Delirium in medical inpatients: adverse outcomes

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Abstract

Introduction

Despite advances in understanding delirium over the past 30 years, adverse outcomes persist. We aim to review the literature pertaining to adverse outcomes, and their causes, associated with delirium in medical inpatients.

Hypothesis

Despite extensive research in delirium to date, delirium patients continue to suffer adverse outcomes. We offer four hypotheses as to why poor outcomes continue to be associated with delirium and propose new areas of research.

Evaluation of hypothesis

Delirium has been associated with institutionalization, increased length of hospital stay, cognitive and functional decline and mortality. Less is known, or even conjectured, in relation to the cause(s) of poor outcomes.

Conclusion

In the evidence gap, we have proposed a number of hypotheses that explore the attrition observed in delirium. These can be understood within the dynamic tension between frailty, emergent illness, triggers, unmet need and survival properties for patients at the limits of redundancy. Further research into the drivers behind poor outcomes is needed.

Introduction

Delirium is defined as an acute disruption of cognition and function in the context of a physiological insult and has been associated with 14%–56% of hospitalized older patients1-5. The importance of studying delirium in medical inpatients has largely been recognized over the past 30 years. Failure to properly diagnose and treat delirium appropriately results in significant morbidity and mortality with attendant healthcare costs6. The incidence of delirium during hospitalization has even been recognized as a sign of the quality of hospital care7.

This paper will review the literature from 1981, representing the first published diagnostic criteria in delirium8, until the present. Adverse outcomes, and their causes, associated with medical inpatients diagnosed with delirium have been examined. Three recent systemic reviews were utilized to determine if any studies reporting on morbidity and mortality associated with delirium also reported on causes of adverse outcomes6,9,10.

While delirium or acute confusional state has been described since Hippocrates9, it was not until the early 1980s that the American Psychiatric Association set forth criteria for diagnosing delirium as a unique psychiatric disorder in the Diagnostic and Statistical Manual of Mental Disorders version three (DSM-III)9. Studies conducted since that time have largely reported whether delirium among hospital inpatients was associated with 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, 3, 6, 12 months and 2 years post-discharge)11-20.

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 outcomes12,14,19. Three subtypes of delirium have been described, hyperactive, hypoactive and mixed.9 Authors have noted that each subtype likely has its own aetiology and pathophysiology, but this awareness has not translated into operationalization of delirium phenomenology19,23.

Furthermore, authors are using the DSM-IV diagnostic criteria for delirium and looking at adverse outcomes from delirium at extended lengths of time, up to 5 years5. Currently, the APA is reviewing the diagnostic criteria for delirium as the DSM-V is set to be released in May 201322.

Most studies report an increase in mortality associated with delirium and additional adverse consequences extending to survivors (Table 1). Survival remains poor even after adjusting for multiple confounders including illness severity, disability and dementia2. Delirium is no longer seen as transitory.11,13-25 In fact, Murray et al.13 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, dependency on caregivers, increased health-care needs, nursing home placements and associated costs.13 Delirium has been consistently shown to be associated with an increased risk of cognitive decline and dementia (as dementia is also a risk factor for delirium)14,15,20. No consensus was seen between the three subtypes with regard to mortality. However, some studies have reported that hypoactive delirium
Table 1  Previous studies reporting outcomes following delirium with summarized findings

