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WHERE NEXT FOR DELIRIUM RESEARCH?

Rowan H Harwood [1], Elizabeth Teale [2]

1. Health Care of Older People, Nottingham University Hospitals NHS Trust
Queen's Medical Centre, Nottingham NG7 2UH
rowan.harwood@nuh.nhs.uk

2. Bradford Institute for Health Research, Temple Bank House,
Bradford Royal Infirmary, Bradford BD9 6RJ
elizabeth.teale@bthft.nhs.uk

Abstract

Clinicians who manage delirium must do so without key information required for evidence-based practice, not least lack of any clearly effective treatment for established delirium. Both the nature of delirium, and the methods used to research it, contribute to difficulties. Delirium is heterogeneous, with respect to motor subtype, aetiology, setting and the co-existence of dementia, and may be almost inevitable towards the end of life. Elements of assessment are subjective, so diagnosis can be uncertain or unreliable. Defining objectives of care and outcomes is sometimes unclear. Better identification and case definition, including seeking biomarkers, stratification by type, or aetiology, and application of more complex models of causation may help. This will likely require further observational epidemiology, imaging, and laboratory-based research before further rounds of large-scale randomised controlled trials. Application of trial methodologies designed for drug treatments of better-defined conditions may have failed to take account of the complexities both of diagnosis and complex intervention in delirium. Both drug and complex intervention trials need sufficient preliminary work to ensure that the right dose, duration or intensity of treatment is delivered and a range of 'intermediate' and 'proximal' outcome measures assessed. Re-purposing of established drugs may provide a source of investigational products. Greater use of alternative research methodologies (qualitative, realist), or adjuvants to trials (process evaluation) will help answer questions about focus, generalisability and why interventions succeed or fail. Delirium research will have to embrace both a 'back to basics' approach with increased breadth of methodologies to make progress.

WHERE NEXT FOR DELIRIUM RESEARCH?

Research is generalizable new knowledge. Clinical practice is best served when informed by rigorous evidence. This includes definition, identification, risk factors and causes, aetio-pathogenesis, prevention, drug and non-drug treatment, consequences, natural history and prognosis. Systematic knowledge allows correct diagnosis, investigation, intervention and information-giving, and the avoidance of myth, presumption, and what does not work. This paper describes some of the gaps in our knowledge of delirium, and the challenges in undertaking clinical research and translating findings into practice.

Is there a problem?

Delirium research funding and effort is relatively small compared with the size of the clinical problem. Recent decades have seen undoubted progress in knowledge about delirium (Inouye et al 2014), but research has not yet answered many important questions to which clinicians, patients and families require answers.

Prevention of delirium represents the ideal, but, at best, a third of incident hospital delirium can be prevented, and prevalent delirium is an equal or greater problem. Clinical recognition of delirium remains poor (Saczynski et al 2014, Kales et al 2003, Bellelli et al 2015). Brief screening tools help (Inouye 2003, Bellelli et al 2014), but depend on adequate training of staff who use them, and are inconsistently applied. On their own they are of insufficient validity to make a definite diagnosis, despite a tendency to interpret them as diagnostic.

Where delirium is detected, optimal strategies for management, symptom control and longer-term follow-up are unclear. Prospective studies have identified poorer cognitive, functional and survival outcomes in individuals following an episode of delirium (Witlox et al 2010, Siddiqi et al 2006, Fick et al 2013). However, the degree to which increased risk results from the neurochemical disturbance of delirium *per se*, the severity of the physiological insult, decompensation in individuals with an underlying tendency to adverse outcomes (confounding by frailty), complications, poor care, or a combination of all these factors is unknown (Teale and Young 2015).

Predictive factors for recovery of delirium, including different symptom patterns and in different clinical contexts are poorly understood, although hypoactive delirium has a poorer prognosis (Jackson et al 2016b).

Further progress requires us to understand why research is difficult, in order to avoid unjustified assumptions and to allow more appropriate study design. Methodologically-based disciplines can

help. For example, epidemiology is the study of the occurrence and causes of disease in populations, exploiting the paradox that the best information about individuals can come from the study of variation in characteristics between groups (Hennekens et al 1987). Heterogeneity in delirium presentation, and the patients it affects, offers a research opportunity. Epidemiological studies are not the only approach or research need, however. In order to advance knowledge we need to convert plausible laboratory, physiological, biochemical and pharmacological principles and hypotheses into practical interventions. Linking these methodologies with clinical research forms the 'first translation gap'. A further challenge is implementation (the 'second translation gap'), the discipline of promoting and evaluating research knowledge in clinical practice (Oborn et al 2010).

Definition and diagnosis

Disease taxonomy has a long history and has evolved with advances in imaging, cell biology, immunology and genetics. Inferring pathologies from clinical manifestations or syndromes (groups of signs and symptoms) is the basis of clinical medicine (Cassell 2004). Where this is possible, it can lead to specific treatment, with the aim of eradicating the disease (cure). This model is inadequate for many modern health problems, in particular chronic and degenerative diseases, multi-morbidity and mental ill-health.

Most mental health diagnoses are syndromes with uncertain or unknown underlying pathology. The process of diagnosis requires an additional search for underlying pathologies and predisposing factors (Zachar and Kendler 2007). The Virchow notion of a single causal factor (originally applied to infectious diseases) is inadequate. A more likely mechanism for syndromes is one of predisposition and precipitant (Laurila et al 2008). These may change with time (for example, changing patterns of drug prescription) and demographic (ageing being associated with loss of cognitive reserve or dementia). Up to two-thirds of cases of delirium have more than one causal factor, and in up to 20% no cause can be found for clinically convincing delirium, despite full investigation (Laurila et al 2008, Rudberg et al 1997, George et al 1997).

