Is "behavioural disturbance" a clinically more useful concept than "delirium" for trials in intensive care medicine?

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"Delirium is common in critically ill patients and is associated with adverse outcomes": an almost universal introduction to studies of delirium in intensive care medicine. Regrettably, each element of this statement is misleading. Delirium is indeed common in the intensive care unit (ICU), but is present in so many forms (hypoactive, agitated, mixed;[1] related to different aetiologies;[2] sedation-related or not[3]) and so dependent on study population and method of assessment as to make studies using unqualified definitions difficult to interpret. Further, this statement is commonly invoked as the rationale for trials of delirium prophylaxis or treatment, with the implicit assumptions that the association with adverse outcomes is causative, and that any negative consequences of intervening will be outweighed by the benefit of breaking this causal link. Neither of these assumptions has been proven, potentially explaining the failure of almost every trial of a pharmacological critical care delirium prevention or treatment strategy.[4,5] Illustrating this point, a protocol of no sedation in mechanically ventilated patients, in comparison to primarily propofol-based standard care, resulted in more agitated delirium (incidence 20% *v* 7%) but more ventilator-free days.[6] If there is to be any progress in ICU delirium management, a more sophisticated approach to diagnosis is a good place to start.

Broadly, there are three categories of medical diagnosis. The first is exemplified by pregnancy — a condition that is clearly present or absent, and readily identified by a range of clinical and laboratory criteria. The second is not so clearly dichotomised, but is nonetheless based on readily available, repeatable and pathophysiologically meaningful measurements (eg, hypertension). Arterial blood pressure is easily quantified, and it is useful to dichotomise patients as "hypertensive" and "not hypertensive" when deciding whether to commence treatment. However, the threshold blood pressure separating treatment benefit from harm is not obvious, or even simply identified by reference to normal ranges, and thus must be sought from large clinical trials. Delirium falls into the third category. Some patients are clearly delirious (either by the common English language definition or by any formal criteria), and so are candidates for treatment. However, signs of delirium can be subtle, depend on the skill of the clinician to detect them, and (by definition) fluctuate. Logically, and by empiric observation,[7] there are different degrees of severity, and indeed what we call delirium seems likely to be a number of different pathophysiological entities grouped together.[2] These factors all add complexity to trials that seek to dichotomise a "delirious/not delirious" threshold for treatment. Recognising this diagnostic complexity, rather than clinging to arbitrary diagnostic criteria, is critical.

Psychiatry has long struggled to categorise features of the human condition. Recognising the utility of agreed criteria for epidemiology and ultimately drug treatment, psychiatrists introduced the *Diagnostic and statistical manual of mental disorders* (DSM) in 1952.[8] Since inception, accommodating the problems of the third diagnostic category identified above has proved challenging. Currently in its fifth edition (DSM-5),[9] major revisions have been made, such as introducing post-traumatic stress disorder and autism, and removing homosexuality as a mental illness. The DSM-5 defines delirium as:

"A. Disturbance in attention (ie, reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment)." Notably, both attention and awareness must be disturbed. Disorientation alone, which can be corrected by attention to reorientation, does not meet the definition of delirium.

"B. The disturbance develops over a short period of time (usually hours to a few days), represents an acute change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day." This element requires knowledge of a patient's baseline, often not the case in critical care.

"C. An additional disturbance in cognition (eg, memory deficit, disorientation, language, visuospatial ability, or perception)." Notably, there is no mention of behavioural disturbance — a common occurrence in acute medicine.

"D. The disturbances in Criteria A and C are not better explained by a pre-existing, established or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal such as coma."

"E. There is evidence from the history, physical examination or laboratory findings that the disturbance is a direct physiological consequence of another medical

condition, substance intoxication or withdrawal (ie, due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple aetiologies."

The validity of any diagnostic definition is the degree to which it allows measurement of the condition it is designed to identify. Validity has several theoretical elements, including "content validity" (the degree to which the elements of the definition identify all of the components of the condition), "criterion validity" (how much the definition agrees with other measures thought to be valid), "discriminant validity" (how the definition distinguishes the condition from other, similar conditions) and "face validity" (does the definition "make sense"?). By these criteria, the DSM-5 definition has some validity, albeit with the caveats identified above. However, unlike the first two diagnostic categories, there is no gold standard. The concept of diagnostic accuracy in delirium is arbitrary and largely without meaning.

