

## Clinical application, the use of dexmedetomidine in intensive care sedation

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### Abstract

Optimal sedation strategy in the critically ill should achieve effective analgesia, targeted sedation and reduced risk of delirium and agitation. Whilst there is no single agent that can achieve these goals for all patients, a multimodal approach may optimise the use of different agents through multiple modes of action and reduce possible adverse events. This practice review provides an evidence based and expert opinion on the practical aspects of dexmedetomidine use as part of multimodal ICU sedation.

Dexmedetomidine, when compared to conventional sedatives and opiates, has been demonstrated to be associated with both sedative and analgesic sparing effects, reduced delirium and agitation, minimal respiratory depression and predictable and desirable cardiovascular effects.

In the intensive care setting, dexmedetomidine has been effectively used in post operative analgesia and sedation of high risk and complex surgical patients, and during transition from other conventional sedatives. Critically ill patients requiring ventilation for more than 24 hours and patients who experienced emergent agitation and or delirium have also been successfully managed with a dexmedetomidine regimen.

Supplementary sedation and analgesia in addition to dexmedetomidine may be required to optimise comfort and safety in critically ill patients. Dexmedetomidine cannot be used to achieve deep sedation or to control acutely agitated or combative patients; therefore additional and rescue conventional sedatives may be required in some patients.

A loading dose is unnecessary in most patients and if given, may increase the risk of hypotension and bradycardia. Although the current licensed dose is 1 µg/kg/hr, the maximum dose of dexmedetomidine used in ICU sedation clinical trials is 1.5 µg/kg/hr. Dexmedetomidine must not be given as a bolus at any time to avoid exaggerated cardiac depression.

Dexmedetomidine infusion has dose dependent central nervous system and cardiovascular system effects with bradycardia and hypotension as the commonest side effects. It produces a state of sympatholysis, central sedation with significant synergy with other sedatives and analgesics. A starting dose in most patients is 0.4 µg/kg/hr with hourly titration to achieve desired sedation. Withdrawal or addition of conventional sedatives and analgesics can be used to fine tune the desired sedation target and achieve optimal analgesia. There is no need to stop dexmedetomidine infusion prior to extubation. Withdrawal of dexmedetomidine was not associated with any nervous or cardiac manifestations of withdrawal.

Dexmedetomidine is relatively contraindicated in patients with recent free microvascular flap surgical procedures, cerebrovascular surgery or with a risk of vasospasm or severe liver dysfunction and its safety has not been established in pregnancy.

**Key words:** Dexmedetomidine, sedatives, delirium, practice guidelines, intensive care.

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Sedation and analgesia are common interventions in intensive care and constitute an integral part of the care of critically ill patients. However, there is no consensus on the best combination of agents or strategies to manage sedation and analgesia effectively and safely, and in particular in patients who need prolonged mechanical ventilation.

The current Clinical Practice Guidelines for the provision of sedation and analgesia in critically ill adults were drafted in 2002 and are supported by studies that largely apply to a North American practice of intensive care rather than an Australasian practice. (1) Benzodiazepines and other gamma-aminobutyric acid (GABA) agonists remain the most frequently used agents for sedation in the intensive care environment. (2)

Numerous studies have demonstrated that the drugs currently used for sedation are associated with adverse events, particularly when combined with opiates. (3-10) Regardless of the agent or agents used, it is important to monitor the depth of sedation, allowing a rational “targeted sedation practice.” The Richmond Agitation Sedation Scale (RASS) (11) has good reliability and validity and is increasingly recommended for use, though many others are also used. Furthermore, titration and interruption of sedative infusions may be an important tool to maintain patients within a predefined target sedation range. (3,12)

Monitoring and early detection and treatment of delirium is pivotal to the overall quality of any sedation strategy. Critical care clinicians can detect delirium at the bedside with the Confusion Assessment Methods in Intensive Care (CAM-ICU) and the Intensive Care Delirium Screening Check List, both of which are simple and well validated clinical tests. (13,14)

An integrated sedation strategy should aim to assess and achieve adequate analgesia, maintain the level of sedation at a pre-assigned sedation target, reduce the overall use of GABA agonists and opiates and prevent, monitor and manage delirium in its early stages. A recent large multi-centre trial has shown that the choice of sedative agent is important. (15)

In contrast to the GABA agonists and opiates, dexmedetomidine has a unique mechanism of action. It

combines sedative, anxiolytic, sympatholytic, anti-delirious and analgesic sparing properties with minimal respiratory depression. (16,17)

Whilst no single agent has all the desirable properties of an ideal agent, an ideal strategy would provide effective analgesia, anxiolysis, and reduce the risk of delirium and agitation with minimal cardio-respiratory depression. After cessation, there should be no symptoms of dependence, tolerance or rebound.

