Journal Pre-proofs

Recognition, Prevention, and Treatment of Delirium in Emergency Department: An Evidence-Based Narrative Review

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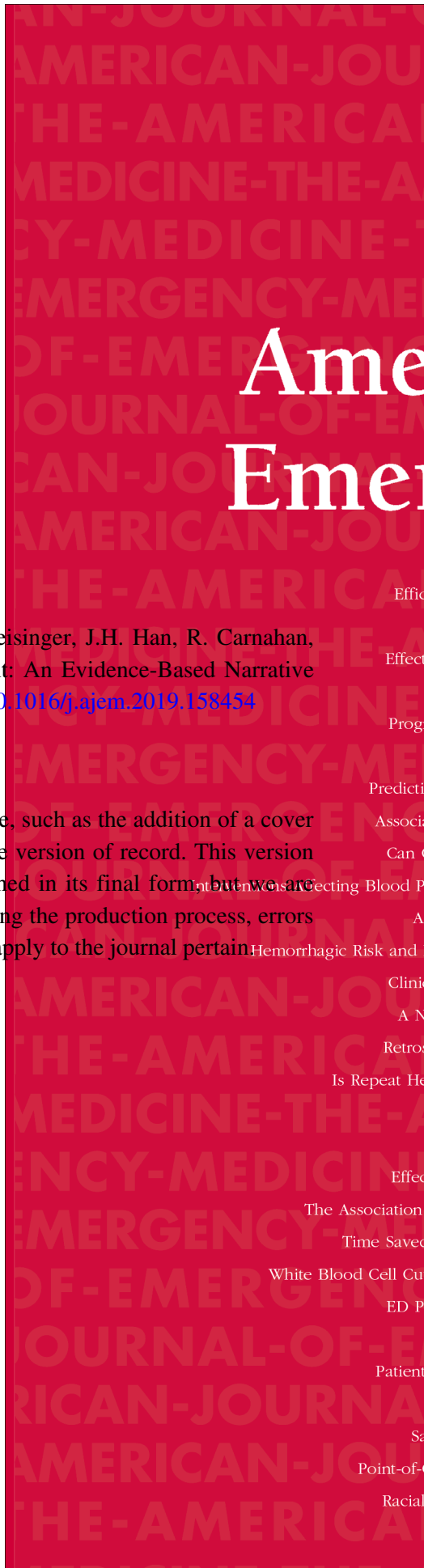
PII: S0735-6757(19)30603-5
DOI: https://doi.org/10.1016/j.ajem.2019.158454
Reference: YAJEM 158454

To appear in: *American Journal of Emergency Medicine*

Received Date: 23 August 2019
Revised Date: 13 September 2019
Accepted Date: 16 September 2019

Please cite this article as: S. Lee, M. Gottlieb, P. Mulhausen, J. Wilbur, H. Reisinger, J.H. Han, R. Carnahan, Recognition, Prevention, and Treatment of Delirium in Emergency Department: An Evidence-Based Narrative Review, *American Journal of Emergency Medicine* (2019), doi: https://doi.org/10.1016/j.ajem.2019.158454



Abstract

Background:

Delirium is an acute disorder of attention and cognition that is common, serious, costly, under-recognized, and potentially fatal. Delirium is particularly problematic in the emergency department (ED) care of medically complex older adults, who are being seen in greater numbers.

Objective:

This evidence-based narrative review focuses on the key components of delirium screening, prevention, and treatment.

Discussion:

The recognition of delirium requires a systematic approach rather than a clinical gestalt alone. Several delirium assessment tools with high sensitivity and specificity, such as delirium triage screen and brief Confusion Assessment Method, can be used in the ED. The prevention of delirium requires environmental modification and unique geriatric care strategies tailored to the ED. The key approaches to treatment include the removal of the precipitating etiology, re-orientation, hydration, and early mobilization. Treatment of delirium requires a multifaceted and comprehensive care plan, as there is limited evidence for significant benefit with pharmacological agents.

Conclusion:

Older ED patients are at high risk for current or subsequent development of delirium, and a focused screening, prevention, and intervention for those who are at risk for delirium and its associated complications are the important next steps.

