

Considerations in the delivery of optimized ICU sedation

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Introduction

The spectacle of the intensive care unit (ICU) patient sedated to the point of appearing moribund is familiar to viewers of TV hospital dramas. Unhappily, this parody has had (and retains) some basis in fact^{1,2} and should receive greater attention because there is now a widely agreed consensus that inappropriate sedation (meaning levels of sedation too far either above or below constantly varying goals) in the ICU may contribute in a detrimental way to the longer-term health and well-being of many patients.³⁻⁵

Our aim in this position paper is to examine current themes, unmet (or under-appreciated) needs and opportunities in sedation practice for adult ICU patients. Our method is to identify the goals of sedation and then discuss the procedures for the attainment of those goals, bearing in mind that the goals themselves may vary from patient to patient and for any individual patient according to their clinical course and progress. Our perspectives and ideas are based on personal and shared experiences of ICU practice but in many cases are not supported by a great weight of evidence from controlled trials. This essay is thus a subjective – but we hope thought-provoking – assessment of sedation practice; it is not a systematic analysis. Sedation practice in the paediatric ICU will not be examined in detail and there will be no discussion of sedation as an element in end-of-life palliation (for

perspectives on which see, among others, Lo et al.⁶, Levy et al.⁷ and Rietjens et al.⁸), but the significance of such uses must be acknowledged.

One other point to be acknowledged immediately is that several of our ideas and suggestions require active and continuing scrutiny of patients. That, in turn, often implies or requires a patient:staff ratio as close as possible to 1:1. There are obvious cost implications in such a requirement: we do not claim to have solutions to the challenges of funding.

The spectrum of sedation goals

The goals of analgesia and sedation (especially those of analgesia) are perceived differently by the patient, his/her family and the medical profession. From the patient's point of view, analgesia, comfort, preservation of day/night cycles (including natural sleep), lack of nuisances such as ambient light and noise, and concerns such as quality of bed are important. Physicians and nursing staff are also committed to providing analgesia and comfort, but other considerations may shape their perspectives. A simple example of the non-congruence of views is offered by perceptions of mechanical ventilation: for staff there is an emphasis on optimizing patient-ventilator synchrony whereas for many patients the dominating feature of ventilation is the discomfort associated with the endotracheal tube.⁹

Separately, it needs to be noted that developments in ventilator technology have exerted a marked influence on sedation practice. One consequence of these advances is that we consider that the phrase 'adaptation to a ventilator' should cease to be part of clinical vocabulary: it is wholly feasible now to think and speak in terms of adapting the ventilator to the patient, a change in terminology that may seem trivial but which is, in fact, of great significance. Indeed, the feasibility of delivering mechanical ventilation without the need for wholesale use of neuromuscular blockade is essential to the realization of the cooperative and awake patient. (In Germany and elsewhere the avoidance of neuromuscular blockade is a measure of the quality of care.)

Additional medical goals include haemodynamic stability, preservation of metabolic homeostasis, immobility, muscular relaxation, preservation of diaphragmatic function and modulation of the stress/immune response, the facilitation of diagnostic and therapeutic interventions as well as considerations such as programmed withdrawal from sedation. This last may be directed toward the end of sedation but may also be directed at other goals; for example, the neurological evaluation of a patient who will thereafter continue to be sedated. One additional item that deserves attention is the short- and long-term effect of sedation on factual recollection. It might be anticipated that deeper

levels of sedation are associated with less factual recollection. Whether or not this is a good thing is an open question. There are claims that better factual recall may reduce the risk of later deleterious psychological effects of an ICU stay.¹⁰ However, not all research into that subject reaches the same conclusion,¹¹ and the parallel widespread evidence that excessive sedation has inherent deleterious effects thus creates a tension between two goals for which at present there is no universal response.

Figure 1 illustrates our view of some areas of therapeutic priority in sedation. This is an extensive set of criteria but by no means exhaustive: consideration of only the desirable features of candidate drugs would include: rapid onset/offset of action; minimal or no adverse effects; and no increase in overall costs of care. No existing or emerging sedative or sedation regimen fulfils all of these requirements.

Several important points emerge from this depiction. The first is that no existing or emerging drug or regimen fulfils all of the requirements. A second implicit consideration is that the hierarchy of requirements may vary according to the stage of sedation. Thirdly, the issue of unmet needs in ICU sedation cannot be limited to the pharmacology of sedative drugs. The origins of unfulfilled needs may be systemic or organizational, and not only pharmacological.

For instance:

1. Adequate knowledge exists and recommendations for best practice have been formulated, but implementation of this knowledge and guidance is suboptimal. Examples include: (i) the (non-) use of analgesia and sedation scales;^{2,12} and (ii) the non-avoidance of sedation drug overdosage (e.g. non-use of daily sedations stops¹³). Underuse of delirium scales may be included in this category but that deficit may be seen as part of a larger difficulty with delirium among ICU patients.^{14,15}

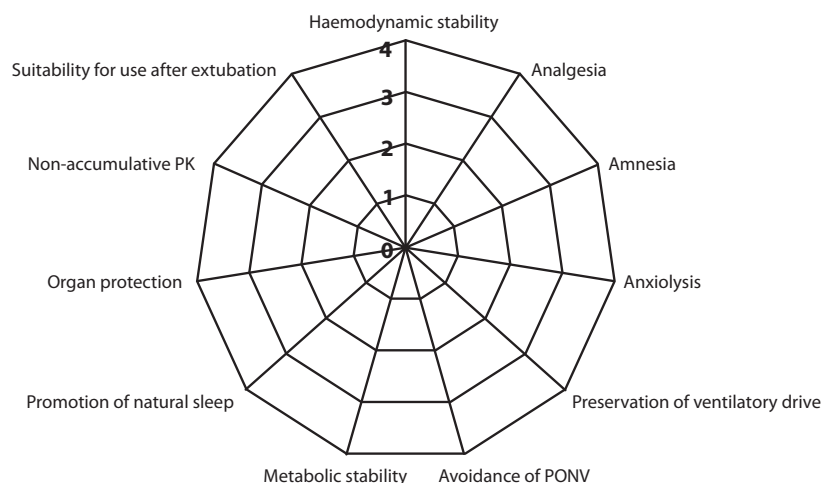


Fig. 1. The 'web of priorities' in ICU sedation: factors relevant to the clinical profile of drugs that may be used for sedation in the adult ICU. Higher scores in any domain indicate greater fulfilment of the desired therapeutic effect. PK: pharmacokinetics; PONV: postoperative nausea and vomiting. Organ protection refers to the possibility of modulating tissue/organ ischaemia-reperfusion. Non-accumulative PK refers both to relatively short contextual half-lives (minutes to hours but not days) and to the absence of active metabolites that prolong the pharmacodynamic effect of the parent drug. Metabolic stability refers to the lack of interference with nutritional substrates (e.g. lipids are provided by propofol) and also to the lack of effect on other metabolic processes as encountered in the propofol infusion syndrome (disruption of fatty acid oxidation and the mitochondrial electron transport chain).

2. Knowledge is incomplete and further research is required before robust principles of good practice can be developed:

- a. Prevention of delirium. Progress in this area may be especially challenging because 'delirium' is not a single entity and its causes are numerous, ranging from withdrawal from drugs (medical and recreational) to postoperative delirium, and to confusion in the elderly
- b. Sleep disturbances, prevention and treatment
- c. Postoperative/post-ICU cognitive dysfunctions
- d. Post-traumatic stress disorder (PTSD)
- e. ICU-acquired weakness.

3. Pharmacology concerns arising from the fact that the pharmacodynamic behaviour of drugs (and their pharmacokinetic profiles) in the very ill patients encountered in ICU practice may differ significantly

from their effects in healthy volunteers or less ill patients:

- a. Development of tolerance to drugs, development of dependence to drugs, and withdrawal reactions.
- b. Delayed emergence from sedation (including build up of active drug metabolites in renal failure, etc.)
- c. Non-availability of drugs (or regimens) relevant to needs of ICU patients identified in (2) above.

