Tackling delirium: a crucial target for improving clinical outcomes

Abstract

Delirium is a common and debilitating syndrome in hospitalised patients, and its impact on mortality, morbidity and duration of hospital admission is increasingly apparent. Delirium is a complex phenomenon, for which there is no specific treatment, but research over the last decade has revealed contributing factors, many of which are modifiable, and preventative strategies have demonstrated benefit. This review highlights the importance of reducing the impact of delirium on hospitalised patients, and summarises the current evidence for strategies to achieve this. Current recommendations focus on the pre-emptive implementation of multi-modal non-pharmacological interventions to reduce the occurrence of delirium in the first place, and routine monitoring using validated tools to identify delirious patients early. Potential therapies for established delirium remain controversial.

Key points:

- Delirium is associated with a higher mortality, morbidity and longer stays in hospital, with negative impact on quality of life long after discharge.

- Delirium is grossly underdiagnosed, and must be screened for daily in hospital patients

- Multicomponent, non-pharmacological interventions have proven effective in decreasing the occurrence of delirium.

- Evidence for the benefit of pharmacological approaches to delirium prevention or treatment remain limited.

Introduction

Delirium is a common affliction, its presence detected in approximately one fifth of general hospital inpatients [1], and its incidence increasing to 30% in the elderly [2] and 80% of the critically unwell [3]. Perhaps because of its ubiquity, it is easy to dismiss as merely an unavoidable consequence of illness, but delirium is independently associated with increased mortality, as well as longer stays in hospital, and on the intensive care unit [4]. Each additional day of delirium is associated with an average of 10 extra days in hospital and a 10% increased risk of death, with an association of long-term cognitive impairment [5]. MRI has shown an association between the duration of delirium and cerebral atrophy and white matter disruption [6].

Various theories have been proposed to describe the pathophysiology underlying delirium, including cerebral inflammation altering the blood-brain-barrier and changes in neurotransmitter levels, such as reduced cholinergic activity or increased catecholamine serotonergic activity [7]. More recently, it has been proposed that the features of delirium may be a clinical manifestation of circadian rhythm disruption [8]. Both illness and the hospital environment itself disrupt the usual 24 hour cycles that govern human behaviour (such as sleeping, waking, eating and physical activity), physiological indices (temperature, heart rate, urine output) and intracellular processes (gene expression, enzyme activity and mitochondrial function) [9]. The circadian oscillation in these diverse functions is synchronised to the time of day, through the light-dark cycle and other cues such as regular feeding times. One of the early signs of

delirium is inversion of the sleep-wake cycle, and this has led to the hypothesis that delirium may represent the observable signs of underlying circadian dysrthythmia, the impact of which extends much deeper, affecting a multitude of cellular and organ system functions. Prevention, identification and treatment of delirium are key priorities for improving clinical outcomes for all patients admitted to hospital. Here we review the current evidence for strategies to reduce the impact of delirium on hospital patients.

Diagnosing delirium

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) delirium is a disturbance in attention (reduced ability to focus, sustain and shift attention), awareness and cognition over a short period of time (hours to a few days) and fluctuates in severity during the course of the day [10]. Delirium can manifest in three different ways: hyperactive (agitated), hypoactive (withdrawn) and mixed (alternating periods of hyperactive and hypoactive). The most common type is mixed followed by hypoactive delirium[11]. The form of delirium most likely to go unrecognised is hypoactive delirium, and it is associated with the worst prognosis [12]. The presence of delirium is consistently underdiagnosed, with detection rates by clinical staff as shown to be as low as 25% [13]. Diagnosis requires regular and repeated screening as, without it, the majority of delirium cases go unnoticed [1] The National Institute of Health and Care Excellence (NICE) recommends that all patients are observed at least daily for recent changes or fluctuations of usual behaviour, and if present, a formal assessment must be carried out to confirm the diagnosis. All patients in an intensive care unit should be formally assessed for delirium at least once every 12 hours using a validated screening tool[14]. The Confusion Assessment Method (CAM) is the most widely used in clinical practice [15], and has been adapted for the Intensive Care Unit (CAM-ICU) [14].

Other screening tools were recently reviewed, including the Delirium Rating Scale (found to be most useful for psychiatric and geriatric patients), and the Nurses' Delirium Screening Checklist (best for recovery room setting) [15].