This clinical review is designed to provide intensive care clinicians with an appropriate and safe strategy for the use of a dexmedetomidine-based sedation regimen in critically ill patients.

### **The pharmacology and clinical effects of dexmedetomidine**

Dexmedetomidine has a very high affinity to  $\alpha_2$  receptors and is about eight times more potent than clonidine. (16)

The distribution half life is 6 to 8 minutes, and after a steady state IV infusion the elimination half life of 2 hours. Dexmedetomidine has a volume of distribution of 1.3 L/kg with a 94% protein binding, primarily to albumin and  $\alpha_1$  glycoprotein. It is metabolised almost completely in the liver to inactive metabolites while less than 5% is excreted unchanged. Therefore, its clearance in liver dysfunction is significantly impaired but clearance is unaffected by severe renal dysfunction. (16)

Dexmedetomidine produces a dose-dependent sedation with peak effect reached 45 to 60 minutes after commencement of an infusion. Patients are easy to rouse and less likely to be disoriented or uncooperative. Dexmedetomidine has a strong synergistic effect with other sedatives and opioids, with a 50 to 70% reduction in propofol, midazolam and opioid requirements having been observed. (17)

The respiratory effects of dexmedetomidine include minimal depression of minute volume with no clinically relevant changes in response to PaCO<sub>2</sub> and PaO<sub>2</sub> even at plasma levels of up to 8 ng/ml. High dose infusion can lead to loss of muscle tone with potential for airway obstruction in non intubated patients. (18)

The cardiovascular effects of dexmedetomidine are highly predictable. In the absence of a loading dose, an average of 10% fall in systolic blood pressure, heart rate and cardiac output has been observed when a dose of 1 µg/kg/hr is used.

Dexmedetomidine produces a state of sympatholysis with significant reduction in plasma and CSF levels of noradrenaline. However, dexmedetomidine has been shown to produce vasoconstriction in denervated arteries and therefore its use in patients with microvascular free flaps and cerebrovascular disease should be avoided.

### **Dexmedetomidine in intensive care sedation**

Most of the early use of dexmedetomidine has been in patients who were ventilated for less than 24 hours after major surgery, (19,20) as its approval was restricted to 24 hours at a maximum dose of 0.7 µg/kg/hr. These reports demonstrated that about 60% of patients required no additional sedation and 45% no additional analgesia. (21)

A recent randomised controlled trial in 306 cardiac surgery patients showed that dexmedetomidine, at a median dose of 0.49 µg/kg/hr, provided effective sedation and targeted analgesia without an increase in hypotension or vasopressor requirements. Furthermore, dexmedetomidine treatment significantly reduced the duration of delirium and promoted early extubation when compared with morphine based regimen. (21)

Until recently, few studies have examined the use of dexmedetomidine for longer than 24 hours in critically ill medical and surgical patients. (7,22) These reports demonstrated that dexmedetomidine significantly reduced the need for additional sedative and analgesic drugs. More importantly, it has become clear that the dose in mechanically ventilated medical ICU patients may exceed 0.7 µg/kg/hr when used for short term post surgical patients.

In a comparative study with lorazepam, dexmedetomidine infused for longer than 24 hours up to 1.5 µg/kg/hr in ventilated critically ill patients led to a significant reduction in delirium and number of days in coma. (23) Dexmedetomidine has also been successfully used in the management of

emergence delirium after failure of conventional therapy in a cohort of critically ill mechanically ventilated patients. (24) In this study, the average dose used was 0.79 µg/kg/hr and resulted in 86% of patients achieving a target Motor Activity Assessment Scale (MAAS) (25) within 12 hours. Similar results were shown in 111 patients treated for emergence delirium as assessed using the Ramsay sedation score. (26) A recent randomised pilot study demonstrated the superiority of dexmedetomidine over haloperidol in the treatment of agitated delirious ventilated ICU patients. (27)

