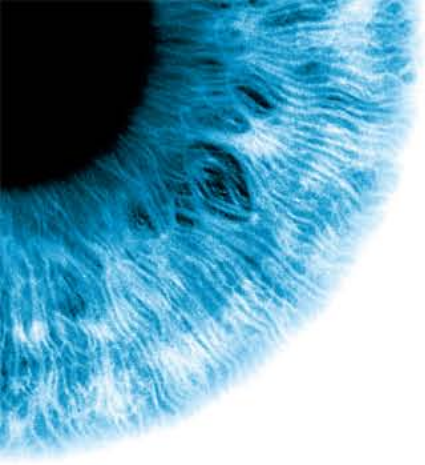

Delirium: Evidence Update April 2012

A summary of selected new evidence relevant to NICE clinical guideline 103 'Delirium: diagnosis, prevention and management' (2010)

Evidence Update 14

Evidence Updates provide a regular, often annual, summary of selected new evidence published since the literature search was last conducted for the accredited guidance they update. They reduce the need for individuals, managers and commissioners to search for new evidence and inform guidance developers of new evidence in their field. In particular, Evidence Updates highlight any new evidence that might reinforce or generate future change to the practice described in the most recent, accredited guidance, and provide a commentary on the potential impact. Any new evidence that may impact current guidance will be notified to the appropriate NICE guidance development centres. For contextual information, Evidence Updates should be read in conjunction with the relevant clinical guideline, available from the NHS Evidence topic page (www.evidence.nhs.uk/topic/delirium). NHS Evidence is a service provided by NICE to improve use of, and access to, evidence-based information about health and social care.

Evidence Updates do not replace current accredited guidance and do not provide formal practice recommendations.

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Contents

Introduction

This Evidence Update identifies new evidence that might reinforce or generate future change to the practice laid out in the following reference guidance:

[1]Delirium. NICE clinical guideline 103 (2010). Available from www.nice.org.uk/guidance/CG103

A search was conducted for new evidence published between 17 August 2009 and 28 November 2011. A total of 348 pieces of evidence were identified and assessed, of which 17 were selected for the Evidence Update (see Appendix A for details of the evidence search and selection process). An Evidence Update Advisory Group, comprised of subject experts, reviewed the prioritised evidence and provided a commentary.

Feedback

If you have any comments you would like to make on this Evidence Update, please email contactus@evidence.nhs.uk

[1] NICE-accredited guidance is denoted by the accreditation symbol

Key messages

The following table summarises what the Evidence Update Advisory Group (EUAG) decided were the key messages from the Evidence Update. It also indicates the EUAG's opinion on whether new evidence identified by the Evidence Update reinforces or has potential to generate future change to the current guidance listed in the introduction.

The relevant NICE guidance development centres have been made aware of this evidence, which will be considered when guidance is reviewed. For further details of the evidence behind these key messages and the specific guidance that may be affected, please see the full commentaries.

The section headings used in the table below are taken from the guidance.

	Effect on guidance	
Key message	**Potential change**	**No change**
Think delirium • Evidence shows that persistent delirium is associated with poor outcomes in terms of mortality and cognition, supporting the need to be aware of delirium. • Evidence supports the need for vigilance in patients presenting with hypoactive delirium, which has been shown to be associated with prolonged delirium.		✓ ✓
Risk factor assessment • Specific groups of medications may be potential risk factors for development of delirium, however evidence is currently limited and further research is required. • Use of the 10-item tool, PRE-DELIRIC (prediction of delirium in ICU patients), to assess the risk of patients in intensive care for developing delirium may be a consideration for future guidance reviews. A risk-assessment tool is not currently recommended.	✓	✓
Interventions to prevent delirium • Evidence showing that multidisciplinary care reduces the incidence of delirium supports current advice on delivery of care to people at risk of delirium. • Evidence suggests that prophylactic fascia iliaca compartment block and the use of light sedation with propofol reduce the incidence of peri-operative delirium in patients undergoing surgery for hip fractures, supporting current advice to use appropriate pain management.		✓ ✓

Key message	Effect on guidance	
	Potential change	No change
• Limited evidence suggests that low-dose melatonin[2] reduces the incidence of delirium in patients admitted to acute care units, but further work is required to establish the actions and role of melatonin.		✓
Treating delirium • Implementation of a multi-component delirium abatement programme does not reduce the duration of delirium. • New evidence is consistent with current recommendations to consider use of haloperidol[3] or olanzapine[4] for short-term treatment of delirium.		✓ ✓

[2] At the time of publication of this Evidence Update, melatonin did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.
[3] At the time of publication of this Evidence Update, haloperidol did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.
[4] At the time of publication of this Evidence Update, olanzapine did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.

1 Commentary on new evidence

These commentaries analyse the key references identified specifically for the Evidence Update, which are identified in bold text. Section headings are taken from the guidance.

Think delirium

An introductory section of NICE clinical guideline (CG) 103 ('Think delirium') notes the need to be aware that people in hospital or long-term care may be at risk of delirium, with potentially serious consequences. Evidence supports this recommendation.

