
UNIVERSITÉ DE LAUSANNE – FACULTÉ DE BIOLOGIE ET DE MÉDECINE

INSTITUT UNIVERSITAIRE DE MÉDECINE SOCIALE ET PRÉVENTIVE

CENTRE D'ÉPIDÉMIOLOGIE CLINIQUE

Directeur : Professeur Fred Paccaud

DEPARTEMENT DE PSYCHIATRIE

SERVICE DE PSYCHIATRIE DE LIAISON

Chef de département : Professeur Patrice Guex

Delirium : Guidelines for general hospitals

THÈSE

préparée sous la direction du
Professeur associé Bernard Burnand
et du
Professeur Friedrich Stiefel

et présentée à la Faculté de biologie et de médecine de
l'Université de Lausanne pour l'obtention
du grade de

DOCTEUR EN MÉDECINE

WM
204
M.c

par
Laurent Michaud

BHTE 3441

Médecin diplômé de la Confédération Suisse
Originaire d'Avenches (VD)

Lausanne

2007

Etat confusionnel aigu à l'hôpital général : développement de recommandations pour la pratique clinique

("Delirium: Guidelines for general hospitals" Article publié dans le Journal of Psychosomatic Research)

Introduction

L'Etat Confusionnel Aigu (ECA) est très fréquent à l'hôpital général. Malgré ses conséquences majeures en terme de morbidité, de mortalité et d'utilisation des services de santé, il est sous-diagnostiqué et sous-traité. Dans le but d'améliorer sa prise en charge chez le patient adulte, des Recommandations pour la Pratique Clinique (RPC) couvrant les aspects de prévention, de diagnostic et de traitement ont été développées.

Méthode

Une recherche de littérature a d'abord identifié les RPC, les revues systématiques, les essais contrôlés randomisés et les études de cohorte sur l'ECA. La qualité des RPC et des revues systématiques ainsi que le niveau de preuve des études ont été détaillés. Un document couvrant l'ensemble de la prise en charge de l'ECA a été élaboré à partir des sources de meilleure qualité pour chaque sujet.

Environ 400 recommandations ont ensuite été tirées de ce document. Elles ont été soumises à un panel multidisciplinaire d'experts des Hospices-CHUV. Les membres du panel ont évalué l'appropriation des recommandations en utilisant une approche valide et explicite. Cette approche prenait en compte tant le niveau de preuve des recommandations que l'expérience clinique des membres du panel. Les recommandations issues de ce processus ont été catégorisées du plus haut au plus bas degré de recommandation (de A à C) en tenant compte d'une part des niveaux de preuve, d'autre part du degré de consensus entre les experts.

Le document complet ainsi que les recommandations ont finalement été soumis à deux experts internationaux reconnus dans le domaine de l'ECA. Leurs remarques ont été prises en compte dans le document définitif. Ce document, ainsi qu'un résumé des recommandations et un algorithme de prise en charge de l'ECA, ont été mis à disposition des soignants sur l'Intranet des Hospices-CHUV.

Résultats :

La plupart des recommandations étaient basées sur des preuves de faible niveau (1.3 % d'essais contrôlés randomisés et de revues systématiques; 14.3% d'essais non randomisés et 84.4 % d'études de cohorte et d'opinions d'experts). Une large majorité de ces recommandations (71.1 %) a toutefois été considérée comme appropriée par les experts. La fréquence et l'utilité du dépistage de l'ECA, le rôle de la contention physique et les indications à l'utilisation de benzodiazépines ont été les sujets les plus controversés au sein du panel. Les données de la littérature et les résultats de la consultation du panel d'experts tendent à favoriser la prévention de l'ECA et sa prise en charge non pharmacologique. Par ailleurs, l'halopéridol reste le traitement de premier choix, le rôle des antipsychotiques atypiques étant toujours incertain.

Discussions :

Ces RPC sont les premières, à couvrir tous les champs de l'ECA, de la prévention aux traitements pharmacologiques. Elles sont basées sur une méthodologie originale combinant les preuves existantes et une consultation formalisée d'experts. Cette méthodologie a permis de pallier partiellement à l'absence de preuve de bon niveau pour la plupart des sujets étudiés. Ce travail a par ailleurs mis en lumière de nombreux sujets controversés, qui devraient être la cible de prochaines recherches.

Au niveau local, ces RPC visaient à améliorer la qualité des soins. Une étude est en cours dans deux services du CHUV pour évaluer l'effet de leur implantation sur les pratiques cliniques.

Review article

Delirium: Guidelines for general hospitals

Laurent Michaud^{a,b}, Christophe Büla^c, Alexandre Berney^b, Vincent Camus^{d,e},
Rachel Voellinger^{a,b}, Friedrich Stiefel^b, Bernard Burnand^{a,*},
the Delirium Guidelines Development Group¹

^aClinical Epidemiology Center, Institute of Social and Preventive Medicine, University Hospital, Lausanne, Switzerland

^bPsychiatry Service, University Hospital, Lausanne, Switzerland

^cService of Geriatric Medicine, CHUV and CUTR Sylvana, Epalinges, Switzerland

^dService of Old Age Psychiatry, University Hospital, Lausanne, Switzerland

^eClinique Psychiatrique Universitaire, Centre Hospitalier Régional Universitaire and Faculté de Médecine, Université François-Rabelais, Tours, France

Received 30 May 2006; received in revised form 25 September 2006; accepted 3 October 2006

Abstract

Objective: Delirium is highly prevalent in general hospitals but remains underrecognized and undertreated despite its association with increased morbidity, mortality, and health services utilization. To enhance its management, we developed guidelines covering all aspects, from risk factor identification to preventive, diagnostic, and therapeutic interventions in adult patients. **Methods:** Guidelines, systematic reviews, randomized controlled trials (RCT), and cohort studies were systematically searched and evaluated. Based on a synthesis of retrieved high-quality documents, recommendation items were submitted to a multidisciplinary expert panel. Experts scored the appropriateness of recommendation items, using an evidence-based, explicit, multidisciplinary panel approach. Each recommendation was graded according to this

process' results. **Results:** Rated recommendations were mostly supported by a low level of evidence (1.3% RCT and systematic reviews, 14.3% nonrandomized trials vs. 84.4% observational studies or expert opinions). Nevertheless, 71.1% of recommendations were considered appropriate by the experts. Prevention of delirium and its nonpharmacological management should be fostered. Haloperidol remains the first-choice drug, whereas the role of atypical antipsychotics is still uncertain. **Conclusions:** While many topics addressed in these guidelines have not yet been adequately studied, an explicit panel and evidence-based approach allowed the proposal of comprehensive recommendations for the prevention and management of delirium in general hospitals.

© 2007 Elsevier Inc. All rights reserved.

Keywords: Diagnosis; Treatment; Clinical epidemiology; Confusional state; Delirium; Nonpharmacological therapy; Prevention; Screening; Systematic review

* Corresponding author. Institut Universitaire de Médecine Sociale et Préventive (IUMSP), Bugnon 17, CH-1005 Lausanne, Switzerland. Tel.: +41 21 314 7255; fax: +41 21 314 4954.

E-mail address: bernard.burnand@chuv.ch (B. Burnand).

¹ The members of the Delirium Guidelines Development Group are as follows: Laurent Michaud, MD (Clinical Epidemiology Center, Institute of Social and Preventive Medicine, University Hospital, Lausanne, Switzerland); Psychiatry Service, University Hospital, Lausanne, Switzerland); Alexandre Berney, MD (Psychiatry Service, University Hospital, Lausanne, Switzerland); Christophe Büla, MD (Service of Geriatric Medicine, CHUV and CUTR Sylvana, Epalinges, Switzerland); Vincent Camus, MD (Service of Old Age Psychiatry, University Hospital, Lausanne, Switzerland); Clinique Psychiatrique Universitaire, Centre Hospitalier Régional Universitaire and Faculté de Médecine, Université François-Rabelais, Tours, France); Rachel Voellinger MD (Clinical Epidemiology Center, Institute of Social and Preventive Medicine, University Hospital, Lausanne, Switzerland);

Psychiatry Service, University Hospital, Lausanne, Switzerland); Friedrich Stiefel, MD (Psychiatry Service, University Hospital, Lausanne, Switzerland); Bernard Burnand MD, MPH (Clinical Epidemiology Center, Institute of Social and Preventive Medicine, University Hospital, Lausanne, Switzerland); Thierry Buclin, MD (Division of Clinical Pharmacology, University Hospital, Lausanne, Switzerland); François Chevalley, MPH (Orthopedic Department, University Hospital, Lausanne, Switzerland); Olivier Lamy, MD (Service of Internal Medicine, University Hospital, Lausanne, Switzerland); Yves Dorogi, RN (Psychiatry Service, University Hospital, Lausanne, Switzerland); Mauro Oddo, MD (Intensive Care Department, University Hospital, Lausanne, Switzerland); Patrick Schoettker, MD (Department of Anesthesiology and Prehospital Emergency Medicine University Hospital, Lausanne, Switzerland); Joseph Ghika, MD (Service of Neurology, University Hospital, Lausanne, Switzerland); Armin von Gunten, MPhil, MD (Service of Old Age Psychiatry, University Hospital, Lausanne, Switzerland).