From theory to actions

No matter how much knowledge is accumulated in one domain, practitioners are faced with the question: "What should we do?" We therefore propose the following action plan.

Determine whether the patient requires analgesia, sedation, or both

Analgesia and sedation are important aspects of ICU practice, relied on to ease the patient's experience of an often unavoidably stressful

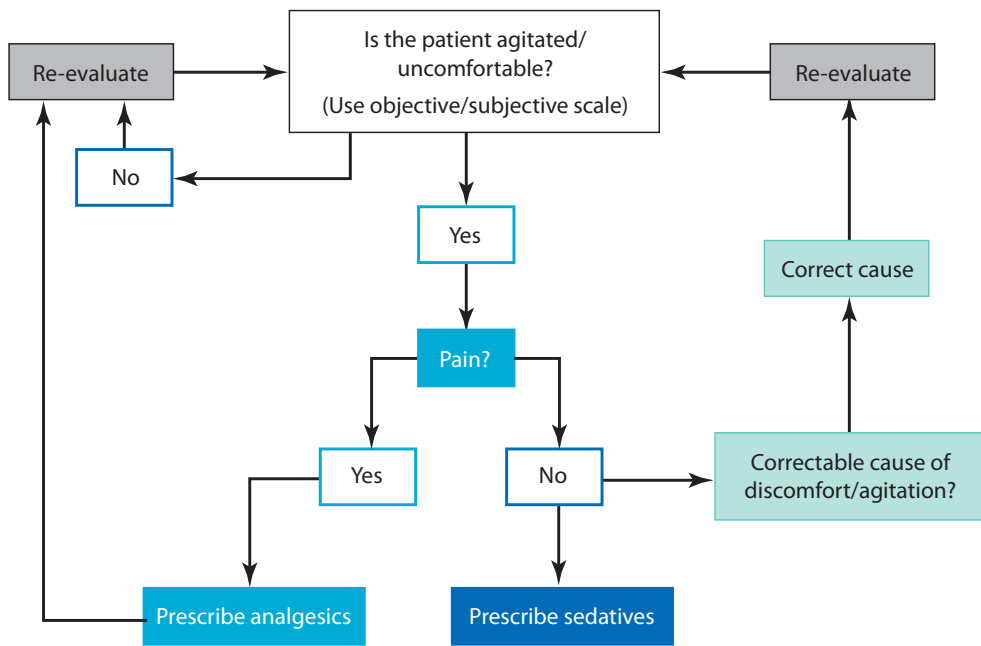


Fig. 2. Proposed pre-evaluation algorithm for the identification of ICU patients who may require analgesia, sedation or both. ('Comfort' is a difficult concept to define. In some studies it has been evaluated using visual analogue scales from 1 [acceptable] to 10 [unbearable].) Comfort criteria evaluated in clinical studies have included the time of the first transfer from bed to chair, first oral feeding and speech recovery (see Blot et al.²⁰ for an example of such criteria in action). A low patient:staff ratio (1:1 if possible) is an important element in the effective monitoring of patient comfort.

environment, and to eliminate pain, anxiety, delirium and other forms of distress. Use of analgesics and sedatives is particularly widespread among patients who require mechanical ventilation and associated neuromuscular blockade,¹⁶ but is by no means limited to that category of patient.

Emphasis on pain and pain relief should be mandatory, because pain (whether of idiopathic or iatrogenic origin) is for many patients a principal source of ICU-related distress. However the phrase 'analgesia and sedation' is deceitful in that it suggests these two objectives are synonymous and in some way interchangeable: they are not. Pain requires the use of pain-relieving drugs (or other relevant measures), not the use of sedation. Failure to differentiate clearly between patients who need sedation and patients who need analgesia is the first of the unmet needs of sedation.

This issue is complicated by the evolution of analgesia-based sedation (ABS), notably the use of remifentanyl

as the unique or main drug for "sedation". Sedative effects may also be achieved with morphine (usually when slightly overdosed) and, in general, the continuous infusion of opioids has hypnotic-sparing effects that may be construed as, or confused with, sedative effects. However, isobolographic analyses suggest that the opioids are not per se sedatives.¹⁷ Clinical studies such as that of Strøm et al.¹⁸ of 'no-sedative' protocols based on the sole use of low-dose morphine boluses are implicitly predicated on that view.^a We therefore consider it important to maintain the distinction between need for analgesia and need for hypnotics, and to assert that fully satisfying these two needs requires two distinct categories of pharmacological agents.

Hence, our first proposal is that a structured algorithm such as that illustrated in Figure 2 should be used routinely for the pre-evaluation of patients, in order to differentiate those who are truly candidates for sedation from those who need pain relief or some change to their environment.

Drugs for sedation

The major classes of sedative drugs comprise the benzodiazepines, propofol and the α_2 -agonists. Opioids must be considered separately, as discussed above.

Extensive commentary on the properties of individual drugs within these classes would be superfluous, though it maybe remarked that notwithstanding the penetration of agents such as remifentanyl and the α_2 -adrenergic agonist dexmedetomidine, there is still significant reliance on propofol, benzodiazepines and opioids. Instead we offer Figure 3 (on pages 4 and 5) as a summary, in simple visual format, of our estimation of how well these various drugs fulfil the priorities identified in Figure 1.

One notable omission from the web depicted in Figures 1 and 3 is delirium. This does not signify that we do not regard delirium prevention and management as priorities in ICU care – they certainly are priorities. However, the spectrum of ICU

^a Whether the extent of in-study use of supplemental sedatives in patients randomized to morphine-only medication in the study of Strøm et al.¹⁸ supports or rebuts that view is an unresolved point between us. Inter alia we add our support to the observation by Brochard¹⁹ that "a protocol of no-sedation implies more than simply not giving patients sedatives." We note also that the unit in which Strøm et al. conducted their research had a reported patient:nurse ratio of 1:1. We consider this to be a fact with practical significance beyond the limits of that study.

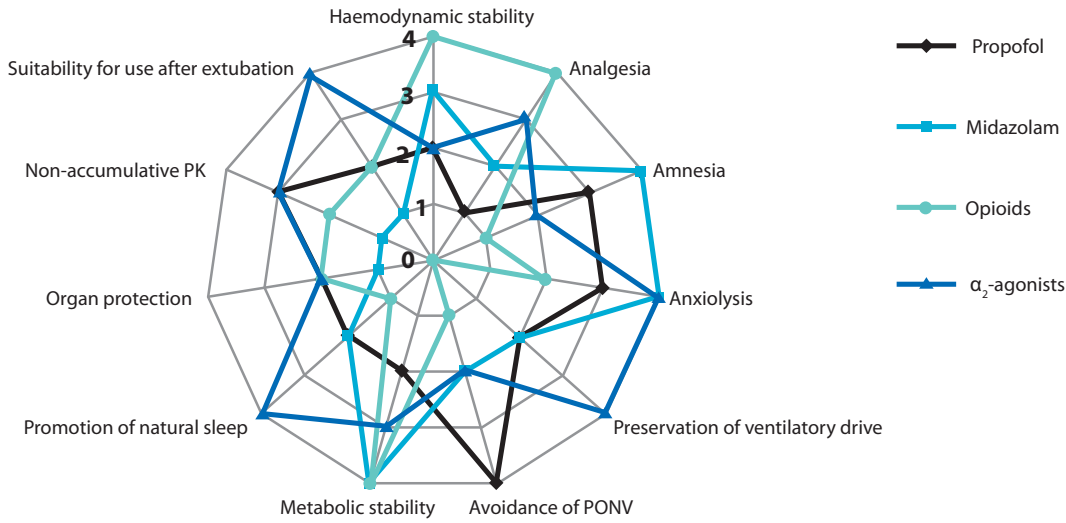


Fig. a.

