Curr Geri Rep (2014) 3:237–244
DOI 10.1007/s13670-014-0102-9

Recent Advances in Delirium Recognition and Management

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Published online: 26 September 2014
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Abstract Delirium is a common syndrome in the elderly and is associated with high mortality and negative health outcomes. Over the last few years, there has been considerable research on delirium. This article summarizes recent studies. The initial literature search conducted for this article revealed over 2,000 articles published from January 2010 through March 2014. The initial list was refined to around 100 original research articles for closer review. Despite considerable research, there have been no breakthroughs in new treatment modalities for this rather complex yet common problem.

Keywords Delirium · Prevention · Management · Treatment · Elderly · ICU · Anesthesia · Post-surgery · ECT · Animal model · Antipsychotics · Melatonin · Ramelteon · Dexmedetomidine · Emergence delirium

Introduction

Delirium, a syndrome that disproportionately affects the geriatric population, is highly prevalent in patients after anesthesia and surgery, those who are critically ill, and patients admitted to the ICU or medical floors of general hospitals. Its prevalence ranges from 10–30 % in medically ill hospitalized elderly patients and about 10–40 % in hospitalized elderly patients in general [1]. The incidence of delirium is high in patients with a preexisting major/minor cognitive disorder (as per DSM-5; previously known as dementia in DSM- IV), making it an important risk factor. Furthermore, the presence of coexisting major neurocognitive disorders complicates the diagnosis of delirium. Delirium has been a focus of research as well as the subject of hospital quality improvement initiatives, largely because of its multifactorial etiology, lack of progress in terms of treatment modalities, and the huge cost and quality implications on the overall healthcare system. It has been noted that the presence of delirium [1] is associated with a significant elevation in mortality risk for elderly patients, both during hospitalization and in the 6–12 months after discharge. The association remains even after controlling for the severity of the underlying illness and other confounding factors. Delirium by itself can lead to longer hospital stays and increased attendant costs. It also affects the type of placement that a patient requires post-hospitalization,-such as a nursing home rather than home.

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Case Report

Mrs. E, a 92-year-old woman with a history of hypertension, dementia, and glaucoma, was brought to the hospital with complaints of weakness, diarrhea, rectal pain, and bleeding for the last month, and was found to have invasive adenocarcinoma. Psychiatric consultation was requested because, over the course of her initial hospital stay, she became increasingly confused and paranoid, was experiencing visual/auditory hallucinations, and was intermittently agitated, removing IV lines and not complying with treatment. Laboratory tests showed evidence of a urinary tract infection, for which treatment was started. The patient was also started on a low dose of risperidone 0.25 mg BID PO, and the dose was gradually increased over the course of a few days, with notable improvement in her delirium. This shows that delirium can be reversible even in the presence of significant medical problems.

Screening for and Diagnosis of Delirium

In order to study delirium, it must be identified and diagnosed appropriately. In addition to a standard clinical interview, several screening tools and scales have been developed to identify patients with delirium. These include the Delirium Symptom Interview, Delirium Rating Scale, revised version (DRS-R-98), Memorial Delirium Assessment Scale (MDAS), Confusion Assessment Method (CAM), CAM-ICU, and the Clinical Assessment of Confusion-A (CAC-A) -and CAC-B. The most commonly used scale is the Confusion Assessment Method, developed by Inouye et al., where screening for delirium is positive if symptoms are acute at onset and have a fluctuating course, and the patient exhibits inattentiveness *plus* disorganized thought *or* altered consciousness.