Introduction

Delirium is an acute change in cognition with altered consciousness and impaired attention that fluctuates over time [1]. It is a frequent condition seen in general hospitals. Its prevalence ranges from 11% to 33% on admission [2–4], and its incidence during hospital stay ranges between 3% and 56% [2,3,5,6]. Delirium is associated with adverse outcomes, including increased morbidity, increased mortality, and increased health services utilization [7–15]. Despite these observations, delirium recognition rates are low (12–43%) [4,16–18], and its management remains inadequate in up to 80% of patients [16]. This suggests lack of preventive and screening activities, missed diagnoses, and inappropriate management of diagnosed delirium. Beneficial changes following guidelines implementation have been demonstrated in several domains [19]. Following the adaptation [20] and implementation [21] of guidelines for depression in general hospitals, we undertook the development of new specific guidelines covering all relevant aspects of the management of delirium among adult patients in general hospitals.

Methods

We chose to start with a strategy of adapting published guidelines, where available, in order not to perform a new valid high-quality work that had been previously conducted [22]. Thus, we first searched to identify high-quality clinical practice guidelines and completed our sources of information with systematic reviews and, in the absence of such documents, clinical trials and cohort studies, when appropriate. The main steps of guidelines development were: (a) a systematic literature search; (b) the rating of each basic element of recommendation (recommendation item) derived from the literature by a multidisciplinary expert panel, using nominal group technique [23]; (c) the incorporation of approved recommendation items in specific recommendations; and (d) a review of the final recommendations by international experts. This process was conducted by the first author, a psychiatry resident, assisted by a development team (senior psychiatrist and senior clinical epidemiologist), in collaboration with a multidisciplinary expert panel representative of the future users of the guidelines. The panel included 14 experts: four psychiatrists (two specialized in old age psychiatry), one geriatrician, one psychiatric nurse, one neurologist, one intensive care clinician, one intensive care nurse, one general internist, one anesthetist, one orthopedic surgeon, one clinical epidemiologist, and one pharmacologist.

Literature search

The aim of this search was to identify existing guidelines and systematic reviews on delirium in adults and in the elderly. Delirium in children was beyond the scope of this research project. Two different search strategies were

performed, based on a previously developed and tested strategy (www.chuv.ch/ceplic/RPC_strat.html). Medline, PsychINFO, Web of Knowledge, EMBASE, and the Cochrane Library databases were used to identify publications in English and French from 1997 to August 2004 with the keywords “delirium,” “confusion,” “hallucination,” and “delusion.” Articles were selected through a three-step screening process based on reviews of the title, abstract, and content of the paper. Additional references from bibliographies were reviewed and included if considered of relevance. The sites of the National Guideline Clearinghouse (www.guideline.gov), the Guidelines International Network (www.g-i-n.net), the National Institute for Clinical Excellence (www.nice.org.uk), the New Zealand Guidelines Group (www.nzgg.org.nz), the Scottish Intercollegiate Guidelines Network (www.sign.ac.uk), and national psychiatric associations were examined. In addition, specific searches were developed for topics (such as risk factors for delirium, prevention of delirium, and physical restraints) not covered by recent guidelines or systematic reviews. Medline, PubMed, EMBASE, and the Cochrane Library were used without time limitations for these searches. Detailed literature search strategies are available from the authors on request. The literature search was updated for the submission of this article. It was repeated using the same methodology for the period from January 2004 to February 2006.

Results of literature search

Searches on guidelines identified 1550 papers, including 519 articles in Medline, 67 articles in PsychINFO, 724 articles in the Web of Knowledge, and 240 articles in EMBASE. Four guidelines were identified in Medline [24–27]. No additional guidelines were found in PsychINFO, the Web of Knowledge, or EMBASE. One additional guideline was identified on an Internet site [28], and another was identified through contacts with delirium experts [29]. Searches on systematic reviews identified 3178 papers, including 2099 articles in Medline, 334 articles in PsychINFO, 724 articles in the Web of Knowledge, and 21 articles in the Cochrane Library. Sixteen systematic reviews [7,12,30–43] were found in Medline, one in the Web of Knowledge [44], one in EMBASE, [45] and one in the Cochrane Library [46]. No additional systematic review was found in PsychINFO. One systematic review was identified on an Internet site [47]. Altogether, 5 guidelines and 19 systematic reviews were therefore identified. The results of literature search update are not detailed here because of space limitations but are available from the authors on request. No new guidelines were retrieved by updating. Five systematic reviews were identified [48–52]. The quality of retrieved guidelines was evaluated with the Appraisal of Guidelines for Research and Evaluation instrument (www.agreustrust.org) by two independent raters (L.M. and R.V.). Systematic reviews were evaluated by the first author using the Cochrane Library criteria [53] and existing references [54,55]. The six most important domains assessed were: (a) clarity of the clinical

question examined; (b) quality and extent of the literature search; (c) inclusion criteria; (d) quality of the methodological evaluation of retrieved studies; (e) review method; and (f) meta-analysis, if present. Based on this evaluation, their results were considered relevant or not to drawing related recommendation items.

Development of recommendations

The retrieved literature was synthesized by selecting, for each topic (i.e., prevention, risk factors, screening, diagnosis, and management), the most appropriate source of evidence, according to the quality of the study and the level of evidence. Based on the quality of available literature, the level of evidence according to the Oxford classification (see Table 1 and www.ccbm.net/levels_of_evidence.asp) was determined for each recommendation item. Drafts of recommendation items were reviewed by and discussed with the expert panel. About 400 recommendation items, covering risk factors, prevention, identification, diagnoses, and management of delirium, were identified. In the first round, the appropriateness of recommendation items was rated separately by each member of the expert panel, using an adapted RAND appropriateness method [23]. The experts scored each recommendation item on a Likert scale ranging from 1 (*extremely appropriate*) to 9 (*extremely inappropriate*). The experts were asked to take into account in their vote both the result of literature synthesis (with its level of evidence) and their clinical experience. Votes were aggregated into four categories (*appropriate*, *uncertain*, *inappropriate*, and *disagreement*) according to the median vote of the experts and the level of intrapanel disagreement. Disagreement was defined as the occurrence of at least 4 of 14 experts voting in one to three categories and at least four others voting in seven to nine categories. In the absence of disagreement, a recommendation item was classified as appropriate (median=1–3), uncertain (median=4–6), or

inappropriate (median=7–9). All items on which disagreement occurred were classified as uncertain. After analyzing the first round of ratings, the experts received an individualized feedback document featuring their own initial rating and the panel median rating for each recommendation item. Recommendation items with disagreement were discussed by the experts at two additional panel meetings and were subsequently rated individually a second time.

Following this process, recommendations were graded for each recommendation item through a rating that combined the level and quality of evidence, and the degree of appropriateness and consensus among the experts. The grade of recommendation was based on the level of evidence (i.e., Oxford classification: Level I=*Grade A*; Levels II and III=*Grade B*; Levels IV and V=*Grade C*). In the case of a very high appropriateness rating (defined by a median vote of 1, i.e., extremely appropriate) and consensus among the experts, a superior grade of recommendation was chosen (e.g., Level II on the Oxford classification with very high appropriateness rating and consensus among panelists implies a Grade A recommendation). Grading definitions are shown in Table 1. The final draft was reviewed by two international experts in delirium and revised according to their comments. The results of literature update were synthesized by the first author and discussed with all authors. Some changes were introduced in the text, and relevant modifications were submitted to the expert panel. Changes in recommendations resulting from the update are mentioned in the tables.

Presentation of guidelines

The guidelines consist of a full-text document and a summary algorithm developed for implementation, which are both accessible to hospital staff through the intranet system of the University Hospital of Lausanne. To enhance readability, the present paper focuses on the most important recommendations, while the entire guidelines are summar-

Table 1
Levels of evidence and grades of recommendation

Levels of evidence*	Grades of recommendation
Level I RCT Systematic reviews of RCT (homogeneous) Systematic reviews	Grade A: Based on fair evidence or on acceptable evidence with a high consensus between experts (Level I evidence, or Level II/III evidence with high consensus)
Level II Non-randomized controlled trials	Grade B: Based on acceptable evidence or on sufficient evidence with a high consensus between experts (Level II/III evidence, or Level IV/V evidence with high consensus)
Level III Prospective cohort studies	
Level IV Retrospective cohort studies and case-control studies	Grade C: Based on acceptable evidence (Level IV/V evidence with sufficient consensus between experts)
Level V Case reports and published expert opinions	Grade I (i): There is no sufficient evidence or no sufficient consensus to formulate any recommendation (i.e., studies or expert opinions are contradictory) (Note: In this case, the decision must be made by considering particular circumstances and the clinical experience of the practitioner.)

