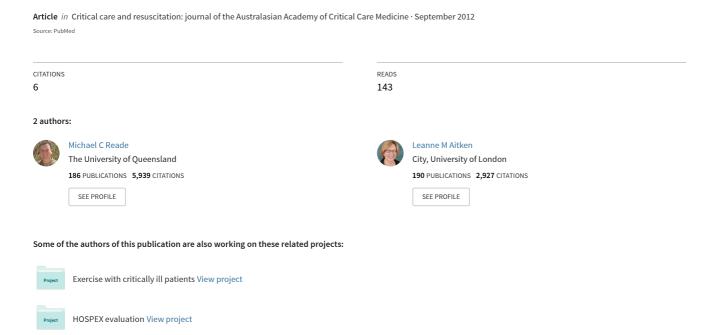
The problem of definitions in measuring and managing ICU cognitive function



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Michael C Reade and Leanne M Aitken

The Austin Hospital intensive care unit recently assessed its introduction of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). 1,2 Interpretation of the findings was the subject of much private correspondence and the letters to the editor in the March 2012 issue of Critical Care and Resuscitation. As clinician–researchers focused on delirium and sedation, we welcome this debate and make no further comment on the issues raised, other than to refer to what we feel were the reasonable conclusions of the original paper.² However, in submitting other aspects of this work for publication, we were struck by one reviewer's opinion that "Tools like the CAM-ICU may be useful screening tools to guide treatment; however, they do not diagnose delirium. That requires reference to *Diagnostic* and statistical manual of mental disorders, fourth edition (DSM-IV)³ and someone trained in its use". We note debate over whether assessment tools such as the CAM-ICU diagnose delirium or really only identify patients who if they could be more fully assessed would be likely to meet more broadly accepted diagnostic criteria. After reflecting on the nature of medical diagnoses, and the potentially costly and harmful implications of over-, under- or misdiagnosis caused by inappropriate definitions, 4,5 as researchers confronting the challenges of identifying delirium and the related concepts of "adequate" sedation and analgesia, here we highlight several issues that we hope will stimulate debate, and ultimately better outcomes.

The need for diagnostic definitions

Medical conditions can benefit enormously from definitions. For centuries, clinicians appreciated that severe infection produced symptoms that could ultimately prove fatal, but not until 1992 with the publication of consensus definitions of sepsis⁶ did it become possible to understand the epidemiology of this condition and to have standardised criteria for entry into clinical trials. The authors of the sepsis definitions recognised their limitations:⁶ lack of understanding of the relative importance of the chosen diagnostic features; variations clinicians might apply in obtaining data; the confounding effect of heterogeneous treatment approaches; and the knowledge that they were most likely grouping together many different pathophysiological conditions. Nonetheless, practical utility and lack of a better alternative have seen the definitions endure. Current defini-

ABSTRACT

- Epidemiology and clinical trials require valid, repeatable definitions that ideally dichotomise patients into having, or not having, a clinical condition.
- Some conditions are clearly dichotomous, such as pregnancy; others such as hypertension or obesity rely on defining a threshold on an objective scale.
- Defining delirium and "adequate" sedation and analgesia
 in the intensive care unit is more difficult, as there is no
 universally agreed scale that quantifies the relative
 importance of various diagnostic features, distinguishes
 features merely observed from those actively sought,
 quantifies severity or fluctuation over time, or accounts for
 the variable approaches of clinicians and the effects of
 assessment environment and pharmacological treatment.
 Definitions of delirium and adequate sedation and
 analgesia therefore vary by assessment method and
 context, making studies using different methods and
 personnel not necessarily comparable.
- Although there is no simple solution, we suggest better awareness of these problems will be helpful. Further, we propose a simplified categorisation to facilitate clinical communication and treatment in the ICU.

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tions of delirium and adequate sedation have these and more limitations, and as yet no single consensus definition of either has emerged. We wish to explore why.