A well conducted multicentre randomised double blind controlled trial has compared dexmedetomidine with midazolam in ventilated medical and surgical ICU patients for longer than 24 hours. (15) Three hundred and seventy five patients expected to be mechanically ventilated for longer than 24 hours were randomised to receive midazolam or dexmedetomidine titrated to an equivalent level of sedation. Both fentanyl and open label midazolam were used to supplement pain and additional sedation requirements. Titration of the study medication infusion included interruption (4-hourly) and reduction aimed to maintain light sedation (RASS -2 to +1). The main results from this study can be summarised as follows:

1. In both groups a comparable target RASS range was achieved (77.3% of patients vs. 75.1%).
2. The maximum dose of dexmedetomidine used was 1.4 µg/kg/hr, with more than 60% patients requiring an infusion dose greater than 0.7 µg/kg/hr.
3. At enrolment more than 55% of patients were delirious in both groups.
4. There was a 22.6% absolute reduction in incidence and 48% reduction in the duration of delirium achieved with dexmedetomidine compared to midazolam in all patients, and in patients who were delirious at enrolment.
5. There was a significant reduction in extubation time (1.9 days, 34% absolute risk reduction) in the dexmedetomidine group.
6. A shorter median length of stay in ICU (1.3 days) in the dexmedetomidine group was not statistically significant (p=0.24).
7. There was comparable additional fentanyl usage in both study groups.
8. Dexmedetomidine treated patients had significantly

higher nurse-to-patient cooperation and communication assessment.

9. Dexmedetomidine treated patients had fewer infections than midazolam treated patients.
10. More dexmedetomidine patients needed open label midazolam on the first day of study infusion, but overall, the median doses required were comparable.
11. The most common adverse event with dexmedetomidine was bradycardia (42% as defined by protocol) with 4.9% of patients requiring intervention (cessation of study drug and or atropine administration). Conversely, tachycardia and hypertension were observed significantly more in the midazolam group with a comparable incidence of hypotension in both groups.

## Managing dexmedetomidine infusion in the critically ill

### *Dexmedetomidine administration*

Dexmedetomidine is best diluted in 5% dextrose to a weight adjusted infusion of 1 ml/hr=0.1 µg/kg/hr for all body weights (**Table 1**). If possible, it should be given through a separate line and infusion device clearly marked “DO NOT BOLUS”. Intensive care staff should become familiar with the unique characteristics of dexmedetomidine sedation, particularly the state of “rousable sedation” where patients respond promptly to verbal stimuli or light touch.

A loading dose is usually unnecessary and not recommended due to the risk of hypotension.

There is no need to stop or wean a dexmedetomidine infusion prior to extubation.

Similarly, there is no need to wean the infusion slowly.

Some patients will require additional sedation and analgesia. This should be prescribed and made available with the following options, but dosage kept to a minimum by targeting a pre-defined sedation score:

1. Dexmedetomidine is NOT a sedative that can be used for immediate control of a very agitated or combative patient. Therefore, rescue sedation can be provided with 1-3 mgs bolus of midazolam or 30-50 mgs propofol repeated as necessary.
2. Additional sedation: Small increments of midazolam

1-2 mgs on need basis can fine tune targeted sedation. However, this should be followed by an increase in dexmedetomidine infusion by 0.1-0.2 µg/kg/hr. If the desired sedation target requires frequent boluses of additional sedatives, aim to maximise the infusion rate of dexmedetomidine up to 1.5 µg/kg/hr prior to starting infusions of other sedative agents such as midazolam or propofol. If such an infusion is deemed necessary, the smallest dose of midazolam, propofol or other sedative is recommended. The dose of midazolam should not exceed 2-3 mg/hr and propofol should be minimised (0.5-1 mg/kg/hr) to minimize any associated hypotensive effects.

3. Additional analgesia: Morphine 1-2 mg or fentanyl 10-20 µg IV boluses to ensure adequate analgesia. Other opioids or analgesics can be used according to the clinician’s preference and the individual patient’s clinical status. This should be followed by an increase in dexmedetomidine infusion by 0.1-0.2 µg/kg/hr.
4. Delirium and agitation: Haloperidol 2.5-5 mg IV repeated boluses, or olanzapine 1.25-2.5 mg orally can be added if severe delirium and agitation occurs. It is expected that the dexmedetomidine infusion should be at its maximum (up to 1.5 µg/kg/hr) when using these medications.

A dexmedetomidine infusion has a predictable cardiovascular effect such that within an hour of commencing an infusion of 1.0 µg/kg/hr, a 10% drop in systolic blood pressure and a 10-15% drop in heart rate are expected. This may be exaggerated in patients who receive a loading dose, or who are hypovolaemic or receiving other vasodilators. Initial management should be targeted at restoring intravascular volume with 10 ml/kg fluid bolus. Otherwise, management should not differ from that of any other critically ill patient.