* Data from the Oxford classification (www.ccbm.net/levels_of_evidence.asp).

ized in Tables 2–8. References could not be included in the current tables for publication, but the full-text document indicates references for every recommendation (available from the authors on request).

Results

The 392 recommendation items on delirium that were submitted to the expert panel resulted in about 5500 ratings (response rate=94%). Most recommendation items had a low level of evidence (Level I, 1.3%; Level II, 6.1%; Level III, 8.2%; Level IV, 6.6%; Level V, 77.8%). However, of the recommendation items, 71.1% were considered by the experts as appropriate, 21.7% were considered uncertain, and 7.2% were considered inappropriate. A permanent disagreement remained among the experts in only 3.8% of

propositions, which were classified into the uncertain recommendation. The dispersion of votes was shown to be related to the level of evidence, with interquartile range (IQR) being 1 for Level I, 4 for Level V, and between 2 and 3 for Levels II–IV. On the other hand, this dispersion was similar between the experts working in the field of psychiatry and those practicing somatic medicine (IQR=4). The frequency and usefulness of screening for delirium, the role of physical restraints, the benefits of electroencephalogram (EEG) and lumbar puncture (LP), and selected indications for benzodiazepines in agitated delirium in younger adults were the most controversial topics among the panelists.

Risk factors

One systematic review studied risk factors for delirium [30]. Since this publication, 21 prospective studies have

Table 2
Risk factors for delirium

	Predisposing factors (on admission)	Grade	Precipitating factors (during stay)	Grade	Aggravating factors	Grade
General factors	Age >70 years	A				
	Severity of illness	A				
Central nervous system factors	Cognitive impairment	A	Stroke	A		
	Depression in the elderly	B	Central nervous system pathological process	B		
	Sensory impairment	B				
	Previous stroke	B				
Metabolic factors	Preoperative electrolyte disturbances	B	Metabolic, electrolyte, and endocrine disturbances	A		
	Preoperative dehydration	B	Fever	C		
	Dehydration	C				
Other systemic factors			Infections	A		
			Pain	B		
			Traumatism	C		
			Hypoperfusion, hypoxia, and cardiac or pulmonary failure	B		
			Organ failure	C		
Substance-related factors	Alcohol abuse	B ^a	Drug or toxic withdrawal	A		
	Number of drugs before admission	B	Number of drugs and number of psychotropic drugs	B		
	Number of psychotropics before admission	B	Anticholinergic drugs	B		
			Opioids	C		
Environmental factors				B	Intensive care unit	B
	Sensory deprivation or overload	C ^a	Physical restraints	B		
					High number of room changes	B
					Absence of a clock	B
					Absence of glasses	B

Please refer to Table 1 for grading definitions.

Patients who are older (>70 years), severely ill, or cognitively impaired are most vulnerable to delirium. They should be first targeted for the identification of other risk factors (B).

Whenever possible, cognitive impairment, fever, dehydration, pain, and electrolytic disturbances should be systematically detected using, for example, a checklist (B).

New drug treatments should be introduced with caution (C).

Any treatment change should be considered with caution, especially with regard to psychotropic drugs, anticholinergic drugs, and opioids (C).

Pain should be adequately managed (C).

Physical restraints should be avoided (C).

In surgical patients, postoperative perfusions and transfusions should be used cautiously (C).

^a Recommendation modified by the updating of guidelines.

Table 3
Recommendations for the prevention of delirium

General recommendations	Specific recommendations	Grade
Detect and treat cognitive impairment	Routine screening of cognitive functions and delirium, whenever possible, using standardized instruments (e.g., MMSE or BOMC on admission, and CAM during hospital stay)	A
Favor high-quality sleep	Cognitively stimulating activities adapted to the patient	C
	Nonpharmacological sleep promotion	A
	Noise reduction; use of low-level lighting; avoidance of constant lighting	A
Minimize drug side effects	Maintenance of a normal sleep–wake cycle	A
	Limitation of the total number of drugs	C
	Avoidance or cautious use of the following medications: <ul style="list-style-type: none"> • Psychotropics, especially hypnotics and benzodiazepines • Anticholinergic drugs • Opioids 	C
Prevent/correct electrolytic disturbances and dehydration	Stimulation of adequate hydration; use of fluid balance charts	A
	Biochemical screening; early management of electrolyte disturbances	B
	Hypodermoclysis if oral intake is inadequate	C
Improve communication and orientation	Regular verbal communication; use of short sentences; frequent information on place, reason for hospitalization, and daily activities; whenever possible, involvement of patient in the process of care; information and reassurance about medical procedures	B
	“On-time” clocks and calendars; familiar artifacts, whenever possible (i.e., posters); avoidance of ward or room transfers; continuity of care	B
Limit sensory underload or overload	Screening for visual and hearing impairment; provision of visual and hearing aids; adequate lighting; use of nightlights; avoidance of blind rooms (without windows)	A
Involve and inform significant others	Information of proxies regarding delirium; encouragement of visits to the patient and involvement in orientation; nursing and feeding; support of proxies	C
Avoid malnutrition and vitamin deficiencies	Nutritional support and/or vitamin supplements for high-risk groups (i.e., B vitamins for alcoholic abusers)	B
Prevent or treat withdrawal	If middle-aged adults are at high risk for alcohol withdrawal, prevention with benzodiazepines	A
	Clomethiazole for prevention of withdrawal in the elderly	B
	Systematic screening for alcohol abuse	B
Do not use physical restraints	Protocol for physical restraints	A
Favor mobilization	Avoidance of immobilization; education regarding hazards of bed rest	A
	Limiting the use of catheter and intravenous line; avoidance of the use of Foley catheter	B
	Early mobilization protocol; evaluation by physiotherapist, whenever necessary	B
Optimize operative conditions	Stimulation of mobility; performance of self-care and daily activities	B
	Adequate analgesia; patient-controlled analgesia, if feasible	B
	Prevention of postoperative hypotension/hypoxemia	C
Consider interventions on the system	Maintenance of postoperative hematocrit level at >30%	C
	Staff education	A
	Development and implementation of guidelines regarding harmful procedures (i.e., physical restraints, polymedication, unnecessary catheters)	B
	Adequate staff allocation	B
	Involvement of volunteers and family	C

Please refer to Table 1 for grading definitions.

investigated this topic [17,56–75]. In addition, one systematic review studied postoperative risk factors for delirium [76]. According to Inouye and Charpentier [59] and Inouye [77], risk factors were grouped into predisposing and precipitating factors. Predisposing factors are baseline conditions that increase the risk of delirium, while precipitating factors are triggers that cause delirium. Although this distinction may seem artificial, it was adopted because it clarifies the potential contribution of these conditions to the

multifactorial pathway leading to delirium. This classification also provides a framework for preventive interventions, one of the aims of the development of the present guidelines. The contribution of drugs, most often considered as precipitating factors, was examined by means of a specific literature search [59,78–82]. In one study, environmental factors were found to aggravate diagnosed delirium [83]. Table 2 summarizes the risk factors for delirium and the general recommendations for identification.

Table 4
Standardized instruments for delirium

	Screening on admission	Grade	Screening during stay	Grade	Diagnosis	Grade	Rating of severity	Grade
Instrument	MMSE	C	CAM/BOMC	C	CAM	C	DRS or MDAS	C
Use	On admission	C	Depending on the situation, at least twice a week	C	To assist in diagnosis	C	To rate severity	C
Users	Medical or nursing staff with adequate training	C	Medical or nursing staff with adequate training	C	Medical or nursing staff with adequate training	C	Medical or nursing staff with adequate training	C

Please refer to Table 1 for grading definitions.

Diagnosis may be based on *DSM-IV* or *ICD-10* criteria, a standardized instrument, or both (B).

Prevention

Systematic reviews [7,31,39,47,51] and recent studies on delirium prevention [5,84–90] led to the examination of a series of potential interventions. Multicomponent intervention strategies based on a specialized delirium consultation team and/or specific staff training were shown to prevent delirium in surgical and medical inpatients [5,7,31,39,47,51,84–89], while pharmacological prevention through haloperidol was unable to lower its incidence [90]. Patients at risk for delirium, such as elderly persons (≥ 70 years), severely ill individuals, and patients with cogni-

tive impairment, should be the target of nonpharmacological preventive interventions (Table 3). However, only a few interventions are based on sound evidence, and cost concern is an important barrier to their implementation.