The specific diagnosis of delirium is based on the newly revised DSM-5 criteria for delirium, where the key diagnostic feature is the disturbance in attention and awareness, in contrast to what was referred to in the DSM-IV as "disturbance in consciousness". Another change in the DSM-5 is the addition of specifiers. Based on duration, delirium is sub-classified as *acute* (lasting a few hours or days) or *persistent* (lasting weeks or months), which reflects research findings that symptoms of delirium can be more chronic. Delirium can also be subdivided based on motor activity. Patients can present as *hyperactive* (increased psychomotor activity that may be accompanied by mood lability, agitation, and/or refusal to comply with medical care), *hypoactive* (sluggishness, lethargy that approaches stupor), or *mixed level of activity* (normal or fluctuating level of psychomotor activity, with impaired attention and awareness (*see* Liptzin and Levkoff, 1992)

Animal Model

Although delirium affects higher cognitive functions and is clinically relevant in humans, animal models can be helpful in understanding the underlying pathophysiology. To date, no general animal model has been developed. However, several animal models [2•] have studied the role of interleukins (IL-1 β), gamma-aminobutyric acid (GABA), dopamine (DA), and acetylcholine (ACH) in delirium, although additional studies are needed to understand their specific roles. An animal model could also be helpful in testing intervention strategies.

Prevention and Treatment of Delirium

Identifying and removing the underlying precipitant (medical illness, surgery, anesthesia, or drugs) is the mainstay of treatment for patients with delirium. The pathogenesis of delirium is rather complex, with an ongoing interplay between predisposing and precipitating factors, patient characteristics (e.g., age, preexisting cognitive disorder, malnutrition), and risk factors during hospitalization (decreased vision, decreased hearing, immobility, indwelling catheter, medication, sleep deprivation). Many of these factors are modifiable and are part of a plan to prevent or treat delirium. As noted below, many pharmacological agents have been studied for the prevention and treatment of delirium.

Pharmacological Prevention Studies

There is some evidence in the literature that delirium can be prevented. Prevention, if possible, is preferred over treatment, and delirium prevention has been studied in several settings.

Given a nearly twofold risk of delirium observed in non-cardiac surgeries among anemic patients, Baldini et al. [3] reviewed data from the Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS) and identified 67 patients who were treated with liberal transfusion to maintain Hgb >10 g/dl, and 72 patients who received transfusion only when they exhibited symptoms of anemia or with Hgb <8 g/dl. MDAS ratings were assessed five days after treatment, and no significant differences in reduction of delirium severity were noted. This suggests that delirium was multifactorial in nature and that controlling for one variable such as low Hgb was unlikely to affect the course of delirium.

Inouye and colleagues [4] designed a multicomponent intervention strategy targeting frequent reorientation, noise reduction, cognitive stimulation, vision, hearing, hydration, and early mobilization. This strategy, termed the Hospital Elder Life program, has been shown to be effective in preventing the initial development of delirium and reducing the total number of days of delirium. It was found that once an initial episode had occurred, however, the intervention had no significant effect on the severity of delirium or the likelihood of its recurrence. The important implication of this pivotal study was that primary prevention was probably the most effective strategy. This multicomponent intervention strategy was adopted within the Dutch Hospital Care System [5•], and the results and benefits noted in the initial study were found to be replicable.

Antipsychotics

Several antipsychotic agents have shown some effect in preventing delirium. A meta-analysis by Teslyar et al. [6•] looked at five randomized controlled trials on the use of prophylactic antipsychotics in elderly postoperative patients. Despite the small number of trials and other limitations in this meta-analysis, antipsychotics did seem to have a protective role in reducing the risk of postoperative delirium. Another meta-analysis by Gilmore et al. [7] showed that antipsychotics

decreased the incidence but not the duration or severity of delirium. The authors concluded that, given the risk of adverse events, universal use of antipsychotics in patients at risk for delirium was not advised, despite the preventive effects of the drugs. There were various limitations in these meta-analyses, including differences in patient age across studies, antipsychotics/doses used, types of surgery, anesthesia, and other medications used. In a randomized double-blind placebo-controlled prophylaxis trial, perioperative administration of olanzapine was found to be associated with a significantly lower incidence of delirium [8]. The study conducted at an orthopedic hospital, enrolled 495 elderly patients undergoing elective knee/hip replacement surgery. The incidence of delirium was significantly lower and the time to onset of delirium was significantly longer in the olanzapine group compared to the placebo group. Wang et al. [9] conducted a prospective randomized double-blind placebo-controlled trial in of 457 patients admitted to the ICU post-surgery, and found that IV haloperidol prophylaxis reduced the incidence of postoperative delirium. It is interesting to note that patients in this study had different surgeries, and duration of surgery and anesthesia was longer for patients in the haloperidol group. Hakim et al. [10] studied the effect of treating subsyndromal delirium on the incidence of clinical delirium. The authors found that patients with subsyndromal delirium after on-pump cardiac surgery who were treated with risperidone had a lower incidence of clinical delirium compared to the placebo group. Larger studies are clearly needed to study the long-term effect of treatment of subsyndromal delirium.