A systematic review by **Cole et al. (2009)** evaluated the incidence and outcome of persistent delirium in older hospital patients (aged ≥ 50 years). Persistent delirium was defined as a cognitive disorder consistent with the accepted diagnostic criteria for delirium at admission (or shortly after admission) and which continued until discharge or after discharge. Eighteen prospective studies with a total of 1322 patients (mean ages 72–89 years, median age 82 years) satisfied criteria for inclusion in the review. Persistent delirium appeared to be common and was recorded for 44.7% (95% confidence interval [CI] 26.8 to 63.7%) of patients at discharge; combined proportions of patients with persistent delirium at 1, 3 and 6 months after discharge were recorded as 32.8% (95% CI 18.4 to 47.2%), 25.6% (95% CI 7.9 to 43.4%) and 21% (95% CI 1.4 to 40.6%) respectively. Patients with persistent delirium had poorer outcomes with respect to mortality, nursing home placement, function and cognition, compared with patients who recovered from delirium.

A systematic review by **Dasgupta et al. (2010)** assessed factors associated with persistence of delirium in patients with acute illness. Twenty-one prospective observational studies satisfied criteria for inclusion in the review (including a total of 1953 patients; studies ranged in size from 33 to 290 patients with six studies including more than 100 patients). The patients and treatment settings were varied, and included mixed medical-surgical units, medical, surgical, geriatric, psychiatric, cancer and palliative care units. Parameters assessed in the studies included characteristics pertaining to the patient, the nature of delirium and the patients' other illnesses.

Although the definition used varied, rates of persistent delirium ranged from 0% to 78%. No meta-analysis was conducted due to the heterogeneity of populations and settings. In a narrative review of the evidence, persistence of delirium was significantly ($p \leq 0.05$ or as defined in the individual study) associated with hypoactive delirium (in four of six studies), increasing severity of delirium (in five of eight studies), cognitive impairment (in seven of 11 studies), multiple comorbidities (in three of eight studies) and hypoxic illness (in two of three studies). However, the authors noted limitations to the analysis, including the observational nature and size of the studies in the review.

Fong et al. (2009) undertook a secondary analysis of data from a prospective cohort study of patients with Alzheimer's disease, to determine the effect of delirium on the course of cognitive function. The analysis assessed cognitive function in 408 patients with dementia who developed delirium (n = 72) or did not develop delirium (n = 336) in the course of their illness, identified by case ascertainment from retrospective chart review. The primary outcome was the rate of cognitive decline (based on changes in the score for the Information-Memory-Concentration [IMC] subtest of the Blessed Dementia Rating Scale over time). Patients with Alzheimer's disease who had episodes of delirium suffered a significant acceleration in their cognitive decline compared with the controls. For patients who developed delirium, the average decline (based on the IMC) of 2.5 points a year accelerated to 4.9 points a year after an episode of delirium ($p = 0.001$). By contrast, patients with Alzheimer's disease who did not develop delirium did not show a significant acceleration of

change in cognitive decline (2.4 vs 3.2 points a year, p = 0.07). The authors concluded that delirium prevention strategies targeted at patients with Alzheimer's disease may be beneficial in delaying cognitive decline.

Key references

Cole MG, Ciampi A, Belzile E et al. (2009) Persistent delirium in older hospital patients: a systematic review of frequency and prognosis. Age and Ageing 38: 19–26.
Full text: www.ageing.oxfordjournals.org/content/38/1/19.full.pdf

Dasgupta M, Hillier LM (2010) Factors associated with prolonged delirium: a systematic review. International Psychogeriatrics 22: 373–94.
Abstract: www.journals.cambridge.org/action/displayAbstract?fromPage=online&aid=7453576

Fong TG, Jones RN, Shi P et al. (2009) Delirium accelerates cognitive decline in Alzheimer disease. Neurology 72: 1570–75.
Abstract: www.neurology.org/content/72/18/1570.abstract

1.1 Risk factor assessment

NICE CG103 identifies factors that indicate a person in hospital or long-term care may be at risk of delirium, including age 65 years or older, cognitive impairment, current hip fracture or severe illness.

A systematic review by **Clegg and Young (2011)** assessed randomised controlled trials (RCTs), prospective cohort studies and case-control studies evaluating the relationship between medications and the risk of delirium in hospitalised patients or long-term care residents. Fourteen studies (including 4652 patients) satisfied criteria for inclusion in the review. The primary outcome measure was the rate of delirium, based on the Diagnostic & Statistical Manual for Mental Disorders (DSM) or the International Classification of Diseases Volume 10 (ICD 10) criteria or a diagnostic tool validated against the DSM or ICD 10.

