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Outcomes in delirium: same but different

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Summary

Delirium has been associated with institutionalization, increased length of hospital stay, cognitive and functional decline and mortality. Research in the last thirty years has recognized that accurate diagnostic criteria allow for targeted interventions for those suffering from delirium. However, despite the advances made in understanding delirium, adverse outcomes persist.

This article will first review how the evolution of diagnostic criteria has fostered improvements in the recognition of delirium and facilitated the development of therapeutic strategies. Second, we discuss how this foundation in approach to delirium has influenced outcomes and the evidence for causality. Finally, the candidate factors responsible for propagating adverse events are considered and future research direction outlined.

Key words: delirium, institutionalization, mortality, inpatients, outcome assessment

Background

Delirium is defined as an acute disturbance of consciousness associated with acute illness. Common in hospitalized older patients, with a prevalence ranging from 14 to 56%, its transience belies its health impact.[1–3] The importance of studying delirium in medical in-patients has largely been recognized over the past thirty years. Delirium may be preventable and yet it remains poorly recognized.[4] Adverse health outcomes may be exacerbated by failure to properly diagnose and appropriately treat delirium. Significant morbidity and mortality (with attendant health care costs) escalate with poor management.[3] The incidence of delirium during hospitalization has even been recognized as a sign of the quality of hospital care.[5]

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Since the American Psychiatric Association first published diagnostic criteria for delirium in 1981, there has been a wealth of research on the aetiology, diagnosis, treatment, prevention and outcomes associated with delirium. This body of work has yielded a greater understanding of delirium as representing a unique cognitive disorder, albeit with multifactorial causes. However, there clearly remains an essential need to conduct additional research. In particular, an appreciation of the reasons for the poor outcomes associated with delirium is important. This paper will review the literature from 1981 until the present to determine the causes of adverse outcomes associated with medical in-patients diagnosed with delirium and discuss possible mechanisms within and beyond the delirium knowledge horizon.

Search methods

A search of four databases was conducted using the search terms ‘delirium’, ‘outcome’, ‘mortality’, ‘institutionalization’ and ‘long term care’. In addition, bibliographies of each of the articles were reviewed as well as three systemic reviews for further detailed analysis of the topic.[3,6,7] Full details of the search methods can be obtained from the corresponding author.

Changing criteria for delirium diagnosis

Descriptions of delirium abound in medical, religious and literary sources since antiquity.[7–9] However, it was not until the early 1980s that the American Psychiatric Association introduced criteria for diagnosing delirium as a psychiatric disorder in the Diagnostic and Statistical Manual of Mental Disorders, version three (DSM-III).[10] While advances were being made in medical treatment for dementia, comparable developments were not witnessed in the field of delirium.[11] The DSM-III criteria for delirium focused on

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clouding of consciousness, perceptual disturbance and incoherent speech, memory impairment and acute onset of clinical features and related etiology.[10,12] Utilizing these criteria for diagnosing delirium, authors researched the connection between a diagnosis of delirium with outcomes such as mortality, length of hospital stay, cognitive impairment, persistence of symptoms and increased hospital charges when compared with those suffering from dementia or other controls.[11–16] These authors struggled with how to disentangle delirium when superimposed upon dementia or other medical illnesses (e.g. urinary tract infections, structural brain diseases).[15,17]

Despite the numerous studies on delirium as a unique mental disorder and the recognition of the correlated adverse outcomes, authors pointed out that delirium continued to go undiagnosed especially among older people. These early studies continued to view delirium as merely a transitory (acute) state from which a patient could recover, die, transition to dementia (chronic), or transition to a functional psychosis.[17,18] In fact, many of these early studies tied the severity of illness ('neural noise' rather than delirium itself) as a key predictor of the likelihood of recovery.[17] Given these results, authors repeatedly pointed out that early recognition, assessment and treatment of delirium might result in lower mortality and decreased financial burden on institutions treating delirious medical in-patients.[12,14,15] In addition, early treatment was seen as an effective means of preventing partial or total damage to brain function and decreasing length of hospital stay.[16,17] Other research confirmed delirium as an independent predictor of outcome.[16,19,20] Future studies were called for to search for a cause of acute cognitive disorders as well as early recognition of risk factors and potential treatment of delirious older patients.[16]

