

Three key areas in progressing delirium practice and knowledge: recognition and relief of distress, new directions in delirium epidemiology, and developing better research assessments

Abstract

Delirium presents formidable challenges: it affects 1 in 4 of older hospitalised adults, greatly elevates the risk of multiple short- and long-term complications including dementia, and causes significant distress. Delirium care remains generally poor. Yet there are clear grounds for optimism; the last decade has seen impactful policy advances and a tripling of research output. Here we highlight three linked areas which have strong potential to transform delirium practice and knowledge in the near term.

Delirium-related distress is strikingly under-represented in practice guidance and research. Proactive recognition combined with effective clinical responses based on good communication provides a critical and largely untapped opportunity to improve care.

Delirium epidemiology research is well-positioned to produce novel insights through advanced prospective designs in populations such as emergency medical patients with detailed pre-, intra- and post-delirium assessments allied with fluid, imaging and other biomarkers.

Research-grade assessment of delirium currently involves a chaotic array of tools, methods and diagnostic algorithms. Areas for development: expand and analytically distinguish the range of features assessed (including distress), optimise feature assessment including use of validated neuropsychological tests where possible, produce standardised algorithms which incorporate explicit pathways from features to diagnosis, and create new fine-grained approaches to the measurement of severity.

Delirium practice and knowledge show accelerating growth; this is encouraging but much of the necessary progress is still to come. Innovation in these three highlighted areas, as well as many others, will open up exciting possibilities in enhancing the care of patients with this common and often devastating condition.

1 Introduction

There may be no other acute medical condition with the range of challenges that delirium currently presents. It affects 1 in 4 older hospitalised adults, is linked with at least an 8-fold risk of future dementia, causes significant distress in patients and carers, and greatly increases the risk of mortality and other complications [1, 2]. Despite this we still fail to educate our staff and organise our healthcare systems across the world such that it is the norm that delirium is optimally prevented, reliably detected and effectively managed.

We have neither standard evidence-based multidomain treatment methods nor pharmacological interventions that target delirium-related encephalopathy [2, 3]. We do know that in hospitalised patients up to a third of incident delirium can be prevented through multicomponent interventions [4], but such interventions have not been routinely embedded in healthcare systems. Delirium remains a major clinical problem without a corresponding public health response [5].

Yet this picture is changing. Research output continues to expand rapidly: in PubMed in 2001, there were 113 publications with 'delirium' in the title; and this number has tripled each decade since (n=338 in 2011; and n=1061 in 2021). Three thriving international delirium organisations have been founded in the last 15 years: the European Delirium Association, the American Delirium Society and the Australasian Delirium Association. Delirium has a higher profile than ever through initiatives like the annual World Delirium Awareness Day that began in 2016. Policymakers in many countries are intervening through sponsoring national guidelines and standards [6-8], and mandating delirium detection at scale, for example, by adopting the 4AT tool in hip fracture patients in entire national clinical populations [9].

There are many fronts along which understanding of delirium and related patient care could advance; recent reviews such as by Wilson and colleagues provide comprehensive coverage [1]. Here we highlight three linked areas which, in our view, have strong potential to transform delirium care: improving clinical practice now through recognition and relief of delirium-related distress, developing future understanding through new directions in delirium epidemiology, and strengthening the quality of delirium research overall by addressing fundamental conceptual, empirical and methodological challenges in evolving better research-grade assessment of delirium.

2 Recognition and relief of distress in delirium

2.1 Distress as a serious complication of delirium

We have long known that delirium often causes distress (from the Latin *distringere*, to 'stretch apart') for the affected person, their family and clinicians. Patients who experienced delirium in hospital have reported feeling frightened, anxious, perplexed, helpless, frustrated, disconnected or lonely during delirium, and afterwards, ashamed, guilty and fearful of its return [10, 11]. Family members and clinicians also experience distress and communication challenges in response to delirium [12]. Some relevant quotes are shown in Box 1.