Screening and diagnosis

Screening for delirium may improve its detection, as suggested by several studies and previous guidelines [24,26,28,91]. However, only a few studies of variable methodological quality investigated this issue [92–94]. Despite this relative lack of evidence, a consensus was reached

Table 5
History, physical examination, and additional investigations

		Grade
History	Full drug history, including over-the-counter drugs	B
	Substance abuse (e.g., alcohol, recreational drugs, etc.)	B
	Previous delirium	B
	Sensory deficits and/or aids (e.g., hearing aid, glasses, etc.)	B
	History by proxies	B
Status	Neurological examination	B
	Evidence of alcohol abuse or withdrawal	B
	Nutritional status	C
First-step investigations	Full blood count	B
	Electrolytes (sodium, potassium, and calcium)	B
	Renal function (blood urea nitrogen and creatinine)	B
	Urine analysis	B
	Blood gases	C
	Liver function tests (alanine amino transferase, aspartate amino transferase, and bilirubin)	C
	Glucose	C
Investigations for selected indications	HIV serology	B
	Blood levels of drugs	B
	Blood and urine cultures	B
	Urinal screening for toxics	B
	Vitamin B ₁₂ and folate serum levels	B
	Antinuclear antibodies	B
	Screening for heavy metals	C
	Systemic lupus	C
	Urinary porphyries	C
	Ammonium	C
	Magnesium and phosphate	I
	Albumin	I
	Alkaline phosphatase	I

Please refer to Table 1 for grading definitions.

The identification and treatment of underlying causes is the cornerstone of delirium management (B).

Potentially involved drugs should be stopped early, biochemical disturbances should be corrected, and antibiotic treatment should be rapidly introduced for infections (B).

History by proxies should be determined to differentiate delirium from dementia and to document previous cognitive status (B).

Table 6
Indications for standard EEG, brain imaging, and LP

	Indications	Grade
EEG	Differentiation of delirium from nonconvulsive or temporal lobe epilepsy	C
	Identification of encephalitis	C
	No cause identified in refractory and persistent delirium	C
	Usefulness of EEG in differentiating delirium from dementia	I
Brain imaging	Cerebral CT	
	Focal neurological signs	C
	Development of delirium after head injury or fall	C
	Patients with pathology potentially associated with intracranial processes (e.g., metastatic cancer)	C
	No cause identified in refractory and persistent delirium	C
	Magnetic resonance imaging	
	Patients with pathology potentially associated with intracranial processes (e.g., metastatic cancer)	C
	Other indications ^a	I
LP	Meningism and fever and/or headache	A
	Meningism only	B
	If headache and meningism only, or if no cause is identified in refractory and persistent delirium ^a	I

Please refer to Table 1 for grading definitions.

^a In these indications, the usefulness of magnetic resonance imaging and LP is uncertain and should be appreciated by a specialist.

to recommend systematic screening for delirium in at-risk patients. Screening should be conducted with standardized validated tools [37]. Instruments identifying cognitive impairment, such as the Mini-Mental State Exam (MMSE) [95] and the Blessed Orientation–Memory–Concentration (BOMC) [96,97], show the best clinimetric properties for delirium

screening (Table 4). Moreover, the MMSE proved to be helpful in monitoring the development and resolution of delirium in geriatric patients [98]. The gold standards for diagnosing delirium are the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* or *International Classification of Diseases, Tenth Revision (ICD-10)* criteria, but their

Table 7
Pharmacological treatment

	Recommendations	Grade
Indications for drug treatment	Avoidance of systemic pharmacological treatment	B
	Uncontrollable agitation despite nonpharmacological interventions	B
	Danger to the patient, staff, or others	B
	Anxiety in agitated or hallucinating patients	B
	Need to control agitation, to perform an investigation, or to provide treatment	C
	Uncertain indication	
	Hypoactive delirium	I
Type of drugs	Haloperidol	B
	Risperidone ^a	C
	Quetiapine ^a	C
	Clomethiazole	C
	Clozapine ^a	C
	Olanzapine ^{a,b}	C
	Benefit of chlorpromazine uncertain	I
Indications for atypical antipsychotics	Contraindication to classical antipsychotics	C
	Side effects of classical antipsychotics	C
Combinations with benzodiazepine	No benzodiazepine in the elderly (>70 years)	C
	Indications in younger adults	
	Uncontrollable agitation while on antipsychotic treatment	C
	Caution required given the potential side effects of these substances in delirium	C
	Uncertain indications	
	Lack of response to antipsychotic treatment	I
	Tolerance to only low doses of antipsychotics	I

Please refer to Table 1 for grading definitions.

Electrocardiogram of patients treated with antipsychotics should be monitored to detect QT interval prolongation (risk of “torsade de pointes”) (B).

Benzodiazepines as monotherapy are reserved for delirium caused by alcohol or benzodiazepine withdrawal as single cause. Whenever another cause is suspected, a combination of haloperidol and benzodiazepines should be used (B).

Vitamin supplements should be instituted in patients with possible B-vitamin deficiencies (i.e., alcohol abuser or malnourished) (B).

Sedation may be indicated in end-of-life care (B).

Cholinergics, such as physostigmine, may be useful in delirium caused by anticholinergic medications (I).

^a Clinicians should pay attention to possible cerebrovascular events induced by these medications in the elderly.

^b Recommendation modified by the updating of guidelines.

Table 8
Other recommendations

	Recommendations	Grade
Dangerous patients	Physical restraint is an exceptional measure that may be indicated if <ul style="list-style-type: none"> • Other less restrictive means have failed <i>and</i> • The patient's behavior puts self and/or staff and/or others at risk Restraints should be used only after discussion with the patient, proxies (including those with durable power of attorney), and nursing staff. The use of a restraint protocol is mandatory to monitor evolution over time. Reevaluation of restraint use should occur periodically, as frequently as every 15 min in the acute phase.	C
Specialized referral	Referral to a specialist (psychiatrist, old age psychiatrist, geriatrician, neurologist, etc.) may be required if: <ul style="list-style-type: none"> • Delirium is unresponsive to treatment • There is important agitation with possible need for physical restraint • There are doubts about management 	C
Informed consent	Informed consent should not be signed by a delirious patients as one's competency is altered	C

Please refer to Table 1 for grading definitions.

external validity does not seem satisfying [99]. *ICD-10* criteria are considered more specific but less sensitive than *DSM-IV* criteria [100,101], but both classifications identify conditions that seem to share a similar prognosis [102]. Other instruments may also be useful in diagnosing delirium [103]. Among them, the Confusion Assessment Method (CAM) has been validated and extensively studied [104], and a special version for use in the intensive care unit (Confusion Assessment Method for the Intensive Care Unit) is available [105]. The Delirium Rating Scale (DRS) [106,107] or the Memorial Delirium Assessment Scale (MDAS) [108] may be useful in rating the severity of delirium. Table 4 summarizes recommended instruments and their proposed use.

Investigation and treatment

The management of delirium includes: (a) the identification and treatment of all potential underlying causes (precipitating factors); (b) the provision of supportive care; and (c) the selection of appropriate pharmacological treatment for behavioral symptoms, when necessary. The identification and treatment of underlying causes is the cornerstone of delirium management. Medical history should be gathered from patients and proxies, and physical examination should be conducted in every patient [7,24,26,91,109,110]. Depending on information and clinical examination, additional investigations may be considered. Some investigations are recommended for every patient, while others are proposed in selected indications (Table 5). The utility of EEG, LP, and brain imaging (CT/MRI) is a much debated topic in the literature and has also been a subject of controversy in the expert panel (Table 6). Supportive care interventions include all preventive interventions listed in Table 2 [5,111–113]; their aim is to restore physiological conditions and to reorient the patient. These interventions should be considered for all delirious patients. Specific therapeutic interventions and nurse-directed care seem to have a beneficial effect on the evolution of delirium in surgical [7,44,47] and medical [5,51,88,89,114] inpatients.

Sound evidence supporting specific indications for drug treatment in delirium is still lacking (Table 7) [52]. A consensus to avoid systemic drug treatment of delirious patients was reached by the experts. When pharmacological treatment seems appropriate, antipsychotics are considered first-choice medications. Haloperidol has been shown to be efficient in treating symptoms of delirium [115] and to have a positive effect on the severity and duration of delirium [90]. For safety reasons, an electrocardiogram should be obtained as soon as feasible (risk of QT interval prolongation and arrhythmia) [116,117]. The usefulness of new atypical antipsychotics has been debated in the literature. Some evidence indicate that olanzapine [118–121] and quetiapine [122] have efficacy similar to that of haloperidol, with fewer side effects, in delirious patients; risperidone showed similar efficacy and side effects [123]. Numerous authors advocate that results from trials in dementia patients suffering from behavioral and psychological symptoms allow the recommendation of new atypical antipsychotics in delirium. These drugs have been associated with a potential increased risk of cerebrovascular events and mortality in dementia patients [124,125], leading the Food and Drug Administration to issue a warning advising avoidance of their use for this indication (www.fda.gov/cder/drug/infopage/antipsychotics/default.htm). However, the results of numerous randomized controlled trials (RCT) on this subject were recently studied by high-quality systematic reviews [48–50], yielding no definitive answer on this potential risk. Moreover, an additional retrospective study showed a higher risk of death associated with the use of conventional versus atypical antipsychotics [126]. Given these conflicting data and considering the fact that the studied population included patients with dementia rather than patients with delirium, haloperidol was considered to be the preferred pharmacological treatment for delirium. Taking into account that several atypical antipsychotics have also been reported to cause delirium, probably because of their anticholinergic effect [127–129], they were recommended with a lower grade of recommendation. New data available in the future might affect this specific recommendation. Benzodiazepines

are not as efficient as antipsychotics and may even precipitate confusion [78–80,130]. They are only recommended as first-choice drugs for alcohol-related or benzodiazepine-related withdrawal [131]. Following the American Psychiatric Association guidelines, young patients who tolerate only minimal doses of antipsychotics could benefit from a combination of benzodiazepines and antipsychotics [91]. Cholinergics [114,132,133], mianserine [134], ondansetron [135], and melatonin [136] have also been studied and could be useful in some situations, while donepezil seems to have no beneficial effect [137]. Clomethiazole is advocated by some authors [138,139] and recommended as a second-line treatment by the experts, based on their positive clinical experience. The pharmacological treatment of delirium is summarized in Table 7. Recommendations for the management of dangerous patients, referral for specialized consultation, and issues concerning informed consent are presented in Table 8.