Propofol is a widely used hypnotic in anaesthesia and ICU sedation. Its main interest, as compared to other hypnotics (such as midazolam) used for ICU sedation, is its non-accumulative PK. Its limitations are illustrated in the radar analysis: it has no intrinsic analgesic properties, does not promote natural sleep and may give rise to propofol infusion syndrome (see text); in many countries, its prolonged use (for several days) is forbidden. Its use after extubation is difficult because it does not preserve, at high doses, ventilatory drive. In postoperative patients admitted to the ICU in particular, propofol decreases the incidence of PONV.

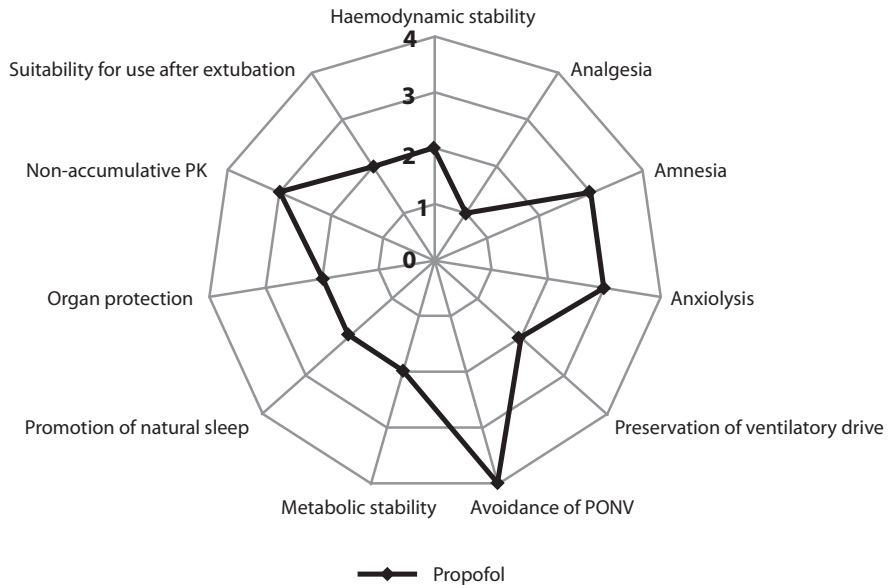


Fig. b.

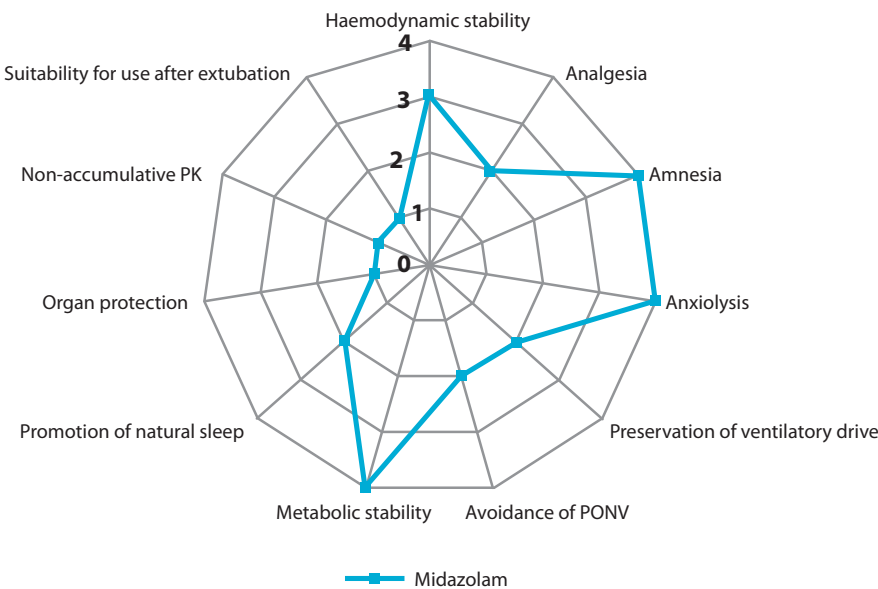


Fig. c.

Midazolam is also widely used for ICU sedation. Its haemodynamic stability is better than that of propofol. It provides amnesia and anxiolysis, but it accumulates after several days of administration, especially in patients with impaired renal and hepatic function and in elderly patients. As a class, benzodiazepines promote the occurrence of delirium. Midazolam is not suitable for sedation after extubation because it alters ventilatory drive.

Opioids have strong analgesic effects but provide no amnesia or anxiolysis. From a pharmacokinetic point of view, this class of drug is very heterogeneous, and includes drugs that have very long contextual half lives (fentanyl and to a lesser extent sufentanil), drugs with active metabolites (morphine) that prolong the pharmacological effect, especially in patients with renal failure, and drugs with very short contextual half lives (e.g. remifentanyl) that are consistent with very rapid elimination (minutes) even after days of administration. Given the relatively restricted use of remifentanyl for ICU sedation, it has been considered that, as a class, opioids have accumulative PK. They do not promote natural sleep. Their effect on ICU delirium is complex. Lack of analgesia (as discussed in the text) can trigger delirium. Morphine can also trigger delirium, and in many patients morphine withdrawal is associated with the disappearance of delirium. See the text for a more detailed discussion on analgo-sedation.

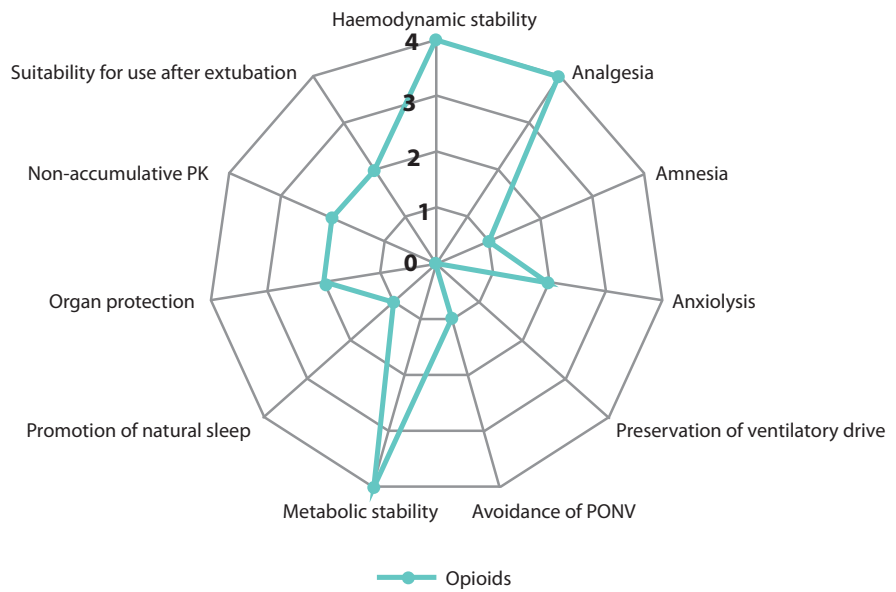


Fig. d.

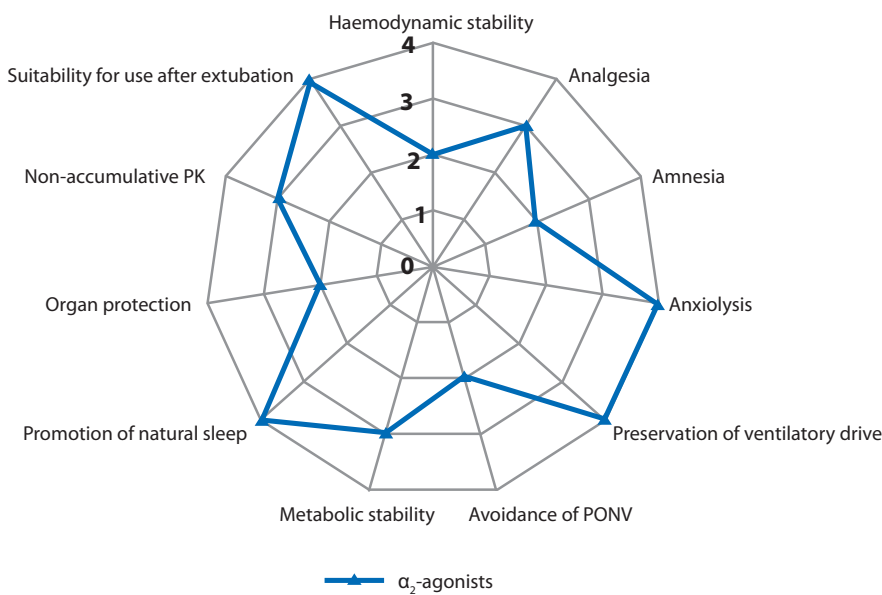


Fig. e.