Among the most distressing features of delirium reported by patients are disturbed cognition (confusion, disorientation decreased language ability), increased *and* decreased psychomotor activity, hallucinations and delusions, difficult emotions, and insomnia [13-15]. The underlying illness or injury, being in hospital and receiving medical treatment, and common delirium sequelae such as falls, pressure areas, cognitive, psychological and functional decline, longer hospital stay, and nursing home placement, are additionally all inherently stressful and likely compound patients' and carers' distress both during and after delirium [2, 6, 16]. Distress can occur with any episode of delirium, though contexts where patients are seriously ill and more likely to die, such as in critical and palliative care, may further increase the risk of distress [11, 17].

2.2 Research gap: treating distress in delirium

Given the consistency of research and anecdote that delirium is often profoundly distressing, it is remarkable how under-evolved is the development of therapeutic clinical responses to distress. A factor in this neglect of distress as a specific therapeutic target may be the decades-long widespread and even routine practice of using psychotropic drugs as an attempted intervention for delirium and its symptoms, including distress [18]. That is, the assumption that drugs are effective in treating distress in delirium may have obscured the need for alternative approaches.

The reliance on drugs in routine practice is particularly concerning given the lack of supporting evidence [2]. For example, a recent cross-setting systematic review reported that antipsychotics made no difference to sedation status, delirium duration, hospital length of stay or mortality (low-moderate evidence), with insufficient evidence regarding delirium severity, and higher incidence of potentially harmful cardiac effects, compared with placebo [19]. Patients receiving palliative care

may face additional risks of harm, with a double-blind randomised controlled trial of risperidone versus haloperidol versus placebo reporting significantly lower symptom scores, fewer extrapyramidal effects, lower use of crisis midazolam, and better survival in participants receiving placebo [20]. The evidence also indicates that benzodiazepines are neither safe nor effective for patients with delirium [21, 22]. A 2020 Cochrane Review included just two small trials of low-very low certainty and concluded the evidence does not support using benzodiazepines for delirium [22]. Even if there were more and higher quality trials, the host of known harms such as dizziness, accidents and cognitive impairment suggests that benzodiazepines might not ultimately demonstrate net benefit for patients with delirium [23].

Recent clinical guidelines [7, 8] have taken account of this evidence, and recommend against routine prescribing of psychotropic drugs. Based on expert consensus rather than evidence, guidelines do, however, allow for use of drugs only for intractable distress or imminent risk of harm to the patient or others. Such use will be in small minority of cases; notably, the 2021 Australian Delirium Clinical Care Standard includes a quality indicator measuring rates of antipsychotic use in patients with delirium [8]. Guidelines also recommend that non-pharmacological approaches should be tried first, with cautious dosing and very short courses of treatment [7, 8].

With respect to broader approaches to the treatment of delirium, there is a very limited number of trials of multidomain treatment and to our knowledge there are no robust trials of non-pharmacological multidomain approaches to the treatment of distress [2]. Taken together, this constitutes a serious gap. Expert consensus supports limited use of psychotropic drugs in the conditions mentioned above, but studies with appropriate distress-specific outcome measures are clearly required to substantiate this. The next section considers the strong potential for non-pharmacological approaches to managing distress in delirium.

2.3 Developing non-pharmacological approaches to the management of distress in delirium

Fortunately, the failure to consider distress as a research topic will likely soon shift, because 'emotional distress' is included in new core outcome sets for delirium intervention trials [24, 25]. Developing a precise definition and measures for this outcome will be challenging, however. Firstly because, as noted above, delirium almost always occurs amidst myriad other sufferings. Secondly, delirium-related distress is not only experienced emotionally, but also cognitively, physically, relationally and spiritually; that is, by the 'whole person' [11]. These points indicate that delirium-related distress is a complex phenomenological entity which therefore could be assessed and

measured (as well as targeted) in a range of different ways (See Figure 1). For example, screening for its presence using a yes/no dichotomy; numerical rating scales; or a 'distress thermometer', such as developed by the National Comprehensive Cancer Network for cancer-related distress [26].

Measurement of *specific emotions* during delirium is another avenue, which might be achieved by using Patient Reported Outcome Measurement Information System (PROMIS®) short forms for anxiety, anger, and emotional and behavioural dyscontrol [27]. Qualitative descriptors (that is, words, stories) are a more natural way for patients to share their subjective experiences and feasibly could be integrated into delirium intervention trials [28]. Determining patients' distress through observational methods, including family rating when patients are unable to communicate could be explored, as could integration of distress items into existing delirium screening tools. The possible ways to identify and measure distress in delirium are likely more numerous than just these, given its multifaceted nature.