Discussion

The development and implementation of guidelines is an important preliminary step to improve delirium management, given its high occurrence in patients hospitalized in general hospitals and highly variable care practices. A recent survey showed that only two countries in Europe possess a guideline for the diagnosis and treatment of delirium [140]. The present guidelines thus constitute a significant contribution from several perspectives. First, from a methodological standpoint, these guidelines are important because they were developed using rigorous methodology based on an extensive literature review and appraisal that included a formal evaluation of existing guidelines and covered all aspects of delirium management. This methodology also included formal consultation with an expert panel of diverse professional and specialty backgrounds that completed a structured appropriateness rating by means of nominal group technique, which is especially well-suited for areas of uncertainty. The guidelines were finally reviewed by international experts, and the literature update conducted just before submission confirmed most recommendations. Second, this work is also important because, to our knowledge, these guidelines are the first to cover, in English, the entire spectrum of delirium management in general hospitals: risk factors identification, preventive and diagnostic strategies, and pharmacological and nonpharmacological treatments. Finally, another contribution of this work is to identify several topics that need to be investigated in future research, such as the usefulness of systematic screening in different populations, the effectiveness of nonpharmacological management, and the place of drugs of anecdotal use (i.e., cholinergics).

Despite the rigorous methodology used, some areas remain with uncertainty, and several key recommendations deserve further comments. First, there exists consensus

among the experts to emphasize the prevention of delirium. Emerging data support this strategy, and efforts should be made to implement prevention programs in at-risk populations in general hospitals. Second, atypical antipsychotics, which have been increasingly used over the past years and have been supported by some empirical evidence, were not recommended as first-choice drugs mainly because of recent data on cerebrovascular adverse events in the elderly. This position might be modified once additional data are available. Third, pharmacological treatment is not systematically recommended to treat delirious patients. Consensus was reached about when and under which circumstances pharmacological treatment is appropriate; that is, in situations where the patient's condition (e.g., agitation) prevents adequate care (e.g., pulling out a central intravenous line) or puts the patient or the nursing staff at risk (e.g., physical aggressiveness).

Several difficulties were encountered while developing these guidelines. First, only a few and incomplete guidelines on delirium existed. A simple adaptation of previous high-quality guidelines was therefore considered not adequate, and the literature search was extended to systematic reviews, RCT, and cohort studies. Levels of evidence were frequently not specified in the guidelines and had to be evaluated from source studies. Finally, most of the topics discussed in these guidelines had not been adequately studied. Therefore, only low levels of evidence appeared in the literature, and diverging strategies were recommended by different authors. To overcome these difficulties, the multidisciplinary panel approach allowed an explicit and systematic examination of proposed recommendation items, which were developed based on existing evidence. This strategy, combining evidence-based knowledge and the consultation of an expert panel, is increasingly being used in the field of psychiatry [141] and somatic medicine [142]. Our literature search retrieved a high proportion of low levels of evidence, thus highlighting the benefits of the experts' consultation. Moreover, the consultation triggered discussions of topics on which diverging expert opinions were found in the literature. During the formalized meetings and voting process, recommendation items often had to be clarified within the expert panel. This certainly improved the quality of our guidelines, but involved heavy logistic support and strong commitment from all the experts.

These guidelines will be implemented in several wards at our university general hospital, and their ability to change practice will be evaluated. A recent review on adherence to mental health guidelines showed that interventions such as academic detailing (visiting of practitioners by colleagues or specially trained staff to present and discuss guidelines), continuous quality improvement, or feedback may not be sufficient to change practice [143]. Additional clinical resources and redesigning of the system seem to be necessary to improve practice, according to current evidence on guidelines implementation [19]. Moreover, changes tend

to return to preintervention level after the cessation of intervention. Recent interventions to improve the management of delirium highlighted the need to enhance guidelines [144] or educational package [145] implementation by follow-up and teaching sessions. We intend to take into account our previous experiences on the implementation of guidelines on depression in general hospitals [21] and the results of the abovementioned studies when implementing these guidelines on delirium.

In conclusion, the development of these guidelines required an extensive literature search and a formalized multidisciplinary expert panel approach to achieve consensus on topics not yet adequately investigated by research. Major efforts will be needed to implement these guidelines in clinical practice, to enhance the application of evidence-based recommendations, and, thus, to improve patient care. Initiatives such as those from the Cochrane Library's recent protocols [146–148] and additional clinical research are mandatory to help improve the quality and the evidence base of such guidelines.

Acknowledgments

We thank Anne Gerber, RN (Intensive Care Department, University Hospital, Lausanne, Switzerland), for participating in the delirium guidelines group. We also thank Dr. M. Cole (McGill University, Montreal, Canada) and Dr. R. Gonthier (University of Saint-Etienne, France) for reviewing the full document; Patrick Taffé for statistical advice; and Valérie Pittet for logistic and informatics support.