The authors highlighted the paucity of evidence about the risk of delirium associated with use of different medications. Studies on opioids, benzodiazepines and antihistamines were of moderate quality (multivariate and matched analyses) and the remainder of the identified evidence was of low or very low quality (univariate analyses). The risk of delirium appeared to be increased with the use of opioids (odds ratio [OR] = 2.5, 95% CI 1.2 to 5.2, two studies), benzodiazepines (OR = 3.0, 95% CI 1.3 to 6.8, one study) and dihydropyridines (OR = 2.4, 95% CI 1.0 to 5.8, one study). Findings with antihistamines were inconclusive (OR = 1.8, 95% CI 0.7 to 4.5, one study). A single high quality RCT showed no increased risk with use of haloperidol (OR = 0.9,95% CI 0.6 to 1.3). A noted limitation of the study was its reliance on a single reviewer.

The study indicates that specific groups of medications may be potential risk factors for development of delirium, however evidence is currently limited and further research is required.

An observational multicentre study by **van den Boogaard et al. (2012)** used routinely available data collected within the first 24 hours of admission to intensive care units (ICU) to develop and validate a method for assessing the risk of delirium developing in patients in critical care, the PRE-DELIRIC (prediction of delirium in ICU patients).

Five ICUs with 3056 patients participated in the study. A total of 1613 consecutive patients in one ICU were used to develop the prediction model and another 549 patients from the same hospital were used for initial validation of the tool; 894 patients from four other hospitals were used for external validation of the tool. PRE-DELIRIC comprised 10 risk factors (age, acute physiology and chronic health evaluation-II score, admission group, coma, infection, metabolic acidosis, use of sedatives, use of morphine, urea concentration, urgent admission).

The main outcome measure was the development of delirium (defined as at least one positive Confusion Assessment Method [CAM]-ICU screening) during ICU admission.

The prognostic ability of PRE-DELIRIC to distinguish between patients with and without delirium was estimated by using the area under the receiver operating characteristics curve (AUROC). The PRE-DELIRIC model was more successful in identifying people at risk of delirium (AUROC = 0.87, 95% CI 0.81 to 0.93) than the clinical prediction of ICU nurses (AUROC = 0.59, 95% CI 0.49 to 0.70) or physicians (AUROC = 0.59, 95% CI 0.49 to 0.70) in a sample of 124 patients assessed within 24 hours of admission to the ICU.

The use of the PRE-DELIRIC method for specialist clinical assessment of the delirium risk in patients in intensive care may be a consideration for future guidance reviews. A risk-assessment tool is not currently recommended.

Key references

Clegg A, Young JB. (2011) Which medications to avoid in people at risk of delirium: a systematic review. Age and Ageing 40: 23–9.
Full text: www.ageing.oxfordjournals.org/content/40/1/23.full.pdf+html

van den Boogaard M, Pickkers P, Slooter AJC et al. (2012) Development and validation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for intensive care patients: observational multicentre study. British Medical Journal 344: e420.
Full text: www.bmj.com/content/344/bmj.e420

1.2 Indicators of delirium: at presentation

No new key evidence was found for this section.

1.3 Interventions to prevent delirium

Multidisciplinary care

A cluster RCT by **Boorsma et al. (2011)** evaluated the impact of a multidisciplinary integrated care intervention on the general quality of care and quality of life of elderly patients with physical or cognitive impairment in residential care facilities.

The RCT involved 10 residential care facilities (340 participating residents) that were randomly assigned to the multidisciplinary integrated care intervention (5 care facilities, 201 residents) or usual care (5 care facilities, 139 residents). The complex intervention was based on identification and monitoring of disabilities caused by chronic disease, and included a comprehensive geriatric assessment of functional health. Data from a web-based Residential Assessment Instrument (RAI) were used to provide a 3-monthly overview of 32 risk-adjusted quality of care indicators, which were summed to provide the first primary outcome for the study.

The second primary outcome for the study was health-related quality of life based on a short-form 12-item version of the Rand Health Insurance Study questionnaire. It should be noted that prevention of delirium was a peripheral focus for the study, and was one item in the 32-item RAI. Blinded assessment of the patients was undertaken at baseline and 6 months after study initiation.

Compared with usual care, application of the integrated care plan was associated with improved quality of care for the elderly residents, with a significantly lower total score of the 32-item quality of care indicator (a lower score indicated better outcomes; mean difference = –6.7, medium effect size = 0.72, p = 0.009). The occurrence of delirium (new or persistent) was reduced in the intervention group (adjusted OR = 0.27, 95% CI 0.10 to 0.69). With respect to limitations, it should be noted that this study used a non-validated method for delirium case ascertainment.

This evidence supports the advice given in NICE CG103 to ensure that care for people at risk of delirium is multicomponent and delivered by a multidisciplinary team.

Key reference

Boorsma M, Frijters DHM, Knol DL et al. (2011) Effects of multidisciplinary integrated care on quality of care in residential care facilities for elderly people: a cluster randomized trial. Canadian Medical Association Journal 183: E724–32.
Full text: www.cmaj.ca/content/183/11/E724.full.pdf+html

Bright light therapy

As part of a multicomponent intervention package to prevent delirium delivered by a multidisciplinary team, NICE CG103 recommends the use of appropriate lighting. Using bright light therapy is not considered in the current guideline.