### *Specific patient groups*

1. High risk complex surgical patients (**Figure 1**)

Dexmedetomidine can be used in patients expected to be ventilated for up to 48 hours after complex surgery. The dose range is 0.2-0.7 µg/kg/hr without the use of a loading dose. The infusion should be commenced in the operating room 30 minutes before skin closure or immediately after surgery. Typical patients in this category include those with:

1. Compromised respiratory function due to chronic

- airways disease.
- 2. Difficult airway and sleep apnoea, particularly in obese patients.
- 3. Anxiety and apprehension.
- 4. A history of delirium following previous operations.
- 5. Narcotic intolerance or history of abuse.
- 6. A critical need for cardiovascular stability, in particular the avoidance of blood pressure swings, such as after thoracic aneurysm repair or aortic valve replacement.
- 7. Elderly patients.

## 2. Complex ICU patients requiring ventilation for more than 24 hours (**Figure 2**)

In this group dexmedetomidine infusion can safely be continued for longer than 24 hours with a dose greater than 0.7 µg/kg/hr, (15) and no loading dose is necessary. Infusion should start at 0.4 µg/kg/hr for one hour then increased by 0.1 to 0.2 µg/kg/hr every 30 minutes as necessary while other sedation agents are titrated accordingly.

Patients who require non-invasive ventilation may benefit from an infusion of dexmedetomidine if they develop claustrophobia, agitation or intolerance to mask or nasal ventilation. However, this should not be an alternative to intubation in patients who would clearly benefit from invasive mechanical ventilation.

*Transitioning of IV sedation to dexmedetomidine (Figure 3)*  
Clinicians often transition patients who have been on other IV sedatives to dexmedetomidine based sedation in preparation for weaning and extubation. In such patients, an infusion of dexmedetomidine without a loading should be started at 0.4 µg/kg/hr for 2 hours before stopping other sedative medications. Concurrent sedative and/or narcotic therapy can then be preferentially weaned 2 hours after initiating dexmedetomidine infusion. The dexmedetomidine dose can be titrated by 0.2 µg/kg/hr every 30 minutes to the maximum desired dose to achieve light sedation ('responsive to touch or name', 'calm and cooperative' or 'restless but cooperative'). Rescue sedation (midazolam 1 mg and/or propofol 25-30 mg) can be given episodes of agitation. Other ICU interventions should continue as clinically indicated.

Additional analgesia can be given as (1-2 mg morphine or 10-20 µg fentanyl) if required. Ventilator weaning should continue as clinically appropriate. Dexmedetomidine infusion can be discontinued once no longer required, at the discretion of the treating physician.

## 3. Patients with emergence delirium and/or agitation

This usually occurs upon weaning from mechanical ventilation or upon reduction in the levels of conventional sedation and/or narcotic agents. This group of patients often require the highest level of dexmedetomidine infusion at a dose often greater than 0.7 µg/kg/hr. Again no loading dose is necessary.

The infusion should be commenced at 0.4 µg/kg/hr for one hour and increased by 0.1 to 0.2 µg/kg/hr every 30 minutes as necessary while other sedation agents are titrated accordingly over a 4 to 6 hour period. The dexmedetomidine infusion can be increased during this process as desired whilst other agents are weaned or added as deemed necessary.

Organic causes of delirium and agitation must be excluded.

## *Patients in whom dexmedetomidine is not recommended*

### 1. Safety reasons:

1. Refractory haemodynamic instability, including:
  - a. Systolic blood pressure of less than 90 mmHg or a mean BP less than 60 mmHg despite significant vasopressor support, such as vasopressin > 2 units per hour or noradrenaline or adrenaline > 0.2 µg/kg/min or dobutamine > 10 µg/kg/min.
  - b. Heart rate less than 55 beats per minute, not induced by beta-blocking agents.
  - c. High grade atrioventricular block in the absence of pace maker.
2. Microvascular free flap procedures, as α2 agonists may cause direct vasoconstriction and reduction in flap blood flow.
3. Severe liver dysfunction (Child-Pugh class C).
4. Recent acute epilepsy or uncontrolled seizure activity.
5. Neurovascular patients including those with recent intervention for a cerebral aneurysm or arterio-

venous malformation, particularly patients within 7 days of aneurysmal or traumatic subarachnoid haemorrhage or those considered at high risk of vasospasm.