Key words: Delirium, Emergency Department, Prevention, Treatment

1. Introduction

Delirium is an acute global brain dysfunction that is highly prevalent in acute care settings.[1,2] The frequency of delirium in the emergency department (ED) is reported to be 10% to 13% among older patients and increases to 22% to 42% in the inpatient setting.[3-6] Among patients with delirium, the overall mortality rate is increased threefold and is comparable to patients with myocardial infarction or sepsis.[7] Delirium is also associated with prolonged hospital stays, subsequent functional and cognitive decline, increased risk of falls, and a higher likelihood of skilled nursing facility placement.[7-10] Moreover, delirium can lead to long-term cognitive deficits even after the recovery from the acute illness.[11,12] The national burden of delirium on the United States healthcare system ranges from $38 billion to $152 billion each year.[13] The pre-hospital setting is another care environment where emergency medical service and law enforcement encounter patients with delirium and associated safety issues related to agitation during transfer.[14] Delirium is challenging to diagnose in the ED, with up to 80% of diagnoses being missed in the ED setting[15] With 57% of hospitalizations for older adults entering through ED, it is essential for emergency clinicians to understand how to screen, prevent, and treat patients with delirium.[16,17]

2. Methods

We searched PubMed and reference lists from relevant original research articles and systematic reviews using the terms “delirium”, “encephalopathy” and “organic brain syndrome” for articles published in English from 1996 to June 2019. Non-human studies, case reports, and case series were not included. We also hand-searched conference proceedings and relevant journals. As this was intended as a narrative review, we did not perform a meta-analysis on the data. A total of 117 articles was included in this review based on relevance as determined by the authors. (Figure 1)

3. Pathophysiology

3.1. Delirium Definition

Diagnostic criteria for delirium have evolved over time to indicate generalized brain dysfunction occurring in the different clinical settings. The core features included in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria are A) Disturbance in attention and awareness, B) Develops over a short period of time, C) Additional disturbance in cognition, D) Attention and cognition are not from a pre-existing or evolving neurocognitive disorder, and not from severely reduced arousal (coma).[18] The DSM-5 is viewed as somewhat more restrictive than compared with previous DSM editions as it states these conditions do not occur in the context of a severely reduced level of arousal.[19,20] Some have advocated for a more inclusive interpretation of Criteria A and D, and to consider those who are unable to engage in cognitive testing as being inattentive.[21]

3.2. Clinical Phenotypes

Delirium is a heterogeneous syndrome and has multiple phenotypes. Delirium is frequently phenotyped by psychomotor activity: hypoactive, hyperactive, and mixed. Hyperactive delirium is characterized by motor agitation, restlessness, and sometimes aggressiveness. Hypoactive delirium is characterized by motor retardation, apathy, slowing of speech, and patients can appear to be sedated. Mixed delirium is a combination of hyperactive and hypoactive delirium. Hypoactive delirium is the most common subtype and easier to miss because of its subtle clinical presentation.[22] The spectrum of hyperactive delirium includes excited delirium syndrome (ExDS), which has traditionally been used in the forensic literature to describe findings in a subgroup of patients with delirium who suffered lethal consequences from their untreated severe agitated behaviors.[23] Hypoactive carries the worst prognosis and has been associated with poorer in-hospital and long-term mortality.[24,25]

4. Diagnosis

4.1. Clinical Assessment Tools

ED healthcare providers miss delirium in 67% to 76% of cases.[22,26] A chief complaint of “altered mental status” is 98.9% specific for delirium but only 38% sensitive, making this insufficient for delirium

monitoring.[21] Therefore, delirium must be actively looked for using a delirium assessment. The Confusion Assessment Method (CAM) is the most widely studied delirium assessment and was derived from the DSM criteria.[27] It includes evaluation of four features: 1) altered mental status and fluctuating course, 2) inattention, 3) disorganized thinking and 4) altered level of consciousness.[27] For a patient to meet criteria for delirium, both features 1 and 2, and either 3 or 4 must be present. Based upon a meta-analysis of 12 studies, the CAM's sensitivity and specificity are 86% and 93%, respectively.[28] Because the CAM's features are subjectively determined by clinical observation, it is operator dependent and requires extensive training. Its diagnostic performance may be lower in raters with limited training or clinical experience.[28] It can also take 5 minutes to perform which may not be feasible for the busy ED environment.[28]