Alpha₂-agonists are mainly represented by clonidine and dexmedetomidine. These drugs are strong anxiolytics and have intrinsic analgesic properties in addition to their sedative effects. They promote endogenous sleep, preserve ventilatory drive and can be safely used after extubation, which is unique among the drugs discussed in this article. They have other interesting effects that have not been fully explored, such as organ protection. Clonidine and dexmedetomidine have very different pharmacokinetic properties, with dexmedetomidine having non-cumulative PK. Because of the difference in PK between the two drugs, reflected by a non-cumulative PK score of 4 for dexmedetomidine and 2 for clonidine, the average value for the class is 3, as shown in the figure.

Fig. 3. Radar analysis of major ICU sedative drugs. Higher scores in any domain indicate greater fulfilment of the desired therapeutic effect. The relative values for each item reflect the authors' opinions based on the literature. See sub-legend to Fig. 3d for a fuller discussion of intra-class differences in non-accumulative PK for opioids, particularly remifentanyl.

Pain and sedation scales

There is an extensive repertoire of robust, validated and reproducible pain and sedation scales suitable for the ICU, and we do not propose to consider these in detail^b (see references 23–31, for examples).

The more pressing issue attaching to these scales is their widespread non-application in routine practice. Procedural and administrative arrangements vary too widely between countries and units for us to offer any single recommendation for addressing this deficit, but we consider ensuring the systematic use of these scales to be a major target in the development of sedation practice. This could be achieved quickly if there were a commitment (at the unit level and above) to make systematic pain assessment (albeit with perhaps imperfect instruments) part of routine practice.

^b *Electroencephalographic-based measures/calculations such as the bispectral index, spectral entropy and auditory-evoked potential have been evaluated for this purpose but remain for the moment tools of research rather than of clinical decision making.^{32–40} The demonstration of limited correlations between the Ramsay/Richmond Agitation–Sedation Scale scores and blood concentrations of sedative drugs in older ICU patients⁴¹ is an additional illustration of the pitfalls that can arise from reliance on ‘objective’ measures of sedation in the ICU and of the importance of clinical indices (with their corollary, vigilance on the part of staff).*

presentations encompassed by the term ‘delirium’ is so extensive and various that we consider the term cannot helpfully be included in such a highly reductionist depiction of the profiles of various classes of sedative drugs. Further discussion of this aspect of sedation practice follows later in this review.

The goals identified in Figures 1 and 3 do not, of course, present in isolation from the patient’s wider clinical circumstances. It is essential to address the goals of sedation in the context of a patient’s course through sedation, starting with induction. Clinical reasoning for sedation should start with a statement of the sedation goals for any given day and anticipate shifts of those goals in ensuing days. The way to assure responsiveness to the patient’s changing needs is to use scales that measure objectively the level of analgesia and sedation, and actively look for the presence/absence of delirium (see Sidebar ‘Pain and sedation scales’).

Induction of sedation

An algorithm for the induction of sedation appears in Figure 4.

Titration of duration of sedation need not be an immediate goal, but early thought must be given to whether the patient is likely to require deep and/or prolonged sedation. Deep sedation will likely be necessary for patients with intracranial hypertension, severe ARDS and other conditions – the use of the vague term ‘deep sedation’ acknowledges the lack of evidence on which to base definitive guidance in this area. Use of deep sedation (approximating to surgical anaesthesia) is certainly necessary in patients who require neuromuscular blocking agents (NMBAs). Use of similar sedation in patients who require mechanical ventilation varies between countries, partly in response to varying attitudes to the use of NMBAs in this situation.

Patients with severe alterations in cardiovascular function and limited oxygen delivery may require a reduction in oxygen consumption (VO₂) in order to avoid tissue hypoxia.

For many other patients, however, sedation must be configured to preserve respiratory drive and avoid respiratory muscle (especially diaphragm) dysfunction.

Alterations to the anticipated duration of sedation in response to the clinical progress of the patient may require the initial sedative regimen to be re-considered; Figure 4 outlines how regimens may change with the duration of sedation, but these suggestions are only a framework – detailed evaluation of the needs of individual patients is essential. Avoidance of over-sedation is a central consideration, and regular and repeated use must be made of sedation scales to titrate and monitor the level of sedation (see Sidebar ‘Pain and sedation scales’).

The emphasis in Figure 4 on the daily re-evaluation of pain status should be noted: experience of pain may fluctuate during an ICU admission and the fact that pain may have been excluded as a source of discomfort during pre-evaluation (see Figure 2) does not mean that it can thereafter be disregarded. Also of note is the advice to evaluate sedation using quantitative scales in order to ensure that dosages of sedative drugs are kept to the minimum needed to achieve the target level of sedation (see Sidebar ‘Pain and sedation scales’).

Controversial possibilities

In patients not requiring profound depth of sedation several interesting (i.e. controversial) possibilities present themselves. Among these is the use of a single agent with analgesic properties to deliver relatively short-term sedation. Examples of this type of agent are dexmedetomidine (or clonidine in some countries) and remifentanyl; ketamine and the volatile anaesthetics may also be included in this category.²¹ There is ample evidence for the clinical effectiveness and benefits of ABS in the adult ICU, even if not all reports are fully affirmative.²² It is clear that, in many individual cases, sole use of remifentanyl (primarily as an