6. Pregnancy or breast feeding.

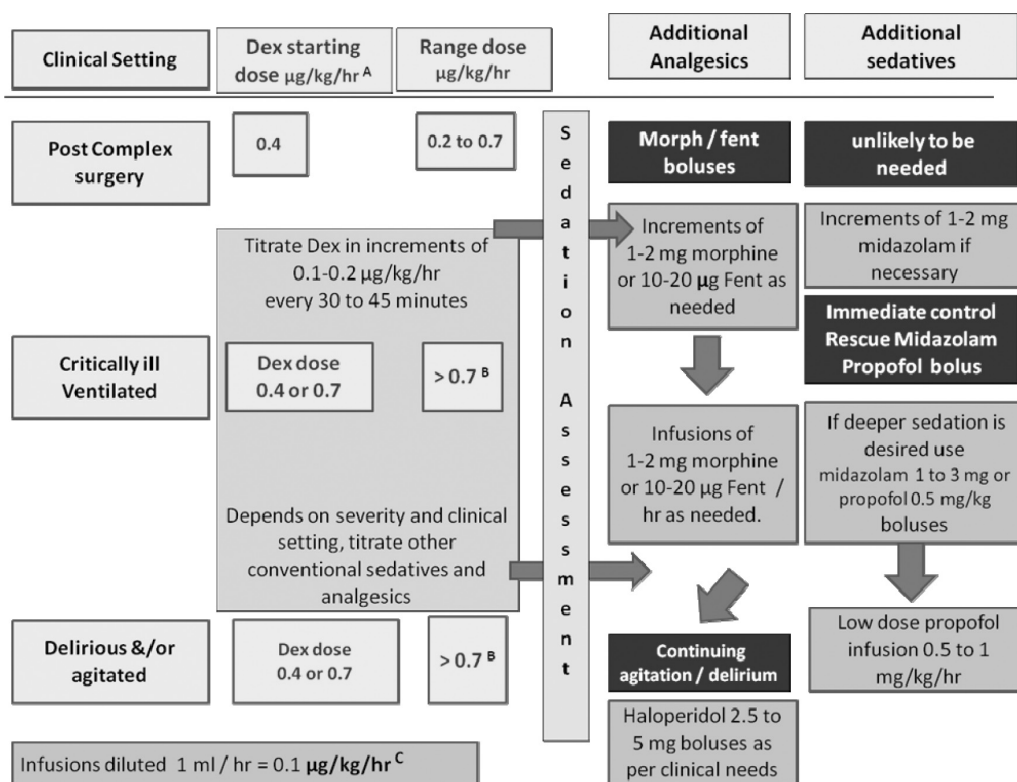
## 2. Inappropriate use

1. Deep sedation, for example in the control of

intracranial hypertension or to facilitate high frequency or controlled ventilation in acute lung injury.

2. Concomitant use of neuromuscular blocking drugs other than for intubation.
3. Acute encephalopathy that is not delirium induced.
4. Convulsive state.

### Recommended dexmedetomidine dose requirements and additional sedation and analgesia



Legend: Dex=dexmedetomidine; Fent=fentanyl.

<sup>A</sup>. Infusions should always start at 0.4  $\mu\text{g}/\text{kg}/\text{hr}$  for one hour and be increased thereafter as required. Assessment of sedation and pain scales should be performed as part of ongoing evaluation at least every 4 hours.

<sup>B</sup>. The maximum dose above 1  $\mu\text{g}/\text{kg}/\text{hr}$  is not identified or approved. However, according to published literature, it is reasonable to use a dose up to 1.5  $\mu\text{g}/\text{kg}/\text{hr}$ .

<sup>C</sup>. This can be achieved by adjusting the volume of 5%DW or N/S added to 200  $\mu\text{g}$  (full vials of dexmedetomidine) so that every ml contains 0.1  $\mu\text{g}/\text{kg}$  of dexmedetomidine. This will also avoid discarding any dexmedetomidine, thereby avoiding any wastage.

NB: Additional sedation and analgesia should be kept to a minimum but can be given as described above in the text and guided by sedation targets and the adequacy of pain relief.

## Institution and department in which work was performed

Various institutions, co-ordinated from Prince of Wales Hospital, Intensive Care Services, Barker Street, Randwick, New South Wales, Australia.