Homogeneity in the 'outcome variable' of an epidemiological or clinical investigation is fundamental. If the study is not (mostly) of a single condition, the ability to identify associated, or potentially-causal, factors is reduced. Delirium is a clinical diagnosis, but diagnosis is difficult. Mimics include dementia with Lewy bodies, progression of vascular dementia, the impact of a disorientating, overstimulating and overwhelming environment (for example, hospitalisation) in someone with dementia or intellectual disability, sleep deprivation, or pain (Sampson et al 2014).

The cardinal feature of delirium is impaired attention, but there is a danger that the two are seen as synonymous. In order for attention to be assessed, there must be sufficient arousal (the patient must be alert enough to be assessed). In the absence of another cause of reduced conscious level, patients too drowsy to be assessed should be classified as having inattention (European Delirium Association 2014). Whilst important for test sensitivity, this reduces specificity, resulting in 'false positives'. Testing attention invariably tests other cognitive or sensory modalities (memory, calculation, language, vision), which can cause problems; for example, many people with dementia cannot recite the months of the year backwards, a commonly-used clinical test for attention. Other features of the delirium syndrome are also important (onset or change, fluctuation, cognitive impairment, motor restlessness or retardation, psychosis, emotional control or lability, autonomic dysfunction), but many of these are also difficult to detect. Aphasia can make assessment of memory, attention or logical thought impossible. Barriers to valid and reliable detection of delirium include the training required to identify clinical signs, or administer diagnostic tests, the fluctuating nature of delirium, and the possibly subjectivity in assessment.

Diagnostic research has concentrated on identification of diagnostic algorithms or tests, and validating these against the 'gold standard' of clinical research diagnostic criteria (Adamis et al 2010). This is necessary and useful, but unless both sensitivity and specificity are very high, study of incidence and prevalence will be incorrect. Poor validity in case definition or outcomes measurement prevents meaningful research. Research into biomarkers for delirium has been limited and no objective delirium test with acceptable diagnostic accuracy has been identified.

In delirium research, this has several important implications:

1. Definition is to some extent arbitrary (witness changing Diagnostic and Statistical Manual diagnostic criteria over the years) (Sepulveda 2015)
2. Diagnostic criteria assembled for the purposes of taxonomy or research must be operationalised for clinical use
3. Conceptualising delirium as a 'disease' may be misleading
4. The validity of a clinical diagnosis is not necessarily secure.

Heterogeneity in delirium, and those who develop it

Delirium is currently held to represent a single condition, but is varied in its presentation and features, and may represent a number of different conditions, based on:

1. Motor subtype (hyper- vs hypo-active)

2. Aetiology (neurological infections, neurological injury or disease, systemic infections, anticholinergic drugs, other drugs, drug or alcohol withdrawal, electrolyte disturbance, renal or liver failure, hypoxia, vascular disease).

3. Setting (surgical vs medical vs intensive care units vs palliative care)

4. The presence or absence of prior dementia.

The argument for these being a single condition is fulfilment of diagnostic criteria for the syndrome. The argument against is the possibility of different causal mechanisms (and lack of evidence of a single common final pathway), and different natural history and prognosis. The solution is to study these groups separately, which requires large numbers of study participants and most likely, multi-centred research. Imaging or biochemical clinical aetiological research may help, if biomarkers for different sub-types or strata can be identified.

Particular evidence for heterogeneity in the delirium syndrome relates to recovery. Delirium is typically described as reversible cognitive impairment, but is also associated with high mortality (Siddiqi et al 2006). In published series, 40% of delirium has resolved within 24h, but 30% persists more than a month and 21% more than 6 months (Cole et al 2009).

A major emerging hypothesis is that episodes of delirium cause permanent cognitive damage, and this represents a mechanism through which dementia deteriorates (Davis et al 2012, Fong et al 2015). An alternative hypothesis is that delirium is a manifestation of frailty resulting from poor reserve to maintain homeostasis, disproportionate physiological impact of relatively minor insults, and risk of incomplete recovery following decompensation (Teale and Young 2015). This is supported in some series where survival, cognitive and functional recovery have all been poor (Whittamore et al 2014). Cognitive failure may, in medical/geriatric and palliative care settings, be a function of frailty and multi-system failure in those approaching the end of life, and therefore not 'treatable' or reversible.

Most delirium occurs on a background of prior dementia and this poses particular problems (Fick et al 2013, Fick et al 2002, Mukadem and Sampson 2011, Morandi et al 2017). Many of those admitted with delirium without a prior dementia diagnosis will either have undiagnosed dementia, or their families describe clear if subtle signs of prior cognitive problems not reaching the diagnostic threshold, indicating 'frail brains' (Jackson et al 2016a). It can be argued that in the context of acute physical illness and the hospital setting it is impossible to distinguish delirium, dementia and delirium superimposed on dementia. For example in hospital, sleep is often disturbed due to the effects of illness, day time inactivity, environmental noise, or dementia itself. Many older people

'nap' during the afternoon. Those who sleep poorly at night may do so in the day, or become irritable and unable to sustain focus on mentally taxing tasks. Does this represent delirium or merely sleep deprivation? Is sleep deprivation a cause of delirium or does it just cause similar symptoms? Similar arguments hold for pain and constipation. 'Cognitive spectrum disorders' – defining a range of cognitive conditions in acute hospitals, including delirium, delirium superimposed on dementia and dementia, has been proposed as an alternative, with the final diagnosis to be determined at follow-up (Reynish 2015). This is not to deny the existence of delirium, but to acknowledge our inability to identify it as an entity in some situations, whilst acknowledging the similar needs of other groups (such as people with dementia or intellectual disabilities) when in a crisis which may have medical, mental health or social origins.