Some aspects of the human condition are clearly dichotomous. One cannot be a "little bit" pregnant. However, most conditions are not so simple. In some cases, a nebulous concept, such as obesity or hypertension, can be defined using an easily measured quantity such as body mass index or blood pressure. Disease diagnosis should be made with reference to associations in population data between certain values and poor outcome. Unfortunately, time-honoured definitions (such as a blood pressure of 140/90 mmHg equating to hypertension) can be difficult to shake even in the face of strong epidemiological evidence. However, such diagnostic problems are insignificant in comparison to conditions unable to be easily characterised on objective and intuitively valid scales. Consider intelligence. While clearly on a continuous scale, it can some-

times be helpful to dichotomise intelligence — for example, for competitive admission to an educational course. Quantifying intelligence illustrates the problems arising when a condition becomes defined by a method of testing (such as an IQ test), the results of which may be influenced by culture, do not equally quantify the spectrum of intellectual capacity (such as linguistic, logical, musical, spatial, and interpersonal) and do not measure adaptability or capacity to learn. While at extremes there might be broad agreement on the "diagnosis" (sufficiently intelligent for a particular task, or not), between these extremes attempts to dichotomise are reliant on the assessor, the circumstances, the duration of observation, and other characteristics that influence the relationship between the assessor and the assessed. If wanting to understand the associations of being "intelligent" or if one felt "intelligent" people might be particularly appropriate for an intervention, variable dichotomisation becomes a problem. Epidemiological studies and clinical trials are facilitated by categorisation — yet some aspects of the human condition are very difficult to categorise, much less dichotomise.

The definition and diagnosis of delirium

In recent years, intensivists and ICU nurses have increasingly recognised the prognostic significance and possible opportunities for prevention and treatment of delirium. However, diagnostically, delirium is a concept analogous to intelligence. At extremes, clinicians have little difficulty identifying delirium's presence or absence, even if their understanding of the term is somewhat vague. The problem lies between the extremes. This is where a diagnostic definition — such as that for sepsis — may be most helpful, even if somewhat arbitrary. However, unlike the white cell count and fever of sepsis that are routinely measured, identifying the features of delirium in a patient depends on whether they are actively sought, understanding the effects of pharmacotherapy, and the subjective interpretation of patient responses. Further complicating the diagnosis, an inherent characteristic of delirium is that it constantly fluctuates — making assessment over time important. Finally, delirium is most intuitively manifest in speech — but many ICU patients cannot speak because of their endotracheal tube.

Delirium is a term in common use in the English language, unlike a clinical term such as sepsis. This makes any diagnostic definition potentially at odds with the common understanding of the term, and calls into question the argument that any one clinical definition is innately superior to any other. Many studies make reference to the DSM-IV as the gold standard.^{1,8-13} The DSM-IV criteria for delirium are:

A. Disturbance of consciousness (ie, reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention.

- **B.** A change in cognition or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established or evolving dementia.
- **C.** The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.
- **D.** There is evidence from the history, physical examination or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.³

These criteria are open to interpretation, dependent on the time and effort expended in their assessment and the skill and perspective of the assessor, as well as knowledge of the "normal" behaviour of the individual so as to be able to recognise "disturbance", "change" or "fluctuation". Understanding a person's normal behaviour can take a lifetime of observation. There is no guidance on what duration of abnormal behaviour should be perceived as a change and not an isolated action. Importantly, these criteria are not at all tailored to intubated critically ill patients. For example, how should an intubated patient, perhaps distracted by pain or anxiety, be assessed for reduced ability to focus attention? How is a fluctuating course assessed in patients receiving varying rates of sedatives or boluses of sedating analgesics? Is critical illness per se, in the absence of laboratory data such as hypernatraemia or hypoxaemia, sufficient evidence that the mental status is a direct consequence of a "general medical condition"?

In response to the need for a clear and simple operational definition of delirium, assessment tools more applicable to the ICU have been developed. Among these are the CAM-ICU,¹ Intensive Care Delirium Screening Checklist (ICDSC),¹⁴ Delirium Detection Score, 15 the abbreviated Cognitive Test for Delirium (CDT), 16 and the Nursing Delirium Screening Scale 17 (Table 1). The CAM-ICU and CDT report the result of an active assessment at a single time point, whereas the others ask whether various manifestations of delirium have been observed over a period. The various scales have been compared with each other 12,18,19 with mixed results. We do not recommend one approach over another, but note that the CAM-ICU has emerged as the most commonly used tool for research^{12,20} and in clinical practice.²¹ All scales attempt to dichotomise delirium as being present or not, despite the fact that all but the CAM-ICU are a numerical score and that subthreshold scores for at least one of the scales (the ICDSC) have been found to correlate with outcome.²²

