Delirium
An Evidence-Based Medicine (EBM) Monograph for Psychosomatic Medicine Practice

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Delirium – EBM Summary

INTRODUCTION

Objective and methods
This monograph summarizes current knowledge related to the diagnosis, epidemiology, etiology, and management of delirium. The monograph is based on the guideline ‘delirium’ of the National Institute of Clinical Excellence (NICE) [1], as well as on systematic reviews and pivotal trials. The quality of the evidence discussed in this monograph is graded as ‘high’, ‘moderate’, ‘low’ or ‘very low’, following the ‘Grading of Recommendations Assessment, Development and Evaluation’ (GRADE) system, which was developed by the Cochrane Center [1]. Readers are encouraged to consult the recommended readings for more detailed information (Appendix A).

Definition and symptoms: Delirium is an acute neuropsychiatric disorder characterized by a disturbed level of consciousness with reduced ability to focus, sustain, or shift attention, and accompanied by changes in cognition, such as memory deficits, disorientation, speech and language disturbances, delusions and perceptual abnormalities. These changes in cognition are not better accounted for by a pre-existing or evolving dementia. In addition, sleep-wake cycle disturbance, increased or decreased motor activity, and emotional disturbances are often present. The disturbance typically develops over a short period of time and tends to fluctuate during the course of the day [2]. Clinically, a distinction between hyperactive and hypo-active delirium is often made on the basis of motor activity. Though this may be clinically useful, it has not found its way into the classification systems.

Diagnosis: The gold standard for the diagnosis of delirium are the criteria of the 4th edition of the Diagnostic and Statistical Manual (DSM IV; codes 291.0 to 293.0 and 780.09) or the 10th edition of the International Classification of Disease (ICD 10; code F05) [2, 3].

Prevalence and incidence: The occurrence of delirium depends on the setting.
- In the general population, the reported prevalence is low and ranges from <0.05 to 0.4%, with a higher prevalence in older people of 1.1% in those over 55 years [4, 5].
- For hospital inpatients, a median prevalence of 21.4%, a median incidence of 15.2%, and a median occurrence rate of 22% is reported on general medical wards. In the NICE guideline the term ‘occurrence rate’ is used when there is overlap between prevalence and incidence data, such as may occur when in incidence studies prevalent delirium upon entering the study is not excluded.
- The occurrence rate on general surgical wards is reported to be 44%; no data on prevalence and incidence rates in this setting are available [1].
- Occurrence rates are higher on Intensive Care Units, with a occurrence rates reported as high as 80%, depending on type of ICU [1].
- In long term care, low quality evidence shows a median occurrence rate of 15.9% [6].

Risk factors: Delirium is currently seen as the resultant of a complex interaction of predisposing and precipitating factors [7]. High quality evidence identifies the following risk factors for incident delirium:
- Older age
- Cognitive impairment
• Visual impairment [1]

Moderate quality evidence identifies the following risk factors for incident delirium:
• Illness severity
• Comorbidities
• Infection
• Fractures
• Vascular surgery
• Presence of a bladder catheter [1].

Moderate to low quality evidence identifies the following risk factors for persistence of delirium:
• Cognitive impairment
• Medical comorbidity
• Vision impairment
• Use of physical restraints [1].

Low level evidence identifies the following risk factors for increased severity of delirium:
• Number of room changes
• Absence of clock or watch
• Cognitive impairment
• Not wearing glasses [1].

Low level of evidence shows no, or no clinically relevant, association for incidence or severity of with a variety of variables, such as sex, mobility, hearing impairment, incontinence, dehydration and polypharmacy [1]. Clinical experience however supports close attention for polypharmacy as a contributing cause of delirium.

**Prognosis:** Delirium has a number of negative prognostic implications.

High quality evidence
• Increased length of hospital stay, particularly for ICU patients [1, 9, 10]
• Increased and earlier post-discharge institutionalization [1]

Moderate to high quality evidence
• Increased mortality: the mortality of delirium patients during their hospital stay is 22 – 76%; the mortality in the first year after discharge is 35 – 40% [8].

Moderate quality evidence
• Delirium is a risk factor for cognitive decline and dementia after 3 years [1]

Low quality evidence.
• Delirium predisposes for worse functional abilities and activities of daily living [1] No study reported on the consequences of delirium for health related quality of life [1]

**Costs:**
Several studies have demonstrated significantly increased costs of health care for patients who develop delirium [9, 10]. One study estimated these costs to be at least 2.5 times greater per day for delirious patients compared to non-delirious patients [11].

**SCREENING AND ASSESSMENT**

Most health care providers recognize that delirium is a serious, underdiagnosed problem, but a minority routinely screen for delirium and few use a specific tool for assessment [12]. Failure to detect delirium has been associated with poorer outcomes, including increased mortality.
[13], while explicit recognition of delirium has been associated with lower mortality and shorter inpatient stays [14].