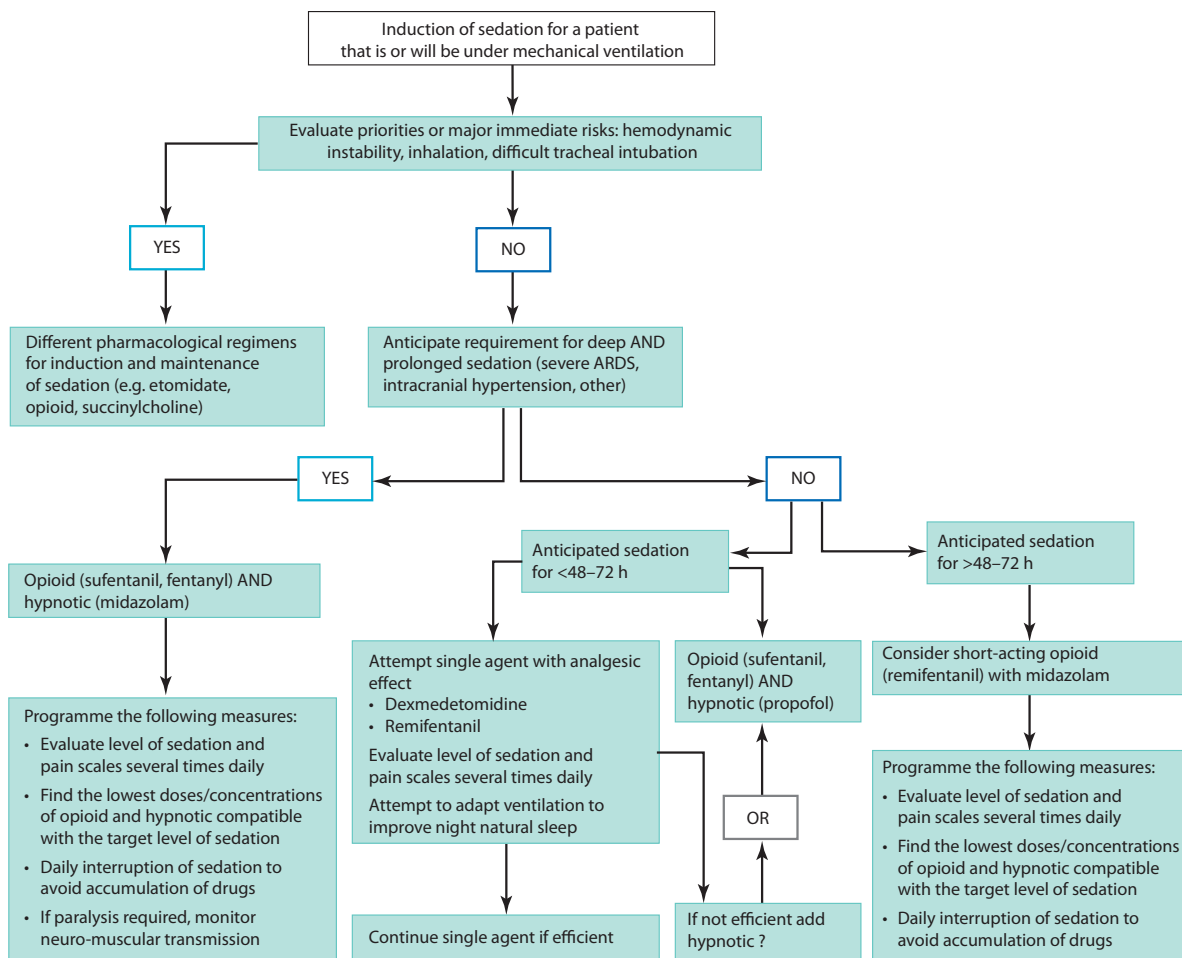


Fig. 4. Decision tree of matters to be considered in the induction of sedation.

analgesic) is associated with demonstrable sedative effects. Nevertheless, the notion of sedation based on what primarily is an analgesic agent is a problematic one. Many practitioners would regard this application as unproven or at least not proven to an adequate degree. We entirely respect that point of view but feel that there is just about sufficient evidence of value for this option not to be automatically excluded. The clinical circumstances and presentation of individual patients are important in determining whether single-agent analgo-sedation should be attempted; selected postoperative patients admitted to the ICU for a relatively brief period of observation and recovery might be candidates for this approach.

It might be expected that the pharmacokinetic qualities of drugs would be influential in relation to the planned or anticipated duration of sedation. Certainly it remains the case that, in patients in whom drug accumulation might be expected and for whom it would be detrimental, consideration should be given to shorter-acting drugs. However, if, as shown in Figure 4 and practised in many centres, ICU sedation now includes routine daily sedation stops, the potential for drug accumulation is greatly reduced. Where sedation stops *are* practised we see no unsustainable tension in the use of longer-acting sedatives for patients likely to be sedated for relatively short periods of time. Conversely, we consider that use

of a short-acting agent such as remifentanyl to provide long-duration sedation may be advantageous when programmed (temporary) withdrawal of sedation is required, as for example in the repeated evaluation of central nervous system function.

Targets in ongoing sedation

Figure 5 outlines our proposals for procedures to be followed during the maintenance of sedation. The continuing need for daily review and systematic assessment of sedation level is re-emphasized. Other important requirements include reassessment of the goals of sedation, monitoring for the development of tolerance and the avoidance of propofol infusion syndrome (PRIS).^{42,c}

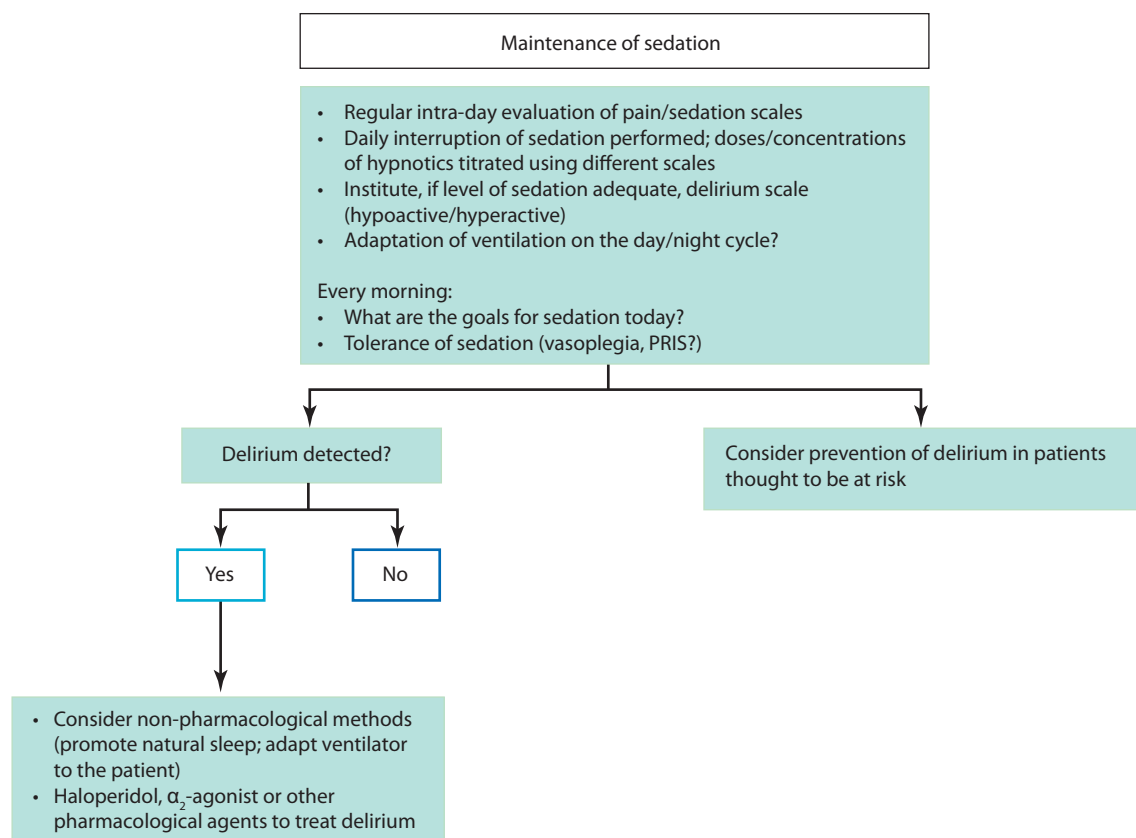


Fig. 5. Proposals for the monitoring of sedation and for delirium prevention. PRIS: propofol infusion syndrome.

There should be complementary efforts to identify patients who have developed delirium or are at risk of doing so. Delirium prophylaxis is feasible and we strongly favour prevention over treatment. The background to this emphasis on delirium is considered in the next part of this essay.

Delirium as a complication of sedation

There are indications that poorly configured sedation may play an important role in the development of delirium, which in turn is associated with worse outcomes in mechanically ventilated ICU patients.^{38,43–47} Delirium appears to be substantially under-recognized in the ICU,⁴⁸ not least because efforts at detection

appear not to be applied consistently even when it is official policy to do so.⁴⁹

Critically ill patients are typically exposed to numerous factors that may precipitate delirium (Table 1). Many of these factors are modifiable, though whether they each attract sufficient attention in the context of usual ICU practice is unclear: this may represent a missed opportunity in delirium prevention. Two factors experienced by most ICU patients are (i) exposure to sedative and analgesic medications and (ii) sleep deprivation or fragmentation. The delirium risk associated with both of these factors is potentially modifiable, as discussed below.

Early diagnosis of delirium is the key

to its successful management. The principal instruments for delirium recognition in the ICU are the Confusion Assessment Method for the ICU (CAM-ICU)⁵¹ and the Intensive Care Delirium Screening Checklist (ICDSC),⁵² both of which appear to work well.^{47,53–55} It is more important to use one of these scales than to deliberate too long over which one to use: the ability of ICU staff to identify delirium without these aids has repeatedly been found to be alarmingly low.