Melatonin

There have been some studies postulating a link between exogenous melatonin and lower incidence or severity of delirium. A systematic review by Jonghe et al. [11] looked at the effectiveness of exogenous melatonin on circadian rhythm disturbances in patients with dementia. Two of the randomized clinical trials in the review showed improvement with melatonin, as did five case reviews. Since dementia is a risk factor for development of delirium, and circadian sleep disturbances overlap between the two disorders, it was postulated that melatonin might have a positive role in treatment of delirium. Two trials [12, 13] have shown evidence of a reduction in the incidence of delirium. Results of a randomized double-blind placebo controlled trial in 145 patients admitted to general medical wards who were randomly assigned to melatonin or placebo [12] showed a lower risk of delirium in the treated group (12 % vs. 31 %). In another study [13], 300 patients undergoing elective surgery with spinal anesthesia were randomly assigned to four groups: control, melatonin, midazolam, and clonidine). The incidence of delirium was found to be lower in patients in the melatonin group. In a group of 62 patients who had developed postoperative delirium, treatment with melatonin was found to be successful in more than half of the patients, but there was no statistically significant difference between groups. A recent editorial (de Rooij et al, 2014) [14••] summarizing the above-referenced studies suggested a possible role for melatonin in prophylactic treatment of delirium.

Ramelteon

In addition to studies of melatonin, a multicenter randomized placebo-controlled trial of 67 patients in the ICU and general wards by Hatta et al. [15••] showed that ramelteon (a melatonin receptor agonist) administered at night to hospitalized elderly patients may provide protection against delirium.

Dexmedetomidine

A growing body of evidence over the years has shown dexmedetomidine as a promising agent, not only for the prevention, but also for the treatment of ICU-related delirium. A meta-analysis of eight clinical trials including five double-blind randomized trails by Xia and colleagues [16] showed that dexmedetomidine significantly reduced length of stay in the ICU and risk of delirium compared to propofol. Hypertension and bradycardia were notable side effects of dexmedetomidine in this meta-analysis. Larger, well-defined trials are needed to define the role of dexmedetomidine in the prevention and treatment of delirium. The Dexlirium Study (Silverstein, personal communication) is a multicenter study funded by the National Institute on Aging that is studying the use of dexmedetomidine in the prevention of delirium and cognitive dysfunction in elderly post-surgical patients.

Sedation and Delirium

In the ICU, adequate levels of sedation represent a primary target of care, but sedation therapy is associated with side effects: hemodynamic instability, difficulty weaning off the ventilator, dysrhythmias, and above all, delirium.

Several preventive studies in the ICU have looked into the relationship of sedation and sedative options with the incidence of delirium. Shehabi and colleagues [17] assessed the feasibility and safety of delivering goal-directed sedation (light sedation using dexmedetomidine as the primary sedative agent) with standard sedation (midazolam and/or propofol). Outcome measures that were studied included cumulative dose of sedative, analgesic and antipsychotic agents received by both groups throughout the study, proportion of patients with delirium, and number of delirium-free days. The number of patients who received propofol (p=0.046) and midazolam (p=0.036) was significantly higher in the "standard sedation" group (33.55, 0.3) compared to the group with early goal-directed sedation (EGDS) (9.89, 0.06). An equal

number of patients experienced one or more positive CAM-ICU ratings during the study, but the number of patient-days with a negative CAM-ICU assessment was 58 % in the EGDS group vs. 47 % in the standard sedation group. The study was unblinded with a small sample size (n=37), however, which was a limitation.