Assessment consists of establishing the diagnosis, assessing severity and assessing clinical risks. Of the available diagnostic instruments, the Confusion Assessment Method (CAM) is preferred in a clinical setting, since it has the highest positive and lowest negative likelihood ratio (LR) (positive LR 9.6; 95% CI 5.8 – 16.0; negative LR 0.16; 95% CI 0.09 – 0.29) (moderate quality evidence) (http://www.healthcare.uiowa.edu/igec/tools/cognitive/CAM.pdf) [1, 15]. The MMSE score had the lowest discriminatory properties (moderate quality evidence) [15]. The MMSE should not be used alone to diagnose delirium.

In the ICU setting, moderate to high quality evidence shows that the CAM-ICU has the best data supporting its use, with positive LRs ranging from 13.42 to 36.36 [1]. Although there are a number of rating scales available for assessment of severity, no recommendation for a specific scale can be given. For most delirium rating scales, low to moderate evidence supports their use in the assessment of severity of delirium. [1, 16].

TREATMENT

Treatment of delirium consists foremost of treatment of the underlying medical condition. In addition, there is evidence that symptomatic treatment, including non-pharmacological and pharmacological treatment may be beneficial to the patient. (For a list or randomized pharmacological trials, see Appendix B).

Non-pharmacological treatment
There is moderate to very low quality evidence that suggests that enhanced treatment strategies for people with delirium are more effective than usual care. However, the various mono- and multi-component interventions vary substantially and most of the studies provide lower quality evidence, with much uncertainty around the results. For this reason, the NICE guideline development group abstained from recommending a specific strategy. There was consensus however that interventions targeting better orientation may be helpful in clinical practice [1].

Pharmacological symptomatic treatment
Antipsychotics
Moderate to low quality evidence shows that antipsychotic medications are effective in the treatment of symptoms of delirium. Compared to treatment with placebo, treatment with an antipsychotic medication is associated with a higher proportion of remission in patients, and a reduced severity of delirium. In one small study, haloperidol (0.25 – 10mg/d), risperidone (0.25-4mg/day), and olanzapine (1.25 – 20mg/day) were equally effective in treating delirium, with few adverse effects [17]. There is no consistent evidence on whether haloperidol results in more or more severe extrapyramidal side effects than olanzapine or risperidone [1]. Although some studies have evaluated the differential response to pharmacological treatment in patients with various motor subtypes of delirium, the low quality of available evidence does not allow any conclusion or recommendation in this respect.

Other medication
There is no evidence to support the use of benzodiazepines in the treatment of delirium not related to alcohol or benzodiazepine withdrawal [1]. There is no current evidence for the efficacy of cholinesterase inhibitors as treatment for delirium [1, 18-21]. In critically ill patients, treatment of delirium with the cholinesterase inhibitor rivastigmine is associated with increased mortality [21].

**Prevention**

*Nonpharmacological prevention:*
Mono-component interventions: there is no evidence of the effect of subcutaneous versus intravenous fluids on the incidence, duration or severity of delirium, both in a hospital setting and in a long term care setting (low quality evidence) [1].
Multi-component interventions: low quality evidence shows that multi-component interventions based on targeting modifiable risk factors (such as cognitive impairment, sleep deprivation, immobility, vision impairment, hearing impairment, dehydration), reduces the incidence of delirium (RR 0.66; 95% CI 0.46 to 0.95), reduces average delirium duration, and reduces the number of patients with urinary incontinence after 6 months follow up (RR 0.80; 95% CI 0.65 to 0.99). There was no difference in mortality, delirium severity, the median length of stay in hospital, post-discharge institutionalisation, the incidence of delirium after 6 months follow up, and the MMSE score after 6 months follow up [1].

*Pharmacological prevention:*

**Antipsychotics**
The NICE guideline summerizes that moderate to low quality evidence suggests that prophylactic treatment with typical antipsychotics does not reduce the incidence of delirium in hospital patients. One low quality RCT (level 2 evidence) with risperidone showed a significant reduction in delirium incidence (RR 0.35; 95% CI 0.16 to 0.77) which corresponds to a number needed to treat of 5 (95% CI 3 to 14) [22]. Another study with olanzapine (level 2 evidence) showed a decreased incidence but longer duration and severity of delirium in postoperative patients after joint surgery [23]. In contrast with this conclusion, a recent RCT of 457 patients after surgery randomized to haloperidol 0.5mg IV bolus and 0.1mg/hr continuous infusion for 12 hours versus placebo showed decreased incidence of delirium and shorter duration of ICU stay [24]. Prophylactic treatment with haloperidol may reduce the severity and duration of delirium, as well as the length of hospital stay [25].