## Disclaimer

The management strategies outlined in this manuscript represent the views of the authors. They are by no means the only way of managing sedation in the critically ill ventilated patient and may not necessarily be the best. Although the content of the clinical application is believed to be accurate, the contributors and their institutions take no responsibility for any adverse event resulting from the use of these

applications. Readers are advised to check doses of drugs from the relevant manufacturers' data sheets.

The use of dexmedetomidine beyond 24 hours and at a dose greater than 1 µg/kg/hr is currently not approved in Australia and New Zealand.

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**Table 1.** Dosage spread sheet for constant infusion rate per kg per hour of dexmedetomidine

Patient's body weight (Kg)	Total dose (micrograms) dexmedetomidine added	Volume of dexmedetomidine to be added into sodium chloride 0.9% bag (mL)	Infusion rate 1 mL/hour= µg/kg/hour	Volume to be removed from 0.9% sodium chloride 50 mL bag (mL)	Final total volume in each infusion bag (mL)
40	200	2	0.1	2.0	50.0
45	200	2	0.1	7.6	44.4
50	200	2	0.1	12.0	40.0
55	200	2	0.1	15.6	36.4
60	200	2	0.1	18.7	33.3
65	200	2	0.1	21.2	30.8
70	200	2	0.1	23.4	28.6
75	200	2	0.1	25.3	26.7
80	400	4	0.1	4.0	50.0
85	400	4	0.1	6.9	47.1
90	400	4	0.1	9.6	44.4
95	400	4	0.1	11.9	42.1
100	400	4	0.1	14.0	40.0