There are a number of potential problems with these approaches to delirium diagnosis. First, there appears to be different subtypes of delirium, with the hypoactive manifestation being more common²³ and associated with worse outcome,²⁴ but potentially more difficult to diagnose. None of the scores differentiate "hyperactive" from "hypoactive"

Scale	Scale elements	Classification of results	
	Patient must be sufficiently awake (RASS score ≥ -3) to be able to be assessed	Positive or negative	
	The following criteria are assessed: an acute change from mental status baseline OR fluctuating mental status during the past 24 hours; and more than two errors in a 10-point test of attention to voice or pictures		
	If the above two criteria are positive and the RASS score is 0, the patient is delirious		
	If the RASS score is 0, test for disorganised thinking using four yes/no questions and a two-step command; more than one error means the patient is delirious		
Intensive Care Delirium Screening Checklist ¹⁴	Patient must show at least a "response to mild or moderate stimulation". Then score one point for each of the following features observed: anything other than "normal wakefulness"; inattention; disorientation; hallucination; psychomotor agitation; inappropriate speech or mood; sleep/wake cycle disturbance; symptom fluctuation	A score ≥ 4 is positive for delirium (noting scores of 1 to 3 have been termed "subsyndromal delirium" ²²)	
	Orientation: 0, 1, 4 or 7 points, depending on orientation to person, place, time	A score ≥ 8 is positive for	
	Hallucinations: 0, 1, 4 or 7 points, depending on frequency and severity	delirium	
	Agitation: 0, 1, 4 or 7 points, depending on severity		
	Anxiety: 0, 1, 4 or 7 points, depending on severity		
	Myoclonus/convulsions: $0 = \text{none}$; $1 = \text{myoclonus}$; $7 = \text{convulsions}$		
	Paroxysmal sweating: 0, 1, 4 or 7 points, depending on severity		
	Altered sleep-waking cycle: 0, 1, 4 or 7 points, depending on severity		
	Tremor: 0, 1, 4 or 7 points, depending on severity		
Abbreviated Cognitive Test for Delirium ¹⁶	Two components of an original nine found to be the most discriminant and practical for the diagnosis of delirium: visual attention span (0–14-point proprietary Wechsler Memory Scale-revised); yes/no recognition memory for common pictured objects (0–12-point scale involving recalling the number and identity of pictures shown)	A score < 11 is positive for delirium	
Nursing Delirium Screening Scale ¹⁷	Score 0, 1 or 2 points for abnormalities in each of the following categories: disorientation; inappropriate behaviour; inappropriate communication; illusions/hallucinations; psychomotor retardation	A score ≥ 2 is positive for delirium	

delirium. Even if both these forms reflect different manifestations of the same pathophysiological process, it is unlikely that both will respond to the same treatment. Sedating antidelirium medications would seem counterproductive in patients already "hypoactive". This makes understanding trial results difficult. For example, in the single placebocontrolled trial demonstrating efficacy of drug treatment for delirium, 25 other than noting 28%-33% of patients were at least "agitated" at baseline, it is unclear whether the intervention (quetiapine, an antipsychotic with marked sedative properties²⁶) was most effective in hyper- or hypoactive delirium. Second, even if the relatively simple distinction between hyper- and hypoactive delirium can be drawn, it is unclear whether the non-specific diagnosis of a condition with such a multifactorial aetiology will be a useful guide to therapy. Third, the relative importance of various features of these scales is unknown. Only one study²⁷ has ever assessed the prevalence of elements of a score, or their response to treatment. Fourth, we wonder whether instruments such as the CAM-ICU, which identify up to 80%²⁸ of mechanically ventilated patients as delirious at some point in their ICU stay, are really identifying a

condition that exists as a separate entity to critical illness per se. While many studies report delirium as a predictor of outcome statistically independent of severity of illness and comorbidity, the adjustment made for severity of illness is usually the Acute Physiology and Chronic Health Evaluation Il score at the time of ICU admission, which may poorly represent severity of illness at the time of assessment, or Sequential Organ Failure Assessment score, which can be heavily influenced by stable premorbid organ function and sedation. Fifth, most of the published literature in which these scales have been used report assessments made by trained research staff rather than bedside clinical staff with competing priorities for attention. Only three published studies have assessed the CAM-ICU as performed by bedside nurses. The first found inter-rater reliability was better with the CAM-ICU than with unstructured assessments, but reported no data on delirium incidence.29 Incidence data are important: the two subsequent studies suggested the CAM-ICU, when performed by bedside nurses, might be relatively insensitive compared with either DSM-IV criteria, 13 or to unstructured assessments by nursing staff.2