*Other medication:*
Riverstigmine and donepezil do not reduce the duration of delirium, nor the length of stay in the ICU or in the general hospital (moderate quality evidence). Prophylactic treatment with risperidone did not reduce the length of hospital stay (level 2) [1, 26].

**QUALITY INDICATORS**

**Organization of detection and management:**
The available evidence does not allow for recommendation of a specific model of organization of delirium detection and management. However, the NICE guideline as well as available reviews and position papers stress the importance of a systematic and proactive approach to delirium identification and treatment. The approach to delirium should include systematic screening for patients with delirium risk factors, and then systematically following them for potential incident delirium and administer interventions known to help prevent
delirium. Once delirium is established, adequate pharmacological and non-pharmacological treatment should be provided. Follow-up contacts can be provided if indicated in order to taper medication or to follow the cognitive status of the patient.

Specific quality indicators
The following indicators provide insight into the quality of the organization of detection and management of delirium:

- The presence of an institutional protocol for delirium, based on a professional guideline
- The availability of professionals with expertise in delirium (psychiatrist/geriatrician) on a 24/7 basis
- Percentage of patients over 65-years that has been screened for delirium risk factors on admission or pre-operatively
- Percentage of patients at high-risk for delirium that is screened for incident delirium during the first few days of admission or post-operatively
- When delirium is present, treatment with antipsychotic medication is considered, unless medically contraindicated and benzodiazepines are avoided unless a clear reason for using them is provided (e.g., alcohol withdrawal).

(Based on: Inspectie voor de Gezondheidszorg (IGZ), Nederlandse Vereniging van Ziekenhuizen (NVZ), Nederlandse Federatie van Universitair Medische Centra (NFU), Orde van Medisch Specialisten (OMS): Quality indicator set for general hospitals: 2010. Utrecht, Health Care Inspectorate of the Netherlands, 2009.)

References


Appendix (Additional Materials)

A) Recommended Readings
B) Annotated List of Randomized Clinical Trials
C) Assessment and Scales
D) Areas for Future Research
E) Multiple choice question(s)
APPENDIX A

Recommended Readings

Relevant practice guidelines:

Relevant literature:

Relevant websites:
- American Delirium Society: http://americandeliriumsociety.org
- European Delirium Association: http://www.europeandeliriumassociation.com
- Hospital Elder Life Programme (HELP, Yale University School of Medicine, New Haven, USA): http://www.hospitalelderlifeprogram.org/public/public-main.php
APPENDIX B

Annotated List of Randomized Pharmacological Trials

A. ACUTE TREATMENT

Antipsychotics


30 hospitalized patients with AIDS were randomly assigned (double-blind) to receive low-dose chlorpromazine, low-dose haloperidol or lorazepam if they developed a delirium. The antipsychotics effectively treated the delirium while the benzodiazepine arm was terminated after it appeared to be ineffective while also causing side effects.


In this randomized trial (N=73), olanzapine and haloperidol reduced delirium symptoms to a similar degree; olanzapine had less EPS.


Small randomized trial (double-blind) of 28 patients that found no clear differences between a 7-day course of risperidone or haloperidol in patients with delirium.


Small randomized trial (N=40) comparing amisulpride with quetiapine for the treatment of delirium. Both interventions were comparable with regards to side effects and reduction of delirium symptoms.


36 patients with delirium received ancillary quetiapine in this small RTC (double-blind, placebo-controlled). All patients received as needed haloperidol. The added quetiapine led to more sedation but also reduced the duration of delirium and agitation.

In this double-blind, placebo-controlled RTC, 101 ventilated ICU patients received either haloperidol, ziprasidone or a placebo for 21 days. There were no differences in side effects or “days spent alive without delirium or coma.”


Small randomized trial (N=32) that found no clear difference between risperidone and olanzapine in treating acute delirium.


Small RTC (double-blind, placebo-controlled) of 42 patients that showed benefit from quetiapine for the treatment of delirium. With treatment, it resolved faster.

**Acetylcholinesterase Inhibitors**


Very small RTC (double-blind, placebo-controlled) trial in 15 patients who were treated for delirium with either rivastigmine or placebo. The duration of delirium was comparable.


Major multicenter RTC (double-blind, placebo-controlled) that examined if adding rivastigmine (12 mg TDD) to haloperidol in patients diagnosed with delirium would be helpful. The approach has face validity as cholinergic load is often increased in delirium. However, the intervention was not helpful. Worse, rivastigmine prolonged the delirium and increased mortality (22% in treatment group vs. 8% on placebo; p=0.07). The trial was prematurely terminated by the DSMB after 104 patients were enrolled because of the interim mortality findings.