Figure 1. Post complex surgical procedures

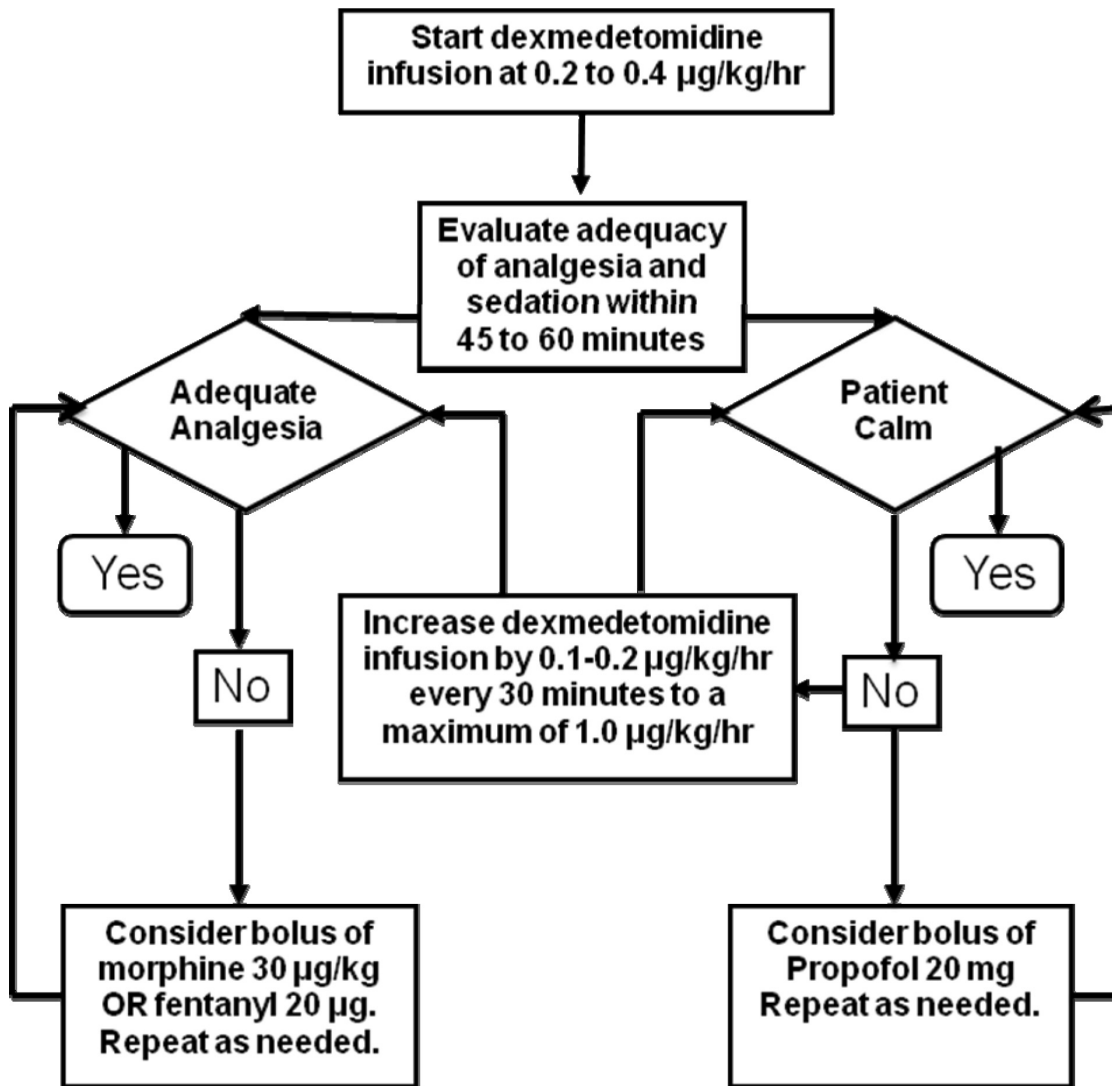


Figure 2. Critically ill ventilated patients

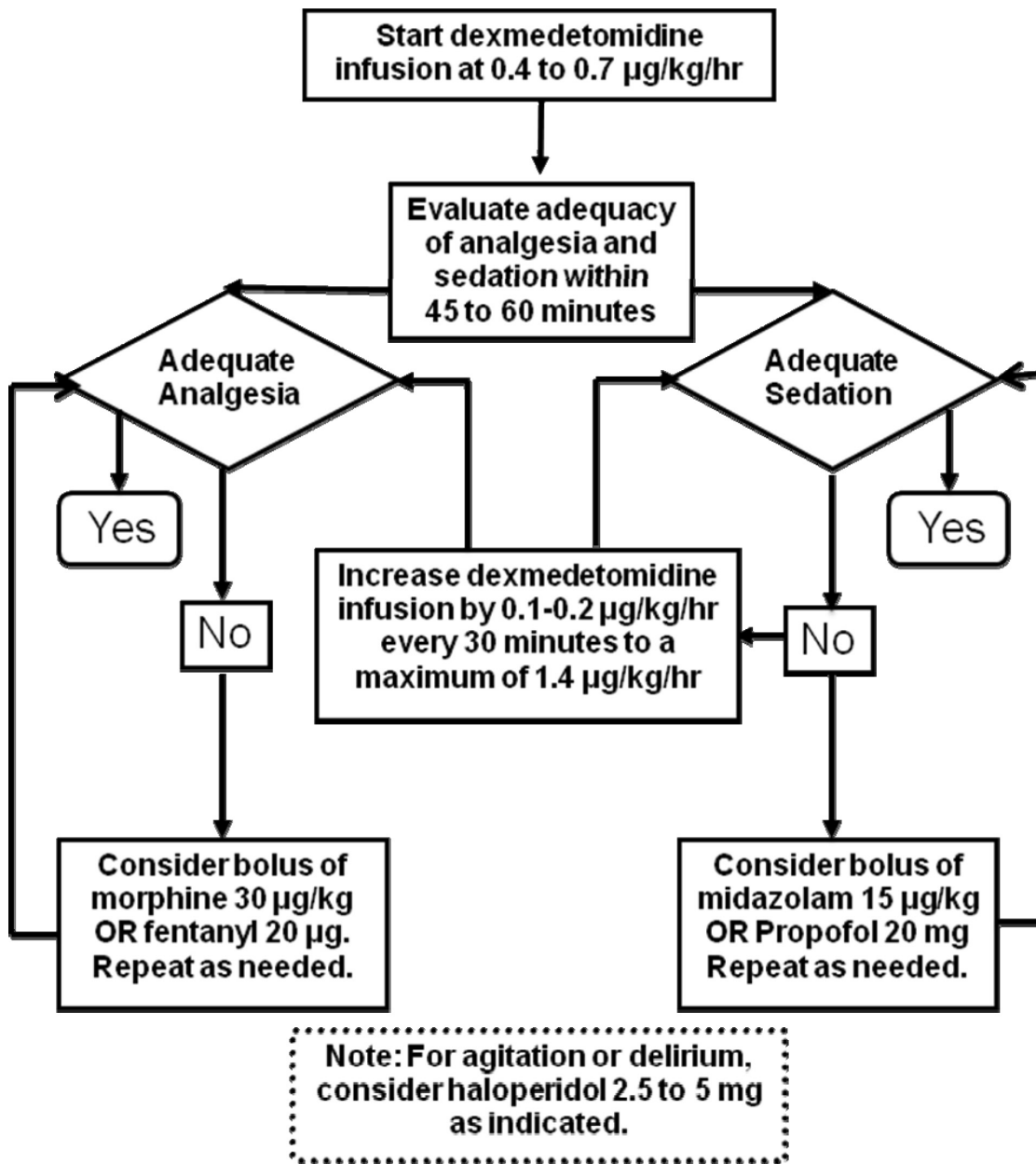