Objectives of care

Healthcare need is the potential to benefit from an assessment or therapeutic intervention. Benefit is often stated in terms of 'health gain', a change in measureable health status, such as disease presence, function or quality of life, but could include prevention, palliation, information-giving or reassurance, or family and carer support. If delirium is an unavoidable part of dying, or a non-specific driver of crises in people with dementia or frailty, then the goals of treatment should focus primarily on relieving distress and optimising function, in contrast to those in whom delirium is an unpleasant epiphenomenon arising in the course of a primary medical disorder, where the goal is cure or disease control. There has been virtually no research on symptom control in delirium, as an outcome *per se* (Partridge et al 2013).

Instead, research has focused on delirium occurrence or resolution. This has advantages, especially for research efficiency (the outcome reflects the condition of primary interest), but there are limitations. If the assessment is at least in part subjective, an opportunity for ascertainment bias is introduced. This is of particular concern in trials of complex interventions where blinding is difficult, and may result in a tendency to overstate the size of treatment effects. More objective outcomes (death or care home placement) or 'distal outcomes' (disability or quality of life) can be measured to avoid bias, but may be relatively infrequent, compromising statistical power, or subject to multiple causes or influences (such as co-morbidity, or socio-economic circumstances), making treatment effects specific to delirium harder to discern (Teale and Young 2015).

As well as pathologies, problems can be defined at the level of organs or anatomical parts (impairments, such as pain, poor visual acuity, attention, memory loss or delusions), tasks or capabilities (walking, reading, social behaviour), activity or participation (successful function in a

physical and social environment, taking account of contextual factors) (World Health Organization 2001). This opens the possibility of intervention at the palliative, functional, social and environmental level. To date these approaches have been little studied.

Avoidance of complications or unintentional harm is an important mechanism for health gain in older people, and the avoidance of healthcare associated harm is the focus of worldwide political action (Department of Health 2016). Interference with, or resistance to, necessary medical intervention, falls and fractures, pressure ulcers, deconditioning, malnutrition, distress, affront to identity and depersonalisation, and post-traumatic stress disorder are delirium-specific examples. These will not necessarily be captured by focus on delirium prevention or recovery, but are important patient-centred outcomes in their own right.

Issues with the existing delirium evidence base

Evidence-based practice requires valid evidence. Research evidence in delirium is incomplete, and varies in quality, so interpretation and appreciation of limitations is required. Lack of evidence of benefit is not the same as evidence of lack of benefit. Avoiding therapeutic nihilism requires us to work with uncertainty.

Both prevention and treatment trials are hard to do, because of the complex packages of measures necessary, the time-frame for recruitment and intervention, and the pressures and competing priorities of emergency healthcare. Trials may be confined to efficacy trials in exemplar conditions (such as hip replacement) when logistics are more easily controlled, and delirium rates high. This raises questions of generalisability; it does not prove that evidence is not generalisable, but introduces uncertainty. Alternatively, non-randomised clinical studies may be undertaken (Slaets et al 1997, Inouye et al 1999, Holt et al 2013), which are pragmatic, and provide evidence, if carefully done and interpreted. However, they are prone to bias, uncertainty about causal relationships, and misleading conclusions.

The absolute priority given to randomised controlled trials may need to be reconsidered. Because trials are difficult, they are often small (although there are many delirium trials with several hundreds of participants). Type 2 statistical error is falsely rejecting the null hypothesis because of insufficient statistical power – trials too small to be sure that results were unlikely to have arisen by chance. Power depends on outcome event rates rather than size alone; there are several recent examples of good-sized but underpowered trials (Hempenius et al 2013, Jeffs et al 2013). Small size also limits the ability to explore variations by subgroups (treatment by subgroup interaction). A recent pragmatic multicentre cluster randomised controlled feasibility trial of a multicomponent

delirium prevention intervention concluded that a definitive trial in routine care would require 2300 participants in each arm (Young et al 2015, Green et al 2016), which would be expensive and logistically challenging. Meta-analysis increases precision in effect size, but concerns remain about heterogeneity in interventions and publication bias (a tendency for negative trials not to be published) (Siddiqi et al 2016a, Hshieh et al 2015, Martinez et al 2012, Al-Quadheeb et al 2014, Gilmore and Wolfe 2013).

Drug trials require a lot of preliminary work to ensure that they have the best chance of success, and this has not always been done in delirium, including lack of dose-ranging, determination of optimal duration of treatment or timing of outcome assessment.

A trial measures a difference between two treatments, or an active treatment and none. Standard clinical trials recognise the problems of protocol violation and crossover, and to an extent simple drug trials can cope with this without losing interpretability (although size of treatment effect will be underestimated). The design of trials (randomisation, stratification or minimisation, permuted blocks, and sufficient size) to ensure baseline balance between groups, and analysis by intention-to-treat, is designed to ensure that results are unbiased (results are unlikely to be due to any factor other than treatment). Control groups serve to eliminate the effects of time, natural history, comorbidity, intercurrent illness, attention and measurement. Ideally a placebo or sham control is used, which is feasible in drug trials, but less so for complex interventions. It is often impossible to have a truly 'inactive' or untreated control group, so interpreting treatment effect sizes becomes difficult: a 'negative' trial may merely indicate dilution of the treatment effect, or that both treatment conditions were effective.