Primary prevention of delirium

The most effective strategy for reducing the impact of delirium is to prevent its occurrence in the first place. Delirium is precipitated by multiple factors, all of which must be addressed. Risk factors for delirium are divided into four domains [16]. The first two: patient characteristics (such as age, alcohol use, smoking) and chronic pathology (such as pre-existing cognitive impairment) are important for identifying those most at risk, for prioritisation in any delirium prevention strategy. The latter two, acute illness and the environment, may be amenable to modification and offer a target for reducing delirium and improving clinical outcomes. Multicomponent strategies which minimise these risk factors have consistently demonstrated efficacy in reducing delirium incidence. A recent systematic review and meta-analysis including 14 interventional studies concluded that multi-modal non-pharmacological interventions can be effective in preventing delirium and falls during a hospital admission in the elderly, with 11 studies showing decreases in delirium incidence (odds ratio 0.47, 95% CI 0.42-0.76), and rate of falls reduced by 64% in two randomised or matched trials [17]. These bundles typically include measures to ensure adequate oxygenation, hydration, nutrition and analgesia. They prompt staff to facilitate mobilisation, as well as provide necessary aides for vision and hearing. Modifications to the environment may help in reducing circadian disruption, by promoting daytime cues such as adequately bright light to simulate the light intensity of outdoors and supporting physical activity and social interaction in the day. Relatives should be actively encouraged to visit and bring cues

such as photographs and familiar music. Patients should be reminded verbally of the time, date and location. Provision of easily visible clocks and calendars aid in active reorientation. At night, reducing sleep interference by minimising bright light, loud noises and avoidable clinical interventions, will promote sleep. In a cohort study in a mixed ICU, the implementation of a bundle of environmental interventions to promote sleep led to an increase in qualitative as well as quantitative measures of sleep, which in turn led to a reduction in the incidence and duration of delirium from 33% to 14% [18]. The bundle consisted of reducing the monitor alarms, telephone ringtones, providing eye masks, dimming the lights during nighttime, minimising non-clinical discussions around patients' bed spaces, orientating the patients to time and place and date, documenting regular CAM-ICU assessments, addressing pain, assessing patients for sedation hold and setting sedation targets. Figure 1 summarises the key components of an evidence-based delirium prevention strategy.

As yet, there is insufficient evidence of benefit from any prophylactic pharmacological strategies. Only two trials have demonstrated reductions in postoperative delirium incidence with prophylactic administration of antipsychotics, such as intravenous haloperidol (0.5 mg bolus followed by 0.1mg/hr infusion for 12 hours) [19], and oral risperidone (0.5 mg twice daily) [20] but trials have been inconsistent. Administration of the exogenous form of the circadian hormone melatonin (0.5 mg once nightly), was associated with a lower delirium incidence (12%) in elderly medical patients compared to placebo (31%) [21] but again, results from other studies have been conflicting [22].

Treatment options for established delirium

Despite the success of non-pharmacological strategies for the prevention of delirium, very few studies have assessed their efficacy in the treatment of established delirium. The first priority is to identify and treat any modifiable organic causes such as pain, hypoxia, acidaemia and other metabolic derangements, infection and haemodynamic instability [22]. Other organic causes, non-clinical seizures, hypertensive encephalopathy and intracerebral haemorrhage, should be ruled out on the basis of history, examination and investigation when appropriate. It is important to review all drug side effects and drug interactions, or the impact of withdrawal of drugs, particularly in the context of pre-existing alcohol/substance abuse. The following classes of drugs have been implicated in contributing to delirium: opioids, antidepressants, anticonvulsants, antihistamines, anstipsychotics, antimuscarinics and steroids. Less familiar, include assorted agents such as furosemide, ranitidine, atenolol and digoxin [14]. Although often a necessary evil in the ICU, sedative medications and deeper levels of sedation are associated with increased risk of delirium, with benzodiazepines appearing to be the worst culprits [23].