An RCT by **Ono et al. (2011)** assessed the effect of bright light therapy on the frequency of post-operative arrhythmia and acute delirium in patients hospitalised for an oesophagectomy as corrective treatment for throat cancer. Bright light therapy may have the potential to address the impaired circadian rhythm that is a feature of delirium.

A total of 22 patients (all male) were randomly assigned to the bright light therapy group (n = 10) or the control group (n = 12) the day after surgery, following removal of ventilation. Starting on day 2 after surgery, patients assigned to the bright light therapy group underwent 2 hours of bright light exposure for 4 days. Patients in the control group were kept in normal light conditions. All patients were assessed twice daily from day 1 to day 6 for post-operative arrhythmia and post-operative delirium (using the Japanese version of the NEECHAM confusion scale and defined in accordance with DSM 4th edition text revision [DSM-IV-TR] diagnostic criteria).

Although the frequency of post-operative delirium was lower in the bright light therapy group than the control group (one of 10 patients vs five of 12 patients), the difference did not reach statistical significance. The small study population and negative findings mean that no firm conclusions can be drawn regarding the effect of bright light therapy on the incidence of delirium.

Key reference

Ono H, Taguchi T, Kido Y et al. (2011) The usefulness of bright light therapy for patients after oesophagectomy. Intensive and Critical Care Nursing 27: 158–66.
Abstract: www.intensivecriticalcarenursing.com/article/S0964-3397%2811%2900026-7/abstract

Pain management

Adequate pain management was identified in NICE CG103 as an important component to be included in a multicomponent intervention to prevent delirium.

A systematic review by **Abou-Setta et al. (2011)** of 83 studies (64 RCTs, five non-RCTs and 14 cohort studies) assessed pain management in adults following acute hip fracture. The studies assessed nerve blockade (n = 32), spinal anaesthesia (n = 30), systemic analgesia (n = 3), traction (n = 11), multimodal pain management (n = 2), neurostimulation (n = 2), rehabilitation (n = 1) and complementary and alternative medicine (n = 2). Study outcomes identified by the investigators as clinically important included acute pain (≤ 30 days), chronic pain (≤ 1 year), 30-day mortality and the frequency of serious adverse events (that is, delirium, myocardial infarction, renal failure and stroke).

The effect of regional nerve blockades in the management of acute pain and reducing the risk of delirium was not statistically significant (OR = 1.20, CI 0.27 to 5.40). The systematic review included a large number of varied studies with varying interventions, resulting in a heterogeneous data set, limiting the ability to draw clinically relevant conclusions from this evidence.

A prospective, single centre RCT by **Mouzopoulos et al. (2009)** assessed the prophylactic effect of pain management with fascia iliaca compartment block (FICB) on perioperative delirium after hip surgery in patients (aged ≥ 70 years) who were considered to be at intermediate or high risk of developing delirium. A total of 219 eligible patients were randomly assigned to FICB (n = 108) or placebo (n = 111); both treatment groups were well balanced with respect to the number of patients considered at intermediate (85 and 89 patients respectively) or high (17 and 16 patients respectively) risk of delirium.

The primary endpoint was the incidence of perioperative delirium, which was defined using the DSM-IV and assessed using the CAM. The frequency of delirium in the FICB prophylaxis group (10.78%, 11 of 102 patients) was significantly lower than that recorded in the placebo group (23.8%, 25 of 105 patients, relative risk [RR] = 0.45, 95% CI 0.23 to 0.87). Subgroup analysis showed no difference between FICB prophylaxis and placebo in the incidence of delirium in patients considered at high risk of delirium (RR = 0.84, CI 0.47 to 1.52). By contrast, there was a significant reduction in the frequency of delirium in patients who received FICB prophylaxis (two of 85 patients) compared with placebo (15 of 89 patients) in the intermediate risk patient group (RR = 0.13, CI 0.03 to 0.53).

The authors concluded that FICB prophylaxis prevents the occurrence of delirium in intermediate-risk patients. However, the clinical applicability of these data is limited as the FICB in the study is not comparable with UK practice.

A single centre, double-blinded RCT by **Sieber et al. (2010)** evaluated the impact of restricted sedation depth with propofol during spinal anaesthesia for hip fracture surgery in elderly patients (aged ≥ 65 years) on the incidence of post-operative delirium. The depth of sedation during surgery was assessed using processed electroencephalography with bispectral index (BIS). A total of 114 patients were randomly assigned to light (BIS of ≥ 80) or deep (BIS of approximately 50) sedation with propofol in a ratio of 1:1. Sedation and analgesia for patient positioning and lumbar puncture were first achieved in both groups with either an intravenous bolus of propofol or midazolam with optional fentanyl. No more than 2 mg of midazolam was used, and no further midazolam was given after spinal anaesthesia was initiated. Post-operative delirium was assessed using the CAM.