References

- [1] American Psychiatric Association. Diagnostic and statistical manual of mental disorder, text revision. 4th ed. Washington (DC): American Psychiatric Association, 2000.
- [2] Bucht G, Gustafson Y, Sandberg O. Epidemiology of delirium. *Dement Geriatr Cogn Disord* 1999;10:315–8.
- [3] Lindsay J, Rockwood K, Rolfsen DB. The epidemiology of delirium. In: Lindsay J, Rockwood K, Macdonald AJ, editors. *Delirium in old age*. New York: Oxford University Press, 2002. pp. 27–50.
- [4] Elie M, Rousseau F, Cole M, Primeau F, McCusker J, Bellavance F. Prevalence and detection of delirium in elderly emergency department patients. *CMAJ* 2000;163:977–81.
- [5] Inouye SK, Bogardus ST, Charpentier PA, Leo-Summers L, Acampora D, Holford TR, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med* 1999;340:669–76.
- [6] Inouye SK. Delirium in older persons. *N Engl J Med* 2006;354:1157–65.
- [7] Cole MG, Primeau FJ, Elie LM. Delirium: prevention, treatment, and outcome studies. *J Geriatr Psychiatry Neurol* 1998;11:126–37.
- [8] Marcantonio ER, Flacker JM, Michaels M, Resnick NM. Delirium is independently associated with poor functional recovery after hip fracture. *J Am Geriatr Soc* 2000;48:618–24.
- [9] McCusker J, Cole M, Abrahamowicz M, Primeau F, Belzile E. Delirium predicts 12-month mortality. *Arch Intern Med* 2002;162:457–63.
- [10] McCusker J, Cole MG, Dendukuri N, Belzile E. Does delirium increase hospital stay? *J Am Geriatr Soc* 2003;51:1539–46.
- [11] Inouye SK, Rushing JT, Foreman MD, Palmer RM, Pompei P. Does delirium contribute to poor hospital outcomes? A three-site epidemiologic study. *J Gen Intern Med* 1998;13:234–42.
- [12] McCusker J, Kakuma R, Abrahamowicz M. Predictors of functional decline in hospitalized elderly patients: a systematic review. *J Gerontol A Biol Sci Med Sci* 2002;57:M569–77.
- [13] Franco K, Litaker D, Locala J, Bronson D. The cost of delirium in the surgical patient. *Psychosomatics* 2001;42:68–73.
- [14] Leslie DL, Zhang Y, Holford TR, Bogardus ST, Leo-Summers LS, Inouye SK. Premature death associated with delirium at 1-year follow-up. *Arch Intern Med* 2005;165:1657–62.
- [15] Marcantonio ER, Kiely DK, Simon SE, John Orav E, Jones RN, Murphy KM, et al. Outcomes of older people admitted to postacute facilities with delirium. *J Am Geriatr Soc* 2005;53:963–9.
- [16] Hustey FM, Meldon SW. The prevalence and documentation of impaired mental status in elderly emergency department patients. *Ann Emerg Med* 2002;39:248–53.
- [17] Morrison RS, Magaziner J, Gilbert M, Koval KJ, McLaughlin MA, Orosz G, et al. Relationship between pain and opioid analgesics on the development of delirium following hip fracture. *J Gerontol A Biol Sci Med Sci* 2003;58:76–81.
- [18] Farrell KR, Ganzini L. Misdiagnosing delirium as depression in medically ill elderly patients. *Arch Intern Med* 1995;155:2459–64.
- [19] Grimshaw JM, Thomas RE, MacLennan G, Fraser C, Ramsay CR, Vale L, et al. Effectiveness and efficiency of guideline dissemination and implementation strategies. *Health Technol Assess* 2004;8:iii-72.
- [20] Voellinger R, Berney A, Baumann P, Annoni JM, Bryois C, Buclin T, et al. Major depressive disorder in the general hospital: adaptation of clinical practice guidelines. *Gen Hosp Psychiatry* 2003;25:185–93.
- [21] Michaud L, Voellinger R, Burnand B, Stiefel F. Major depressive disorders in the general hospital: how to implement guidelines. *J Psychosom Res* 2006;60:455–9.
- [22] Fervers B, Burgers JS, Haugh MC, Latreille J, Mlika-Cabanne N, Paquet L, et al. Adaptation of clinical guidelines: literature review and proposition for a framework and procedure. *Int J Qual Health Care* 2006;18:167–76.
- [23] Fitch K, Bernstein SJ, Aguilar MD, Burnand B, LaCalle JR, Lazaro P, et al. The RAND/UCLA appropriateness method user's manual. Santa Monica (CA): RAND Corporation, 2001.
- [24] Jacobi J, Fraser GL, Coursin DB, Riker RR, Fontaine D, Wittbrodt ET, et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult [erratum appears in *Crit Care Med* 2002;30:726]. *Crit Care Med* 2002;30:119–41.
- [25] Foreman MD, Mion LC, Tryostad L, Fletcher K. Standard of practice protocol: acute confusion/delirium NICHE Faculty [Review; 24 refs]. *Geriatr Nurs* 1999;20:147–52.
- [26] Rapp CG, Mentes JC, Titler MG. Acute confusion/delirium protocol. *J Gerontol Nurs* 2001;27:21–33.
- [27] American Psychiatric Association. Practice guideline for the treatment of patients with delirium. *Am J Psychiatry* 1999;156(Suppl 5):1–20.
- [28] British Geriatrics Society. Delirium guidelines. www.bgs.org.uk [Internet site] 2003.
- [29] Alexopoulos GS, Silver JM, Kahn DA, Frances A, Carpenter D. Treatment of agitation in older persons with dementia. *Postgraduate medicine, special report*, 1998.
- [30] Elie M, Cole MG, Primeau FJ, Bellavance F. Delirium risk factors in elderly hospitalized patients. *J Gen Intern Med* 1998;13:204–12.
- [31] Cole MG, Primeau F, McCusker J. Effectiveness of interventions to prevent delirium in hospitalized patients: a systematic review. *CMAJ* 1996;155:1263–8.
- [32] Cole MG, Primeau FJ. Prognosis of delirium in elderly hospital patients. *CMAJ* 1993;149:41–6.

- [33] Fick DM, Agostini JV, Inouye SK. Delirium superimposed on dementia: a systematic review. *J Am Geriatr Soc* 2002;50:1723–32.
- [34] Yildiz A, Sachs GS, Turgay A. Pharmacological management of agitation in emergency settings. *Emerg Med J* 1920:339–46.
- [35] van der Mast RC, Roest FH. Delirium after cardiac surgery: a critical review. *J Psychosom Res* 1996;41:13–30.
- [36] Dyer CB, Ashton CM, Teasdale TA. Postoperative delirium A review of 80 primary data-collection studies. *Arch Intern Med* 1995;155:461–5.
- [37] Smith MJ, Breitbart WS, Platt MM. A critique of instruments and methods to detect, diagnose, and rate delirium. *J Pain Symptom Manage* 1995;10:35–77.
- [38] Stuck AE, Siu AL, Wieland GD, Adams J, Rubenstein LZ. Comprehensive geriatric assessment: a meta-analysis of controlled trials. *Lancet* 1993;342:1032–6.
- [39] Draper B. The effectiveness of old age psychiatry services. *Int J Geriatr Psychiatry* 2000;15:687–703.
- [40] Morrison RS, Chassin MR, Siu AL. The medical consultant's role in caring for patients with hip fracture. *Ann Intern Med* 1998;128(12 Part 1):1010–9.
- [41] Morita T, Tsuneto S, Shima Y. Definition of sedation for symptom relief: a systematic literature review and a proposal of operational criteria. *J Pain Symptom Manage* 2002;447–53.
- [42] McNicol E, Horowicz-Mehler N, Fisk RA, Bennett K, Gialeli-Goudas M, Chew PW, et al. Management of opioid side effects in cancer-related and chronic noncancer pain: a systematic review 1. *J Pain* 2003;4:231–56.
- [43] Viganò A, Dorgan M, Buckingham J, Bruera E, Suarez-Almazor ME. Survival prediction in terminal cancer patients: a systematic review of the medical literature. *Palliat Med* 2000;14:363–74.
- [44] Cole MG. Delirium: effectiveness of systematic interventions. *Dement Geriatr Cogn Disord* 1999;10:406–11.
- [45] Wheeler M, Oderda GM, Ashburn MA, Lipman AG. Adverse events associated with postoperative opioid analgesia: a systematic review. *J Pain* 2002;3:159–80.
- [46] Jackson KC, Lipman AG. Drug therapy for delirium in terminally ill patients. *Cochrane Database Syst Rev* 2004;(2):CD004770.
- [47] Britton A, Russell R. Multidisciplinary team interventions for delirium in patients with chronic cognitive impairment. *Cochrane Database Syst Rev* 2000;(2):CD000395.
- [48] Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA* 2005;294:1934–43.
- [49] van Iersel MB, Zuidema SU, Koopmans RT, Verhey FR, Olde Rikkert M. Antipsychotics for behavioural and psychological problems in elderly people with dementia: a systematic review of adverse events. *Drugs Aging* 2005;22:845–58.
- [50] Carson S, McDonagh MS, Peterson K. A systematic review of the efficacy and safety of atypical antipsychotics in patients with psychological and behavioral symptoms of dementia. *J Am Geriatr Soc* 2006;54:354–61.
- [51] Milisen K, Lemiengre J, Braes T, Foreman MD. Multicomponent intervention strategies for managing delirium in hospitalized older people: systematic review. *J Adv Nurs* 2005;52:79–90.
- [52] Jackson KC, Lipman AG. Drug therapy for delirium in terminally ill patients [Systematic review]. *Cochrane Database Syst Rev* 2006.
- [53] Clark M, Oxman AD. *Cochrane Reviewers' Handbook* 4.1.5 [updated April 2002]. In: *The Cochrane Library, Issue 2*. Oxford: Updated Software, 2002.
- [54] Oxman AD, Cook DJ, Guyatt GH. Users' guides to the medical literature: VI. How to use an overview Evidence-Based Medicine Working Group. *JAMA* 1994;272:1367–71.
- [55] Greenhalgh T. Papers that summarise other papers (systematic reviews and meta-analyses). *BMJ* 1997;315:672–5.
- [56] Andersson EM, Gustafson L, Hallberg IR. Acute confusional state in elderly orthopaedic patients: factors of importance for detection in nursing care. *Int J Geriatr Psychiatry* 2001;16:7–17.
- [57] Edlund A, Lundstrom M, Brannstrom B, Bucht G, Gustafson Y. Delirium before and after operation for femoral neck fracture. *J Am Geriatr Soc* 2001;49:1335–40.
- [58] Galanakis P, Bickel H, Grading R, Von Gumpfenberg S, Forstl H. Acute confusional state in the elderly following hip surgery: incidence, risk factors and complications. *Int J Geriatr Psychiatry* 2001;16:349–55.
- [59] Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons Predictive model and interrelationship with baseline vulnerability. *JAMA* 1996;275:852–7.
- [60] Litaker D, Locala J, Franco K, Bronson DL, Tannous Z. Preoperative risk factors for postoperative delirium [see comments]. *Gen Hosp Psychiatry* 2001;23:84–9.
- [61] Lynch EP, Lazor MA, Gellis JE, Orav J, Goldman L, Marcantonio ER. The impact of postoperative pain on the development of postoperative delirium. *Anesth Analg* 1998;86:781–5.
- [62] Marcantonio ER, Goldman L, Orav EJ, Cook EF, Lee TE. The association of intraoperative factors with the development of postoperative delirium. *Am J Med* 1998;105:380–4.
- [63] Martin NJ, Stones MJ, Young JE, Bedard M. Development of delirium: a prospective cohort study in a community hospital. *Int Psychogeriatr* 2000;12:117–27.
- [64] Rolfson DB, McElhaney JE, Rockwood K, Finnegan BA, Entwistle LM, Wong JF, et al. Incidence and risk factors for delirium and other adverse outcomes in older adults after coronary artery bypass graft surgery. *Can J Cardiol* 1999;15:771–6.
- [65] Sasajima Y, Sasajima T, Uchida H, Kawai S, Haga M, Akasaka N, et al. Postoperative delirium in patients with chronic lower limb ischaemia: what are the specific markers? *Eur J Vasc Endovasc Surg* 2000;20:132–7.
- [66] Schneider F, Bohner H, Habel U, Salloum JB, Stierstorfer A, Hummel TC, et al. Risk factors for postoperative delirium in vascular surgery. *Gen Hosp Psychiatry* 2002;24:28–34.
- [67] Vazquez F, O'Flaherty M, Michelangelo H, Quiros R, Garfi L, Janson J, et al. Delirium incidence in elderly inpatients. *Med B Aires* 2000;60:555–60.
- [68] Zakriya KJ, Christmas C, Wenz JF, Franckowiak S, Anderson R, Sieber FE. Preoperative factors associated with postoperative change in confusion assessment method score in hip fracture patients. *Anesth Analg* 2002;94:1628–32.
- [69] Dai YT, Lou MF, Yip PK, Huang GS. Risk factors and incidence of postoperative delirium in elderly Chinese patients. *Gerontology* 2000;46:28–35.
- [70] Bohner H, Hummel TC, Habel U, Miller C, Reinbott S, Yang Q, et al. Predicting delirium after vascular surgery: a model based on pre- and intraoperative data. *Ann Surg* 2003;238:149–56.
- [71] Korevaar JC, van Munster BC, de Rooij SE. Risk factors for delirium in acutely admitted elderly patients: a prospective cohort study. *BMC Geriatr* 2005;5:6.
- [72] Yildizeli B, Oguzhan Ozyurtkan M, Batirel HF, Kuscü K, Bekiroglu N, Yuksel M. Factors associated with postoperative delirium after thoracic surgery. *Ann Thorac Surg* 2005;79:1004–9.
- [73] Yoshimura Y, Kubo S, Shirata K, Hirohashi K, Tanaka H, Shuto T, et al. Risk factors for postoperative delirium after liver resection for hepatocellular carcinoma. *World J Surg* 2004;28:982–6.
- [74] Santos FS, Velasco IT, Fraguas R. Risk factors for delirium in the elderly after coronary artery bypass graft surgery. *Int Psychogeriatr* 2004;16:175–93.
- [75] Freter SH, Dunbar MJ, MacLeod H, Morrison M, MacKnight C, Rockwood K. Predicting post-operative delirium in elective orthopaedic patients: the Delirium Elderly At-Risk (DEAR) instrument. *Age Ageing* 2005;34:169–71.
- [76] Bitsch M, Foss N, Kristensen B, Kehlet H. Pathogenesis of and management strategies for postoperative delirium after hip fracture: a review [see comment]. *Acta Orthop Scand* 2004;75:378–89.
- [77] Inouye SK. Delirium in hospitalized older patients: recognition and risk factors. *J Geriatr Psychiatry Neurol* 1998;11:118–25.

