic and sedative actions are mediated via reduced transmission in the locus coeruleus (major noradrenergic centre of the central nervous system).
- It causes anxiolysis and sedation without the respiratory depression



The α_2 adrenoceptor is a G_i-protein coupled receptor. In the resting state, guanosine diphosphate (GDP) is bound to the α subunit of the G protein, which is itself bound to the receptor.

1. Dexmedetomidine binds to the α2-adrenoceptor resulting in a conformational change in the receptor. This results in activation of the Gα subunit, and the exchange of GDP for guanosine triphosphate (GTP).
2. The Gβγ subunit dissociates from the GTP-Gα complex and activates inward rectifier K^+ channels, causing K^+ efflux and hyperpolarisation of the nerve terminal.
3. Hyperpolarisation of the cell membrane in turn inhibits voltage gated Ca^{2+} channels.
4. Reduced intracellular calcium impairs secretion of neurotransmitters such as noradrenaline.
5. In parallel, the activated Gα-GTP complex inhibits adenylyl cyclase, reducing cAMP production which has multiple downstream effects.

- Valuable opioid-sparing effect

- Dose-dependent reduction in mean arterial pressure and heart rate.

- Reduction in cerebral blood flow and a clinically insignificant increase in $PaCO_2$

- Nausea has been suggested to be between 1% and 10%.

- Dexmedetomidine has not been shown to impair adrenal steroid synthesis.

Dosing and Administration

- Dexmedetomidine is administered intravenously. at an infusion rate of 0.7 mcg/kg/h using actual body weight.

- It should then be titrated gradually to the desired level of sedation within the range of 0.2 to 1.4 lg/kg/h.

- UK licensing information does not recommend the use of a loading bolus.
- Steady state is achieved in 1 hour.

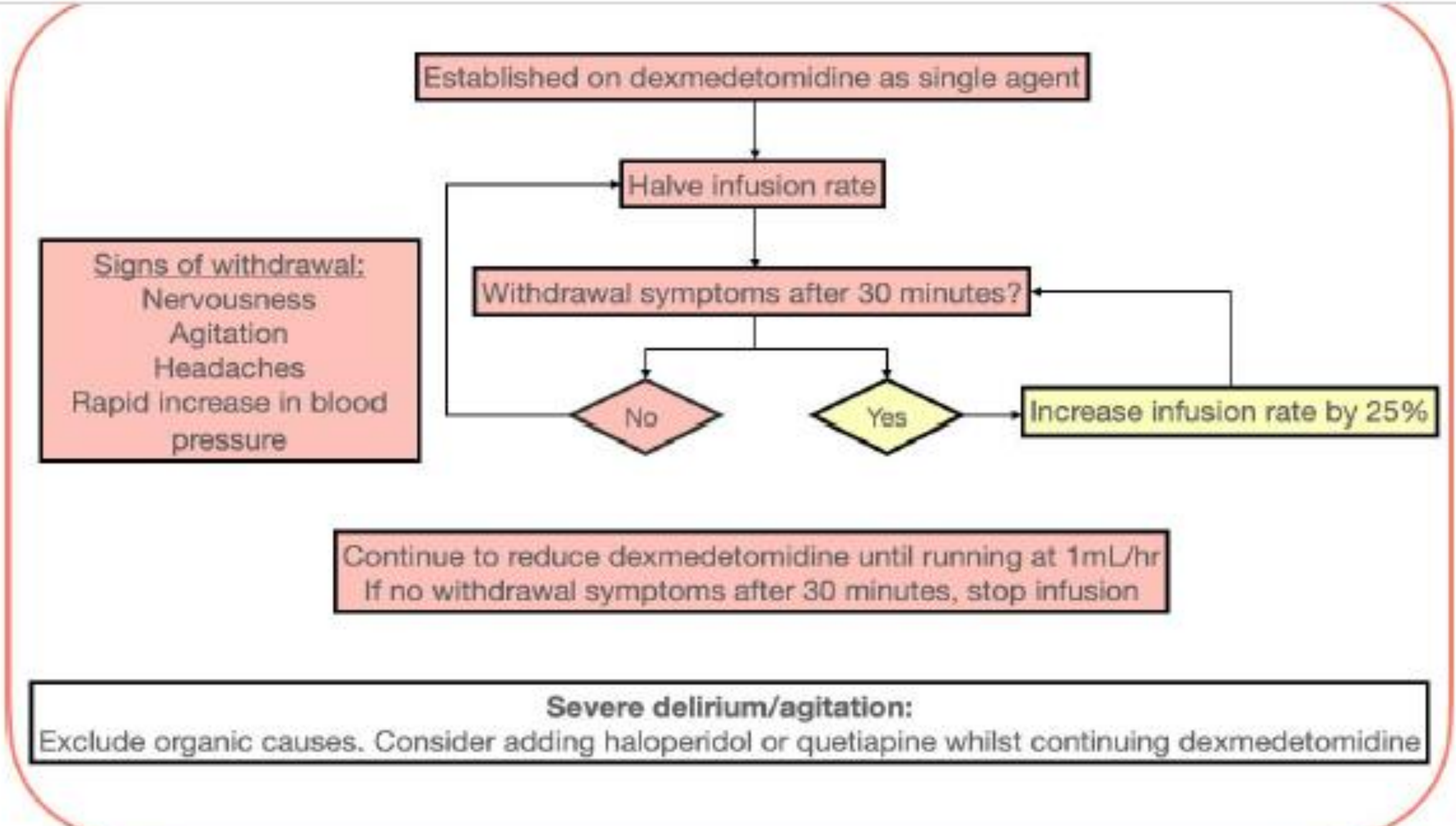
- Dexmedetomidine permit it to be continued at a lower dose during and immediately after extubation.