A single main trial outcome is specified because of the possibility of chance associations when multiple outcomes are used, and the risk of exploitation by (commercial) vested interests when such associations are reported. However, these considerations are less relevant to complex interventions (Medical Research Council 2008, Goldberg et al 2013). There are many dimensions of health experience, from disease-specific physiological or functional measures, through generic health status, quality of life and psychosocial variables such as experience and satisfaction. Defining what constitutes a 'good' outcome is particularly troublesome for frail older people. If it is not possible to prevent or treat delirium, attenuation of symptoms (or reduction in the distress they cause) may be an appropriate outcome. However, measurement of these patient-focused outcomes is challenging, especially in individuals who may be unable to communicate how they are feeling (Goldberg and Harwood 2013).

Increasingly, trials are cluster randomised (at the level of a ward or hospital rather than the individual; for example, Siddiqi et al 2016b). This introduces additional problems with contamination and cluster effects, requiring inflated sample sizes.

There are many practical difficulties in undertaking delirium research. Researchers may defer performing delirium assessments, or clinical staff may deter researchers from approaching patients at the point of determining trial eligibility if they are frail or unwell (when they are most at risk from delirium). Missing delirium assessments may occur when patients are unavailable or unwilling to undergo testing. The hierarchical nature of data obtained from repeated assessments, managing missing data, and determining delirium duration and severity from longitudinal data (especially where there is fluctuation) are challenges for data analysis.

The evidence for benefit of delirium prevention interventions

The preventative paradigm aims to influence behaviour at individual, organisational or societal levels. Delirium is more common amongst patients treated in some ways than others; delirium can be caused or prevented. Regional anaesthesia (for example, Williams-Russo 1995, Marino et al 2009), use of dexmedetomidine sedation in intensive care units (Pasin et al 2013, Su et al 2016), proactive ortho-geriatric consultation (Marcantonio et al 2001, Lundström et al 2007), and post-acute rehabilitation out of hospital (Siddiqi et al 2016a, Caplan et al 2006) all have credible supportive evidence for prevention from randomised controlled trials. There is evidence to support delirium prevention through multicomponent interventions: meta-analysis of randomised trials demonstrate an overall beneficial effect (Hshieh et al 2015, Martinez et al 2012), but the effect is diluted in routine care settings, and there is no consensus on the critical components of these interventions. Benefit may simply represent attention to basic care (mental stimulation, hydration, nutrition, correction of sensory impairment, mobility, sleep promotion) and avoidance of harmful practice.

Much delirium does not appear to be preventable, and in some circumstances (e.g. advanced frailty, or at the end of life), delirium may be all but inevitable. For those with frailty, disproportionate physical and cognitive decompensation may occur in response to what may be considered to be a relatively minor insult and this, rather than the severity of the insult *per se*, is likely to contribute to poor outcomes. It may make more sense to investigate generic interventions in frailty (including targets such as falls, nutrition, immobility and incontinence) rather than delirium-specific interventions alone. In many 'medical' disciplines, including intensive care and palliative care, there are multiple competing priorities, which may have conflicting impacts on outcomes, including the

occurrence of delirium. Analgesia is an example: painful diseases, pain itself and analgesic drugs may all cause delirium. There may be a trade-off between avoidance of deconditioning and immobility and the occurrence of in-patient falls. Delirium prevention will form part of a comprehensive package.

The evidence for delirium treatment interventions

The 1999 American Psychiatric Association guideline on delirium stated (amongst much good advice) that 'antipsychotic medications are the pharmacologic treatment of choice' (American Psychiatric Association 1999). This advice was based largely on custom and practice. Since then, many trials have investigated single agent drug treatments, notably antipsychotics, pro-cholinergics and cholinesterase inhibitors, melatonin, and benzodiazepines (for example, Page et al 2013, de Jonghe et al 2014, van Eijk et al 2010). Some suggest a treatment effect, but none, nor any meta-analysis, provides evidence beyond reasonable doubt. Similarly complex interventions including geriatric assessment, delirium units and management advice and follow-up have also suggested treatment effects without any certainty (for example, Cole et al 1994, Cole et al 2002, Baldwin et al 2004, Pitkälä et al 2006, Goldberg et al 2013). Current guidance from the UK National Institute for Health and Clinical Excellence (NICE) acknowledges the paucity of evidence for treatment of delirium, and is unable to recommend the routine use of any pharmacological agent (National Institute for Health and Clinical Excellence 2010). Overall it is fair to say that no treatment intervention has convincing evidence of efficacy or effectiveness.

Solutions

The first requirement is for basic clinical, imaging, biomarker and epidemiological research systematically to investigate how delirium might subdivide, or (as current thinking holds) represent a single entity. This will require funders to support work one step removed from clinical trials and their immediate impact on clinical practice. More accurate information on phenomenology, prevalence, incidence, associations, risk factors, and natural history is required on a scale not previously attempted, including for subgroups (e.g. those with dementia and frailty) and subtypes (e.g. hyper- vs hypoactive delirium, or by cause).