- [78] Brown TM. Drug-induced delirium [Review; 114 refs]. *Semin Clin Neuropsychiatry* 2000;5:113–24.
- [79] Gray SL, Lai KV, Larson EB. Drug-induced cognition disorders in the elderly: incidence, prevention and management. *Drug Saf* 1999; 21:101–22.
- [80] Carter GL, Dawson AH, Lopert R. Drug-induced delirium Incidence, management and prevention. *Drug Saf* 1996;15:291–301.
- [81] Marcantonio ER, Juarez G, Goldman L, Mangione CM, Ludwig LE, Lind L, et al. The relationship of postoperative delirium with psychoactive medications. *JAMA* 1994;272:1518–22.
- [82] Gaudreau JD, Gagnon P, Harel F, Roy MA, Tremblay A. Psychoactive medications and risk of delirium in hospitalized cancer patients. *J Clin Oncol* 2005;23:6712–8.
- [83] McCusker J, Cole M, Abrahamowicz M, Han L, Podoba JE, Ramman-Haddad L. Environmental risk factors for delirium in hospitalized older people. *J Am Geriatr Soc* 2001;49:1327–34.
- [84] Aizawa KI, Kanai T, Saikawa Y, Takabayashi T, Kawano Y, Miyazawa N, et al. A novel approach to the prevention of postoperative delirium in the elderly after gastrointestinal surgery. *Surg Today* 2002;32:310–4.
- [85] Marcantonio ER, Flacker JM, Wright RJ, Resnick NM. Reducing delirium after hip fracture: a randomized trial. *J Am Geriatr Soc* 2001;49:516–22.
- [86] Milisen K, Foreman MD, Abraham IL, DeGeest S, Godderis J, Vandermeulen E, et al. A nurse-led interdisciplinary intervention program for delirium in elderly hip-fracture patients. *J Am Geriatr Soc* 2001;49:523–32.
- [87] Lundstrom M, Edlund A, Lundstrom G, Gustafson Y. Reorganization of nursing and medical care to reduce the incidence of postoperative delirium and improve rehabilitation outcome in elderly patients treated for femoral neck fractures. *Scand J Caring Sci* 1999; 13:193–200.
- [88] Naughton BJ, Saltzman S, Ramadan F, Chadha N, Priore R, Mylotte JM. A multifactorial intervention to reduce prevalence of delirium and shorten hospital length of stay. *J Am Geriatr Soc* 2005;53: 18–23.
- [89] Lundstrom M, Edlund A, Karlsson S, Brannstrom B, Bucht G, Gustafson Y. A multifactorial intervention program reduces the duration of delirium, length of hospitalization, and mortality in delirious patients. *J Am Geriatr Soc* 2005;53:622–8.
- [90] Kalisvaart KJ, de Jonghe JFM, Bogaards MJ, Vreeswijk R, Egberts TCG, Burger BJ, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. *J Am Geriatr Soc* 2005;53:1658–66.
- [91] Trzepacz P, Breitbart W, Franklin J, Levenson J, Martini DR, Wang P. Practice guideline for the treatment of patients with delirium. In: American Psychiatric Association, editor. *American Psychiatric Association practice guidelines for the treatment of psychiatric disorders: compendium 2002*. Washington (DC): The American Psychiatric Association, 2002. pp. 29–66.
- [92] Lacko L, Bryan Y, Dellasega C, Salerno F. Changing clinical practice through research: the case of delirium. *Clin Nurs Res* 1999; 8:235–50.
- [93] Rockwood K, Cosway S, Stolee P, Kydd D, Carver D, Jarrett P, et al. Increasing the recognition of delirium in elderly patients. *J Am Geriatr Soc* 1994;42:252–6.
- [94] Gaudreau JD, Gagnon P, Harel F, Roy MA. Impact on delirium detection of using a sensitive instrument integrated into clinical practice. *Gen Hosp Psychiatry* 2005;27:194–9.
- [95] Folstein MF, Folstein SE, McHugh PR. “Mini-Mental State” A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–98.
- [96] Katzman R, Brown T, Fuld P, Peck A, Schechter R, Schimmel H. Validation of a short Orientation–Memory–Concentration Test of cognitive impairment. *Am J Psychiatry* 1983;140:734–9.
- [97] Davous P, Lamour Y, Debrand E, Rondot P. A comparative evaluation of the short orientation memory concentration test of cognitive impairment. *J Neurol Neurosurg Psychiatry* 1987;50: 1312–7.
- [98] O’Keefe ST, Mulkerrin EC, Nayeem K, Varughese M, Pillay I. Use of serial mini-mental state examinations to diagnose and monitor delirium in elderly hospital patients. *J Am Geriatr Soc* 2005;53:867–70.
- [99] Liptzin B. What criteria should be used for the diagnosis of delirium? *Dement Geriatr Cogn Disord* 1999;10:364–7.
- [100] Cole MG, Dendukuri N, McCusker J, Han L. An empirical study of different diagnostic criteria for delirium among elderly medical inpatients. *J Neuropsychiatry Clin Neurosci* 2003;15:200–7.
- [101] Laurila JV, Pitkala KH, Strandberg TE, Tilvis RS. The impact of different diagnostic criteria on prevalence rates for delirium. *Dement Geriatr Cogn Disord* 2003;16:156–62.
- [102] Laurila JV, Pitkala KH, Strandberg TE, Tilvis RS. Impact of different diagnostic criteria on prognosis of delirium: a prospective study. *Dement Geriatr Cogn Disord* 2004;18:240–4.
- [103] Zou Y, Cole MG, Primeau FJ, McCusker J, Bellavance F, Laplante J. Detection and diagnosis of delirium in the elderly: psychiatrist diagnosis, confusion assessment method, or consensus diagnosis? *Int Psychogeriatr* 1998;10:303–8.
- [104] Inouye SK, vanDyck CH, Alessi CA, Balkin S, Siegel AP, Horwitz RI. Clarifying confusion: the confusion assessment method A new method for detection of delirium. *Ann Intern Med* 1990; 113:941–8.
- [105] Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et al. Delirium in mechanically ventilated patients—validity and reliability of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *JAMA* 2001;286:2703–10.
- [106] Trzepacz PT, Baker RW, Greenhouse J. A symptom rating scale for delirium. *Psychiatry Res* 1988;23:89–97.
- [107] Trzepacz PT, Mittal D, Torres R, Canary K, Norton J, Jimerson N. Validation of the Delirium Rating Scale—Revised-98: comparison with the Delirium Rating Scale and the Cognitive Test for Delirium. *J Neuropsychiatry Clin Neurosci* 2001;13:229–42.
- [108] Breitbart W, Rosenfeld B, Roth A, Smith MJ, Cohen K, Passik S. The Memorial Delirium Assessment Scale. *J Pain Symptom Manage* 1997;13:128–37.
- [109] Conn DK, Lief S. Diagnosing and managing delirium in the elderly [Review; 44 refs]. *Can Fam Physician* 2001;47:101–8.
- [110] Meagher DJ. Regular review—delirium: optimising management. *BMJ* 2001;322:144–9.
- [111] Gustafson Y, Brannstrom B, Berggren D, Ragnarsson JI, Sigaard J, Bucht G, et al. A geriatric–anesthesiologic program to reduce acute confusional states in elderly patients treated for femoral neck fractures. *J Am Geriatr Soc* 1991;39:655–62.
- [112] Inouye SK, Wagner DR, Acampora D, Horwitz RI, Cooney LM, Tinetti ME. A controlled trial of a nursing-centered intervention in hospitalized elderly medical patients: the Yale Geriatric Care Program. *J Am Geriatr Soc* 1993;41:1353–60.
- [113] Landefeld CS, Palmer RM, Kresevic DM, Fortinsky RH, Kowal J. A randomized trial of care in a hospital medical unit especially designed to improve the functional outcomes of acutely ill older patients. *N Engl J Med* 1995;332:1338–44.
- [114] Pitkala KH, Laurila JV, Strandberg TE, Tilvis RS. Multicomponent geriatric intervention for elderly inpatients with delirium: a randomized, controlled trial. *J Gerontol A Biol Sci Med Sci* 2006;61: 176–81.
- [115] Breitbart W, Marotta R, Platt MM, Weisman H, Derevenco M, Grau C, et al. A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. *Am J Psychiatry* 1996;153:231–7.
- [116] Hassaballa HA, Balk RA. Torsade de pointes associated with the administration of intravenous haloperidol: a review of the literature and practical guidelines for use. *Expert Opin Drug Saf* 2003;2:543–7.
- [117] Okasha A. Psychiatric research in an international perspective The role of WPA. *Acta Psychiatr Scand* 2003;107:81–4.