As early as 1986, studies began demonstrating that the DSM-III criteria for delirium could not be utilized adequately to predict whether patients would recover from cognitive impairment.[12,19] In 1987, the APA published the DSM-III-R (revised edition) setting forth additional criteria for delirium. Around this time, authors also started reporting that the symptoms of delirium were less transitory than previously thought and that the adverse outcomes often lasted up to one year post-discharge. In fact, more than one study noted that symptoms persist at time of discharge in many (as high as 95%) of elderly patients who suffer from delirium during hospitalization.[21,22] The studies between 1990 and 2006 largely continued to report on the adverse consequences of delirium among hospital in-patients with respect to increased length of hospital stay, death in hospital, and mortality, institutionalization, cognitive impairment, functional decline and increased need for care after discharge at varying periods (typically during hospitalization as well as at 1 month, 3 months, 6 months, 12 months and 2 years post-discharge).[13,19,20,21–34] Specifically, Murray *et al*. reported that functional decline could be detected 3 months post-discharge and persist at 6 months. Loss of function alone accounted for reduced activities of daily living (ADLs), dependency on caregivers, increased health care needs, nursing home placements and associated costs.[35] The main outcome studies for delirium are summarized in Table 1.

It should be pointed out that several of these studies recognized the limitations of the contemporary instruments and criteria utilized to assess cognitive function, as well as the need to differentiate the various subtypes of delirium to accurately describe the prevalence of outcomes.[19,22,27] Around this time, support for delirium representing a less transient phenomenon gained wider credence.[13,22,23,35]

The influence of diagnostic criteria on outcomes

In 2000, the APA updated the diagnostic criteria for delirium.[39] Utilizing these, studies continued to report adverse outcomes. Studies reporting associated mortality all showed a detrimental effect of delirium even up to 5 years from the index event but by a varying magnitude.[13,19,25,37,41] The need for long-term care following delirium remains a consistent finding in the delirium literature.[2,21,22,26,28,29,33,36,38] Delirium outcomes are studied in the context of confounders such as severity of illness, disability and dementia and would appear to remain an independent predictor of adverse event.[42]

Conversely, many studies continue to report on improvements in outcomes based on early assessment and targeted interventions. Early and targeted interventions can limit the duration of the symptoms of delirium and prevent adverse outcomes.[40,41] Whilst not reaching the same

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Table 1. *Main outcome study results for delirium in terms of risk of functional decline, nursing home placement, dementia and death*[51]

Author(s)	Diagnostic criteria for delirium	Sample size (*n*)	Follow-up	Outcomes (results) for delirious patients
Rabins[11]	DSM-III	73 psychiatric consultations	1 year	Death (>demented patients)
Fields[12]	DSM-III	115	3 months	Long-term cognitive outcome (DSM-III criteria not predictive of cognitive impairment), $P = 0.26$
Thomas[14]	DSM-III	133	Until discharge or death	Length of stay (+13 days, $P = 0.03$)
Rockwood[18]	DSM-III	80	Until discharge	Recurrence of acute confusion during hospitalization, chronicity of confusion (dementia), resolution of confusional state, no increased length of stay ($P = 0.11$), mortality
Koponen[17]	DSM-III	70	1 year	Decline in function (silent delirium MMSE score 3.5 ± 3.9; $n = 8$, mixed or hyperactive delirium MMSE score 11.1 ± 6.8; $n = 35$ and 9.8 ± 5.9; $n = 27$, $P = 0.01$)
Rockwood[16]	DSM-III	80	6 months	Delay in discharge (OR = 18.38, $P = <0.001$)
Francis[19]	DSM-III-R	229	Until discharge and 6 months post-discharge	Length of stay (12.1 days *vs* 7.2 days for control, $P = <0.001$), institutionalization, mortality (6-month mortality 14.3% for delirious *vs* 10.1% from control, $P = 0.1$)
Ramsay[20]	DSM-III-R	119	Until discharge and 10-week follow-up (for mortality)	Mortality (62% in delirious *vs* 14% in non-delirious, $P < 0.001$), length of hospital stay (not significant)
Francis[23]	DSM-III-R	229	2 years	Mortality, loss of independent living, cognitive decline
Levkoff[13]	DSM-III	325	Admission, 3 and 6 months	Mortality (not associated with increased risk, OR 1.3, 95% CI 0.63 to 2.8), increased risk of institutionalization (7-fold increase, OR 7.3, 95% CI 2.6 to 20.5) and increased length of stay (community, adjusted $t = 4.03$, $P = 0.0001$, institutional, adjusted $t = 4.48$, $P = 0.0001$)
Jitapunkul[24]	DSM-III-R	184	Admission through discharge	Mortality (35% among delirious intrahospital *vs* 16% among non-delirious, $P < 0.01$), risk of institutionalization ($n = 2$ for delirious and $n = 3$ for non-delirious, $P < 0.05$), no significant increase in length of stay (median 20 *vs* 16 days for non-delirious)
Murray[21]	DSM-III	325	Discharge, 3 months, 6 months (compared with admission)	Loss of function 3 months after discharge ($P = 0.009$)
Pompei[25]	DSM-III-R	432		Mortality (higher during hospitalization but not after), length of stay (longer when accompanied by acute illness)
Cole[26]	DSM-III-R	88	Enrolment, 1, 2, 4, 8 weeks later. Is this more of an intervention study?	No improvement in cognitive function at 8 weeks for those receiving targeted nursing care. No significant difference between those receiving targeted nursing care and those not on need for restraints, institutionalization, length of stay, mortality