Management of delirium

Non-pharmacological methods for the prevention of delirium have not been fully evaluated in the ICU setting.⁵⁶ There is no *a priori* reason why they should not work, but many of them rely for their effectiveness on careful

^c PRIS may be seen as a reminder that studies on ICU sedation and sedatives have tended to concentrate on efficacy. Specific assessment of the safety of sedative drugs has been a rarity. We consider it highly desirable that future studies give greater importance to the investigation of side effects and the consequences of complex metabolism (e.g. accumulation of metabolites for morphine). Information of this sort is especially relevant when choosing agents for long-term sedation.

Table 1. Delirium risk factors (from Girard et al.⁵⁰).

| Host factors | Factors of critical illness | Iatrogenic factors |
|--------------------------------|---|---|
| Age (older) | Acidosis | Immobilization (e.g. catheters, restraints) |
| Alcoholism | Anaemia | Medications (e.g. opioids, benzodiazepines) |
| Apolipoprotein E4 polymorphism | Fever/infection/sepsis | Sleep disturbances |
| Cognitive impairment | Hypotension | |
| Depression | Metabolic disturbances (e.g. sodium, calcium, blood urea nitrogen, bilirubin) | |
| Hypertension | Respiratory disease | |
| Smoking | High severity of illness | |
| Vision/hearing impairment | | |

Includes factors associated with delirium in both ICU and non-ICU studies.

and systematic assessments of non-life-threatening factors that currently are not an integral part of everyday practice in many ICUs. Multifactorial protocols, as tested in postoperative non-ICU patients by Marcantonio et al.,⁵⁷ may be transferable to the ICU setting.

Action should be taken to promote natural sleep, which is subject to both quantitative and qualitative impairment in ICU patients (sleep is considered in detail in the next part of this essay). More generally, benefits may be expected from parallel medical efforts to treat conditions such as sepsis, hypoxia or hypotension, all of which can be organic causes of delirium. The success of early rehabilitation programmes in reducing the risk of delirium is also relevant in this context.⁴

There are no formally evaluated non-pharmacological means of treating established delirium, but some of the methods employed in prevention might be useful adjuncts to other interventions.

Medications

The relevance of pain to delirium needs to be recognized. Morrison et al.⁵⁸ reported a very considerable (risk ratio >5) increase in the risk of incident delirium in patients who received less than 10-mg equivalents of parenteral morphine sulphate per day in a hip fracture cohort. Risk of delirium increased ninefold in cognitively functional patients experiencing severe pain.

The dataset for use of drugs in the prevention or treatment of delirium is not extensive.⁵⁹⁻⁶² Overall, the available data are compatible with antipsychotic agents being first-choice therapies both for prophylaxis and for the management of established delirium. First- and second-generation agents appear to be similarly effective and generally well tolerated: a presumption in favour of haloperidol thus seems pragmatic. Atypical antipsychotics may be considered when haloperidol is inappropriate^{63,64} and the recent report by Devlin et al.⁶⁵ of the use of a

combination of haloperidol with quietapine is noteworthy.

With the exception of the work of Rubino et al.,⁶⁶ peer-reviewed experience with clonidine in delirium management has emphasized its use in alcohol withdrawal syndrome; its wider utility is thus unclear. Evidence for a beneficial effect of clonidine in opioid withdrawal is equivocal and the dataset is small.⁶⁷ Recent experience with dexmedetomidine is also limited,^{68,69} but includes an indication of an effect at least comparable to that of haloperidol⁷⁰ and superior to that of midazolam.^{71,d} We therefore nominate this agent as an alternative first-line option for the *prevention* of delirium and as preferable to a benzodiazepine as adjunct therapy for patients who have not had a fully adequate response to haloperidol. This would represent a pharmacologically reasoned approach to delirium medication in which an agent (i.e. haloperidol) that had not produced a sufficient clinical response would be augmented by an agent acting via another mechanism (α_2 -adrenoceptor agonism). We would not advocate dexmedetomidine as a routine alternative to haloperidol in established cases of delirium until there are data on this subject. The haemodynamic effects of such combination therapy are for the moment not published.

Cochrane reviewers in 2009 were able to identify *no* adequately controlled trials to support the use of benzodiazepines in the treatment of delirium due to causes other than alcohol withdrawal among hospitalized patients.⁶¹ We are of the view that benzodiazepines should not be used for the management of delirium not arising from alcohol withdrawal. Even in that setting, dexmedetomidine may be a preferred option.^{72,73} Phasing out the use of benzodiazepines for delirium would represent a considerable shift in current practice (see, e.g., Salluh et al.⁷⁴), but is a development that we believe would improve standards of sedation.

^d It is worth noting that for the most part the studies identified by Campbell et al.⁶² used haloperidol doses below the expert-endorsed range and, with the exception of the study by Reade et al.,⁷⁰ none evaluated the effects of haloperidol infusion.

Amnesia

Amnesia is another aspect of the ICU experience that requires attention. Links between ICU-related stressor events,¹¹ delirium, sleep disturbance and amnesia are widely accepted but hard to demonstrate in any conclusive way. Moreover, even though up to about one-third of ICU patients^{11,91} may report no recall of their time in ICU, robust correlations between later outcomes and amnesia, delirium, wakefulness and sedative exposure can be highly elusive if not contrary-seeming;⁹¹ some of the most persistent predictors of post-ICU psychological difficulties are age, baseline health and the severity of the index ICU event,¹¹ with apparently limited relation to sedative use (except as a proxy for severity of illness).

Furthermore, the proposition that amnesia arising from sedation is a good thing (because it expunges the recall of stressful and distressing experiences) is not universally supported. In particular, Jones and colleagues¹⁰ have articulated the idea that amnesia during an ICU stay – which these authors suggest may have its origins in (among other things) exposure to sedative drugs and sleep deprivation – may lead to worse outcomes because the lack of recalled real events allows delusional memory to dominate the patient's recollection. This, in turn, may dispose to a variety of unwanted psychological sequelae, including post-traumatic stress disorder (PTSD).^e In this model, profiling of amnesia as a positive feature of sedative therapy (see, e.g., references 92 and 93) may be an error.

^e *The role of stress hormone effects in recall of traumatic memory and the possible significance of such effects in the suppression of PTSD symptoms by therapeutic means is beyond the scope of this paper but perhaps an area of promise for future research (see Schelling⁹⁴).*

Finally, it may be noted that the incidence of delirium in the intervention group (the 'no sedation' arm) of the study by Strøm et al.¹⁸ was higher than that in the control group. This study was in effect restricted to a specific subpopulation of medical and surgical ICU patients (namely those with respiratory failure and a long median duration of ventilation) and this finding from a 'no sedation' protocol based on low-dose morphine may not be applicable to other patient types. This observation is a reminder, however, that avoidance of sedation is not a guarantee of avoidance of delirium. The role of morphine in this experience of delirium is unclear but cannot be discounted.

Sleep deprivation and disruption

Disruption of sleep and the consequences of sleep disruption are not confined to ICU patients, or even to hospitalized patients^{75–77} (sleep disruption may also affect staff⁷⁸).

Sleep and the effects of sleep deprivation and/or fragmentation in the ICU patient have been the subject of several recent reviews and commentaries (see, e.g., references 79–82), and have been associated with a range of physiological and psychological effects, including delirium, which may adversely affect the course of recovery.^f

Sleep interruption/deprivation in the ICU has both quantitative and qualitative dimensions (Table 2), and there is no single conclusive remedy to this challenge. However, careful selection of sedative(s) might play a part in minimizing the effects of sleep deprivation, and this makes the effects of different drugs on the quality of sleep a consideration in the development of a sedative regimen.