Various studies have compared the effect of a benzodiazepine vs. non-benzodiazepine sedation regimen on the length of ICU stay, duration of ventilation, and incidence of delirium. A meta-analysis of six trials [18] suggested that use of dexmedetomidine- or propofol-based sedation reduced the length of ICU stay and duration of mechanical ventilation compared to benzodiazepine. However, larger controlled studies would be necessary to study the impact of non-benzodiazepine sedation on the prevalence of delirium.

Donepezil

In a randomized controlled trial by Marcantonio et al. [19] to determine the effect of donepezil in reducing the prevalence and severity of delirium in patients undergoing hip fracture repair, no significant differences were found between donepezil and placebo.

Anesthesia and Delirium

Postoperative delirium (POD), especially in elderly patients, is a frequent reason for a psychiatric consultation service request. Two multifactorial but modifiable etiologies of delirium are anesthesia and surgery, and two randomized controlled trials looked into the link between depth of anesthesia and postoperative delirium. Chan et al. [20] (n-=921) conducted a randomized double-blind prospective study to determine whether BIS-guided anesthesia reduced postoperative delirium and cognitive decline. The investigators found a lower incidence of delirium in the BIS-guided group compared to routine care at baseline after surgery. There was no difference in rates of postoperative cognitive dysfunction at one week post-surgery, but the rate was reduced at three months post-surgery. The study included only those patients whose surgery was expected to last for more than two hours, and so it is unclear whether the results are generalizable to surgery of a shorter duration. Another randomized controlled trial, a single-blind study by Radtke et al. [21], showed that monitoring the depth of anesthesia decreased the rate of postoperative delirium. A BIS score of less than 20 was significantly associated with increased incidence of delirium. The STRIDE study (A Strategy to Reduce the Incidence of Postoperative Delirium in Elderly Patients; (Sieber, personal communication) is a single-site randomized double-blind clinical trial funded by NIH, the aim of which is to study the impact of sedation level (light vs. heavy) on the incidence and severity of postoperative delirium as well as the rate of mortality one year post-surgery.

Blood Transfusion and Delirium

In a study by Behrends et al. [22] the perioperative data of 472 patients undergoing major non-cardiac surgery was analyzed to investigate the impact of perioperative blood transfusion on the incidence of postoperative delirium. The authors found that intraoperative blood transfusion of more than 1000 ml RBC increased the risk of delirium in the first postoperative day. While additional research is needed to study this variable, it is worthwhile to keep in mind that transfusion could be a factor in the incidence of delirium.

Psychoeducation and Delirium

The effect of perioperative psychoeducation on the incidence of delirium was investigated by Lee et al. [23] in a retrospective comparative study between 49 patients who received psychoeducation and 46 patients who received standard care. The incidence of postoperative delirium was found to be significantly lower in the intervention group. Although there were several limitations to the study, it did provide a way to study non-pharmacological interventions to prevent delirium.

Treatment Studies

Antipsychotics

Typical antipsychotics such as haloperidol have been the primary agent of choice in the treatment of symptoms of delirium such as agitation. Clinicians have been challenged to look for other alternatives in view of the risk of EPS, QTc prolongation, and torsades with haloperidol use.

Maneeton et al, [24] conducted a seven-day prospective randomized double-blind controlled trial in 52 medically ill patients with severe delirium in order to compare the efficacy and tolerability of haloperidol and quetiapine. The study reported a reduction in delirium severity in both the haloperidol and quetiapine groups, but there was no significant difference between groups in either the mean subscale scores or rates of remission. Extrapyramidal symptoms were noted in some patients in the haloperidol group, whereas this was not seen in the quetiapine group, for which hypersomnia seemed to be the most common adverse event. The study had many limitations. The study population was small and younger in age (<65 years), and patients with hypoactive delirium and renal or hepatic failure were excluded. Only a small number of patients experienced EPS on haloperidol, but this could be because of the small sample size.