**B. PROPHYLAXIS**

**Antipsychotics**


Large RTC (double-blind, placebo-controlled) of 430 patients over age 70 that examined if short-term, low-dose haloperidol (1.5 mg/day) treatment can prevent post-
operative delirium following hip surgery. The incidence of delirium was similar: 15.1% for the treatment group and 16.5% for the placebo group. However, those patients who developed delirium had a less severe delirium of shorter duration if they had received prophylactic haloperidol.


120 patients received a one-time sublingual dose of 1 mg risperidone or placebo immediately following regaining consciousness after elective cardiac surgery. The intervention reduced the risk of developing delirium (11.1% in the treatment group vs. 31.7% in the placebo group).


Large RTC (double-blind, placebo-controlled) of 400 patients that examined if peri-operatively administered olanzapine (5 mg before and after surgery) would reduce delirium in elderly patients admitted electively for joint replacement surgery. While intervention reduced the incidence of delirium, the duration and severity of delirium was greater in the intervention group; nonetheless, dismissal to home rather than a rehabilitation facility was greater in the olanzapine-intervention group.

**Acetylcholinesterase Inhibitors**


120 patients scheduled for elective cardiac received short-term, peri-operative rivastigmine (double-blind, placebo-controlled). The incidence of post-operative delirium was 30% in the placebo group and 32% in the treatment group.

**Melatonin**


165 medically admitted patients age 65 or above received low-dose melatonin (0.5) at night to see if delirium was prevented. The intervention effectively reduced the incident of delirium as determined by CAM (12% with melatonin vs. 31% with placebo).

(This was a double-blind, placebo-controlled RTC.)
APPENDIX C

Assessment and Scales

Many delirium scales are available. The choice of instrument depends on a number of factors, including time for completion, amount of training required, experience of the rater, the purpose of the scale (diagnosis, screening, severity measurement), and the clinical setting.

The scales listed below are the best in terms of psychometric properties and wide validation in multiple clinical settings/patient groups (see EBM main text for details regarding psychometric properties).

For non-psychiatric clinicians: Screening and diagnosis
- For the ICU: CAM-ICU: http://www.mc.vanderbilt.edu/icudelirium/docs/CAM_ICU_worksheet.pdf

For psychiatric clinicians: Severity rating and diagnosis
- Memorial Delirium Assessment Scale (MDAS) http://www.delirant.info/DreamHC/Download/MDAS.pdf

For nurses: Screening
- Neelon and Champagne Confusion Scale (NEECHAM)

References


APPENDIX D

Areas of Future Research

- Determination of best pharmacological treatment
  - It remains unclear if and when second-generation antipsychotics are to be preferred over first-generation antipsychotics
  - RCT of amisulpride should be performed (see reference below)
  - Currently, there are no clear indications for the pharmacological prevention of delirium
- Identification of biomarkers that could aid in detection and diagnosis of delirium (including subclinical delirium)
- Comparing efficacy of pharmacologic treatment in certain delirium subtypes (hyperactive versus hypoactive delirium)
- Identification of elements of underlying pathophysiology of delirium and its symptoms
- Further development of prevention and detection strategies and their impact on incidence, mortality, morbidity, and cost
- Identification of elements of psychiatric consultation that have the most impact on clinical and financial outcomes of delirium prevention and treatment
- Development of a new practice guideline that incorporate recent research findings

Reference:
Pintor, L, Fuente, E, Bailles, E, Matrai. S. Study on the efficacy and tolerability of amisulpride in medical/surgical inpatients with delirium admitted to a general hospital. European Psychiatry 2009;24:450-455

_Open label prospective study of 40 hospital inpatients with delirium treated with amisulpride 200-300mg/day for 1 week. Patients treated with amisulpride showed significant improvement in DRS, PANSS and MMSE._
APPENDIX E

Multiple choice questions

Which of the following is a specific quality indicator for delirium care in a hospital?

A. Percentage of patients over 65-years that has been screened for risk factors for delirium upon admission or pre-operatively
B. The percentage of patients who receive a routine psychiatric consultations in the ICU
C. The percentage of orthopaedic patients who receive peri-operative delirium prophylaxis for hip surgery (e.g., an antipsychotic)
D. The percentage of patients with delirium who require restraint

(Correct answer: A.)

What is the best treatment for managing delirium?

A. Haloperidol
B. Valproate
C. Lorazepam
D. Donepezil
E. Citalopram

(Correct answer: A)

Which of the following factors have highest evidence of being associated with delirium?

A. Gender
B. Premorbid cognitive impairment
C. Hypertension
D. Incontinence
E. Social support

(Correct answer: B)

Best assessment for delirium is which of the following?

A. MMSE
B. History from family
C. CAM
D. CT head
E. Review of medications

(Correct answer: C)

Best evidence exists for delirium negatively impacting which of the following?

A. Development of dementia
B. Mortality of caregivers
C. Impairment of ADL’s longterm
D. Length of hospitalization
E. Marital status

(Correct answer: D)