Existing studies of patients' experience of delirium point the way to new treatment targets. Two recent qualitative syntheses reported that patients with delirium felt supported by "*loving, understanding, trusting, respectful, participating, reassuring and positive encounter(s)*", "*familiar everyday routines, daylight, an emotionally neutral or familiar voice, decision-making autonomy and being informed about delirium symptoms and progress*" [10] and "*nurses' presence, kindness, and explanations, and thoughts of family and home*" [11]. Conversely, some patients and carers have reported that feeling not listened to, understood, informed or forgiven by clinicians heightened their sense of isolation, uncertainty or shame [11].

These findings strongly suggest that patients and carers truly value bedrock care: compassionate, respectful interactions, information, family involvement, decision-making support, and stable, natural environments; these kinds of clinical responses and surroundings help to counter the distress of delirium [29]. Therefore, training staff to consciously and skilfully adopt supportive and potentially therapeutic ways to communicate with people with delirium and their family members should be standard practice. This includes sensitivity to the potential for distress arising from a clinical evaluation for delirium [30], for example, by integrating such assessment into conversation and observation and explaining to the patient the reasons for the questions (Box 2). Arguably, re-valuing and operationalising of such simple, humane approaches towards patients with delirium are among the most promising clinical, educational and research avenues to follow.

3 New directions for delirium epidemiology

Epidemiology systematically describes what happens to whom, where and when. Early cross-sectional studies made clear that delirium was prevalent at scale in places of high acuity and frailty [31]. Even so, contemporary delirium prevalence estimates continue to surprise [1], which has implications for the degree to which delirium remains under-detected in multiple healthcare settings [2].

3.1 The natural history of delirium

We have a limited understanding of the natural history of delirium, even within a hospital admission. A systematic review of persistent delirium showed that 36% (95% CI 22% to 51%) of patients still had delirium at discharge (average length of stay 21 days) [32]. Moreover, delirium is already present on admission in around two-thirds of cases [33]. Although we commonly understand delirium onset to occur over hours and days, the exact start point can be challenging to pinpoint. It is especially unclear if pre-existing dementia (which may have its own day-to-day fluctuations in cognition) alters this tempo in either direction. Delirium superimposed on dementia could develop more precipitously. On the other hand, delirium could conceivably evolve more slowly over a week or more. Overall, such questions can only be addressed by an integrated approach to longitudinal assessment starting at an individual's usual place of residence.

3.2 Understanding delirium risk and delirium outcomes

Building on the descriptive data, population studies have begun investigating in more detail the longitudinal relationships between baseline delirium risk and subsequent delirium outcomes [34]. This necessitates reaching back into community samples (where all the pre-delirium risk is measurable) and ascertaining health at follow-up (where many consequences occur) (Figure 2). Prior prospective studies of delirium risk have mostly drawn from elective surgical populations where pre-operative assessments can readily be performed. Such studies have yielded valuable insights into post-operative delirium and its consequences. However, it is important to acknowledge that most delirium occurs in older medical emergency patients, a population with much higher levels of frailty and dementia than elective surgical patients. Additionally, the initial precipitating factors (surgery

versus infection, drug effects, dehydration, etc.) differ in important ways in these two populations, and delirium in emergency medical admissions is likely of longer duration [35, 36].

3.3 Prospective studies in emergency medical patients

Only three population studies have prospectively linked cognitive and functional states in emergency medical patients before, during, and after delirium: the Delirium and Cognitive Impact in Dementia (DECIDE), the Delirium and Population Health Informatics Cohort (DELPHIC), and Cognition and Social Care After Delirium (CASCADE) studies, though full results from the latter cohort are awaited [37-39]. DECIDE went further than previous studies which had retrospectively-ascertained delirium [40, 41] by showing a prospective association with cognitive decline (-1.8 MMSE points (95%CI -3.5 to -0.2) over two years) and incident dementia (OR 8.8, 95%CI 1.9 to 41) [37]. Furthermore, a dose-effect was apparent because multiple delirium episodes, more severe delirium and more than five days of delirium were associated with worse cognition. This was independent of the general effects of being hospitalised [42].