Scale	Scale elements	Explanatory descriptions
Ramsay Sedation Scale (1974) ³⁸	1 Anxious, restless or both	No explanatory descriptions published
	2 Cooperative, oriented and tranquil	
	3 Responding to commands	
	4 Brisk response to stimulus	
	5 Sluggish response to stimulus	
	6 No response to stimulus	
Riker Sedation-Agitation Scale (1999) ³⁹	7 Dangerous agitation	Pulling at endotracheal tube (ETT), trying to remove catheters, climbing over bedrail, striking at staff, thrashing side to side
	6 Very agitated	Requiring restraint and frequent verbal reminding of limits, biting ETT
	5 Agitated	Anxious or physically agitated, calms to verbal instructions
	4 Calm and cooperative	Calm, easily arousable, follows commands
	3 Sedated	Difficult to arouse but awakens to verbal stimuli or gentle shaking, follows simple commands but drifts off again
	2 Very sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
	1 Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands
Motor Activity Assessment Scale (1999) ⁴⁰	6 Dangerously agitated and uncooperative	No external stimulus is required to elicit movement AND patient is pulling at tubes or catheters OR thrashing side to side OR striking at staff OR trying to climb out of bed AND does not calm down when asked
	5 Agitated	No external stimulus is required to elicit movement AND attempting to sit up OR move limbs out of bed AND does not consistently follow commands (eg, will lie down when asked but soon reverts to attempts to sit up or move limbs out of bed)
	4 Restless but cooperative	No external stimulus is required to elicit movement AND patient is picking at sheets or tubes OR uncovering self BUT follows commands
	3 Calm and cooperative	No external stimulus is required to elicit movement AND patient is adjusting sheets or clothes purposefully and follows commands
	2 Responsive to touch or name	Opens eyes OR raises eyebrows OR turns head toward stimulus or moves limbs when touched or name is loudly spoken
	1 Responsive only to noxious stimuli	Opens eyes OR raises eyebrows OR turns head toward stimulus OR moves limbs with noxious stimuli
	0 Unresponsive	Does not move with noxious stimuli
Richmond Agitation Sedation Scale (2002) ⁴¹	+4 Combative	Overtly combative, violent, immediate danger to staff
	+ 3 Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
	+2 Agitated	Frequent non-purposeful movement, fights ventilator
	+ 1 Restless	Anxious but movements not aggressive vigorous
	0 Alert and calm	
	– 1 Drowsy	Not fully alert, but has sustained awakening (eye-opening/eye contact) to voice (>10 seconds)
	– 2 Light sedation	Briefly awakens with eye contact to voice (<10 seconds)
	– 3 Moderate sedation	Movement or eye opening to voice (but no eye contact)
	– 4 Deep sedation	No response to voice, but movement or eye opening to physical stimulation
	– 5 Unarousable	No response to voice or physical stimulation

The attractive notion of a dichotomous diagnosis (delirious or not delirious) is akin to declaring a person intelligent or not intelligent on the basis of an IQ test result. That almost all delirium scales produce a numerical result on an interval scale suggests their authors recognised delirium has grades of severity. If there was a gold-standard test dichotomising delirium, the scores could be subjected to receiveroperating characteristic analysis — but of course this is not possible. Other multifactorial critical illness syndromes have been usefully defined along a continuum of severity; for example, the RIFLE (risk, injury, failure, loss and end-stage) classification of renal impairment³⁰ has been used successfully to define epidemiology and as entry criteria for clinical trials. Any diagnostic approach should be judged by its utility in guiding treatment. Just as intelligence or renal impairment can be usefully dichotomised to guide actions (for example, whether or not to offer a university place, or to start renal replacement therapy), dichotomising delirium (as an indication for treatment) by defining a threshold on a severity scale makes sense. However, the best threshold for treating delirium should be defined with reference to clinical trials, not by an arbitrary decision. The studies "validating" the scores in Table 1 have all used intuitive rather than empirical thresholds for delirium, and comparative validity (defined by utility in predicting prognosis or guiding treatment) has never been assessed.