The DSM-5 delirium definition and its earlier forms have been operationalised for non-verbal ICU patients most commonly as the Confusion Assessment Method for the ICU (CAM-ICU)[10] and the Intensive Care Delirium Screening Checklist (ICDSC).[11] The CAM-ICU reports the result of an active assessment at a single time point, whereas the ICDSC is a score of various signs of delirium observed over a period — either a single 8-hour shift or the previous 24 hours. The ICDSC therefore relies on continuous observation and, thus, may be variably applied depending on nurse to patient ratios and the need for patient interactions. Neither distinguishes hypoactive from agitated delirium unless combined with a sedation score such as the Richmond Agitation Sedation Scale (RASS). Comparisons between the two and the DSM reference standard show varying degrees of sensitivity and specificity that depend, in part, on the proportion of hypoactive versus agitated delirium and the nature and severity of illness of the patients studied.[12] However, studies of sensitivity and specificity comparing with an arbitrary standard, as described above, miss the main point of any diagnostic technique in clinical medicine: to identify a patient group who will benefit from an intervention.

Grouping together the many different types of patients with delirium, especially those with agitated and hyperactive delirium, could explain why many clinical trials have failed to find an effect of drug therapy. For example, the recent MIND-USA trial[13] randomly allocated 566 patients with delirium to placebo, haloperidol or ziprasidone. Most patients (89%) had hypoactive delirium at baseline, defined as a positive CAM-ICU combined with a RASS of 0 or lower. Study group had no significant effect on the primary outcome, median number of days alive without delirium or coma. The Pharmacological Management of Delirium (PMD) trial[14] randomised 351 ICU patients to a multicomponent bundle that reduced exposure to anticholinergic and benzodiazepine medications and prescribed low dose haloperidol, compared with standard care. No distinction was made between hypoactive and agitated delirium. There was no effect on delirium duration or severity. All drugs that have been trialled for ICU delirium have sedating effects. Separating patients with agitated delirium from those with exclusively hypoactive manifestations makes intuitive sense if using such sedating drugs. Indeed, the only multicentre trial to show superiority of one pharmacological treatment strategy over another exclusively recruited patients with hyperactive delirium. Among such patients and in addition to standard care, randomisation to dexmedetomidine (up to 1.5 μg/kg/h), compared with placebo, accelerated resolution of delirium and resulted in more ventilator-free hours at 7 days.[15]

Against this background, the study presented by Young and colleagues[16] in this issue of *Critical Care and Resuscitation* presents a novel approach to the diagnosis of behavioural disturbance, much of which will have been due to delirium. Young et al used the technique of natural language processing to analyse the narrative text entries of 12 375 patients, scanning nearly 70 million words for pre-defined terms indicating behavioural disturbance. Behavioural disturbance was present in 5108/12 375 patients. Like delirium identified in other studies, behavioural disturbance was associated with older age, higher illness severity, medical or unplanned admissions, neurological diagnosis, chronic kidney or liver disease, and requirement for mechanical ventilation and renal replacement therapy. Surprisingly, though, after adjustment for baseline characteristics and illness severity, behavioural disturbance was not associated with increased risk of death. Furthermore, among patients who were mechanically ventilated during their ICU stay, behavioural disturbance was associated with lower hospital mortality (odds ratio, 0.80; 95% CI, 0.65–0.99). The authors speculate this association might be explained if it was the patients who were least unwell who were the most likely to have their sedation lightened, thereby exposing their behavioural disturbance.

Some would criticise Young et al's methodology as less valid than the criteria used by the ICDSC, CAM-ICU or even DSM-5 for diagnosing delirium. Certainly, not all agitation — and most likely behavioural disturbance — is due to delirium. Some will have been "lucid agitation" in response to anxiety, pain, or ventilator dyssynchrony.[17] However, to a clinician, academic validity is less relevant that diagnostic utility. If the current diagnostic tools for delirium had been used in trials to improve the outcomes of patients with delirium, there might be little to improve upon. As this is not the case, the operational definition

of behavioural disturbance used by Young and colleagues can only be a potential improvement. The next step will be to pair this with an intervention and assess if the high incidence of adverse outcomes identified in their study can be improved. Simultaneously testing a diagnostic technique and intervention makes little sense with the first two types of diagnosis identified above, but with the third, in which dichotomising a nebulous and fluctuating condition as present or absent is inherently challenging, it is essential.

Competing interests

No relevant disclosures.

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