The incidence of post-operative delirium was significantly reduced in the light sedation group (19%, 11 of 57 patients) compared with the deep sedation group (40%, 23 of 57 patients, p = 0.02). The mean number of days of delirium during hospitalisation was also lower in the light sedation group (0.5 ± 1.5 days) compared with the deep sedation group (1.4 ± 4.0 days, p = 0.01). The authors concluded that use of light sedation with propofol reduced the incidence of post-operative delirium by 50% compared with deep sedation. However, it is worth noting that this US study used different post-operative treatment pathways than would be applicable in the UK, including a high rate of admissions to the intensive care unit for patients with hip fractures. Further, the study used higher doses of midazolam during initial sedation and analgesia in the light sedation group, which may confound the apparent difference in the incidence of delirium between the groups.

Evidence from these studies supports the advice of NICE CG103, and may provide additional information on appropriate pain management.

Key references

Abou-Setta AM, Beaupre LA, Rashiq S et al. (2011) Comparative effectiveness of pain management interventions for hip fracture: a systematic review. Annals of Internal Medicine 155: 234–45.
Full text: www.annals.org/content/155/4/234.full.pdf+html

Mouzopoulos G, Vasiliadis G, Lasanianos N et al. (2009) Fascia iliaca block prophylaxis for hip fracture patients at risk for delirium: a randomized placebo-controlled study. Journal of Orthopaedics and Traumatology 10: 127–33.
Full text: www.springerlink.com/content/333173814113103q/fulltext.pdf

Sieber FE, Zakriya KJ, Gottschalk A et al. (2010) Sedation depth during spinal anesthesia and the development of postoperative delirium in elderly patients undergoing hip fracture repair. Mayo Clinic Proceedings 85: 18–26.
Full text: www.mayoclinproc_85_1_004.pdf

Medication review

A cluster RCT by **Lapane et al. (2011)** assessed the effect of prospective pharmacy-led monitoring to facilitate early identification of potential adverse drug reactions. The study used software developed by the American Society of Consulting Pharmacists Foundation, the Geriatric Risk Assessment MedGuide (GRAM), which correlates the effects of medications with physical, functional and cognitive decline. The software assists in the problem identification process when evaluating complex medication regimens in older patients and incorporates medical monitoring information into a care plan.

Twenty-five nursing homes (monitored by two pharmacies using GRAM) participated in the study during 2003 (intervention group: 12 nursing homes, 1711 patients, usual care group: 13 nursing homes, 1491 patients) and 2004 (intervention group n = 12, 1769 patients, usual care group n = 13, 1552 patients). The pharmacies generated GRAM reports and monitoring plans within 24 hours of patient admission into the nursing home.

The use of GRAM resulted in interventions for 491 residents (50% aged ≥ 85 years, 33% aged 75–84 years and 18% aged 65–74 years). Newly admitted patients in nursing homes in the intervention group had a lower rate of possible delirium compared with those admitted to homes in the usual care group (adjusted hazard ratio [HR] = 0.42, 95% CI 0.35 to 0.52). However, an indirect method was used to ascertain presence of delirium from routine records, and the actual drug changes made to prevent delirium and other adverse effects were not reported in the article. This evidence supports the advice given in NICE CG103 to carry out a medication review for people at risk of delirium.

Key reference
Lapane KL, Hughes CM, Daiello LA et al. (2011) Effect of a pharmacist-led multicomponent intervention focusing on the medication monitoring phase to prevent potential adverse drug events in nursing homes. Journal of the American Geriatrics Society 59: 1238–45.
Full text: www.ncbi.nlm.nih.gov/pmc/articles/PMC3157676/pdf/nihms314926.pdf

Medication

A double-blind, single centre RCT by **Larsen et al. (2010)** evaluated the effectiveness of prophylactic administration of olanzapine in the prevention of post-operative delirium in elderly patients undergoing elective knee or hip replacement surgery (olanzapine did not have marketing authorisation for this indication at the time of publication of this Evidence Update). A total of 495 patients (aged ≥ 65 years) were randomly assigned to receive olanzapine 5 mg (n = 243) or placebo (n = 252) immediately before and after surgery. The primary outcome was the frequency of delirium, defined in accordance with the DSM 3rd edition revision (DSM-III-R) criteria; secondary outcomes included the time-to-onset, duration and severity (assessed using the Delirium Rating Scale-Revised-98 [DRS-R-98] score) of delirium.

For patients undergoing knee or hip replacement surgery, the incidence of post-operative delirium was lower in the olanzapine group (14.3%, n = 28) compared with the placebo group (40.2%, n = 82, 95% CI 17.6 to 34.3, p < 0.0001). Kaplan-Meier graphical analysis showed that the time-to-onset of delirium was longer for patients in the olanzapine group compared with the placebo group (p < 0.0001). However, delirium that occurred was more severe (DRS-R-98 score = 16.44 vs 14.5, p = 0.02) and of a longer duration (2.2 days vs 1.6 days, p = 0.02) with olanzapine than placebo.

Although not statistically significant, the authors noted that there were slightly more post-operative cardiac complications with olanzapine treatment compared with placebo. Findings from this study were limited in that the patients were only followed-up for 4 days.

This evidence is consistent with current guidance, which recommends new research to define the role of drugs to prevent delirium.