Current pharmacological interventions are based on limited trial evidence of efficacy and have potentially serious side-effects, especially in older people with co-existing dementia. Further drug trials are urgently required based on new and plausible theories of patho-aetiology of delirium to identify potentially novel therapeutic targets, grounded in sound scientific principles. Repurposing of drugs with an existing license and safety record could form the basis of this work. Early phase 2 trials

are required with momentum maintained to bridge the first translational gap for drugs that show promise. Joined-up working between laboratory and clinical researchers would help to identify targets for future drug trials.

A broader view on outcomes is required. In the absence of an objective measure of delirium, reduction in incident delirium and delirium severity are difficult to measure. In some settings (e.g. advanced frailty or palliative care) relief of suffering or distress and maintenance of function is as important as resolution of delirium and restoration of cognition (Cassell 2004).

An area rarely considered in medical research is that of epistemology. The dominant philosophy is positivist – which holds that you should not believe what hasn't been proved, hence the importance of randomised controlled trials, and the approaches used in health technology assessment and prioritisation bodies such as the National Institute for Health and Care Excellence (NICE). This poses an inherent risk. McNamara's fallacy holds that what cannot be measured is not important, or worse, does not exist (Wikipedia 2016). Strictly a randomised controlled trial answers a single question (about drug dose, or configuration of complex services, in a defined group at baseline, on a particular outcome measure). Ensuring these are optimised is important but difficult, and may require a series of trials investigating different subgroups or treatment or outcome variation. Trials are expensive, time-consuming and labour-intensive, making this an ambitious goal. Funders and researchers soon lose interest, often after only a single large trial has been completed.

Realist evaluation investigates what works, for whom, under what circumstances, and why (Wong 2015). It does this by proposing 'middle range theories', or broad propositions defining context, mechanism and outcome, and how they relate. This widens and enhances the study of applicability and generalisability, but in doing so demands we accept different, and less rigorous, quality of evidence. Realism considers, and appraises, any available evidence that might contribute support or contradict a theory. The focus of uncertainty is shifted from doubts about effect size and generalisability inherent in trials methodology, to questions of validity and causality inherent in other research designs. However, trials remain an important source of evidence. Embedding subgroup and process evaluation in trials contributes valuably to realist evaluation. Process evaluation asks why trials may not have shown an anticipated effect through examination of treatment-related problems (fidelity), research-related issues, mechanisms and contextual factors (facilitators, barriers) that provide, explain and determine the necessary conditions for a treatment to be effective (Moore et al 2014). Given the variations around delirium research this is particularly important, but to date little done.

Qualitative methodologies may contribute. Examples include studying the experience and meaning of delirium for patients, carers and staff (for example, Partridge et al 2013, Morandi et al 2015). This in turn, can define treatment goals and patient-centred outcome measures. For staff, understanding interaction with hospital processes, and competing priorities such as throughput and risk, is needed if delirium prevention and treatment programmes are to be successfully implemented. The importance of patient and public participation in all aspects of research has been highlighted in the UK over the past decade in terms of generation of research questions, research delivery, interpretation and impact. The development of outcomes focused on reducing the distressing symptoms of delirium would be well-informed by involving individuals who have experienced delirium.

Conclusion

Despite encouraging progress, delirium research has failed to have sufficient impact on clinical practice. The use of limited and limiting research paradigms – often for justified reasons – has contributed. In the policy arena it has served to explain delirium as 'a disease' that can be prevented, or relatively easily identified and treated, with the presumption that successful treatment of the underlying cause will be followed by cognitive and clinical recovery. This has been influential in guideline development and recommendations for clinical practice. However, there is little existing or emerging evidence to support this paradigm.

Instead we have a syndrome, which shows considerable heterogeneity, and may not be a single condition, bearing a complex relationship with dementia and other causes of physical and neurological frailty. Identification is difficult, and in some settings may be impossible, at least with any degree of certainty. Single causes are the exception not the rule, and a model of predisposition and precipitant may serve better. Reversibility is uncertain and in general, survival, cognitive and functional outcomes are poor for some subgroups at least. The possibility that a simpler disease model may be valid for some groups (for example, post-operatively) remains enticing, and should not be abandoned entirely.

Observational research on aetiology and causal factors is incomplete. The dominance of randomised controlled trials in understanding treatment effects has been unproductive, partly because too little preparatory work has been done before embarking on trials, and secondly because process evaluations have not been used to explain why the results occurred. Fundamental re-evaluation of the approach to delirium research may reveal findings that will drive a necessary step-change in clinical practice.

Declarations

There are no conflicts of interest. This is a review article and has not been subject to ethical review.

References

Adamis D, Sharmab N, Whelan PJP, Macdonald AJD (2010). Delirium scales: A review of current evidence. Aging and Mental Health; 14: 543-555.

Al-Quadheeb NS, Balk EM, Fraser GL, Skrobik Y, Riker RR, Kress JP, Whitehead S, Devlin JW (2014). Randomised ICU trials do not demonstrate an association between interventions that reduce delirium and short term mortality: a systematic review and meta-analysis. Critical Care Med; 42: 1442-54.

American Psychiatric Association (1999). Practice guideline for the treatment of patients with delirium. American Psychiatric Association, Arlington, Virginia.

Baldwin R, Pratt H, Goring H, Marriott A, Roberts C (2004). Does a nurse-led mental health liaison service for older people reduce psychiatric morbidity in acute general medical wards? A randomised controlled trial. Age and Ageing; 33: 472-8.