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Diagnostic criteria for delirium</th>
<th>Sample size (n)</th>
<th>Follow-up</th>
<th>Outcomes (results) for delirious patients</th>
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<tr>
<td>Rabins26</td>
<td>DSM-III</td>
<td>73 psychiatric consultations</td>
<td>1 year</td>
<td>Death (&gt;demented patients)</td>
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<td>Fields35</td>
<td>DSM-III</td>
<td>115</td>
<td>3 months</td>
<td>Long-term cognitive outcome (DSM-III criteria not predictive of cognitive impairment)</td>
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<td>Thomas36</td>
<td>DSM-III</td>
<td>133</td>
<td>Until discharge or death</td>
<td>Length of stay (+13 days)</td>
</tr>
<tr>
<td>Rockwood17</td>
<td>DSM-III</td>
<td>80</td>
<td>Until discharge</td>
<td>Recurrence of acute confusion during hospitalization, chronicity of confusion (dementia), resolution of confusional state, increased length of stay, mortality</td>
</tr>
<tr>
<td>Koponen38</td>
<td>DSM-III</td>
<td>70</td>
<td>1 year</td>
<td>Decline in function</td>
</tr>
<tr>
<td>Rockwood19</td>
<td>DSM-III</td>
<td>80</td>
<td>6 months</td>
<td>Delay in discharge</td>
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<tr>
<td>Francis49</td>
<td>DSM-III-R</td>
<td>229</td>
<td>Until discharge and 6 months post-discharge</td>
<td>Length of stay, institutionalization, mortality</td>
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<td>Ramsay51</td>
<td>DSM-III-R</td>
<td>119</td>
<td>Until discharge and 10-week follow-up (for mortality)</td>
<td>Mortality (&gt;in delirious), length of hospital stay (&gt;in delirious)</td>
</tr>
<tr>
<td>Francis15</td>
<td>DSM-III-R</td>
<td>229</td>
<td>2 years</td>
<td>Mortality, loss of independent living, cognitive decline</td>
</tr>
<tr>
<td>Levkoff11</td>
<td>DSM-III</td>
<td>325</td>
<td>Admission, 3 and 6 months</td>
<td>Mortality (higher), risk of institutionalization (greater), length of stay (increased)</td>
</tr>
<tr>
<td>Jitapunkul42</td>
<td>DSM-III-R</td>
<td>184</td>
<td>Admission through discharge</td>
<td>Mortality (increased), risk of institutionalization (greater), length of stay (no difference)</td>
</tr>
<tr>
<td>Murray13</td>
<td>DSM-III</td>
<td>325</td>
<td>Discharge, 3 months, 6 months (as compared to admission)</td>
<td>Loss of physical function (ADLs)</td>
</tr>
<tr>
<td>Rockwood14</td>
<td>DSM-III and DSM-III-R</td>
<td>168 patients + 5 with delirium</td>
<td>Until discharge or until outcome occurred</td>
<td>Persistence of symptoms (48%), length of stay</td>
</tr>
<tr>
<td>Pompei16</td>
<td>DSM-III-R</td>
<td>432</td>
<td></td>
<td>Mortality (higher during hospitalization but not after), length of stay (longer when accompanied by acute illness)</td>
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<tr>
<td>Cole17</td>
<td>DSM-III-R</td>
<td>88</td>
<td>Enrolment, 1, 2, 4, 8 weeks later Is this more of an intervention study?</td>
<td>Impact of targeted nursing care on cognitive impairment, need for restraints, institutionalization, length of stay, mortality (impact small)</td>
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<tr>
<td>Inouye3</td>
<td>CAM</td>
<td>727</td>
<td>Discharge and 3 months follow-up</td>
<td>New nursing home placement, functional decline (both significant at discharge and at 3 months), mortality (not statistically significant)</td>
</tr>
<tr>
<td>O’Keefe19</td>
<td>DSM-III</td>
<td>90</td>
<td>During hospitalization</td>
<td>Mixed delirium most common subtype. Mortality (no difference between subtypes), illness severity, length of stay (prolonged for those with hypoactive as compared to other subtypes), falls and hospital acquired infections (more common in hyperactive delirium), hypoactive patients more likely to develop pressure sores</td>
</tr>
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</table>
is often associated with worse outcomes, as this subtype often goes unrecognized\(^\text{19,23}\). Despite extensive research on outcomes in the 30 years since the adoption of the DSM-III diagnostic criteria of delirium, our research did not reveal any articles focusing exclusively on causes of adverse outcomes for medical inpatients suffering from delirium. In Rabins et al.\(^\text{26}\), the authors recognized as one of their study’s limitations the failure to address the issue of cause of death. In a study cohort by Rahkonen et al.\(^\text{24}\), institutionalization in delirium was associated with another serious illness, poor home management, repeated falls, depression or progression of cognitive function. Mortality was caused by cardiovascular

<table>
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<th>Table 1 (continued)</th>
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<tr>
<td>Rockwood(^\text{43})</td>
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<tr>
<td>Rahkonen(^\text{24})</td>
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<tr>
<td>McCusker(^\text{20})</td>
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<tr>
<td>McCusker(^\text{44})</td>
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<td>McCusker(^\text{45})</td>
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<td>Villalpan-do-Berumen(^\text{46})</td>
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<td>Leslie(^\text{47})</td>
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<td>Sylvestre(^\text{48})</td>
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<tr>
<td>Andrew(^\text{23})</td>
</tr>
<tr>
<td>Lundstrom(^\text{21})</td>
</tr>
<tr>
<td>Adamis(^\text{2})</td>
</tr>
<tr>
<td>McAvay(^\text{3})</td>
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<td>Eeles(^\text{3})</td>
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disorders, acute pyelonephritis and cerebrovascular disorder. This study did not, however, focus on causes of outcomes but rather etiology of delirium itself. No other study appears to focus exclusively on the cause of adverse outcomes.

Authors have, however, reported on various complications that are associated with delirium. For example, falls with injury, infections (including aspiration pneumonia), pressure sores, malnutrition, oversedation and urinary incontinence have been reported as more common in delirium. Each of these complications may contribute independently to adverse outcomes. Take, for example, falls as a complication of hospitalized elderly patients. Falls have long been known to increase mortality among hospitalized elderly patients. O’Keefe reported that patients suffering from delirium are more likely to suffer a fall than non-delirious patients. However, it appears 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 directly attributable to complications of delirium or arise from other cause(s) altogether.