- [118] Skrobik YK, Bergeron N, Dumont M, Gottfried SB. Olanzapine vs haloperidol: treating delirium in a critical care setting. *Intensive Care Med* 2004;30:444–9.
- [119] Sipahimalani A, Masand PS. Olanzapine in the treatment of delirium. *Psychosomatics* 1998;39:422–30.
- [120] Kim KS, Pae CU, Chae JH, Bahk WM, Jun T. An open pilot trial of olanzapine for delirium in the Korean population. *Psychiatry Clin Neurosci* 2001;55:515–9.
- [121] Breitbart W, Tremblay A, Gibson C. An open trial of olanzapine for the treatment of delirium in hospitalized cancer patients. *Psychosomatics* 2002;43:175–82.
- [122] Sasaki Y, Matsuyama T, Inoue S, Sunami T, Inoue T, Denda K, et al. A prospective, open-label, flexible-dose study of quetiapine in the treatment of delirium. *J Clin Psychiatry* 2003;64:1316–21.
- [123] Han CS, Kim YK. A double-blind trial of risperidone and haloperidol for the treatment of delirium. *Psychosomatics* 2004;45:297–301.
- [124] Wooltorton E. Risperidone (Risperdal): increased rate of cerebrovascular events in dementia trials. *CMAJ* 2002;167:1269–70.
- [125] Wooltorton E. Olanzapine (Zyprexa): increased incidence of cerebrovascular events in dementia trials. *CMAJ* 2004;170:1395.
- [126] Wang PS, Schneeweiss S, Avorn J, Fischer MA, Mogun H, Solomon DH, et al. Risk of death in elderly users of conventional vs atypical antipsychotic medications. *N Engl J Med* 2005;353:2335–41.
- [127] Lim CJ, Trevino C, Tampi RR. Can olanzapine cause delirium in the elderly? *Ann Pharmacother* 2006;40:135–8.
- [128] Centorrino F, Albert MJ, Drago-Ferrante G, Koukopoulos AE, Berry JM, Baldessarini RJ. Delirium during clozapine treatment: incidence and associated risk factors. *Pharmacopsychiatry* 2003;36:156–60.
- [129] Morikawa M, Kishimoto T. Probable dementia with Lewy bodies and risperidone-induced delirium. *Can J Psychiatry* 2002;47:976.
- [130] Marcantonio ER, Goldman L, Mangione CM, Ludwig LE, Muraca B, Haslauer CM, et al. A clinical prediction rule for delirium after elective noncardiac surgery. *JAMA* 1994;271:134–9.
- [131] Mayo-Smith MF. Pharmacological management of alcohol withdrawal: a meta-analysis and evidence-based practice guideline. *JAMA* 1997;278:144–51.
- [132] Burns MJ, Linden CH, Graudins A, Brown RM, Fletcher KE. A comparison of physostigmine and benzodiazepines for the treatment of anticholinergic poisoning. *Ann Emerg Med* 2000;35:374–81.
- [133] Moretti R, Torre P, Antonello RM, Cattaruzza T, Cazzato G. Cholinesterase inhibition as a possible therapy for delirium in vascular dementia: a controlled, open 24-month study of 246 patients. *Am J Alzheimers Dis Other Dement* 2004;19:333–9.
- [134] Uchiyama M, Tanaka K, Isse K, Toru M. Efficacy of mianserin on symptoms of delirium in the aged: an open trial study. *Prog Neuropsychopharmacol Biol Psychiatry* 1996;20:651–6.
- [135] Bayindir O, Guden M, Akpinar B, Sanisoglu I, Sagbas E. Ondansetron hydrochloride for the treatment of delirium after coronary artery surgery. *J Thorac Cardiovasc Surg* 2001;121:176–7.
- [136] Hanania M, Kitain E. Melatonin for treatment and prevention of postoperative delirium. *Anesth Analg* 2002;94:338–9.
- [137] Liptzin B, Laki A, Garb JL, Fingerroth R, Krushell R. Donepezil in the prevention and treatment of post-surgical delirium. *Am J Geriatr Psychiatry* 2005;13:1100–6.
- [138] Gustafson Y, Lundstrom M, Bucht G, Edlund A. Delirium in old age can be prevented and treated. *Tidsskr Nor Lægeforen* 2002;122:810–4.
- [139] Hepp U. Diagnosis and treatment of delirium. *Schweiz Rundsch Med Prax* 2002;91:455–63.
- [140] Leentjens AF, Diefenbacher A. A survey of delirium guidelines in Europe. *J Psychosom Res* 2006;61:123–8.
- [141] Alexopoulos GS, Streim J, Carpenter D, Docherty JP, Expert Consensus Panel for Using Antipsychotic Drugs in Older Patients. Using antipsychotic agents in older patients. *J Clin Psychiatry* 2004;65(Suppl 2):5–99.
- [142] Fass R, Longstreth GF, Pimentel M, Fullerton S, Russak SM, Chiou CF, et al. Evidence- and consensus-based practice guidelines for the diagnosis of irritable bowel syndrome. *Arch Intern Med* 2004;65(Suppl 2):5–99.
- [143] Bauer MS. A review of quantitative studies of adherence to mental health clinical practice guidelines. *Harv Rev Psychiatry* 2002;10:138–53.
- [144] Young LJ, George J. Do guidelines improve the process and outcomes of care in delirium? *Age Ageing* 2003;32:525–8.
- [145] Tabet N, Hudson S, Sweeney V, Sauer J, Bryant C, Macdonald A, et al. An educational intervention can prevent delirium on acute medical wards. *Age Ageing* 2005;34:152–6.
- [146] Siddiqi N, Stockdale R, Holmes J, Britton AM. Interventions for preventing delirium in hospitalised patients [Protocol]. *Cochrane Database Syst Rev* 2006.
- [147] Overshott R, Burns A, Karim S. Cholinesterase inhibitors for delirium [Protocol]. *Cochrane Database Syst Rev* 2005;(2):CD005317.
- [148] Lonergan E, Britton AM, Luxenberg J, Wyller T. Antipsychotics for delirium [Protocol]. *Cochrane Database Syst Rev* 2006;(1):CD005594.