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Table 1. *Continued*

Author(s)	Diagnostic criteria for delirium	Sample size (*n*)	Follow-up	Outcomes (results) for delirious patients
Inouye[2]	CAM	727	Discharge and 3 months follow-up	Discharge: In hospital deaths, not significant (adjusted values unstable and wide CI intervals), length of hospital stay (not achieve statistical significance). 3 month follow-up: Death associated with delirium (OR 1.6, clinical but not statistical significance)
O'Keefe[28]	DSM-III	90	During hospitalization	Mixed delirium most common subtype. Difference found between hypoactive, hyperactive, mixed and no delirium with regard to illness severity ($P < 0.05$), length of stay ($P < 0.005$) and frequency of falls ($P < 0.05$). Mortality rates did not differ between 4 groups
Rockwood[37]	DSM-IV	203 (who survived hospitalization)	3 years (mean 32.5 months)	Delirium an important risk factor for dementia and death. Adjusted hazard ratio for death at follow-up, 1.80 (95% CI 1.11 to 2.92)
Rahkonen[43]	DSM-III-R	51	1 year after discharge to home	Most patients still living at home 1-year after discharge. 20% ($n = 10$) of patients taken into long-term care, 10% ($n = 5$) of patients died. Causes of death were CVD, acute pyelonephritis and cerebrovascular strip
McCusker[29]	DSM-III-R	313	2, 6 and 12 months follow-up after hospital admission	Delirium is an important prognostic factor for functional and cognitive status for at least 12 months after admission. MMSE for delirium only –3.36 (95% CI –6.15 to –0.58, $P = 0.008$). Admission to long-term care by 12 months (OR 1.15, 95% CI 0.33 to 4.05)
McCusker[30]	DSM-III-R	361	2, 6 and 12 months follow-up after hospital admission	Mortality (dementia patients, weak and non-significant effect of delirium; no difference between prevalent and incident delirium; higher for patients with delirium but without dementia, more delirium symptoms)
McCusker[31]	DSM-III-R	359	2, 6 and 12 months follow-up after hospital admission	Length of stay increased for incident delirium (7.78 days, 95% CI 3.07 to 12.48) but not prevalent delirium
Villalpando-Berumen[42]	DSM-III-R	320	In hospital, short-, long-term (up to 5 years after initial delirium event)	Mortality in-hospital (no increase), increased mortality at 5-year follow-up ($P = 0.03$), length of stay longer ($P = 0.02$)
Leslie[33]	DSM-III-R	919 (905 who survived hospitalization)	1-year follow-up	Patients with delirium survived 274 days compared with 321 days for those without delirium (HR 1.62, $P < 0.001$)
Sylvestre[34]	DSM-III-R (CAM)	230	8 weeks (delirium severity), 12 months (survival)	Delirium patients divided into subgroups. Those in 'Worsening' group had largest percentage of death (highest in first 2 weeks, but risk decreased afterward