Bellelli G, Morandi A, Davis DHJ, Mazzola P, Turco R, Gentile S, Ryan T, Cash H Guerini F, Torpilliesi T, Del Santo F, Trabucchi M, Annoni G, MacLullich AMJ (2014). Validation of the 4AT, a new instrument for rapid delirium screening: a study in 234 hospitalised older people. Age and Ageing; 43: 496-502.

Bellelli G, Nobili A, Annoni G, Morandi A, Djade CD, Meagher DJ, MacLullich AM, Davis D, Mazzone A, Tettamanti M, Mannuccio PM (2015). Under-detection of delirium and impact of neurocognitive deficits on in-hospital mortality among acute geriatric and medical wards. Eur J Intern Med; 26: 696-704.

Caplan G A, Coconis J, Board N, Sayers A, Woods J (2006). Does home treatment affect delirium? A randomised controlled trial of rehabilitation of elderly and care at home or usual treatment (the REACH-OUT trial). Age and Ageing; 35: 53-60.

Cassell EJ (2004). The Nature of Suffering and the Goals of Medicine. 2nd edition. New York; Oxford University Press.

Cole MG, Primeau FJ, Bailey RFl (1994). Systematic intervention for elderly inpatients with delirium: a randomized trial. CMAJ; 151, 965-70.

Cole MG, McCusker J, Bellavance F (2002). Systematic detection and multidisciplinary care of delirium in older medical inpatients: a randomized trial. CMAJ; 167: 753-9.

Cole MG, Ciampi A, Belzile E, Zhong L (2009). Persistent delirium in older hospital patients: a systematic review of frequency and prognosis. Age and Ageing; 38: 19-26.

Davis DH, Muniz Terrera G, Keage H, Rahkonen T, Oinas M, Matthews FE, Cunningham C, Polvikoski T, Sulkava R, MacLullich AM, Brayne C (2012). Delirium is a strong risk factor for dementia in the oldest-old: a population-based cohort study. Brain; 135: 2809-16.

De Jonghe A, van Munster BC, Goslings JC, Kloen P, van Rees C, Wolvius R, van Velde R, Levi M, de Haan RJ, de Rooi SE (2014). Effect of melatonin on incidence of delirium among patients with hip fracture: a multicentre, double-blind randomized controlled trial. CMAJ; 186: E547-E556.

Department of Health (2016). NHS Outcomes Framework 2016/7. London, Department of Health. Available at http://digital.nhs.uk/nhsof. Accessed 24th September 2016.

European Delirium Association and American Delirium Society (2014). The DSM-5 criteria, level of arousal and delirium diagnosis: inclusiveness is safer. BMC Medicine; 12: 141

Fick DM, Agostini JV, Inouye SK (2002). Delirium superimposed on dementia: A systematic review. Journal of the American Geriatric Society; 50: 1723–1732.

Fick DM, Steis MR, Waller JL, Inouye SK (2013). Delirium superimposed on dementia is associated with prolonged length of stay and poor outcomes in hospitalized older adults. Journal of Hospital Medicine; 8: 500–505.

Fong TG, Davis D, Growdon ME, Albuquerque A, Inouye SK (2015). The interface between delirium and dementia in elderly adults. Lancet Neurology; 14: 823-32

George J, Bleasdale S, Singleton SJ (1997). Causes and prognosis of delirium in elderly patients admitted to a district general hospital. Age and Ageing; 26: 423-427.

Gilmore ML, Wolfe DJ (2013). Antipsychotic prophylaxis in surgical patients modestly decreases delirium incidence – but not duration – in high incidence samples. A meta-analysis. General Hospital Psychiatry; 35: 370-5.

Goldberg SE, Bradshaw LE, Kearney FC, Russell C, Whittamore KH, Foster PER, Mamza J, Gladman JRF, Jones RG, Lewis SA, Porock D, Harwood RH (2013). Comparison of a specialist Medical and Mental Health Unit with standard care for older people with cognitive impairment admitted to a

general hospital: a randomised controlled trial (NIHR TEAM trial). BMJ; 347: f4132. Accessed 24th September 2016.

Goldberg SE, Harwood RH (2013). Experience of general hospital care in older patients with cognitive impairment: are we measuring the most vulnerable patients' experience? BMJ Quality and Safety 2013 doi:10.1136/bmjqs-2013-001961. Accessed 24th September 2016.

Green J, Teale EA, on behalf of the POD study investigators (2016). A cluster randomised feasibility study of the prevention of delirium (POD) programme for elderly patients admitted to hospital. British Geriatrics Society Spring Conference. http://www.bgs.org.uk/pdf_cms/admin_archive/2016_spring_abstracts.pdf. Accessed 24 September 2016.

Hempenius L, Slaets JPJ, van Asselt D, de Bock GH, Wiggers T, van Leeuwen BL (2013). Outcomes of a geriatric liaison intervention to prevent the development of postoperative delirium in frail elderly cancer patients: report on a multicentre, randomized, controlled trial. PloS One; 8: e64834. Accessed 24th September 2016.

Hennekens CH, Buring JE, Mayrent S (1987). Epidemiology in Medicine. Baltimore: Lippincott, Williams and Wilkins.

Holt R, Young J, Hestletine D (2013). Effectiveness of a multicomponent intervention to reduce delirium incidence in elderly care wards. Age and Ageing; 42: 721-7.

Hshieh TT, Yue J, Oh E, Puelle M, Dowal S, Travison T, Inouye SK (2015). Effectiveness of multicomponent non-pharmacological delirium interventions. JAMA; 175: 512-520.