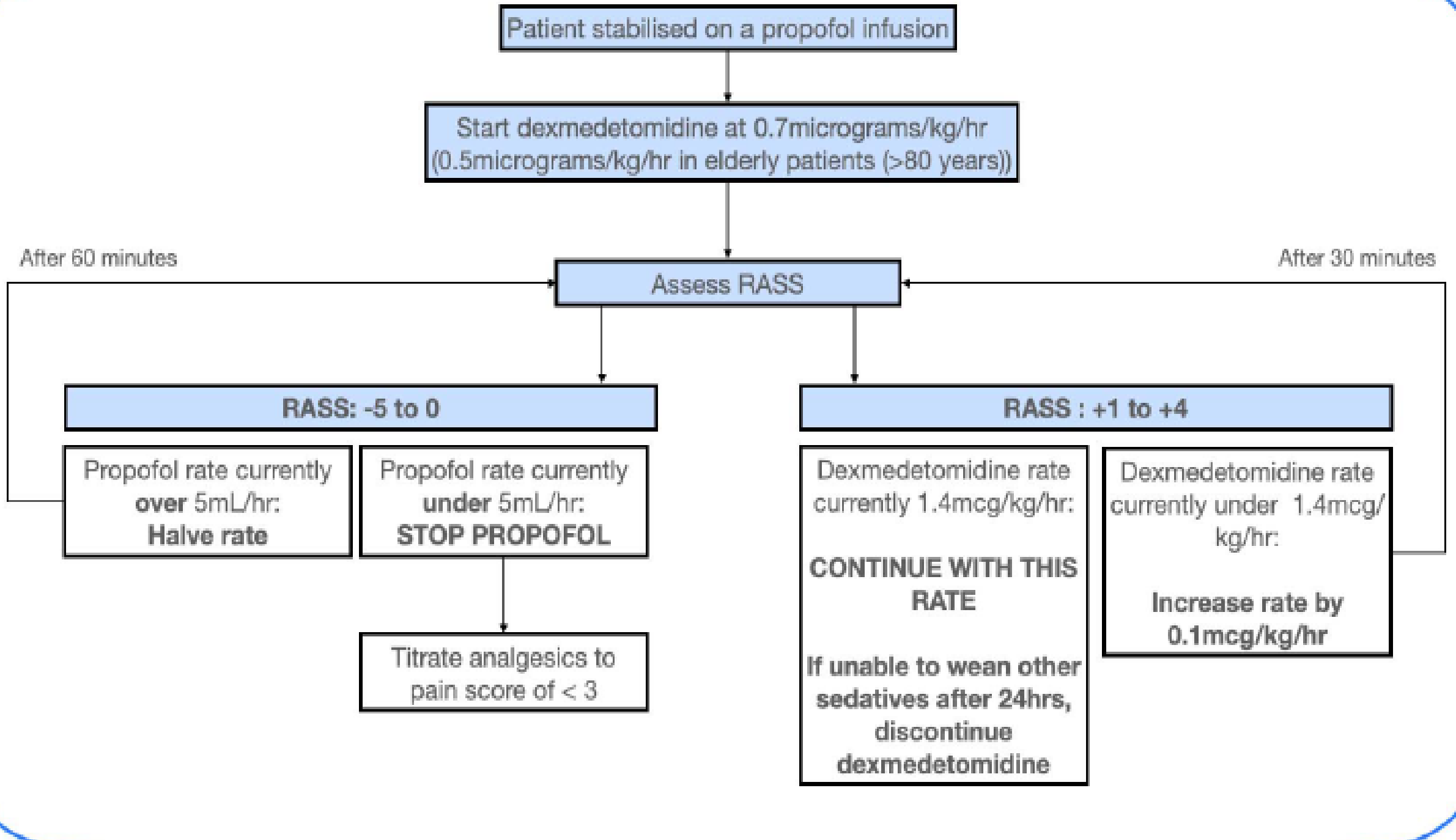
Maintenance dose of *dexdor*® based on a dilution of 8 mcg/ml

8 mcg/ml

1 2 Dose (mcg/kg/hr)