Key reference

Larsen KA, Kelly SE, Stern TA et al. (2010) Administration of olanzapine to prevent postoperative delirium in elderly joint-replacement patients: a randomized, controlled trial. Psychosomatics 51: 409–18.
Full text: www.psy.psychiatryonline.org/cgi/reprint/51/5/409

Melatonin

The effect of melatonin (a pineal gland hormone that may be involved in the sleep/wake cycle) on the incidence of delirium was investigated in a double-blind RCT by **Al-Aama et al. (2011)**. Melatonin did not have UK marketing authorisation for this indication at the time of publication of this Evidence Update. A total of 145 patients (aged ≥ 65 years) admitted through the emergency department into a tertiary care hospital were randomly assigned to receive melatonin 0.5 mg (n = 72) or placebo (n = 73) every night for 14 days or up to discharge.

Patients were assessed every 24–48 hours for delirium, the primary outcome measure, using CAM and the Memorial Delirium Assessment Scale. Patients treated with melatonin had a lower risk of delirium compared with the placebo-treated patients (12.0% vs 31.0%, $p = 0.014$). Furthermore, after exclusion of patients with prevalent delirium at study enrollment (nine patients in the placebo group and five patients in the melatonin group), administration of melatonin still showed a lower risk for delirium (3.6% vs 19.2%, $p < 0.02$).

The authors concluded that nightly administration of low-dose melatonin to patients in acute care units may prevent the onset of delirium. Among recommended interventions to prevent delirium, NICE CG103 advises promotion of good sleep patterns and sleep hygiene. However, no statistically significant effect of melatonin on sleep was seen in this study, and further research is required on the postulated mechanism of action and role of melatonin.

Key reference

Al-Aama T, Brymer C, Gutmanis I et al. (2011) Melatonin decreases delirium in elderly patients: a randomized, placebo-controlled trial. International Journal of Geriatric Psychiatry 26: 687–94.
Abstract: www.onlinelibrary.wiley.com/doi/10.1002/gps.2582/abstract

1.4 Indicators of delirium: daily observations

No new key evidence was found for this section.

1.5 Diagnosis (specialist clinical assessment)

No new key evidence was found for this section.

1.6 Treating delirium

Delivery of care

A cluster RCT by **Marcantonio et al. (2010)** assessed the potential of a nurse-led delirium abatement programme (DAP) to reduce the duration of delirium in patients newly admitted into post-acute care units. The DAP intervention included assessment of delirium within 5 days of admission, identification and correction of common reversible causes of delirium, avoidance of complications associated with delirium, and recovery of function.

Eight facilities were randomly assigned to DAP or usual care. At DAP sites, all nurses in the unit received mandatory training on the DAP. A total of 7794 patients were admitted into the facilities during the course of the study; 2249 patients at the usual care sites and 2495 at the DAP sites were eligible for the study and completed a delirium assessment.

Of these patients, 175 at the usual care sites and 282 at the DAP sites were confirmed by trained researchers as having delirium, and proxy consent was provided for entry into the study. The primary outcome for this study was the persistence of delirium at 2 weeks and 1 month after admission to the post-acute care unit; assessments were undertaken by a blinded assessor using the CAM.

Delirium was detected by nurses in 41% of patients at DAP sites compared with 12% in the usual care sites ($p < 0.001$). However, implementation of the DAP had no impact on the duration of delirium at 2 weeks (68% with DAP vs 66% with usual care) or 1 month (60% with DAP vs 51% with usual care, $p \geq 0.20$). Although NICE CG103 recommends multicomponent interventions delivered by a multidisciplinary team to prevent delirium (see section 1.3), similar advice is not given for treatment of established delirium. Evidence from this study supports the current guidance.

Key reference

Marcantonio ER, Bergmann MA, Kiely DK et al. (2010) Randomized trial of a delirium abatement program for postacute skilled nursing facilities. Journal of the American Geriatrics Society 58: 1019–26. Abstract: www.onlinelibrary.wiley.com/doi/10.1111/j.1532-5415.2010.02871.x/abstract

Pharmacological treatment

Haloperidol, olanzapine and risperidone

A prospective follow-up single-blind RCT by **Grover et al. (2011)** evaluated the efficacy and safety of olanzapine and risperidone compared with haloperidol in patients with delirium (haloperidol, olanzapine and risperidone did not have UK marketing authorisation for this indication at the time of publication of this Evidence Update). A total of 64 patients were randomly assigned to receive treatment with haloperidol (0.25–10.0 mg, n = 20, mean age 44.1 years), risperidone (0.25–4.0 mg, n = 21, mean age 46.5 years) or olanzapine (1.25–20.0 mg, n = 23, mean age 45.4 years).

The primary measure of outcome was the DRS-R-98. Patients treated with olanzapine, risperidone or haloperidol showed significant reduction in DRS-R-98 severity scores over 6 days (−4.126, −3.922 and −4.018 respectively, $p < 0.001$ for all three treatments), but with no significant differences between the treatment groups ($p = 0.282$). The authors concluded that all three medications were equally effective in the treatment of delirium.