Hypothesis
What has been conclusively and repeatedly described, regardless of the measure used, is that poor outcomes are associated with delirium. While it is not entirely clear why adverse outcomes from delirium continue, a number of mechanisms can be hypothesized:

- Adverse outcomes may result from the sum of complications known to be associated with delirium. For instance, falls, injury, lack of awareness of thirst, dehydration and pressure sores. As discussed, however, insufficient research has been conducted to conclude that such complications alone can account for delirium’s adverse outcomes.
- Difficulties in patient communication during delirious episodes create obstacles to delivery of care. This may result in a delirious patient being unable to articulate their primary wishes (such as requiring toileting) with a behavioural change being an expression of unmet need. Health-care practitioners may inadvertently misread these signals and provide treatments to allay ‘aberrant’ behaviour. A cycle of misidentification–mistreatment often follows. Failure of patients to express illness in classical presentations (most notably in hypoactive delirium) may exacerbate this trend with the underlying diagnosis unnoticed and therefore untreated. Often it would seem that patients with delirium die with, and not from, the condition. Many, if not most, patients in the terminal stages of an illness will develop a delirium. However, overrepresentation of this cohort of patients in the reported literature may have biased outcomes unfavourably.
- Delirium itself may be a harbinger of undiagnosed but significant clinical problems, such as frailty, which may propagate poor outcomes in their own right. Frailty has been used as an argument against identifying and treating potentially reversible conditions. Conversely, a philosophy of ‘breaking the butterfly upon a wheel may sometimes be observed’ (Representative Poetry Online - Alexander Pope: Epistles to Several Persons: Epistle to Dr. Arbuthnot: complete poem and commentary) with regards to onerous tests and therapies. Both attitudes may propagate poor outcomes.

Evaluation of hypothesis
The authors have referenced some of their own studies in this hypothesis. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Another way of attempting to understand adverse outcomes is to consider delirium in the context of the fundamental properties represented by the delirious state; a disturbance of consciousness. In this respect, delirium is a manifestation of complex system failure in keeping with other geriatric syndromes. When complex systems fail they do so with the highest order function first, namely consciousness. Consciousness embodies all thoughts embraced whilst awake and aware. As previously argued, disturbance of consciousness is integral to delirium. Not least, consciousness must be implicated because every realm of human thought or behaviour has been tarnished in some way during an episode of delirium.

Complex systems fail once redundancy is exhausted. The reliability theory of ageing states that the properties of failure mechanics also change at the limits of redundancy (when the system is on the brink of failure). At this point, the individual is no longer able to tolerate further deficits (Figure 1) with the insinuation that system collapse or death ensues. The rate of death follows the pattern of susceptibility to any random external event. The patient with delirium and exhausted redundancy (through juxtaposition of frailty, morbidity, illness severity) is highly vulnerable to succumb through stochastic extrinsic events (e.g. infection) that may otherwise be survivable.

Empirical data
The disturbance of consciousness imparts an additional intrinsic–extrinsic interaction that may even
increase the likelihood of death from a myriad of additional causes previously mentioned (poor communication with medical staff, the complications of their delirium and the underlying condition). The kinetics of failure dictates that patients with delirium have a survival rate in keeping with other terminal conditions. Evidence in support of this argument is provided in the adapted survival curves (Figure 1).32.

Consequences of Hypotheses
This data also provides an insight into the potential scope of management interventions on outcome in delirium. It is shown that survival is negatively impacted by delirium. Within the delirium group, mortality is highest amongst those who are also frail (median survival only 88 days). If the survival difference between fitness and frailty for patients with delirium represents the parameters within which management strategies might modify outcomes then this equates to a potential median difference of 271 days. There are numerous assumptions implicit in this argument including that the impact of fitness equates to medical interventions in delirium. Nevertheless, this may serve to illustrate the theoretical magnitude and potential limitations to even successful interventions in delirium management.

Discussion
Delirium imposes a burdensome health (economic and societal) toll that extends across function, institutionalization, mortality and risk of dementia. Despite the advances made in the understanding of outcomes in delirium, barriers still exist in the appreciation of the driving forces for attrition. Only through an understanding of why outcomes in delirium are so poor can the foundation for development of targeted management interventions be developed. Perhaps, this is why management strategies have gained limited ground thus far as they have been modelled on otherwise successful preventative strategies. Intervention strategies may indeed improve post-delirium outcomes34, but there remains no consensus21,32.

We have proposed a number of hypotheses that provide possible mechanisms for continued adverse events in delirium. These can be understood within the dynamic tension between frailty, emergent illness, triggers and survival properties for patients at the limits of redundancy. The physician and their multidisciplinary team may have an important role in modulating this effect. The patient without redundancy at the mercy of the next random adverse event has limited self or environmental awareness and self-agency. Hospital processes designed to serve a cognitively intact individual with efficiency and effectiveness often fail even to detect delirium. If delirium passes unobserved then unmet need is the consequence. Even if recognized, a disproportionate approach to management of delirium, from neglect to iatrogenesis, may result in a cascade of complications. Improved recognition and management of delirium may yet be attainable with the application of good geriatric principles.

Conclusion
Further research into the drivers of poor outcomes is needed and the findings used to develop management strategies in delirium. Future studies must also capture the trajectory of underlying illness, complications and explore how clinical decision-making is modified by delirium. Until we are thus enlightened then it is 'not in our stars, but in ourselves,' and our medical culture that holds the destiny of patients with delirium (Play Script—Text—William Shakespeare: Julius Caesar. Script of Julius Caesar a play by William Shakespeare).
Acknowledgment
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References