Weight (kg)	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0	1.1	1.2	1.3	1.4
50	1.3	1.9	2.5	3.1	3.8	4.4	5.0	5.6	6.3	6.9	7.5	8.1	8.8
55	1.4	2.1	2.8	3.4	4.1	4.8	5.5	6.2	6.9	7.6	8.3	8.9	9.6
60	1.5	2.3	3.0	3.8	4.5	5.3	6.0	6.8	7.5	8.3	9.0	9.8	10.5
65	1.6	2.4	3.3	4.1	4.9	5.7	6.5	7.3	8.1	8.9	9.8	10.6	11.4
70	1.8	2.6	3.5	4.4	5.3	6.1	7.0	7.9	8.8	9.6	10.5	11.4	12.3
75	1.9	2.8	3.8	4.7	5.6	6.6	7.5	8.4	9.4	10.3	11.3	12.2	13.1
80	2.0	3.0	4.0	5.0	6.0	7.0	8.0	9.0	10.0	11.0	12.0	13.0	14.0
85	2.1	3.2	4.3	5.3	6.4	7.4	8.5	9.6	10.6	11.7	12.8	13.8	14.9
90	2.3	3.4	4.5	5.6	6.8	7.9	9.0	10.1	11.3	12.4	13.5	14.6	15.8
95	2.4	3.6	4.8	5.9	7.1	8.3	9.5	10.7	11.9	13.1	14.3	15.4	16.6
100	2.5	3.8	5.0	6.3	7.5	8.8	10.0	11.3	12.5	13.8	15.0	16.3	17.5
105	2.6	3.9	5.3	6.6	7.9	9.2	10.5	11.8	13.1	14.4	15.8	17.1	18.4
110	2.8	4.1	5.5	6.9	8.3	9.6	11.0	12.4	13.8	15.1	16.5	17.9	19.3
115	2.9	4.3	5.8	7.2	8.6	10.1	11.5	12.9	14.4	15.8	17.3	18.7	20.1
120	3.0	4.5	6.0	7.5	9.0	10.5	12.0	13.5	15.0	16.5	18.0	19.5	21.0
125	3.1	4.7	6.3	7.8	9.4	10.9	12.5	14.1	15.6	17.2	18.8	20.3	21.9
130	3.3	4.9	6.5	8.1	9.8	11.4	13.0	14.6	16.3	17.9	19.5	21.1	22.8
135	3.4	5.1	6.8	8.4	10.1	11.8	13.5	15.2	16.9	18.6	20.3	21.9	23.6
140	3.5	5.3	7.0	8.8	10.5	12.3	14.0	15.8	17.5	19.3	21.0	22.8	24.5
145	3.6	5.4	7.3	9.1	10.9	12.7	14.5	16.3	18.1	19.9	21.8	23.6	25.4
150	3.8	5.6	7.5	9.4	11.3	13.1	15.0	16.9	18.8	20.6	22.5	24.4	26.3
155	3.9	5.8	7.8	9.7	11.6	13.6	15.5	17.4	19.4	21.3	23.3	25.2	27.1
160	4.0	6.0	8.0	10.0	12.0	14.0	16.0	18.0	20.0	22.0	24.0	26.0	28.0
165	4.1	6.2	8.3	10.3	12.4	14.4	16.5	18.6	20.6	22.7	24.8	26.8	28.9
170	4.3	6.4	8.5	10.6	12.8	14.9	17.0	19.1	21.3	23.4	25.5	27.6	29.8
175	4.4	6.6	8.8	10.9	13.1	15.3	17.5	19.7	21.9	24.1	26.3	28.4	30.6
180	4.5	6.8	9.0	11.3	13.5	15.8	18.0	20.3	22.5	24.8	27.0	29.3	31.5


Established on dexmedetomidine as single agent
Halve infusion rate
Withdrawal symptoms after 30 minutes?
No
Yes
Increase infusion rate by 25%
Signs of withdrawal:
Nervousness
Agitation
Headaches
Rapid increase in blood pressure
Continue to reduce dexmedetomidine until running at 1mL/hr
If no withdrawal symptoms after 30 minutes, stop infusion
Severe delirium/agitation:
Exclude organic causes. Consider adding haloperidol or quetiapine whilst continuing dexmedetomidine


Patient stabilised on a propofol infusion
Start dexmedetomidine at 0.7micrograms/kg/hr (0.5micrograms/kg/hr in elderly patients (>80 years))
After 60 minutes
Assess RASS
After 30 minutes
RASS: -5 to 0
RASS : +1 to +4
Propofol rate currently over 5mL/hr: Halve rate
Propofol rate currently under 5mL/hr: STOP PROPOFOL
Titrate analgesics to pain score of < 3
Dexmedetomidine rate currently 1.4mcg/kg/hr:
CONTINUE WITH THIS RATE
If unable to wean other sedatives after 24hrs, discontinue dexmedetomidine
Dexmedetomidine rate currently under 1.4mcg/kg/hr:
Increase rate by 0.1mcg/kg/hr

Route	Usual dose range	Onset of action	Time to peak effect	Notes
IV: bolus and infusion	1 μg/kg bolus → 0.2–1.5 μg/kg/h infusion	5–10 min	15–30 min	Bolus dosing may be associated with increase risk of hypotension and bradycardia
IV: infusion alone	0.2–1.5 μg/kg/h infusion	~15 min	60 min	Doses above 1.5 μg/kg/h demonstrate no additional sedative effect
Intranasal	1–4 μg/kg	~10 min	~20 min	Onset of action and time to peak may be slower in adults (onset up to 45–60 min, time to peak up to 90–105 min)
Intramuscular	1–4 μg/kg	?15–20 min	Unclear	Pharmacodynamics not well studied
Sublingual	120 or 180 μg	?45–60 min	?60–120 min	Pharmacodynamics not well studied

Note: Pharmacodynamic information adapted primarily from Weerink et al.,[6] Carlone et al.,[52] Preskorn et al.,[61] Barr et al.,[62] Yu et al.,[63] Yuen et al.,[64] and Bailey et al., .[65]

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Pharmacokinetics

- Dexmedetomidine exhibits a 2-compartment model, with a distribution half-life of 6 minutes.
- It exhibits linear pharmacokinetic within the recommended range not to accumulate in treatments lasting up to 14 days
- 94% protein bound, binding primarily to serum albumin, with a constant degree of binding over a wide range of serum albumin levels.
- Volume of distribution at steady state is estimated at between 1.1 and 2.1 l/kg.