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Table 1. *Continued*

Author(s)	Diagnostic criteria for delirium	Sample size (*n*)	Follow-up	Outcomes (results) for delirious patients
Andrew[36]	DSM-III-R	77	Short (discharge) or long-term (6 months)	Poor recognition of delirium was associated with death and poor functional recovery. (P <0.0001), risk persisted at 6 months (P <0.0001). Agitated delirium was therefore, protective
Lundstrom[40]	DSM-IV	400	Day 1, 3 and 7 after admission	Effect of intervention programme on length of stay and mortality in delirious patients. Length of stay for delirious patients: on intervention ward *vs* control (10.8 ± 8.3 *vs* 20.5 ± 17.2 days, P <0.001). Mortality: P < 0.03
Adamis[42]	DSM-IV (CAM)	94	Within 3 days of admission, every 3 days after until 18 days, day 28	Delirium is not a transient disorder. Initial MMSE as predictor for mortality (P = 0.002). New discharge to care homes, stayed longer in hospital (P = 0.016)
McAvay[38]	CAM	433	1 year	Delirium at discharge is associated with higher nursing home placement and mortality at 1 year follow-up. For those with delirium at discharge: multivariable adjusted HR 2.64 (95% CI 1.60–4.35) for nursing home placement or mortality
Eeles[41]	DSM-IV	278	5 years	Median time to death for those with delirium was 162 days compared with 1444 days for those without (P <0.001), hospital acquired delirium has worst survival at 88 days (though not statistically significant, P = 0.43); residential or nursing home patient placement higher for first 2 years post-delirium; year 1, 40.5 *vs* 17.6%, P = 0.03; year 2, 33 *vs* 15.1%, P = 0.05)
Travers[48]	DSM-IV	493	During hospitalization	Increased in-hospital mortality: OR 5.19, 95% CI 1.27 to 21.25, OR 31.07, 95% CI 9.30 to 103.78)

level of confidence in the findings as observed with successful preventative strategies, there have been notable gains. One cohort study conducted by Lundstrom *et al*., consisting of a nursing intervention programme, showed a reduction in length of hospital stay, reduction in mortality and shorter duration of delirium.[40,41]

The APA recently reviewed the diagnostic criteria for delirium and the DSM-V was released in May of 2013.[1] The new criteria for diagnosing delirium are:

(A) a disturbance in attention (i.e. reduced ability to direct, focus, sustain and shift attention) and awareness (reduced orientation to the environment).
(B) the disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.
(C) an additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability or perception).
(D) the disturbances in criteria A and C are not better explained by another 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 (i.e. due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple aetiologies.

Our search criteria did not show any studies conducted under these newly released diagnostic criteria for delirium as of 28 February 2014.

Subtypes of delirium

Three subtypes of delirium have been described: hyperactive, hypoactive and mixed.[6] Authors have noted that each subtype probably has its own aetiology and pathophysiology, but this awareness has not translated into operationalization of delirium phenomenology. Authors have found that hypoactive delirium often goes undiagnosed and may contribute to poor outcomes associated with this subtype.[28,36]

Again, these studies called for additional investigations into delirium in order to determine the best method to diagnose delirium, the long-term prognosis and define what interventions are possible to prevent or improve the adverse outcomes reported.[19,22,26]

Causes of adverse outcomes

The inception of DSM-III diagnostic criteria of delirium has yielded extensive reporting of outcomes but our research did not reveal any articles focusing exclusively on the causes of adverse outcomes. In the study of Rabins *et al*., the ineffable causes of death in delirium were matched only by their elusive nature.[11] In a cohort study by Rahkonen *et al*., poor outcomes, in the form of institutionalization in delirium, were associated with multiple other factors: another serious illness, poor home management, repeated falls, depression, or progression of cognitive function.[43] Cardiovascular disorders, acute pyelonephritis and cerebrovascular disorder were associated with mortality.[43] These findings were, however, secondary to the primary objective of understanding delirium aetiology. At the time of writing, no other study appears to focus exclusively on causes of outcomes.