DELPHIC linked better baseline cognition with a lower risk of delirium (0.63, 95% CI 0.45 to 0.89) and less severe and shorter delirium. However, if individuals did experience more severe or prolonged delirium, those with high baseline cognition went on to have a disproportionately larger decline in cognition two years later. Together, these studies highlight the advantage of prospective population studies in quantifying the relative contributions of baseline cognition and extent of delirium on long-term cognitive outcomes. These studies also underline the value of detailed delirium ascertainment conducted during the in-patient stay allowing for the crucial parameters of severity and duration to be investigated as potential contributors to short- and long-term outcomes.

3.4 Embedding pathophysiology research into cohort studies

Now that we are gaining a better understanding of the clinical and epidemiological course of delirium, future work could nest serial pathophysiological studies in prospective cohorts. Such studies could integrate detailed fluid, electro-encephalography, and neuroimaging biomarkers, and could also explore the role of genomics, transcriptomics and proteomics. With appropriate analysis and sufficient power, this approach might help identify mechanisms specific to delirium, or shared (or interact with) pathological processes in the dementias [43]. Not only could this elucidate pathways involved in delirium-related neuronal injury, but might also identify which individuals might benefit from interventions to improve cognitive impairment after delirium.

Epidemiological studies have been foundational in understanding the predisposing risk factors and the outcomes of delirium, but there remain many unanswered questions. For example, we lack understanding of what predicts more severe and prolonged or persistent delirium, and despite the strong relationship between delirium and future dementia risk, we know little about how patient factors and delirium features interact to modify this risk. Designing studies that longitudinally examine risk, precipitating factors, delirium features during the episode and outcomes, combining this with more detailed biomarker measurements and integrating endophenotype [44] analysis can begin to push forward our understanding of these crucial issues.

4 Towards better research-grade assessment of delirium

Delirium is a complex syndrome which has multiple domains and parameters that can potentially be measured (Table 1)[45]. Perhaps as a consequence, the field lacks agreed methods for research-grade assessment of delirium: in fact a strikingly disparate assortment of methods is used across studies [46]. The result of this is divergent occurrence and prognosis estimates, and difficulties in interpreting findings from biomarker and interventional studies. Further issues are that delirium status is mostly recorded simply as either present or absent with duration usually not recorded, and when severity is reported, this multifaceted construct is typically analysed as a reductive single linear scale. The development of more consistent and fine-grained delirium research assessments will need to consider several issues, including use of explicit diagnostic algorithms, choosing what features are measured, how individual components are best measured (including objectively or through patient report), capturing delirium severity with consideration of the divergent and varying impact of individual features, agreeing on the key domains for capturing delirium recovery through repeated assessment, incorporating best practice to minimise distress during assessments, and capturing a broader range of parameters such as duration and pre-delirium cognitive status.

4.1 Moving beyond binary diagnosis as an outcome: assessment of specific features

Delirium diagnosis in studies is based on DSM or ICD, or alternatively on delirium tools validated against DSM or ICD. The general approach is to determine the presence or absence of various delirium features and then apply various formulae or algorithms to inform diagnosis. But DSM and

ICD criteria have changed over the past decades, tools vary in what features they assess and how a diagnosis is triggered, and it is often unclear how the information gathered is used to inform diagnostic criteria, leading to several sources of variation [46].

With respect to the features assessed, many tools focus on those essential for diagnosis, such as onset and attention deficits. A drawback of this approach is that it limits analysis of delirium in relation to potential feature-specific effects of intervention studies or outcomes. A significant omission in most delirium study assessments is the measurement of distress, which as noted above is common in delirium. This omission has impeded progress because, in practice, the management of distress and associated agitation and safety concerns, frequently in the context of psychosis, is often the main concern of clinical staff. Further, in the context of delirium, psychotropic drugs are predominantly used to address affective symptoms, not attention deficits, other cognitive impairments or altered arousal [18]. However, drug treatment studies have almost always used outcomes based on a binary ascertainment of delirium, or a single linear scale of severity combining multiple features without distinguishing distress or measuring it from patients' perspectives.