- Dexmedetomidine is extensively hepatically metabolised, including via the CYP450 system.
- All metabolites have negligible pharmacological activity.
- 95 % of an administered dose is renally excreted, with the remainder excreted via the gut.
- There is no requirement for dose adjustment in severe renal failure
- Hepatic dysfunction exposed to increased free drug fractions, leading to prolonged elimination half-life, from approximately 1.9 to 2.5 hours in the healthy subject to up to 7.4 hours in those with severe hepatic impairment reduce maintenance doses in hepatic impairment patients

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Monitoring Requirements

- Patients receiving a dexmedetomidine infusion require continuous electrocardiogram, respiration and blood pressure
- If noninvasive blood pressure monitoring is used, the minimum cycle time should be 5 minutes.
- Two-hourly sedation scores should be performed to aid titration, and the Confusion Assessment Method for the Intensive Care Unit (ICU)
- Delirium scoring should be performed at least every 12 hours
- There is no requirement to measure serum drug levels

Contraindications for the following patients who

- Are hypersensitive to the drug or excipients
- Have unpaced second- or third-degree heart block
- Have uncontrolled hypotension
- Have acute cerebrovascular conditions
- Are concurrently using other alpha-2 agonists, eg, clonidine

Cautions for the following patients who

- Are at risk of exaggerated cardiovascular response, eg, hypovolaemia
- Have spinal cord injury
- Have severe left ventricular systolic dysfunction
- Have concurrent neuraxial anaesthesia
- Are pregnant
- Are breast-feeding
- Have seizures

- **Dexmedetomidine is commonly utilized to achieve light sedation in critically ill patients in the ICU and is currently recommended in the SCCM 2018 and PADIS guidelines.**

- **While further studies are needed, DEX is a versatile medication which may provide benefit in other indications including delirium, sleep, and alcohol withdrawal.**

- **Poor quality of evidence of DEX use in immunomodulation and sepsis, no conclusions for its use can be drawn.**

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Sedation

- In the Society of Critical Care Medicine's (SCCM) 2013 and Pain Agitation/Sedation Delirium Immobility and Sleep Disruption (PADIS) Guidelines use of light sedation in lieu of deep sedation was recommended decrease time to extubation and reduce ICU length of stay (LOS)

- No standard definition of light sedation exists.

- Majority of studies utilize Richmond Agitation and Sedation Score (RASS) (−2 to +1)

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Dexmedetomidine (DEX) an intravenous sedative commonly used in the ICU due to its ability to achieve light sedation without respiratory depression or concern for over sedation

- DEX remains a common sedative of choice, either alone or in combination with other sedatives and analgesics.

- It should be recognized that DEX should not be used for patients requiring deep sedation (RASS: −3 to −5), such as patients receiving continuous infusion neuromuscular blockade With increasing focus on patient-centered outcomes.

- Studies are needed to evaluate DEX for sedation and its effects on long-term outcomes including quality of life, specifically physical impairmen cognitive impairment, and mental health

Table 1. Current Place in Practice and Major Trials.

Author	Trial design	Patients	ICU population	Interventions	Outcomes
Pandharipande et al[3] MENDS	Double-blind, RCT	106	Mixed medical and surgical	DEX vs lorazepam	Time within RASS goal: 80% vs 67%; $P = 0.04$ 28-d mortality: 17% vs 27%; $P = 0.18$
Riker et al[4] SEDCOM	Double-blind, RCT	375	Mixed medical and surgical	DEX vs midazolam	Time within RASS goal: 77.3% vs 75.1%; $P = 0.18$ Days to extubation: 3.7 vs 5.6; $P = 0.01$
Jakob et al[5] MIDEX PRODEX	2 double-blind, RCTs	897	Mixed medical and surgical	DEX vs midazolam DEX vs propofol	Hours on MV vs midazolam: 123.0 vs 164.0; $P = 0.03$ VAS score vs midazolam: ED: 19.7 (15.2-24.2); $P < 0.01$ VAS score vs propofol: ED: 11.2 (6.4-15.9); $P < 0.01$
Shehabi et al[6] SPICE III	Open-label, RCT	3904	Mixed medical and surgical	DEX vs other sedation	MV-free days: 23.0 vs 22.0 90-d mortality: OR: 1.00 (0.87-1.15) 180-d mortality: OR: 1.01 (0.88-1.16)

Abbreviations: DEX, dexmedetomidine; ED, estimated difference; ICU, intensive care unit; MV, mechanical ventilation; OR, odds ratio; RCT, randomized controlled trial; VAS, visual analog scale; RASS, Richmond Agitation and Sedation Score.

- Pandharipande et al DEX resulted in more days alive without delirium or coma and more time at the targeted level of sedation compared with lorazepam.

- Riker et al performed an international RCT comparing DEX and midazolam and found no significant difference between percentage time within target RASS but DEX treated patients spent less time on the ventilator and experienced less delirium.

- Two multicenter RCTs conducted by Jakob et al found DEX to be non inferior to midazolam and propofol in maintaining target sedation level with reduced time to extubation and was associated with improved patient communication with nursing staff as well as decreased delirium.

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SLEEP

- Normal sleep follows 4 different stages identified by conventional somnography that are associated with distinct physiological and neurochemical changes.