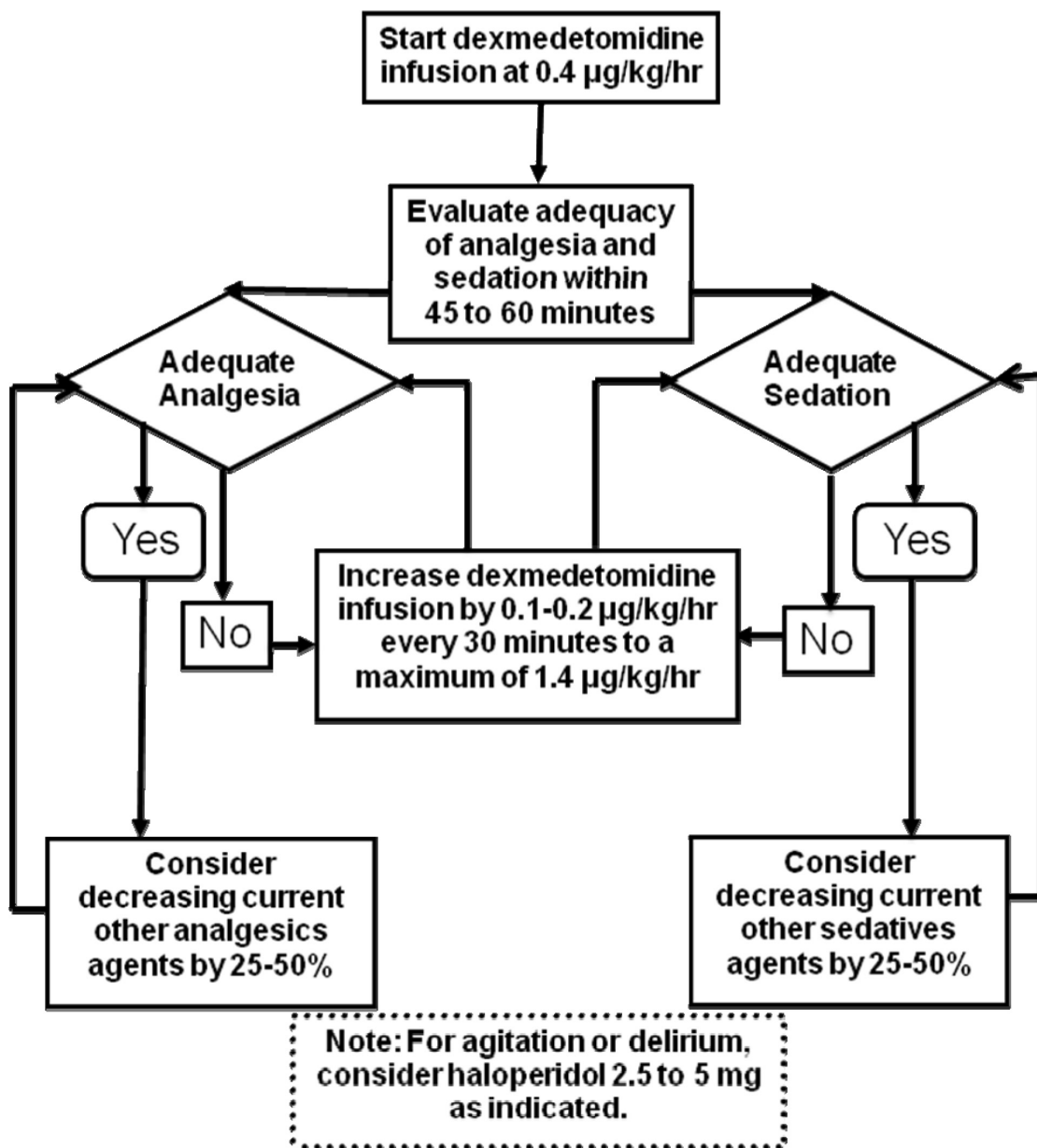


Figure 3. Transition from other sedatives



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