^f *Observations on the deleterious effects of sleep deprivation are based substantially on studies in healthy volunteers. Systematic investigation of the clinical effects of inadequate and/or insufficient sleep in ICU patients is highly desirable. It should be noted also that methods for the objective investigation of sleep are still evolving and that even polysomnography, generally regarded as the benchmark for sleep investigation, has limitations (practical restrictions) in the ICU setting. Bourne et al.⁸³ have reviewed the available methods.*

^g *In the ANIST trial (Acute Neurological ICU Sedation Trial; ClinicalTrials.org identifier 00390871) use of dexmedetomidine (vs propofol, on a background of fentanyl administered for analgo-sedation) has been reported in a small (n=35) mixed ICU population, including patients with or without brain injury, to preserve or enhance cognitive function, as measured in the Adapted Cognitive Exam (ACE), after patients had been brought to a state of calm, awake sedation (Mirski et al.⁸⁶).*

Observations in preclinical and human studies indicate that endogenous sleep pathways (specifically pathways involved in the promotion of non-random eye movement sleep) may also mediate α_2 -mediated sedation, providing a physiological basis for reports that dexmedetomidine-induced sedation produces electroencephalographic (EEG) sleep spindles that qualitatively and quantitatively resemble stage 2 normal sleep.^{84,85} These influences may underpin the 'conscious sedation' observed during use of dexmedetomidine. This property – in our experience unique among mainstream sedative agents – makes dexmedetomidine an interesting resource for the management of sleep disturbance in the ICU and the putative consequences of an ICU stay on long-term cognitive functions.^g

Separately, there are experimental and limited clinical data (in patients undergoing opioid detoxification) to suggest that low-dose propofol is capable of modulating hypothalamic sleep pathways and of evoking EEG spindle oscillations that resemble those seen during normal sleep.^{87,88} These data identify propofol as another resource for the promotion of 'natural' sleep. The doses used for this purpose are well inside the usually acknowledged safe limits for avoidance of PRIS (though see Merz et al.⁸⁹ for a reminder that PRIS may occur even at low doses in exceptional circumstances).

Melatonin therapy may also have promise in the correction of sleep patterns in ICU patients (Current Controlled Trials ISRCTN47578325).⁹⁰

Table 2. Some factors with potential to disrupt normal sleep in the ICU.

ICU environment

- Frequent nursing and care
- Permanent exposure to light
- Permanent exposure to noise

Forced loss of physical activity

Severity of disease

Sepsis

Mechanical ventilation (pressure support ventilator mode)

Sedative and analgesics (propofol, benzodiazepines, opioids)

Antiepileptics, adrenergic agents

Weaning and post-weaning

Weaning from the ventilator and programmed interruption of sedation leading ultimately to its cessation are accepted goals for all patients. In some cases, however, sedation needs to be continued after weaning.

A priority during weaning is to anticipate and avert delirium. Evidence already examined in this review identifies haloperidol and the α_2 -adrenoceptor agonists clonidine (which is used extensively in Germany) and dexmedetomidine as the drugs of choice for this purpose, with the α_2 -adrenoceptor agonists having additional properties that may favour them, including:

- ‘awake sedation’
- lack of depressant effects on respiration^{69,95,96}
- re-synchronization of sleep.

Alpha₂-adrenergic agonists have been shown to be useful for the prevention of withdrawal syndrome in ventilated patients who have received prolonged courses of opioids and/or benzodiazepines.^{97–100} This application may be especially relevant for ARDS patients, in whom prolonged ventilation is often necessary. First reports of the use of dexmedetomidine in weaning patients from non-invasive ventilation are also encouraging,¹⁰¹ but further experience is needed before any conclusions may

be reached or recommendations offered (see also Okabe et al.¹⁰² for a cautionary note on the use of dexmedetomidine).

Our algorithm of clinical reasoning for this phase of sedation appears in Figure 6.

The goals of analgesia/sedation after withdrawal of mechanical ventilation are similar but not identical to those with mechanical ventilation. Although analgesia and patient comfort are still the main goals, avoidance of respiratory depression becomes a major goal. Among sedatives that are presented in the web of priorities shown in Figure 1, only α_2 -agonists do not substantially depress the respiratory drive. A second major goal is promotion of natural sleep, as has been already been discussed.

Volatile anaesthetic-based sedation

Use of volatile anaesthetics for postoperative and ICU sedation in adults has been reported to compare favourably with the use of midazolam or propofol, being in particular characterized by rapid emergence,^{102–105} more rapid extubation and shorter total hospital stay.¹⁰² Not every report of this modality affirms these findings¹⁰⁶ but there is enough positive experience to justify further use and evaluation. Sevoflurane in particular is

considered to exert relatively minor depressant effects on respiration and haemodynamics, both important considerations.¹⁰⁷

Use of volatile anaesthetics is an area of sedation practice very much influenced by developments in (and the economics of) delivery systems (see, e.g., references 108–111], but shows promise as a viable alternative to parenterally administered sedation for mechanically ventilated adult patients in the ICU and for peri-procedural sedation. Concerns that sevoflurane (and, by implication, other fluoride-containing agents) might have an adverse impact on renal function have been at least partly allayed by Röhm et al.;¹⁰⁷ the fact that the drug was used at low dose and for ≤ 24 h in this study may have been relevant to the findings. Cumulative dose-exposure is one aspect of the use of volatile anaesthetics that requires further investigation. In general the absence of a safety database for prolonged exposure to these agents is (and seems likely to remain) the biggest single obstacle to their general use in sedation (Dr PV Sackey, oral communication at ESICM 2011).

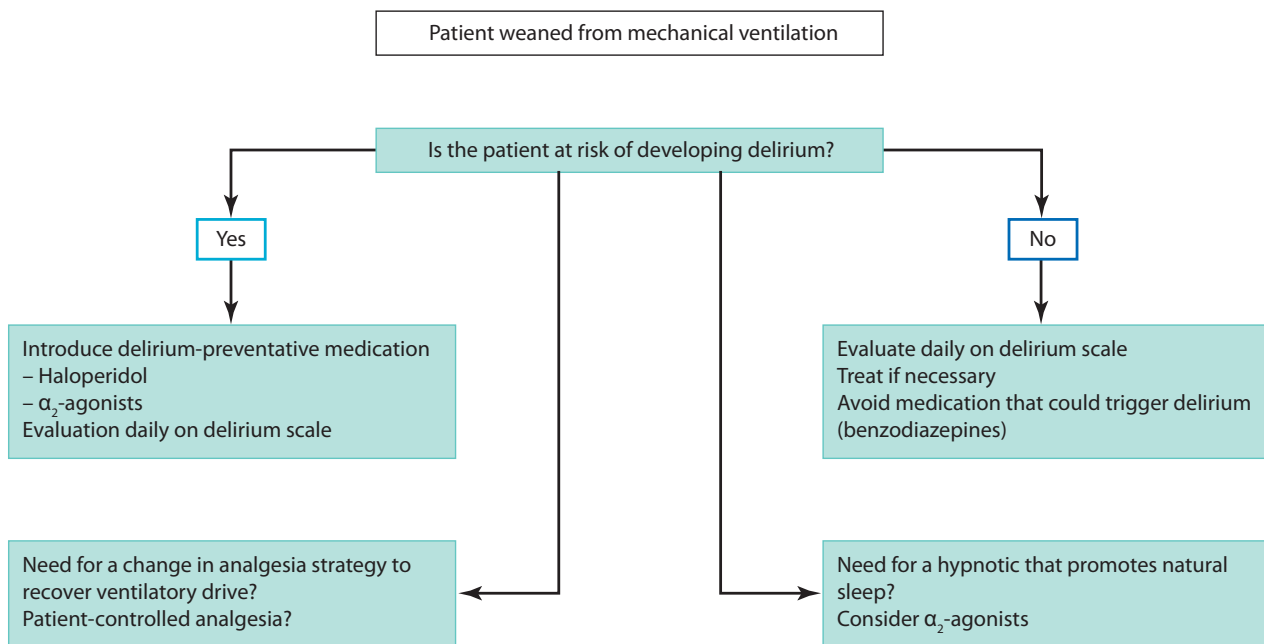


Fig. 6. Decision tree for management of analgesia, sedation and delirium in patients weaned from mechanical ventilation.