4.2 Optimal measurement of specific features of delirium

In DSM and ICD, and in most delirium tools, determining presence of a particular feature is mostly based on the rater's subjective impression following informant history, observation and interview [2, 45]. The interview may incorporate cognitive tests, though mostly without specified scoring thresholds. Yet inter-rater agreement for subjective assessment of attention deficits, the core diagnostic feature of delirium, is moderate at best [47]. Integrating neuropsychological testing into delirium assessment has been hampered both by the limited evidence base and the lack of inclusion of relevant neuropsychological evidence in protocol development [45, 48]. There is now a growing evidence base on neuropsychological approaches in delirium, including in the context of dementia [45, 49, 50]. Some delirium instruments also now incorporate cognitive tests with specified cut-off scores [51-53], though few studies report individual test item sensitivity and specificity. With respect to non-cognitive elements of delirium, some such as level of arousal are relatively well-studied [54], but distress, agitation, visuospatial dysfunction, language deficits, and psychotic features lack agreed, validated methods [55, 56]. Future research grade assessments for delirium could be improved by use of a wider range of component domain tests which are as objective as possible and are individually validated with, where possible, evidence-based cut-off scores. Additionally, assessments and scoring processes need to be feasible to administer at the bedside to all patients

with delirium so that patients not producing speech or who are otherwise unable to engage with the interviewer can be incorporated into the overall assessment outcome rather than excluded.

Conventional neuropsychological tests (for example, digit span, months of the year backward) mostly do not meet all of these criteria, which necessitates the development of novel approaches for the standardised assessment of delirium features along with studies assessing their validity, reliability and usability. As one example, the DelApp is a computerised test implemented on a smartphone which was explicitly developed for objective, standardised assessment of the presence and degree of the arousal and attention deficits characteristic of delirium (that is, deficits in orienting, sustaining and focusing attention)(Figure 3). The DelApp has been shown to have high sensitivity and moderate-to-high specificity in detecting delirium in older hospitalised patients, many of whom with dementia [50], and in non-verbal patients in the ICU [57].

4.3 A multi-faceted measurement model for delirium severity?

The construct of delirium severity is a current focus in the field, though considerable conceptual and empirical uncertainty exists. It lacks a consensus definition, with several potential options including the distress caused during or after the episode, short-term risks including mortality, or risk of long-term adverse outcomes such as dementia. Though single linear severity scores predict outcomes, delirium severity is too complex to be captured fully in such scores, causing issues with scoring and loss of signal. For example, low arousal compromises recording of other severity markers such as hallucinations, giving rise to a paradoxically low score on some scales. Additionally, severity markers differ in their effects: low arousal has disproportionately large effects on prognosis, but possibly a smaller effect on distress than other features such as psychosis [58]. Future assessments of severity should incorporate graded measures of individual features and address psychometric scoring problems such as these. There is also value in considering the integration of qualitative assessments to complement the quantitative measures.

4.4 Priorities for action in research grade delirium assessment

The development of better research grade delirium assessments requires more use of specified and reproducible components that draw from existing best practice but also overcome existing shortcomings, and integrate advances in measurement of individual features, for example from neuropsychological research (Table 1). It is clear that some features of delirium, such as attention deficits, lack agreed measurement methods and for some of these (for example distress) the

development of new methods is required. Explicit diagnostic algorithms using specified measurement methods with agreed cut-off scores are also needed to facilitate study comparisons. Further, analysing delirium not simply as a binary diagnosis or as single linear severity scores but also including individual features will permit richer analysis of the triggers and consequences of these features and potentially shed light on specific beneficial effects of interventions that are currently under-explored. Capturing a broader range of relevant parameters such as delirium duration, pre-delirium cognitive and frailty status, precipitating factors and in-patient complications will further advance knowledge and help lead to a more detailed understanding of delirium, including possible subtypes with different prognoses and treatments [44].

5 Conclusions

We have highlighted three related areas with promise in delirium practice and knowledge: distress, epidemiology, and research assessment. There are however many other topics in the field with similarly exciting potential to influence clinical care and research. These include mandating delirium education [59], incorporating common outcomes including Patient-Reported Outcome Measures in delirium research, developing new ways of encouraging patient and carers into delirium research, developing standardised multidomain treatment strategies, exploiting new opportunities using large scale routine data, and growing the evidence base on the pathophysiology of delirium [2]. With advances along these fronts, in conjunction with support from policymakers, we can be optimistic that we will witness major improvements in delirium care in the coming years.

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