- N1 and N2 are considered lighter sleep stages while N3/N4 and rapid eye movement (REM) are considered restorative sleep

- Sleep disruption in critically ill patients has been shown to impact outcomes related to cardiorespiratory decompensation, metabolic derangements, neurocognitive effects and immunological consequences that can lead to impaired morbidity.

- Patients within the ICU experience a significant amount of sleep fragmentation leading to a reduction in deep N3/N4

- REM sleep stages despite having relatively normal totalsleep times.
- Although sedation has previously been advocated to promote sleep and reverse consequences of sleep deprivation.

- Recent literature has evaluated the effects of sedative agents on sleep quality in critically ill patients γ-aminobutyric acid receptor (GABA) agonists and opioids have been associated with alterations in sleep architecture and a reduction in perceived sleep quality so guidelines recommending against their use for the improvement of sleep in critically ill adults.

- DEX has been explored as a potential pharmacologic intervention for sleep disruption in the ICU due to its unique mechanism of action .

- Dexmedetomidine exert hypnotic action through activation of central presynaptic and postsynaptic alpha-2 receptors within the locus coeruleus to hyperpolarize neurons and reduce NE release, inducing a state of unconsciousness similar to natural sleep

Table 2. Trials of Dexmedetomidine and Sleep.

Author	Trial design	Patients	ICU population	Interventions	Outcomes
Alexopoulou et al[7]	Prospective, before and after study	13	Mixed medical and surgical	Nocturnal DEX vs no sedation	Sleep efficiency: 64.8% vs 9.7%; $P < 0.01$ Sleep fragmentation index: 2.7 times/h vs 7.6 times/h; $P = 0.02$ Sleep at night: 79.0% vs 48.0%; $P = 0.03$ Stage 1 sleep: 13.1% vs 48.0%; $P < 0.01$ Stage 2 sleep: 80.2% vs 47.0%; $P < 0.01$
Wu et al[8]	Double-blind, RCT	76	Noncardiac surgery	Nocturnal DEX vs placebo	Sleep efficiency: 22.4% vs 15.0%; $P = 0.03$ Sleep fragmentation index: 23.9 times/h vs 22.3 times/h; $P = 0.61$ Stage 1 sleep: 56.4% vs 84.2%; $P = 0.04$ Stage 2 sleep: 43.5% vs 14.7%; $P = 0.04$
Skrobik et al[9]	Double-blind, RCT	100	Mixed medical and surgical	Nocturnal DEX vs placebo	Perceived sleep quality: MD: 0.02 (0.42-1.92)

Abbreviations: DEX, dexmedetomidine; ICU, intensive care unit; MD, mean difference; RCT, randomized controlled trial.

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Delirium

- Delirium is an acute onset of deficit in attention and cognition which has been associated with increased hospital stay, long-term cognitive impairment, and a 3-fold increase in 6-month mortality.

- Delirium is highly prevalent in the ICU, affecting 30% to 50% of patients.

Table 3. Trials of Dexmedetomidine and Delirium.

Author	Trial design	Patients	ICU population	Interventions	Outcomes
Pandharipande et al[3] MENDS	Double-blind, RCT	106	Mixed medical and surgical	DEX vs lorazepam	Days alive free of delirium or coma: 7.0 vs 3.0; $P = 0.01$
Riker et al[4] SEDCOM	Double-blind, RCT	375	Mixed medical and surgical	DEX vs midazolam	Prevalence of delirium: 54.0% vs 76.6%; $P < 0.01$
Skrobik et al[9]	Double-blind, RCT	100	Mixed medical and surgical	Nocturnal DEX vs placebo	Delirium-free during ICU admission: 80.0% vs 54%; $P < 0.01$ Nocturnal DEX and delirium: RR: 0.44 (0.23-0.82)
Stollings et al[10]	Prospective, cohort study	103	Mixed medical and surgical	DEX vs lorazepam	DEX concentrations and delirium: OR: 1.10 (0.90-1.30) Lorazepam concentrations and delirium: OR: 13.20 (1.40-120.10)
Shehabi et al[6] SPICE III	Open-label, RCT	3904	Mixed medical and surgical	DEX vs other sedation	Delirium or coma-free days: 24.0 vs 23.0
Hughes et al[11] MENDS2	Double-blind, RCT	422	Mixed medical and surgical	DEX vs propofol	Delirium or coma-free days: aOR: 0.96 (0.74-1.26)
Reade et al[12] DAHLIA	Double-blind, RCT	71	Mixed medical and surgical	DEX vs placebo	Hours to delirium resolution: 23.3 vs 40.0; $P = 0.01$
Chitnis et al[13] DIRECT	Open-label, RCT	67	Cardiothoracic surgery	DEX vs propofol	Incidence of delirium: 24.0% vs 42.0%; $P = 0.19$

Abbreviations: aOR, adjusted odds ratio; DEX, dexmedetomidine; ICU, intensive care unit; MV, mechanical ventilation; OR, odds ratio; RASS, Richmond Agitation Sedation Scale; RCT, randomized controlled trial; RR, relative risk.

- Given that DEX's unique mechanism of action is associated with decreased delirium and improved sleep architecture, it is an attractive option in patients experiencing delirium.

- Based on low-quality evidence, current PADIS guidelines recommend against DEX for the prevention of delirium.

- Guidelines suggest utilizing DEX for delirium in mechanically ventilated adults where agitation is precluding weaning or extubation.