Another randomized double-blind placebo controlled trial was conducted by Girard et al. [25], in which 101 mechanically ventilated patients in the ICU were randomized to receive haloperidol, ziprasidone, or placebo. Neither haloperidol nor ziprasidone was found to significantly increase delirium/coma-free days compared to placebo. The study population in this trial seemed more heterogeneous and rather ambiguously described as "adults" (>18 years), and included mechanically ventilated medical and surgical ICU patients who had an abnormal level of consciousness. As a result, 49 % of patients were delirious upon enrollment and 36 % were comatose, and this difference in baseline characteristics could have led to the lack of response to both antipsychotics.

In a study by Devlin et al. [26] involving 36 subjects, patients on quetiapine were found to have quicker resolution of delirium symptoms compared to placebo. A similar study of 42 patients by Tahir et al. [27] found that the quetiapine group recovered 82.7 % faster than the placebo group. Both studies, however, were underpowered, and thus larger studies with larger dosing of quetiapine are needed to draw definitive conclusions on its effectiveness.

Three prospective studies by Yoon et al. (n=80) [28], Grover et al (n=64) [29•], and Kim et al. [30] looked at the efficacy of haloperidol compared to other antipsychotics, and all studies found evidence that haloperidol, olanzapine, risperidone, and quetiapine were equally efficacious in reducing symptoms of delirium. The first two studies [28, 29•], however, were neither randomized nor placebo-controlled trials, and they were underpowered as well. Another comparative study noted no significant differences in treatment results with aripiprazole compared to haloperidol [31]

Kishi et al. [32] studied the effect of risperidone in the treatment of delirium in advanced cancer patients, and results indicated that 48 % of patients responded to risperidone and 38 % achieved remission. Reduction in severity of delirium was noted in 79 % of patients. However, there was no comparison group.

Ondansetron

Tagarakis et al. [33] conducted a prospective randomized double-blind study in 80 patients after surgery in which they compared the efficacy of ondansetron with haloperidol in treating delirium. A significant improvement in severity of delirium was noted in the ondansetron group, but no other statistically significant differences were noted between the two drugs.

Melatonin and its Agonist Ramelteon

We found no studies on the role of melatonin or ramelteon in reducing the duration or severity of delirium, but there are several case reports. A letter to the editor by Tsuda et al. [34], describes the case of a 100-year-old patient who suffered an episode of delirium while admitted to the ICU with pneumonia. He was started on ramelteon, with notable improvement and reduced severity of delirium. Other cases published by Kimura et al. [35•] and Furuya et al. [36•] have suggested that ramelteon could play a useful role in the treatment of delirium.

Sedation and Delirium

A quality improvement (QI) study in an ICU conducted by Hager et al. [37] looked into sedation and delirium status in patients with acute lung injury. The QI team educated three clinical groups in the ICU on the new CAM-ICU sedation protocol regarding preventive and treatment methods for delirium. At the end of the 20-month study, period-days of continuous sedation infusion had been reduced, increased wakefulness was noted, and the number of days without delirium had increased. While there was improvement in sedation, however, there were several patients who remained comatose or delirious, suggesting that underlying medical severity and less-modifiable factors were present that affected delirium.

Adjuvant Treatment with Bright Light Therapy

Bright light therapy as an adjunctive treatment was studied by Chong et al. [38] in 228 patients admitted to the geriatric medicine department who received evening bright light treatment along with interventions adopted from the HELP program. The duration of delirium was found to be shorter for patients with hyperactive delirium compared to the hypoactive or mixed type. No significant difference was found in length of hospital stay, and no significant improvement in Mini-Mental State Examination (MMSE) score was noted in any delirium subtypes. There was significant improvement in functional status at discharge, particularly in patients with mixed and hyperactive delirium. Improvement in sleep-wake disturbances was seen in all types of delirium, but predominantly in the hyperactive type.