Pharmacological approaches to treating delirium remain controversial. Antipsychotics are most commonly used in patients with hyperactive delirium where there is a risk to safety, but the side effects of the proposed drugs must be balanced against any benefit they may provide. In delirium due to alcohol or benzodiazepine withdrawal, benzodiazepines offer a specific treatment, but otherwise it is advised to avoid these drugs as they can contribute to development of delirium. Although antipsychotics, such as haloperidol, are included in guidelines as potential therapy for established delirium, a recent systematic review of the use of antipsychotics (including haloperidol, risperidone and olanzapine) for the treatment of delirium in elderly patients

demonstrated no improvement in delirium duration, severity, mortality or hospital length of stay, in the 19 identified studies [24]. In one randomised controlled trial of 247 patients in the palliative care setting, those taking haloperidol or risperidone had greater delirium scores compared to those receiving placebo, and mortality rates were higher in those receiving haloperidol [25]. In the intensive care setting, dexmedetomidine, a selective alpha2-adrenoceptor agonist with analgesic and sedative effects, has shown promise in the treatment of hyperactive delirium. In a randomised controlled trial of 74 mechanically ventilated patients, those receiving dexmedetomidine had a shorter duration of delirium and increased number of ventilator-free hours at day 7, compared to those receiving placebo [26]. It is possible that this effect was due to the decrease in the amount of other sedative agents (propofol, opioids and midazolam) required by the treatment group compared to placebo. This finding has been corroborated by the significantly lower prevalence of delirium in mechanically ventilated patients receiving dexmedetomidine for sedation rather than midazolam (54% compared to 77%) in a multicentre international prospective trial of 375 patients[27]. Patients in the dexmedetomidine group also had more delirium-free days, and were extubated sooner than the midazolam group.

Conclusions

Illness and admission to hospital place a patient at risk of developing delirium, which has stark consequences for the individual, reducing their likelihood of survival, and dimishing their quality of life long after hospital discharge. Once established, delirium is difficult to treat, but there is convincing evidence from clinical trials for the effectiveness of comprehensive bundles of care in preventing its onset in the first place. Detection and prevention of delirium should be a key priority for all healthcare

professionals. We recommend auditing delirium incidence, on the wards and in the intensive care unit, and for multidisciplinary clinical teams to take shared responsibility in the implementation of strategies to improve delirium detection and prevention.

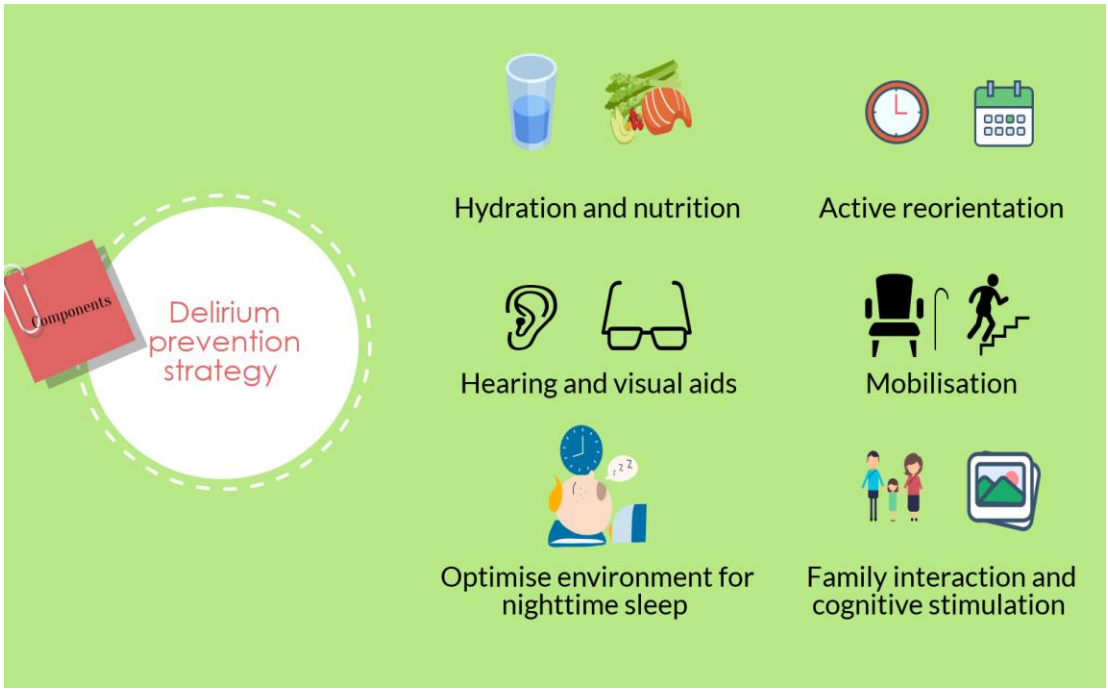

Figure 1. Components of a multi-faceted delirium prevention strategy.

Conflict of interest

The authors have declared no conflicts of interest.

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