Inouye SK, Bogardus ST, Charpentier PA, Leo-Summers L, Acampora D, Holford TR, Cooney LM (1999). A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med; 340: 669-76.

Inouye SK, Westendorp RJG, Saczynski JS (2014). Delirium in elderly people. Lancet; 383: 911–922.

Inouye SK (2003). The Confusion Assessment Method (CAM): Training Manual and Coding Guide; Yale University School of Medicine.

Jackson TA, MacLullich AM, Gladman JR, Lord JM, Sheehan B (2016a). Undiagnosed long-term cognitive impairment in acutely hospitalised older medical patients with delirium: a prospective cohort study. Age Ageing; 45: 493-9.

Jackson TA, Wilson D, Richardson S, Lord JM (2016b). Predicting outcome in older hospital patients with delirium: a systematic literature review. International Journal of Geriatric Psychiatry; 31: 396-403

Jeffs KJ, Berlowitz DJ, Grant S (2013). An enhanced exercise and cognitive programme does not appear to reduce incident delirium in hospitalised patients: a randomized controlled trial. BMJ Open. http://bmjopen.bmj.com/contents/3/6/e002569.full.pdf. Accessed 24th September 2016.

Kales HC, Kamholz BA, Visnic SG, Blow FC (2003). Recorded delirium in a national sample of elderly inpatients: potential implications for recognition. Journal of Geriatric Psychiatry and Neurology; 16, 32–38.

Laurila JV, Laakkonen M-L, Strandberg TE, Tilvis RS, Pitkälä KH (2008). Predisposing and precipitating factors for delirium in a frail geriatric population. Journal of Psychosomatic Research; 65: 249–254.

Lundström M, Olofsson B, Stenvall M, Karlsson S, Nyberg L, Englund U, Borssén B , Svensson O, Gustafson Y (2007). Postoperative delirium in old patients with femoral neck fracture: A randomized intervention study. Aging Clin Exp Res; 19: 178-186.

Marcantonio ER, Flacker JM, Wright RJ, Resnick NM (2001). Reducing delirium after hip fracture: a randomized trial. Journal of the American Geriatrics Society; 49: 516-22.

Marino J, Russo J, Kenny M, Herenstein R, Livote E, Chelly JE (2009). Continuous lumbar plexus block for postoperative pain control after total hip arthroplasty. A randomized controlled trial. Journal of Bone and Joint Surgery American Edition; 91: 29 -37.

Martinez FT, Tobar C, Beddings CI, Vallejo G, Fuentes P (2012). Preventing delirium in an acute hospital using a non-pharmacological intervention. Age and Ageing; 41: 629-634.

Medical Research Council (2008). Developing and evaluating complex interventions: new guidance. London: MRC. www.mrc.ac.uk/complexinterventionsguidance. Accessed 24 September 2016.

Moore G, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, Moore L, O'Cathain A, Tinati T, Wight D, Baird J (2014). Process evaluation of complex interventions: Medical Research Council guidance. MRC Population Health Science Research Network, London.

Morandi A, Davis D, Bellelli G, Arora RC, Caplan GA, Kamholz B, Kolanowski A, Fick DM, Kreisel S, MacLullich A, Meagher D, Neufeld K, Pandharipande PP, Richardson S, Slooter AJC, Taylor JP, Thomas C, Tieges Z, Teodorczuk A, Voyer P, Rudolph JL. (2017). The Diagnosis of Delirium Superimposed on Dementia: An Emerging Challenge. JAMDA; 18: 12-18

Morandi A, Lucchi E, Turco R, Morghen S, Guerini F, Santi R, Gentile S, Meagher D, Voyer P, Fick DM, Schmitt EM, Inouye SK, Trabucchi M, Bellelli G (2015). Delirium superimposed on dementia: A quantitative and qualitative evaluation of informal caregivers and health care staff experience. J Psychosom Res; 79: 272-8.

Mukadem N, Sampson EL (2011). A systematic review of the prevalence, associations and outcomes of dementia in older general hospital inpatients. International Psychogeriatrics; 23: 344-355.

National Institute for Health and Clinical Excellence (2010). Delirium: prevention, diagnosis and management CG103. https://www.nice.org.uk/guidance/cg103/evidence/full-guideline-134653069. Accessed 24th September 2016.

Oborn E, Barrett M, Racko G (2010). Knowledge translation in healthcare: A review of the literature. Cambridge: Judge Business School. Working Paper Series 5/2010. https://www.jbs.cam.ac.uk/fileadmin/user_upload/research/workingpapers/wp1005.pdf. Accessed 24th September 2016.

Page VJ, Ely EW, Gates S, Zhao XB, Alce T, Shintani A, Jackson J, Perkins GD, McAuley DF (2013). Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients (Hope-ICU): a randomised, double-blind, placebo-controlled trial. Lancet Respiratory Medicine; 1: 515-523.

Partridge JS, Martin FC, Harari D, Dhesi JK (2013). The delirium experience: what is the effect on patients, relatives and staff and what can be done to modify this? Int J Geriatr Psychiatry; 28: 804-12.

Pasin L, Landoni G, Nardelli P, Belletti A, Di Prima AL, Taddeo D, Isella F, Zangrillo A (2014). Dexmedetomidine Reduces the Risk of Delirium, Agitation and Confusion in Critically Ill Patients: A Meta-analysis of Randomized Controlled Trials. Journal of Cardiothoracic and Vascular Anesthesia; 28: 1459-1466.