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Alcohol Withdrawal

- Alcohol is CNS depressant, exhibits its effects through increased activity of the inhibitory neurotransmitter GABA and concurrent inhibition of the excitatory neurotransmitter glutamate.

- To maintain equilibrium in the setting of prolonged alcohol use, compensatory functional changes occur by down regulation of inhibitory GABA receptors and increased expression of excitatory N-methyl-D-aspartate (NMDA) receptors the binding site of glutamate.
- With abrupt alcohol cessation, neuronal hyperactivity occurs due to overactivation of the upregulated NMDA receptors and decrease in GABA receptors.

- Symptoms of alcohol withdrawal may range from tremors ,insomnia, tachycardia, more severe complications including delirium tremens, tonic-clonic seizures, and extreme agitation and delirium.

- Benzodiazepines are commonly used to manage alcohol withdrawal due to their mechanism at the GABA receptor.

- Benzodiazepine monotherapy may not be sufficient to control alcohol withdrawal symptoms, leading to frequent and increasing doses that may cause excessive sedation, delirium, respiratory depression, and increased hospital LOS due to its inhibition of NE and central sympathetic output.

- DEX has been utilized for alcohol withdrawal to assist with symptomatic management through reduction in autonomic hyperactivity, leading to improvement in anxiety, agitation, tremor, hypertension, and tachycardia.

- Given DEX's lack of GABA activity, it is important to note that it should not be used alone to prevent or treat withdrawal-related seizures or delirium.

Table 4. Trials of Dexmedetomidine and Alcohol Withdrawal.

Author	Trial design	Patients	ICU population	Interventions	Outcomes
Mueller et al[14]	Double-blind, RCT	24	Medical	DEX (low dose) + BZD vs DEX (high dose) + BZD vs placebo + BZD	Change in 12-h BZD use (DEX vs placebo): −36.5 vs −17.5 mg; $P = 0.03$ Change in 24-h BZD use (DEX vs placebo): −56vs −8 mg; $P = 0.04$ Haloperidol use (DEX vs placebo): 25% vs 50%; $P = 0.36$ ICU LOS (DEX vs placebo): 4.7 d vs 4.0 d; $P = 0.42$
Bielka et al[15]	Open-label, RCT	72	Mixed medical and surgical	DEX + BZD vs BZD	24-h BZD use: 20.0 vs 40.0 mg; $P < 0.01$ Cumulative BZD use: 60.0 vs 90.0 mg; $P < 0.01$ Haloperidol use: 6% vs 31%; $P = 0.02$
Beg et al[16]	Retrospective cohort	67	Mixed medical and surgical	DEX + BZD vs BZD	Cumulative BZD use: 100.5 vs 37.0 mg; $P < 0.01$ Change in BZD use after DEX: 21.0 vs 11.0 mg; $P = 0.10$ Change in CIWA-Ar score after DEX: 14.5 vs 8.5; $P < 0.01$ ICU LOS: 2.9 d vs 1.4 d; $P < 0.01$
Love et al[17]	Retrospective cohort	62	Mixed medical and surgical	DEX vs propofol vs DEX + propofol	Change in CIWA-Ar score: −4.4 vs −4.7 vs −10.4; $P = 0.21$ Need for MV: 14.3% vs 23.1% vs 22.2%; $P = 0.40$ ICU LOS: 5.1 d vs 5.5 d vs 4.1 d; $P = 0.65$

Ludtke et al[18]	Retrospective cohort	32	Mixed medical and surgical	DEX vs propofol ± BZD	Need for MV: 13.1% vs 58.8%; $P < 0.01$ ICU LOS: 53.0 h vs 114.9 h; $P = 0.02$
Rayner et al[19]	Retrospective cohort	20	Mixed medical and surgical	Pre-DEX vs post-DEX	24-h BZD use: 52.7 vs 20.3 mg; $P < 0.01$ 24-h haloperidol use: 12.0 vs 6.4 mg; $P = 0.05$
VanderWeide et al[20]	Retrospective cohort	20	Not specified	DEX vs control	Reduction in 12-h BZD use: −19.9 vs −8.3 mg; $P = 0.04$ Reduction in 24-h BZD use: −29.6 vs −11.0 mg; $P = 0.06$ Need for MV: 40.0% vs 41.0%; $P = 1.00$ ICU LOS: 86.6 h vs 54.0 h; $P = 0.23$
Yavarovich et al[21]	Retrospective cohort	438	Medical	DEX + BZD vs BZD	Pre-ICU LOS: 23.4 h vs 9.3 h; $P < 0.01$ ICU LOS: aOR: 2.14 (1.78-2.57)
Lizotte et al[22]	Retrospective cohort	41	Mixed medical, cardiac, and surgical	DEX vs propofol	Mean reduction in BZD use: 13.5 vs 13.6 mg; $P = 0.93$ Mean reduction in haloperidol use: 7.6 vs 8.0 mg; $P = 0.47$ Need for MV: 14.7% vs 100.0%, $P < 0.01$ ICU LOS: 123.6 h vs 156.5 h; $P = 0.13$

Abbreviations: aOR, adjusted odds ratio; BZD, benzodiazepines; CIWA-Ar, Clinical Institute Withdrawal Assessment for Alcohol scale; DEX, dexmedetomidine; ICU, intensive care unit; LOS, length of stay; MV, mechanical ventilation; RCT, randomized controlled trial.