Given the limitations of the above screening strategies in the emergency setting, newer brief screening instruments have been developed, such as Single Question in Delirium (SQiD), ultra-brief two-item bedside test for delirium (UB-2), and delirium triage screen (DTS) (Table 1, 2).[29-31] Each of these tools have sensitivities above 90% and can be administered within 60 seconds.[29-32] Due to their limited specificities, which range from 49.6%-59.9%, positive screens will need additional assessment. Other instruments such as the CAM, 3D-CAM, CAM-ICU, brief CAM (bCAM), or 4AT can be used for further evaluation.[31] The bCAM is based upon the CAM algorithm and incorporates objective testing to make it easier to use by inexperienced users. This assessment was specifically designed for the ED. It takes approximately 1 to 2 minutes to complete, and has moderate sensitivity (65% to 84%) and excellent specificity (91% to 96%) for delirium in acutely ill older adults.[6,31,33] One potential reason for the bCAM's moderate sensitivity was the low proportion of patients who were positive for altered level of consciousness,[6,33] which can be missed without adequate training.[26]

A 3-minute diagnostic assessment for CAM-defined delirium (3D-CAM) was developed to overcome the significant time required to administer a full CAM assessment. 3D-CAM has a sensitivity of 95% and specificity of 94% for delirium in acutely older patients, but still takes more than 3 minutes and requires

formal training.[34] Additionally, it has not been validated in older ED patients. The combination of UB-2 and 3D-CAM is currently being validated, and its utility will need to be examined.[30] The 4 A's Test (4AT) is another cognitive assessment that can be used to identify delirium and cognitive impairment and takes 2 minutes to perform. It has excellent sensitivity (87% to 93%) and moderately good specificity (70% to 91%) for delirium in acutely ill older adults. [33,35,36] The 4AT is an easy to use instrument that does not require extensive training to apply, but uses cutoff score to diagnose delirium and cognitive impairment.[36-39] One example of assessment in the ED is to combine a concise instrument with high sensitivity and another tool with more specificity, as suggested by the geriatric ED guidelines (Figure 2).

4.2. Underlying Etiology

When a patient meets criteria for delirium in the ED, the ED's primary role is to find the underlying etiology. A clinician should conduct a comprehensive assessment to identify an etiology of delirium. Because delirious patients may not be able to provide an accurate history, obtaining historical information from the patient, emergency medical service (EMS), caregivers and family is crucial. Because adverse drug reactions are a common cause of delirium, the patient's medication list, including non-prescription medications and supplements, should be confirmed. The physical examination should be thorough and include a review of the vital signs. A point-of-care blood glucose measurement is essential and other lab work and imaging studies should be obtained as indicated. Since delirium is characterized by global brain dysfunction, its etiologies are vast. Table 3 includes a list of potential etiologies that providers should consider in patients presenting with delirium.[40] We emphasize that 1) almost any illness can precipitate delirium, 2) patient vulnerability to delirium should be considered, for example, someone may be more prone to delirium with a severe illness when they have pre-existing cognitive impairment, other comorbidities, or take certain medications, 3) most cases of delirium have more than one etiology, and 4) a clinician should not anchor on a urinary tract infection as the cause for delirium, as many older adults may have pyuria as baseline and it may not the cause of delirium.[41]

5. Delirium Treatment

5.1. Non-pharmacological

To date, there is no ED-specific treatment for delirium. Several studies demonstrate effective non-pharmacological approaches to treating delirium in the inpatient setting. For example, Pitalka et al. studied comprehensive geriatric assessments coupled with non-pharmacologic interventions and avoidance of antipsychotics, and demonstrated improved health related quality of life and faster alleviation of delirium. The diversity and multicomponent nature of non-pharmacologic interventions studied to manage delirium makes it difficult to draw conclusions about the efficacy of specific strategies.[42-44]

Nevertheless, non-pharmacological treatments are recommended as the first-line interventions for patients with delirium. They are low-risk and consistent with standards for quality care. These include re-orientation, behavioral intervention, hydration, and ensuring hearing and vision competency. Caregivers should communicate using clear instructions and frequent eye contact. Ready access to hydration and assistance from both medical staff and caregivers is recommended, as a previous study has demonstrated a reduction in the incidence of agitation.[45]

Agitation in delirium is rare, but when a patient experiences agitated behavior, verbal de-escalation is recommended before physical or chemical restraints.[46] If physical restraints are indicated, it is important to monitor the patient closely, and document and remove the restraints as soon as feasible.[47] Nearly half of medical professionals in one study experienced work-related violence during their career, but received limited training for the care of agitated patients.[48-51] Thus, it is imperative for ED staff to receive proper training in the care of agitated patients, which could improve treatment of patients with delirium.