We cannot currently recommend a better approach to the diagnosis of delirium in a research context than one of the scales in Table 1. While the unstructured delirium diagnoses made by Austin Hospital nurses independently predicted ICU mortality and length of stay,² this method is likely to be highly variable between sites and individuals, and so unsuited to epidemiological work or multicentre trials. The Austin study was performed in a unit with a staffing ratio of at least one nurse per patient and in which 85% of nurses had a postgraduate critical care nursing qualification. Unstructured assessments by staff with less constant patient contact might produce different results. For example, subjective assessments by intensivists were found to be markedly less sensitive than DSM-IV-guided assessment by a geriatrician, psychiatrist or neurologist. ¹²

We do not necessarily believe that a new scoring system for delirium is required. However, we do point to the need to understand and account for the method and context of delirium diagnosis. If indeed the CAM-ICU is relatively insensitive or difficult to perform when applied by bedside nurses, then this must be understood when interpreting data collected in this manner rather than by trained research nurses. Ignoring the possibility that delirium is dependent on the nature of the assessor and the conditions of assessment will only confuse. Before the influence of these factors is better understood, returning to the

reviewer's comment in our introduction, it is illogical to think that delirium can *only* be diagnosed, in a dichotomous fashion, with reference to any particular assessment tool

Targeting adequate sedation

While possibly less contentious than diagnosing delirium, a related concept is the monitoring of adequate sedation in the ICU. Lighter sedation convincingly leads to better patient outcomes,31 and using scales to characterise sedation level assists protocolisation, which in some circumstances^{32,33} but apparently not others³⁴⁻³⁶ is also helpful. Suboptimal sedation is reportedly common but highly variable (1%-75%),37 suggesting a common and easily implemented definition of optimal sedation would be invaluable. As with delirium, adequate (but not too deep) sedation is a nebulous concept that has given rise to a variety of scales. The most commonly used are presented in Table 2. Once again, we cannot recommend one scale over another; neither could the Society of Critical Care Medicine (SCCM) in their guidelines.⁴² Extensive comparisons have been published elsewhere.43-45 The Ramsay Sedation Scale, 38 Riker Sedation-Agitation Scale, 39 and Motor Activity Assessment Scale⁴⁰ have more than one criterion defining each level, while the putative improvements of the Richmond Agitation Sedation Scale (RASS)⁴¹ were to define each point using a single feature, and to distinguish clearly between responses to verbal and physical stimuli.

Despite SCCM recommendations,⁴² sedation scales are highly variably implemented worldwide. 46,47 We wonder if whether, despite extensive research to demonstrate interrater reliability and validity, the primary purpose to which these scales is put at the bedside — that is, to facilitate communication between members of the clinical team about the state of the patient and the goals for therapy has been devalued. As clinician-scientists interested in this field, frequently even we have difficulty recalling elements of the various scales. We wonder if, as is the case with delirium diagnosis, prescribing and monitoring sedation might not also take better account of real-world conditions. Sedation scales contain many categories that in practice are often arbitrarily combined. For example, the SCCM recommended patients be kept at a RASS score of 0 to -2;⁴⁸ European guidelines recommended a target Ramsay score of 2 or 3;49 and a recent review37 noted target ranges used in various studies that included Ramsay scores of 2-3, 2-4, 2-5, 3-4 and 4-5, and Riker scores of 1-3, 4 and 3-4. This practical coalescing of categories reflects the simple need of clinicians to target deep sedation (for example, to control intracranial pressure, or when neuromuscular junction blockade is required), moderate sedation (for example, to

Table 3. Suggested essential elements for scales that assist prescription and monitoring of sedatives, analgesics and antidelirium agents in the ICU*