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IMMUNOMODULATION

- DEX-induced immunomodulation have been proposed and demonstrated in the literature.

- Alpha-2 adrenoreceptors are located on T-lymphocytes, and upon activation by agonists such as DEX, T-cell proliferation, T-cell function, and inflammatory cytokine release are suppressed.

- Alpha-2 adrenoreceptors are also found on natural killer cells and receptor activation results in an enhanced immune response with increased cytotoxic activity

- Alpha-2 adrenoreceptor activation leads to an alteration in T-helper 1 and T-helper 2 cell balance. This shift favors T-helper 2 cells inhibits the cellular response, and ultimately leads to an anti-inflammatory state.

- Epidermal growth factor (EGF) receptors in astrocytes are also activated by DEX, and this results in protective effects during neuroinflammation.

- In addition, DEX inhibits key phosphorylation steps in the Janus kinase(JAK) and signal transducer and activator of transcription (STAT) pathway.This pathway ultimately leads to translocation of transcription factors and gene transcription for proinflammatory mediators; therefore, inhibition of the JAK/STAT pathway may decrease inflammation.

- Dexmedetomidine also exerts beneficial effects on mitochondria, reducing reactive oxygen species (ROS) and associated stress-induced cell apoptosis.

- DEX activates the Nrf2/HO-1 pathway resulting in a wide array of immunomodulatory effects including decreased inflammation, oxidative stress, and cell apoptosis which provide organ protection in stressed states.

- Several studies have investigated the use of DEX perioperatively for cardiac surgery or in broad critically ill populations and suggested potential for immunomodulation; however, few reported inflammatory marker measurements

- The studies in cardiac surgery demonstrated a decrease in mortality at various time points including operative, in-hospital, 30 days, 1 year, and even up to 5 years.

- While no inflammatory marker levels were obtained, the authors of these studies suggest the effects of DEX on cardiomyocyte mitochondria and associated decrease in ROS induced cell apoptosis may provide cardioprotective effects

Author	Trial design	Patients	ICU population	Interventions	Outcomes
Ji et al[23]	Retrospective cohort	1134	Cardiothoracic surgery	DEX vs other sedation	Hospital mortality: OR: 0.34 (0.19-0.61) 30-d mortality: OR: 0.39 (0.23-0.66)
Cheng et al[24]	Retrospective cohort	505	Cardiothoracic surgery	DEX vs other sedation	Incidence of stroke: aOR: 0.15 (0.04-0.59) Hospital mortality: aOR: 0.10 (0.03-0.32)
Peng et al[25]	Retrospective cohort	2068	Cardiothoracic surgery	DEX vs other sedation	Incidence of sepsis: aOR: 0.41 (0.18-0.95) 5-y mortality: aOR: 0.61 (0.42-0.89)
Moore et al[26]	Open-label, RCT	103	Mixed medical and surgical	DEX vs other sedation	Serum adrenaline (nmol/L): 0.32 vs 0.38; $P = 0.25$ Serum noradrenaline (nmol/L): 4.27 vs 6.2; $P = 0.09$ Serum total cortisol (mU/L): 515 vs 618; $P = 0.26$

Abbreviations: aOR, adjusted odds ratio; DEX, dexmedetomidine; ICU, intensive care unit; OR, odds ratio; RCT, randomized controlled trial.

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SEPSIS

- There is growing interest in the effects of DEX and its potential benefits within the context of sepsis and septic shock.

- DEX is associated with several mechanisms for immunomodulation. These effects may be especially pertinent in sepsis as immune system dysfunction is known to play a significant role in the syndrome's progression.

- In particular, DEX preserves vagal tone and activity leading to inhibited cytokine synthesis and protection against diseases mediated by inflammatory cytokine release.

- This phenomenon termed the cholinergic antiinflammatory response has been demonstrated in several experimental models of sepsis.

- DEX may also provide hemodynamic benefits in sepsis and septic shock where hypotension causes alpha 2 upregulation of peripheral alpha-2 adrenergic receptors. This receptor upregulation leads to increased sensitivity to catecholamines and improvements in hemodynamics in experimental sepsis models.

- DEX infusion increases venous tone and return, ultimately improving microcirculatory function and hemodynamics.

- These alterations in hemodynamics in addition to immunomodulation present unique mechanisms for potential benefit of DEX in sepsis and septic shock.

- Several studies have investigated the impact of DEX in patients with sepsis or septic shock .