By contrast, complications associated with delirium have been reported. Injurious falls, infections (including aspiration pneumonia), pressure sores, malnutrition, over-sedation and urinary incontinence have been described as more common in delirium.[19,27,28,40,44,45] It is conceivable that each of these complications may contribute independently to adverse outcomes or interact in a multiplicative risk scenario.[46] Several nursing studies have been performed attempting to show that interventions targeted at these complications may reduce adverse outcomes among delirious patients.[40,44] However, it appears that insufficient research has been conducted on the frequency of adverse outcomes resulting from each of these complications in hospitalized delirious patients to allow us to posit whether or not poor outcomes are attributable to complications of delirium or arise from other cause(s) altogether.

Interestingly, studies are again questioning whether the current screening tools are continuing

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to misdiagnose, detect late or miss many cases of medical delirium. Do the shortcomings of the DSM criteria for diagnosing medical delirium continue to result in adverse outcomes? Are new methods for diagnosis needed? In 2014, Bellelli *et al*. suggested that the sensitivity and simplicity of the 4 As Test ('4AT') may help improve outcomes for medical delirium when compared with the DSM-IV-TR criteria, and a number of other ergonomically promising instruments are on the horizon.[4]

As research has progressed and the diagnostic criteria and tools for identifying delirium improved, clarity of reporting on adverse outcomes with delirium has been established. These consequences following delirium are now routinely documented for medical patients, across a multitude of measures. Good medical practice, including early diagnosis and management, may help ameliorate the burden of adverse outcomes. However, the absence of direct evidence to guide an understanding of adverse events is a frustration; as without this, how can treatments be tailored and sophisticated enough for our patients? Longitudinal studies have provided valuable insights into the interrelationship between delirium and dementia.[47] Not only is delirium a risk state for dementia (by an odds ratio of 8.7), but the dementia phenotype is not explained by classical Alzheimer's pathology. Dementia from any sub-type, and certainly not excluding post-delirium dementia, would contribute to the risk of adverse events seen in delirium. Many if not all problems described following delirium might reasonably be shared through the natural history disease of dementia progression. Furthermore, cases of dementia have a prolonged hospital stay. Many of those patients may rightly be termed non-delirious but the nascent dementia and risks it poses in hospital may elevate vulnerability further.

Other possibilities can be considered:

- The sum of numerous complications known to be associated with delirium may be sufficient to drive poor outcomes.
- Impaired communication as part of the delirium syndrome creates obstacles to the identification of patient requirements and their restoration with unmet need a more likely and less obvious predicament.
- The psychopathology incumbent on a diagnosis of delirium poses a barrier to the diagnosis of the condition, its causes and management.
- Delirium itself may represent a global multidimensional risk state, such as advanced frailty, with the inherent risk this poses.
- If a balanced approach to treatment is not assumed then the false paradigm of therapeutic nihilism *versus* the 'breaking of the butterfly upon a wheel'[48] of an aggressive algorithmic approach may threaten further the patient already in a weakened state (comprehensive geriatric assessment offers the best prospect of optimizing outcomes and avoiding such harm from omission or commission).[49,50]
- Delirium is a marker of a failing hospital system in relation to an institution that no longer prioritizes the care of older and vulnerable patients. Not only is delirium more likely, but neglect may prove even more detrimental to outcomes [50]

Further research

Despite the advances made in diagnosing and understanding the causes of delirium, barriers still exist to a fuller appreciation of the causes of poor outcomes. Each of the potential mechanisms for adverse events in delirium proposed requires dedicated study. Quantification of the dementia syndrome post-delirium would add important insights into post-delirium risk and shine a light on the reciprocity between these two conditions. Any study regarding adverse outcomes associated with delirium must also consider more truculent measures: the trajectory of underlying illness, complications, measure global risk states, such as frailty, and explore the interaction between delirium and clinician. Longer-term clinical follow-up is important. Definitive diagnoses, through rigorous clinical, investigative or pathological undertakings are essential. Delirium does not always reveal its secrets in life and so, supplementary post-mortem investigations will also be helpful. Unless such confounders are taken into consideration, important information may be lost from patients who die with, rather than from, delirium. As such, our group intends to conduct further research on specific causes of adverse events associated with delirium in medical patients.

In the final analysis, much has been improved in relation to the quantification of delirium and measurement of the salient clinical end-points. Amidst this change, unfortunately, the aphorism of

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'the more it stays the same' pertains to outcomes. Increased interest in the understanding of outcomes in delirium offers the only real prospect of positive change.

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Conflict of interest

None.

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