Conclusions

We agree with the proposition that the ‘ideal’ ICU sedative regimen should deliver good analgesia while maintaining the patient in a condition of mental and psychological tranquility but also clarity.¹¹² This objective remains elusive: however, reference to Figure 3 indicates some of the possibilities for combination therapy to approach this ideal, both through reducing the dose of individual agents required to achieve a specific degree of effect and by using combinations to compensate for the limitations or deficiencies of particular agents.

Excessive sedation has confirmed adverse clinical consequences and we consider that its widespread routine use should be avoided. Use of sedation to compensate for resource or staff shortages is to be deplored, and is a strong signal of a need for a major review of systems and procedures (and perhaps also attitudes). This is not to say that deep sedation may not retain a place in the ICU, notably in patients who require non-standard forms of ventilatory support and/or neuromuscular blockade. Experts in ICU care have expressed reservations about ‘indiscriminate’ use of

techniques such as daily sedation breaks,¹¹² and that is a perspective that deserves to be respected. The significant principle is that sedation requirements are dynamic and therefore need frequent re-assessment. A summary of measures required for the systematic and responsive monitoring of patient requirements in the ICU appear in Table 3. Among these we would highlight the use of accepted scales *by staff trained in their application* (emphasis added) to quantify pain sedation and the emergence of delirium.

Table 3. Principles for the systematic monitoring of patient requirements in the ICU.
(From Sessler & Pedram,¹¹³ with some amendments and additions.)

1. Develop an interdisciplinary, structured approach for managing sedation and analgesia in the ICU

2. Perform patient assessment and optimize the ICU environment

- a. Identify predisposing and precipitating factors; manage treatable factors
 - b. Identify outpatient medications (medication reconciliation), particularly psychiatric and pain medications; restart medications as appropriate
 - c. Optimize patient comfort and tolerance of the ICU environment: avoid noise; preserve day/night cycles
 - d. Optimize mechanical ventilation settings for patient/ventilator synchrony
-

3. Regularly perform and document structured patient evaluation and monitoring

- a. Establish and communicate treatment goals
 - b. Assess presence and severity of pain, as well as response to therapy
 - c. Assess level of sedation using a validated sedation scale, as well as response to therapy
 - d. Assess presence and severity of agitation using a validated agitation scale
 - e. Identify delirium, and consider regular assessment of delirium, using a validated delirium assessment instrument
-

4. Implement a structured patient-focused management strategy

- a. Select analgesic and sedative drugs based on patient needs, drug allergies, organ dysfunction (particularly renal or hepatic dysfunction), need for rapid onset and/or offset of action, anticipated duration of therapy and prior response to therapy
 - b. Focus first on analgesia, then sedation
 - c. Titrate analgesic and sedative drugs to a defined target, using the lowest effective dose
 - d. Implement a structured strategy to avoid accumulation of medications/metabolites: utilize scheduled interruption or intermittent dosing of analgesic and sedative drugs
 - e. Evaluate and manage severe agitation, including a search for causative factors, and perform rapid tranquilization
 - f. Identify delirium, correct precipitating factors and treat with haloperidol or other neuroleptic drugs
 - g. Avoid potential adverse effects of analgesic and sedative drugs; quickly identify and manage adverse effects that occur
-

5. Anticipate weaning from mechanical ventilation

6. Develop analgesia/sedation plan for after weaning from mechanical ventilation.

Major goals here are:

- provide comfort (analgesia, anxiolysis)
 - promote natural sleep
 - treat withdrawal syndrome from long term sedation before tracheal extubation
 - treat withdrawal syndrome from chronic tobacco or alcohol or psychotrope consumption
 - preserve ventilator drive
 - avoid cough impairment
 - prevent, diagnose and treat delirium
-

Ketamine

Ketamine HCl is probably encountered more in paediatric ICU than in the treatment of adults and as such falls outside the scope of this article. However, this is undoubtedly a useful drug and its combination of analgo-sedative properties plus its very low cost have contributed to its inclusion on the WHO list of essential medicines. This prominence warrants a brief survey of its place in sedation practice.

Ketamine (the S-isomer is often preferred, for its greater potency) is a rapidly acting general anaesthetic; acting primarily via antagonism of N-methyl-D-aspartate receptors in the CNS. It has both analgesic and sedative effects. It may also be used to augment the effects of other analgesics and hence for an opioid-sparing effect (Kapfer B et al. *Anesth Analg* 2005;100:169–74; Neshar N et al. *Chest* 2009;136:245–52).

Ketamine's pharmacokinetic profile makes it suitable for administration to mechanically ventilated patients as a continuous i.v. infusion. Its wider pharmacokinetic/dynamic profile as a fast-on/fast-off agent, which offers procedural sedation with short-term postoperative analgesia has obvious appeal, albeit one at present exploited mostly in paediatrics

(Green SM et al. *Ann Emerg Med* 2011;57:449–61).

Ketamine relaxes bronchiolar smooth muscle and has neutral or even possibly advantageous effects on respiratory function that have led to its being favoured by some commentators for patients with asthma and similar reactive airways diseases (Burburan SM et al. *Minerva Anesthesiol* 2007;73:357–65). (The continuous infusion of intravenous ketamine has been linked to reduction of bronchodilator requirements in patients with refractory bronchospasm [Miller AC et al. *Minerva Anesthesiol* 2011;77:812–20].) More generally, ketamine has been associated, in various human studies, with reduction of airways resistance, and preservation of residual capacity, minute ventilation and tidal volume (Mankikian B et al. *Anesthesiology* 1986;65:492–9). Protective pharyngeal and laryngeal reflexes are preserved in ketamine-treated patients (Green SM et al. *idem*; Green SM, Krauss B. *Ann Emerg Med* 2000;36:480–2).

Ketamine does not routinely cause significant perturbations in cardiovascular indices such as blood pressure, heart rate or vascular resistance (Miller AC et al. *idem*). However, it is not suitable for patients with decompensated heart failure

or cardiogenic shock when its direct negative inotropic effect may be unmasked to the detriment of the patient and should be used with caution (and only in the absence of familiar alternatives) in patients with pulmonary hypertension. Use of ketamine should be avoided in patients with seizure disorders but its generally favourable effects on cerebral blood flow and the absence of any increases in intracranial pressure suggest that it may have value in the sedation of TBI patients.

Clearly ketamine has much to commend it as an analgo-sedative, in theory. However, as noted in a recent review (Miller AC et al. *idem*), the quality of the clinical evidence base for adult use is not as good as might be wished. Additional trials of greater size and rigour are probably needed to establish ketamine as a first-line resource for the adult ICU.

Also to be considered is that use of higher doses of ketamine can produce a 'dissociative state' in which patients may be unable to speak or respond purposefully to verbal commands, whereas lower doses may be associated with psychomimetic effects such as hallucinations (usually short-lasting [<60 min]), and that its use as a sedative in adults can lead to emergence delirium (Giannini AJ et al. *Am J Ther* 2000;7:389–91).

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Peter H Tonner

Peter H Tonner received his medical degrees at the University Hospital Eppendorf, Hamburg, Germany, in 1987. From 1990 to 1992, he accepted a 2-year postdoctoral fellowship at the Department of Anesthesia of the Massachusetts General Hospital/Harvard Medical School in Boston, MA, USA. During this fellowship, he worked with Keith W Miller, D Phil, Edward J Mallinkrodt, Professor of Anesthesia, on molecular mechanisms of anaesthesia. In 2000, Professor Tonner changed to the University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany, where he was rewarded a full Professor of Anaesthesiology in 2002. Since 2006, Professor Tonner has been Chairman of the Department of Anaesthesia, Surgical and General Intensive Care Medicine at the Bremen Heart Center, Klinikum Links der Weser in Bremen and, since 2010, also of the Department of Anaesthesia and Intensive Care Medicine at the Klinikum Bremen Nord, Germany. Professor Tonner has authored more than 100 publications in peer-reviewed journals, along with several book chapters. He has edited several books on clinical and basic science aspects of anaesthesiology. Due to his experience in anaesthesiology and intensive care medicine, Professor Tonner serves as a reviewer for numerous national and international medical journals.



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