Yang et al. [39] studied the effect of adjuvant treatment with bright light combined with antipsychotic medication in a randomized study of 36 patients referred to psychiatry consultation from general medicine and general surgery floors. Patients were randomized to receive risperidone or risperidone plus bright light treatment. Patients in both groups showed a reduction in mean Delirium Rating Scale and Memorial Delirium Assessment Scale scores, but the group treated with risperidone and bright light therapy showed a significantly greater reduction on DRS and total sleep time. No significant difference was found in MDAS between the groups. This study had many limitations, such as small sample size, lack of a control group, and a short period of study (five days). However, these studies provide some evidence that bright light therapy may provide some benefit in the management

of delirium, although randomized controlled trials are needed to confirm this finding.

Emergence Delirium (ED)

Emergence delirium is an acute confusional state lasting 15–20 minutes that occurs immediately upon emergence from anesthesia [40]. While it is not well-studied or well-described in the literature, its incidence ranges from 15–20 % in patients postoperatively, leading to increased use of medications, increased need for staff, and prolonged hospital stay. A model to study emergence delirium is in patients after electroconvulsive therapy. No systematic studies in this population have been conducted, but a case report published by Cohen et al. [41] described emergence delirium in a 71-year-old patient post-ECT, where a dramatic improvement was observed with dexmedetomidine infusion. As mentioned above, meta-analyses have shown the promising role of dexmedetomidine in the prevention of postoperative delirium, but additional research is needed.

Rivastigmine

A clinical trial of rivastigmine [42] for reducing the incidence of delirium in older postoperative patients did not demonstrate any significant effect. This study was stopped prematurely due to information on the potential risk of increased mortality associated with rivastigmine. An earlier randomized double-blind placebo controlled study by Overshott et al. [43], however, did provide some evidence that rivastigmine may be safe and effective in treating symptoms of delirium, although the sample size of patients in the study was too small (n=15) to make any meaningful inference.

Blonanserin

A retrospective chart study [44] by Kato et al. on the efficacy of blonanserin (atypical antipsychotic) in 32 patients in the ICU found that blonanserin was not overly sedating and was fairly well-tolerated, with no incidence of EPS, and a reduction in delirium severity for 96.6 % of patients. The study had many limitations, however, such as the small number of charts reviewed and the fact that it was non-randomized and lacked a control group. Other than incidence of EPS, no mention was made as to whether cardiac complications were observed with blonanserin.

Dexmedetomidine

The use of dexmedetomidine for the treatment of delirium in patients after cardiac surgery was investigated by Yapici et al [45] in a prospective observational study of 72 patients who underwent elective cardiac surgery and had difficulty in weaning off ventilation. The patients were randomized to two treatment arms, standard sedation (Group M) vs. dexmedetomidine (Group D). At 36 hours post-surgery, all patients had a positive CAM-ICU, but at 60 hours, there was a significant difference, with only one patient in Group D with positive CAM-ICU compared to seven patients in Group M. Time to extubation was also shorter for Group D. While the results suggest that dexmedetomidine may be a promising agent in treating delirium associated with prolonged ventilation in an ICU setting, the study was not blinded, did not have a control group, and the sample size was small, so further research is clearly needed.

Conclusions

Given the prevalence of delirium in intensive care units of hospitals, Hackett et al. (1968) referred to the syndrome as “the new madness of medical progress”. In light of the growing elderly population and the high incidence of delirium in hospitalized elderly patients, it is imperative that better strategies for prevention and treatment are developed. Despite the numerous studies in the last few years that are highlighted in this review, the results of research in delirium prevention have been inconclusive, and when delirium does occur, better treatments are needed. And while various medications have been shown to reduce the severity of delirium, definitive results are still lacking. Antipsychotics continue to be the medication of choice in the treatment of delirium, particularly the hyperactive type, leaving patients at increased risk of EPS, acute dystonia, prolonged QTc, torsades, ventricular fibrillation, and even sudden death. Additional studies are needed to validate the efficacy of alternative medications and approaches in the prevention and treatment of delirium.

Compliance with Ethics Guidelines

Conflict of Interest Benjamin Liptzin and Jisha Lovin Kuriakose declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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