Description	Suggested treatment response
Clearly distressed	Address treatable causes of discomfort, eg, bowel function, noise, thirst
	Address, in turn, analgesia, antidelirium agents and sedation; or if an intervention is the cause of the agitation and is no longer required (eg, the endotracheal tube), discontinue the intervention
Not obviously distressed, but when actively assessed is found to require analgesia or antidelirium agents	Use, in turn, analgesia and antidelirium agents
Calm and cooperative	Continue current therapy
Unable to assess for pain or delirium, as the patient is insufficiently interactive	Lighten, in turn, sedation then antidelirium or analgesic agent (depending on situation); unless there is a specific indication for deep sedation such as control of intracranial pressure, requirement to tolerate unusual ventilation pattern or requirement for neuromuscular junction blockade
	Not obviously distressed, but when actively assessed is found to require analgesia or antidelirium agents Calm and cooperative Unable to assess for pain or delirium, as the patient is insufficiently

make distressing procedures tolerable), adequate sedation only just sufficient to allow a patient to tolerate essential interventions such as an endotracheal tube (accepting this may require no sedation at all), or insufficient sedation, accepting the consequence of agitation or distress (applied briefly, to facilitate assessment or extubation). We suspect that in many of the studies that found numerical sedation targets were rarely prescribed, clinicians had agreed on a less formal plan to target one of these four levels.

Targeting adequate analgesia

The third arm of the ICU cognitive triad, pain, confounds the assessment of both delirium and sedation. Pain is the most common memory patients have of an ICU.50 Proper identification of pain is important, as an "analgesia-first" approach is associated with reduced ventilation time.³¹ As pain is a seemingly intuitive concept, assessment of analgesia is often overlooked. International guidelines all identify self-reporting of pain as the gold-standard assessment. 42,51 Unfortunately self-report is not realistic in many ICU patients, who require alternative methods of pain assessment. Physiological indicators such as blood pressure and heart rate have traditionally been relied upon, but their relationship with pain in the critically ill is inconsistent. 52,53 ICU behavioural pain scales such as the Behavioural Pain Scale⁵⁴ and the Critical-care Pain Observation Tool (CPOT)⁵⁵ assess facial expression, body movements and compliance with the ventilator, while the CPOT also includes muscle tension and the option to substitute ventilator compliance with vocalisation for extubated patients. The ability of these instruments to reliably and accurately identify and quantify pain in non-verbal critically ill patients has not been confirmed.⁵⁶ Clinical experience suggests that differentiating between pain and other possible causes of worrying facial expressions or ventilator compliance is difficult and highly dependent on the expertise of the clinician undertaking the assessment.

We contend that the presence and severity of pain in critically ill patients cannot be identified through the use of a single instrument. Instead, a combination of strategies including self-report if possible, a behavioural assessment instrument, physiological indicators, and an understanding of the likely sources of pain in each patient should be used. In clinical practice, pain quantification is only important when balancing the risk and benefit of analgesia. Extensive experience with patient-controlled analgesia outside the ICU suggests patients do this most effectively for themselves.⁵⁷ If patient-controlled analgesia is impossible in the critically ill, an empirical approach using titrated analgesics is likely to be more effective than arbitrarily defining a score that warrants treatment.

Towards simple and valid scales for cognitive management in clinical practice

The problems described with the various tools to diagnose delirium and adequate analgesia and sedation most likely reflect the origin of many of them as research rather than clinical tools. For delirium, a proper understanding of the features of the condition and its variation over time require more than a dichotomous description. For sedation, clinical practice really only requires four categories: deep, moderate, adequate and insufficient, while for analgesia, patients either have pain that should be treated or they do not. Sedation, analgesia and delirium control are interdepend-

ent, meaning treatment of one of these elements will impact on measurement of the other two. In Table 3, we present this as a simplified coding system that we hope might facilitate better clinical communication, if not of sufficient complexity for research.

Conclusion

We have identified a number of problems with the definitions of delirium and adequate sedation and analgesia, but other than formalise the structure we suspect many clinicians already use to manage cognitive function in the ICU, we have not proposed any alternatives. Indeed, we argue that the nature of these clinical conditions prevents their diagnosis in the same manner as many other manifestations of critical illness. We are therefore left with imperfect but essential tools that need to be properly understood. From this confusing state, we hope consensus definitions can emerge that minimise the effect of observer variation and context, are equally applicable to research and practice, and characterise severity and fluctuation over time. The most important goal of scales used to measure delirium, sedation and analgesia is to identify strategies that first, identify patients at higher risk of adverse outcome independent of other markers of disease severity, and second, identify patients who will benefit from therapy. Putative strategies should be compared against these goals, not by their faithfulness to theoretical or time-honoured definitions. To do so will require testing both by researchers and bedside clinicians, and an open mind rather than loyalty to a particular approach.

Competing interests

None declared.

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