This study was limited in that it had no placebo control arm so provides no evidence that the treatments shortened the duration of delirium. Further, randomisation allocation concealment was unclear with blinding of assessors only, duration of patient follow-up was limited to 6 days, and the patient numbers in each treatment group were low. In addition, the relatively young patient population was unrepresentative of the 'real-world' population that is usually affected by delirium.

Evidence from this study is consistent with NICE CG103, which recommends haloperidol and olanzapine for the treatment of delirium. Although the study provides some evidence of similar outcomes with risperidone, further studies that overcome the limitations of this evidence are required before the clinical value of risperidone in the treatment of delirium can be established. NICE CG103 contains a detailed research recommendation about the most effective medication for treating delirium.

Key references

Grover S, Kumar V, Chakrabarti S (2011) Comparative efficacy study of haloperidol, olanzapine and risperidone in delirium. Journal of Psychosomatic Research 71: 277–81.
Abstract: www.jpsychores.com/article/S0022-3999%2811%2900043-2/abstract

Rivastigmine

A double-blinded RCT by **van Eijk et al. (2010)** evaluated the effect rivastigmine, a cholinesterase inhibitor, on the duration of delirium in critically ill patients. Rivastigmine did not have UK marketing authorisation for this indication at the time of publication of this Evidence Update. A total of 6724 patients from six hospitals were screened, of which 648 were confirmed as having delirium (based on the CAM-ICU); 109 patients were randomly assigned to receive treatment with rivastigmine (n = 55, mean age 68 years) or placebo (n = 54, mean age 70 years).

In addition to the usual care based on haloperidol (given to patients in both groups), patients in the rivastigmine group received a starting dose of rivastigmine 1.5 mg twice daily, which was incrementally increased to 6 mg twice daily from day 10 onwards. The primary outcome assessment was the duration of delirium during hospitalisation. Data from the study were reviewed by the unblinded data safety and monitoring board (DSMB) every 3 months.

After the fourth interim analysis of data (104 patients allocated to treatment), the DSMB recommended termination of the study due to a higher incidence of mortality in the rivastigmine group (n = 12, 22%) compared with the placebo group (n = 4, 8%, p = 0.07). As such, the planned sample size of 440 patients was not attained. Furthermore, the median duration of delirium was longer with rivastigmine (5.0 days, interquartile range [IQR] 2.7–14.2) compared with placebo (3.0 days, IQR 1.0–9.3, p = 0.06), and rivastigmine-treated patients stayed in the intensive care unit for significantly longer than control patients (15 days, IQR 9–30 vs 8 days, IQR 3–17, p < 0.0001).

Overall, findings from this study showed that rivastigmine does not reduce the duration of delirium in critically ill patients and may be associated with increased mortality. This evidence is consistent with NICE CG103, which does not include rivastigmine as a recommended treatment for delirium.

Key reference

van Eijk MMJ, Roes KCB, Honing MLH et al. (2010) Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial. The Lancet 376: 1829–37.
Abstract: www.thelancet.com/journals/lancet/article/PIIS0140-6736%2810%2961855-7/abstract#

Benzodiazepines

A Cochrane review by **Lonergan et al. (2009)** of randomised, blinded trials evaluated the efficacy and safety of benzodiazepines in the treatment of delirium not associated with the withdrawal of alcohol.

Only one study met the selection criteria of the review. This study compared the effectiveness of lorazepam (a short-acting benzodiazepine that did not have UK marketing authorisation for this indication at the time of publication of this Evidence Update) with dexmedetomidine (a selective alpha-2-adrenergic receptor agonist that is not currently available for use in the UK) in the treatment of delirium in mechanically ventilated patients (n = 106) in intensive care units. The effectiveness of the medications was assessed based on duration of coma-free and delirium-free days.

A total of 52 patients were treated with dexmedetomidine and 51 patients were treated with lorazepam; the study did not have a placebo control group. Patients treated with dexmedetomidine had an increased number of days free from delirium and coma (mean 7 days, range 1–10 days) compared with lorazepam-treated patients (mean 3 days, range 1–6 days, p = 0.01). The authors noted the scarcity of evidence, and that further research is

needed for the use of benzodiazepines in non-alcohol withdrawal related delirium. Evidence from this review is consistent with NICE CG103, which does not include benzodiazepines as recommended treatment for delirium.

Key reference
Lonergan E, Luxenberg J, Areosa Sastre A (2009) Benzodiazepines for delirium. Cochrane Database of Systematic Reviews Issue 4: CD006379.
Full text: www.onlinelibrary.wiley.com/doi/10.1002/14651858.CD006379

1.7 Information and support

No new key evidence was found for this section.

2 New evidence uncertainties

During the development of the Evidence Update, the following evidence uncertainties were identified that have not previously been listed on the NHS Evidence UK Database of Uncertainties about the Effects of Treatments (DUETs).