5.2. Pharmacological

5.2.1. General Considerations

Drug treatment for delirium has been extensively studied. Since there are no robust mortality or long-term benefits, the goal of pharmacological therapy should be to control agitation and calm the patient, while

avoiding oversedation.[52] In specific circumstances, such as agitation, they may have a role in the treatment, but this is usually in the minority. Whenever possible, the oral route is preferred over injections to minimize discomfort of injection, subsequent agitation and arrhythmia.[53]

5.2.2. Benzodiazepines

Benzodiazepines act as positive allosteric modulators on the gamma aminobutyric acid (GABA)-A receptor. Evidence on benzodiazepine use in delirium not related to sedative withdrawal is limited, but these drugs can worsen delirium and are generally not recommended for management of agitation in delirium. One Randomized Controlled Trial (RCT)[54] and two partially-controlled trials assessing the impact of benzodiazepines[55,56] demonstrated that there is no clear benefit and potential harm to increase the risk of delirium in ventilated patients. In general, benzodiazepines should be avoided except for selected indications such as alcohol withdrawal.[57-59]

5.2.3. Typical Antipsychotics

Haloperidol is a first-generation antipsychotic commonly utilized to treat agitated patients. It is a typical, butyrophenone-type antipsychotic with a high affinity for D2 receptors in the brain.[60] The mean time to sedation is 25 to 28 minutes, with a mean total sedation time of 84 to 126 minutes.[61,62] In a study of palliative care patients, the use of haloperidol for delirium did not demonstrate a significant reduction in delirium severity but was associated with increased mortality.[63] Among postoperative patients, one study found that haloperidol reduced the severity and duration of delirium.[64] A study among patients with acquired immunodeficiency syndrome (AIDS) showed modest reduction in delirium severity with haloperidol, [55] while another study showed a reduction in delirium severity.[65] However, none of these studies showed an improvement in delirium resolution or mortality, and a recent Cochrane review concluded that the use of the antipsychotics did not show strong evidence of treatment effects outside of the intensive care unit.[66]

5.2.4. Second Generation Antipsychotics

The use of typical antipsychotics has been questioned due to a high prevalence of extrapyramidal symptoms, prompting consideration of second-generation antipsychotics.[60,67-69] Second-generation antipsychotics have been reported to have a lower risk of extrapyramidal side effects than typical antipsychotics when used for delirium, but these comparisons were being made against relatively high doses of haloperidol.[70,71] Olanzapine had a faster response time for delirium compared to haloperidol, and low-dose olanzapine was well-tolerated among delirious patients in various settings.[65,72,73] A study on intravenous olanzapine showed a very low rate of akathisia and QTc prolongation on electrocardiogram, with no difference between the intravenous or intramuscular route among ED patients.[74,75] As such, in those rare circumstances in which an antipsychotic may be indicated, olanzapine may be a reasonable alternative for patients who cannot tolerate haloperidol. Olanzapine does have anticholinergic effects, however, which could worsen confusion in some patients. Quetiapine has also been studied in several trials and is generally preferred among patients with a high risk of extrapyramidal symptoms (e.g. Parkinson's disease, Lewy body dementia), though it is important to be aware of its anticholinergic effects. [76-78] Studies have found that quetiapine is comparable to haloperidol for the treatment of delirium. [76-78] Risperidone is another atypical antipsychotic agent which is available in liquid form and was effective for the management of agitated behaviors among patients with delirium in both the emergency department and inpatient setting.[79-82] A recent multi-center RCT comparing haloperidol versus ziprasidone in the ICU setting showed no significant difference in the duration of delirium symptoms.[83]

5.2.5. Ketamine

Ketamine is a dissociative sedative that interacts with a series of receptors, including N-methyl-D-aspartate, nitric oxide synthase, and multiple opioid receptors. It has a rapid onset of action, 2–3 minutes, and lasts 20–30 minutes.[84,85] Ketamine (4–5 mg/kg IM) with and without midazolam (to prevent emergence reactions) was tested in the pre-hospital setting for agitated delirium syndrome. In this study, ketamine achieved rapid and safe sedation to enable a safe transfer for emergency medical services.[86] The use of ketamine in the ED was also tested, and an observational study found more rapid improvement of

agitation compared to midazolam or haloperidol.[87] However, there is limited information available on the safety and efficacy of ketamine in older adults with agitation.[88]

5.2.6. Pharmacological Agents at Glance

Pharmacological agents to treat symptoms of delirium need to be adjusted for older adults to minimize risk of adverse effects. We list these recommendations in Table 4. It is important to note that many of these agents were tested for agitated patients, and not all are specific to those with delirium.