Pitkälä KH, Laurila JV, Strandberg TE, Tilvis RS (2006). Multicomponent Geriatric Intervention for Elderly Inpatients with Delirium: A Randomized, Controlled Trial. Journals of Gerontology: Series A; 61: 176-181.

Reynish E (2015). Prevalence, mortality and readmission of people with dementia, delirium and other cognitive spectrum disorders in the general hospital. European Geriatric Medicine; 6: S177-S8.

Rudberg MA, Pompei P, Foreman MD, Ross RE, Cassel CK (1997). The natural history of delirium in older hospitalized patients: a syndrome of heterogeneity. Age and Ageing; 26: 169-174.

Saczynski JS, Kosar CM, Xu G, Puelle MR, Schmitt E, Jones RN, Inouye SK (2014). A tale of two methods: Chart and interview methods for identifying delirium. Journal of the American Geriatrics Society; 62: 518–524.

Sampson EL, White N, Leurent B, Scott S, Lord K, Round J (2014). Behavioural and psychiatric symptoms in people with dementia admitted to the acute hospital: prospective cohort study. Br J Psychiatry; 205: 189-96

Sepulveda E, Franco JG, Trzepacz P, Gaviria AM, Vinuelas E, Palma J, Ferre G, Grau I, Vilella E (2015). Performance of the delirium rating scale-revised-98 against different delirium diagnostic criteria in a population with a high prevalence of dementia. Psychosomatics; 56: 530-541.

Siddiqi N, House AO, Holmes JD (2006). Occurrence and outcome of delirium in medical in-patients: a systematic literature review. Age and Ageing; 35: 350–364.

Siddiqi N, Harrison JK, Clegg A, Teale EA, Young J, Taylor J, Simpkins S (2016a). Interventions for preventing delirium in hospitalised non-ICU patients. Cochrane Database of Systematic Reviews. 2016, Issue 3. Art.No.:CD005563 DOI:10.1002/14651858.CD005563.pub3.

Siddiqi N, Cheater D, Collinson M, Farrin A, Forster A, George D, Godfrey M, Graham E, Harrison J, Heaven A, Heudtlass P, Hulme C, Meads D, North C, Sturrock A, Young J (2016b). The PiTSTOP study: a feasibility cluster randomized trial of delirium prevention in care homes for older people. Age and Ageing; 45: 652-661.

Slaets JP, Kaufmann RH, Duivenvoorden HJ, Pelemans W, Schudel WJ (1997). A randomised trial of geriatric liaison intervention in elderly medical inpatients. Psychosomatic Medicine; 59: 585-591.

Su X, Meng ZT, Wu XH, Cui F Li HL, Wang DX, Zhu X, Zhu SN, Maze M, Ma D (2016). Dexmetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. Lancet; 388:1893-1902.

Teale E, Young J (2015). Multicomponent delirium prevention: not as effective as NICE suggests? Age and Ageing; 44: 915-917.

Van Eijk MMJ, Roes KCB, Honing MLH, Kuiper MA, Karakus A, van der Jagt M, Spronk PE, van Gool WA, van der Mast RC, Kesecioglu J, Slooter AJC (2010). Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial. Lancet; 376: 1829-37.

Whittamore K, Goldberg S, Gladman JRF, Jones RG, Harwood RH (2014). The diagnosis, prevalence and outcome of delirium in a cohort of older people with mental health problems on general hospital wards. International Journal of Geriatric Psychiatry; 29: 32-403.

Wikipedia (2016). MacNamara's fallacy. https://en.wikipedia.org/wiki/McNamara_fallacy. Accessed 24th September 2016.

Williams-Russo P, Sharrock NE, Mattis S, Szatrowski TP, Charlson ME (1995). Cognitive effects after epidural vs general anesthesia in older adults. A randomized trial. JAMA; 274: 44-50.

Witlox J, Eurelings LSM, de Jonghe JFM, Kalisvaart KJ, Eikelenboom P, van Gool WA (2010). Delirium in elderly patients and the risk of post discharge mortality, institutionalization, and dementia. A Meta-analysis. JAMA; 304: 443-451.

Wong G (2015). Getting started with realist research. International Journal of Qualitative methods: 14: 1-2.

World Health Organization (2001). International Classification of Functioning, Disability and Health (ICF). Geneva: WHO. Available at http://www.who.int/classifications/icf/en/. Accessed 24th September 2016.

Young J, Cheater F, Collinson M, Fletcher M, Forster A, Godfrey M, Green J, Anwar S, Hartley S, Hulme C, Inouye SK, Meads D, Santorelli G, Siddiqi N, Smith J, Teale E , Farrin AJ (2015). Prevention of delirium (POD) for older people in hospital: study protocol for a randomised controlled feasibility trial. Trials 2015 16:340. DOI: 10.1186/s13063-015-0847-2. Accessed 24th September 2016.

Zachar P, Kendler KS (2007). Psychiatric Disorders: A Conceptual Taxonomy. American Journal of Psychiatry; 164: 557-565.

Key words (MeSH)

Delirium, dementia, taxonomy, research design, evidence-based medicine, clinical trials, health status, terminal care

Key points

- Convincing evidence indicated that some delirium can be prevented, but little evidence for effective treatment of established delirium
- Delirium is a heterogeneous syndrome, that can be difficult to diagnose with certainty, which needs to be taken into account in delirium research

- Research has focussed on narrow views of causation and objectives of care, which should be broadened in future
- Research is restricted by a concentration on randomised controlled trials; other research methodologies should be explored in addition.