Risk factor assessment

- The risk of delirium associated with commonly prescribed medicines. www.library.nhs.uk/DUETs/viewResource.aspx?resid=411897

Interventions to prevent delirium

- Bright light therapy for patients at risk of delirium. www.library.nhs.uk/DUETs/viewResource.aspx?resid=411898
- Nerve blockade for reducing the incidence of delirium. www.library.nhs.uk/DUETs/viewResource.aspx?resid=411899

Treating delirium

- The role of benzodiazepines in the control of non-alcohol related delirium in hospitalised patients www.library.nhs.uk/DUETs/viewResource.aspx?resid=412261

Further evidence uncertainties for delirium can be found at www.library.nhs.uk/duets/ and in the NICE research recommendations database at www.nice.org.uk/research/index.jsp?action=rr.

DUETs has been established in the UK to publish uncertainties about the effects of treatment that cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.

Appendix A: Methodology

Scope

The scope of this Evidence Update is taken from the scope of the reference guidance:

- Delirium. NICE clinical guideline 103 (2012). Available from www.nice.org.uk/guidance/CG103

Searches

The literature was searched to identify studies and reviews relevant to the scope. Searches were conducted of the following databases, covering the dates 17 August 2009 (the end of the search period of the most recent Annual Evidence Update) to 28 November 2011:

- CINAHL
- Cochrane Database of Systematic Reviews – Cochrane Library
- Embase
- MEDLINE
- NHS EED
- PsycINFO

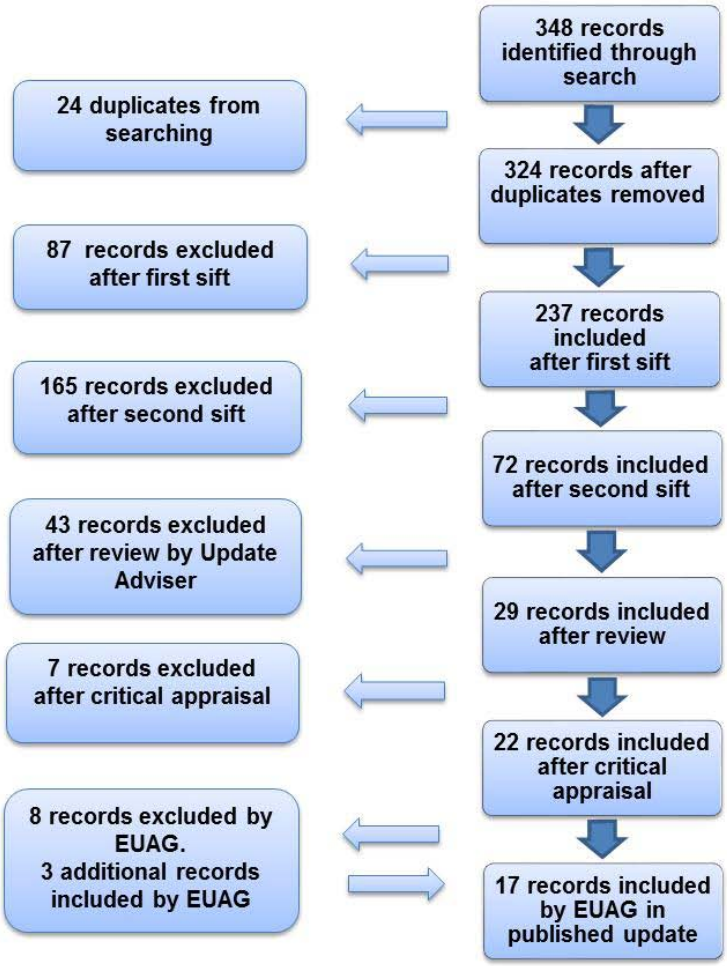
Table 1 provides details of the MEDLINE search strategy used, which was adapted to search the other databases listed above. The search strategy for this EU was based on the scope and search strategy from NICE CG103. The search strategy was used in conjunction with validated Scottish Intercollegiate Guidelines Network search filters for RCTs and systematic reviews (www.sign.ac.uk/methodology/filters.html).

Three other studies (Cole et al. 2009, Fong et al. 2009, van den Boogaard et al. 2012) were also identified outside of the literature search. Figure 1 provides details of the evidence selection process. The long list of evidence excluded after review by the Update Adviser, and the full search strategies, are available on request from contactus@evidence.nhs.uk

Table 1 MEDLINE search strategy (adapted for individual databases)

1	Deliri$.ti,ab.
2	(acute adj2 confusion$) or (“acute confusional state”) .tw.
3	acute adj2 “brain syndrome”.tw.
4	acute adj2 “brain failure”.tw.
5	acute adj2 “psycho-organic syndrome”.tw.
6	acute adj2 “organic psychosyndrome”.tw.
7	terminal$ adj restless$.tw.
8	Toxic confus$.tw.
9	Delirium/
10	Confusion/
11	Or/1-10
12	*psychoses, alcoholic/ or *alcohol withdrawal delirium/
13	*substance withdrawal syndrome/
14	12 or 13
15	11 not 14

Figure 1 Flow chart of the evidence selection process



EUAG – Evidence Update Advisory Group

Appendix B: The Evidence Update Advisory Group and NHS Evidence project team

Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of subject experts who review the prioritised evidence obtained from the literature search and provide the commentary for the Evidence Update.

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