5.3. Delirium Care Bundles

There are two evidence-based care bundles focused on delirium prevention and management: the Hospital Elder Life Program (HELP) and the ABCDEF bundle[89,90] The HELP program focuses on a multicomponent intervention strategy and mobilizes a multidisciplinary team that includes a geriatric nurse specialist, elder life specialists, trained volunteers, and geriatricians (Table 5)[89] The HELP program (Table 5) reduced episodes of delirium for geriatric inpatients, but the program is also resource intensive and requires multiple geriatric specialists[91,92] It is more likely that a care bundle in the ED can adapt part of the six components from the HELP program, such as reducing sleep deprivation while patients are staying in the ED, correcting vision and hearing with environmental adjustment and aids, providing hydration and early mobilization. A newer meta-analysis pooling the results of non-pharmacological multicomponent prevention interventions[93,94] concluded that the number needed to treat (NNT) was 14 to prevent delirium.[95] The ABCDEF bundle was developed for mechanically ventilated patients in the ICU setting and adheres to pain, agitation, and delirium guidelines.[96] The use of the ABCDEF care bundle resulted in an increase in delirium-free days.[90,97,98] However, it has some components that may not be relevant to ED care (e.g. the use of spontaneous awakening and breathing trials). It is imperative to assess which components of the care bundle are feasible and effective in the ED setting.

6. Delirium Prevention

An estimated 30% to 40% of delirium cases are preventable, thus making prevention the most effective strategy for minimizing the occurrence of delirium and related adverse outcomes after hospitalization or discharge.[99] Some studies suggest that increased ED length of stay may increase the risk of incident delirium.[100,101] This implies that avoiding ED boarding time may be a vital delirium prevention strategy.

A study of an inpatient unit found that family members could contribute to delirium prevention by assisting in orientation and participating in the multimodal intervention program as a part of care team.[102] Other non-pharmacological prevention strategies are summarized in the delirium care bundles (Table 5).

Pharmacological agents are a common precipitant of delirium. Prevention strategies to minimize the risk of drugs as a precipitant of delirium are relevant for the ED. These include performing medication reconciliation; avoiding polypharmacy; minimizing use of anticholinergics, benzodiazepines, sleep aids, and metoclopramide whenever possible; using the lowest effective dose of corticosteroids or opioids; assessing for potential dehydration or electrolyte abnormalities in patients receiving diuretics; and monitoring for medication withdrawal syndromes.[103-105]

The prescription of high-risk medications defined by the Beers list is common in the ED.[106] Common medications that can contribute directly to cognitive impairment include sedatives and drugs with anticholinergic properties (e.g., first-generation antihistamines, tricyclic antidepressants, bladder antispasmodics). These drugs should be avoided when possible, especially when less risky alternatives are available. Thus, a routine medication review for these medications is recommended. The use of antipsychotics and other medications for delirium prevention in high-risk patients has been studied in a variety of settings with mixed results.[107-110] Schrijver et al. studied the use of prophylactic haloperidol in ED patients who were at high risk of delirium, but did not find any reduction in hospitalization rates.[111] The current evidence as a whole is not adequate to support pharmacologic prevention strategies as a standard of care.

7. Future Directions

The long-term cognitive deficits experienced by patients after recovery from illness and delirium is an active area of research.[9] Electroencephalography is another modality to identify the pathognomonic slow wave activity seen during encephalopathy.[112,113] Machine learning can identify the high-risk population for delirium, using clinical data from electronic health records to enable automated risk estimation for each patient, and it is important to explore its risk prediction characteristics compared with the conventional risk assessment tools.[114] Dexmedetomidine is a sedative agent frequently used in the ICU, and multicenter RCT studies and meta-analyses showed a lower risk of causing delirium compared to midazolam.[115,116] It is not used in the ED, and its utility needs further clarification. Effective caregiver engagement in the ED and transitions of care to and from the ED are also important strategies to explore in the prevention of delirium.

8. Conclusion

Older ED patients are at high risk for current or subsequent development of delirium, and because of the rate of misdiagnosis and mortality, they benefit from a focused evaluation process involving a routine delirium assessment in the ED.[7,15] Active screening, prevention, and intervention for those who are at risk for delirium and its associated complications are the next steps needed to improve care for older adults under our care and beyond.

Acknowledgments

None.

Conflicts of interest

None.

Funding

Dr. Lee and Dr. Carnahan were supported by a Health Resources and Services Administration Geriatric Workforce Enhancement Program Award, U1QHP28731.

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