Author	Trial design	Patients	ICU population	Interventions	Outcomes
Pandharipande et al[27]	Double-blind RCT, subgroup analysis	63	Mixed medical and surgical	DEX vs lorazepam	Delirium or coma-free days: 6.1 vs 2.9; $P < 0.01$ MV-free days: 15.2 vs 10.1; $P = 0.03$ 28-d mortality: 16% vs 41%; $P = 0.03$
Kawazoe et al[28] DESIRE	Open-label, RCT	201	Mixed medical and surgical	DEX vs other sedation	CRP (mg/dL): 4.9 vs 8.1; $P = 0.03$ PCT (ng/mL): 0.5 vs 0.9; $P = 0.12$ MV-free days: 20 vs 18; $P = 0.20$ 28-d mortality: HR: 0.69 (0.38-1.22)
Miyamoto et al[29]	Open-label, RCT, post hoc analysis	111	Mixed medical and surgical	DEX vs other sedation	6-h lactate clearance: aMD: 18.5 (2.2-34.9); $P = 0.03$ 12-h lactate clearance: aMD: 28.7 (4.8-52.6); $P = 0.02$
Ohta et al[30]	Open-label, RCT, post hoc analysis	201	Mixed medical and surgical	DEX vs other sedation	CRP range (mg/dL): 5.6-20.3 vs 8.3-21.1; $P = 0.03$ PCT range (ng/mL): 1.2-37.4 vs 1.7-52.9; $P = 0.04$ 14-d mortality: 13% vs 21%; $P = 0.16$
Nakashima et al[31]	Open-label, RCT, post hoc analysis	104	Mixed medical and surgical	DEX vs other sedation	SOFA renal subscore at day 4: −1 vs 0; $P = 0.02$ Hospital mortality: 28% vs 52%; $P = 0.01$ 28-d mortality: 22% vs 42%; $P = 0.03$
Liu et al[32]	Open-label, RCT	200	Not reported	DEX vs propofol	Acute kidney injury: 38% vs 60%; $P < 0.05$ Renal replacement therapy: 9.2% vs 14.4%; $P < 0.05$ Days on renal replacement therapy: 3 vs 5; $P < 0.05$

Morelli et al[33]	Open-label, crossover	38	Not reported	DEX vs propofol + remifentanil	NE equivalents before and after DEX: 0.69 vs 0.30 μg/kg/min; $P < 0.01$
Nelson et al[34]	Retrospective cohort	72	Not reported	DEX vs propofol	Hypotension: 29.7% vs 31.4%; $P = 0.99$ Hours to hypotension: 2 vs 1; $P = 0.85$
Benken et al[35]	Retrospective cohort	95	Not reported	DEX vs propofol	Hypotension: 19.4% vs 32.8%; $P = 0.17$ Degree of hypotension: 34.7 vs 47.3 mmHg; $P = 0.03$
Cioccari et al[36]	Open-label, RCT, post hoc analysis	83	Mixed medical and surgical	DEX vs other sedation	Baseline NE equivalent requirement: 0.03 vs 0.04 μg/kg/min; $P = 0.17$ Lower NE/MAP ratio with DEX: RDGM: 1.74 (1.02-2.95); $P = 0.04$
Hughes et al[11] MENDS2	Double-blind, RCT	422	Mixed medical and surgical	DEX vs propofol	Delirium or coma-free days: OR: 0.96 (0.74-1.26) MV-free days: OR: 0.98 (0.63-1.51) 90-d mortality: HR: 1.06 (0.74-1.52)
Aso et al[37]	Retrospective cohort	50 671	Not reported	DEX vs other sedation	28-d mortality: OR: 0.78 (0.73-0.84)

Abbreviations: aMD, adjusted mean difference; CRP, C-reactive protein; DEX, dexmedetomidine; ICU, intensive care unit; HR, hazard ratio; MAP, mean arterial pressure; MV, mechanical ventilation; NE, norepinephrine; OR, odds ratio; PCT, procalcitonin; RCT, randomized controlled trial; RDGM, ratio of difference in geometric means; SOFA, Sequential Organ Failure Assessment.

- High-quality, prospective studies of DEX in patients with sepsis and septic shock are needed to evaluate the immunomodulatory effects in this setting.

- Furthermore, studies involving the measurement of inflammatory and immune system markers as well as the potential for enhanced vascular responsiveness with DEX may be lucrative areas for further research.

- Dexmedetomidine is commonly utilized to achieve light sedation in critically ill patients in the ICU and is currently recommended in the SCCM 2018 PADIS guidelines.

- DEX is a versatile medication which may provide benefit in other indications including delirium, sleep, and alcohol withdrawal.

- Due to the poor quality of evidence of DEX use in immunomodulation and sepsis, no conclusions for its use can be drawn.

- DEX was efficacious in facilitating medical imaging and mixed with efficacy for procedural sedation and sedation of non intubated medical and psychiatric patients.

- DEX is associated with bradycardia and hypotension, which are generally transient and infrequently require medical intervention

- The agents most commonly used to treat intubated patients include sedatives acting on the gamma aminobutyric acid (GABA) receptor, such as benzodiazepines and propofol, as well as the opioid analgesic fentanyl

- Benzodiazepines are highly deliriogenic and may prolong duration of mechanical ventilation and length of stay.

- Propofol can be associated with significant hypotension and with a life-threatening infusion syndrome when used at high doses for very prolonged periods

- Midazolam and fentanyl display context-sensitive durations of action that can produce prolonged and unpredictable deep sedation and coma.

DEX offers several potential advantages over classic GABAergic agents

- Low risk of respiratory depression which permits the use of DEX in patients who are not intubated, undergoing painful procedures, patients being treated with (NIPPV) and patients with psychiatric or toxicologic conditions requiring continuous sedation but not intubated and mechanical ventilated

- Improved sleep quality.

- Analgesia.

- Induction of a state of “cooperative sedation” in which patients can communicate with clinicians.

Randomized controlled trials (RCTs) of mechanically ventilated intensive care unit (ICU) patients have demonstrated that

- DEX reduces
  - Time to extubation.
  - Prevalence of delirium.
  - Duration of mechanical ventilation[18] compared to benzodiazepines.

- DEX improves the ability of ventilated patients to communicate pain to nursing staff compared with midazolam or propofol.

- ICU-based studies also suggest that DEX reduces the risk of delirium and need for intubation in patients undergoing NIPPV.

Thank you