

# Clinical Practice Guideline for Postoperative Delirium in Older Adults

October 10, 2014



American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults

## INTRODUCTION

Postoperative delirium is a common, life-threatening problem in older adults and is recognized as the most common postoperative complication in this age group.<sup>1,2ET</sup> Delirium occurs after surgery in 5% (in low-risk patients undergoing low-risk operations) to 50% (in high-risk patients undergoing high-risk operations) of adults 65 years and older.<sup>3-5</sup> An episode of delirium is associated with a range of deleterious clinical consequences, including major postoperative complications, prolonged hospitalization, loss of functional independence, reduced cognitive function, incomplete recovery, delayed rehabilitation, and even death.<sup>6-12</sup> Health care costs attributed to delirium in the United States currently exceed \$164 billion annually (2011 US dollars).<sup>13</sup> Delirium has been shown to be preventable in up to 40% of cases in some hospitalized older adult populations,<sup>14ET, 15ET</sup> a fact that makes delirium a prime candidate for prevention interventions targeted to improve the outcomes of older adults after surgery.<sup>16</sup>

Delirium represents an acute brain failure that presents with a sudden decline in cognitive function and attention.<sup>17</sup> The diagnosis of delirium can be made using many widely available delirium assessment tools,<sup>18</sup> which evaluate the patient for clinical characteristics such as acute change in mental status, inattention, disorganized thinking, and altered level of consciousness.<sup>18-19</sup> The clinical presentation of delirium varies. Motoric subtypes can vary from hypoactive (eg, withdrawn, decreased motor activity) to hyperactive (eg, agitation, heightened arousal, aggression). Mixed delirium presents with the range of both hyperactive and hypoactive symptoms. Delirium is reported to remain unrecognized in more than half of clinical cases,<sup>20</sup> a finding largely attributed to the fact that hypoactive delirium is typically unrecognized. Risk factors for postoperative delirium include impaired cognition, advancing age, functional impairment, sensory impairment, higher illness severity, and greater chronic disease burden.<sup>3</sup>

The field of delirium research is entering a rapid-growth phase. In the past 30 years, the number of publications on delirium indexed in bibliographic databases such as Medline has increased from <40 per year in the 1980s to nearly 400 per year at present. Given the wealth of recent evidence, an effort to synthesize the information on prevention and treatment of delirium was considered timely and important.

Another major impetus for developing this guideline for postoperative delirium was the result of a survey given to both surgical and nonsurgical specialists participating in the American Geriatrics Society Geriatrics-for-Specialists Initiative (AGS GSI). The purpose of the survey was to identify geriatric competencies, and the need for additional training and guidance for surgical specialists.<sup>21</sup> The survey was completed by more than 50 surgical specialists who represented seven different surgical specialties. Specialists identified delirium as “essential” more than any other topic in the care of older adults. Delirium was the geriatric clinical issue identified as the least understood and for which the knowledge gap for optimal management was greatest. Therefore, having identified lack of knowledge of delirium as the area of greatest need, the American Geriatrics Society (AGS) initiated this postoperative delirium clinical practice guideline project with support from a grant to the AGS GSI from the John A. Hartford Foundation.

The overall goal of this clinical guideline is to improve clinical care of adults 65 years and older through prevention and treatment of delirium in the postoperative setting. While the recommendation statements may apply more broadly, some of the statements will not apply to care specifically in the intensive care unit (ICU), palliative care, and nursing home settings. The recommendations are made based on studies that included both surgical and nonsurgical patient cohorts. The specific aims addressed by the guideline include (1) the nonpharmacologic and pharmacologic interventions that should be implemented perioperatively for the prevention (ie, before delirium occurs) of postoperative delirium, and (2) the nonpharmacologic and pharmacologic interventions that should be implemented perioperatively for treatment (ie, once delirium has occurred) of postoperative delirium. Nonpharmacologic interventions were defined as including behavioral interventions, monitoring devices, rehabilitation, environmental adaptations, psychological and social supports, medication reductions, complementary and alternative medicine, and systems and process changes. The target audience of these recommendations is any healthcare professional or healthcare system who provides care for older adults in the perioperative setting.

For prevention of delirium, the goal of our recommendations is to implement intervention strategies for the primary prevention of perioperative delirium, ie, to prevent delirium before delirium develops. To achieve this goal, the prevention recommendations are made for all older adult surgical patients *at risk* of postoperative delirium but in whom delirium has not yet developed. This guideline defines at-risk older patients as moderate-to-high risk based on previous risk-stratification models, such as those from the National Institute for Health and Care Excellence (NICE) guidelines (at risk defined as having one or more of the following characteristics: age 65 years and older; any cognitive impairment (past or present) and/or dementia, current hip fracture, or severe illness).<sup>22</sup> For surgical patients, predisposing factors of delirium represent an inter-relationship between predisposing patient vulnerability and precipitating factors/insults.<sup>23</sup> In the context of a surgical patient, the extent (or the resultant physiologic stress created by factors such as blood loss, length of operation, or extent of dissection) of the operation is the main determinant of the precipitating insult (eg, the more extensive the operation, the greater the precipitating insult and the higher the delirium rate).

For management of delirium, the goals of the panel's recommendations are to decrease delirium severity and duration, to ensure patient safety, and to improve outcomes in patients with established delirium. To achieve these goals, the following recommendations are made for *all patients with delirium*. The statements are intended to use available evidence to guide clinical care and are not intended to discourage or prevent research.

The guideline was purposefully limited to the specific aims described and is not intended to be comprehensive of all topics related to postoperative delirium. Delirium screening and diagnosis generally, and studies related to ICU sedation specifically are not addressed in this guideline, because they

represent topics recently addressed in other high-quality systematic reviews and guidelines.<sup>18,22,24</sup> There are many validated tools to diagnose delirium, and this guideline is not intended to comprehensively review delirium diagnosis or screening tools. ICU studies were included that were directly pertinent to delirium prevention and treatment, and not solely addressing ICU sedation. The topics of ICU delirium and ICU sedation in the critical care environment (eg, mechanically ventilated patients) has been recently covered in a separate guideline statement, and were not intended to be covered in the present guideline.<sup>24</sup> Topics considered by the panel, for which there was not enough evidence to make a recommendation statement, were: administration of general anesthesia versus neuroaxial anesthesia to prevent delirium,<sup>25–26</sup> choice of one anesthetic agent over another agent,<sup>25</sup> choice of specific anesthetic agents,<sup>25</sup> use of neuroaxial anesthesia postoperatively to prevent delirium,<sup>25</sup> single-component nonpharmacologic prevention and treatment of delirium,<sup>22</sup> and prescription of melatonin to prevent delirium.<sup>27ET,28ET</sup> It is important to note that many of the studies used to formulate some of the recommendations are in nonsurgical patients, a fact that makes extrapolating the findings to surgical patients less ideal in comparison to studies performed in surgical patients since the etiology of delirium in nonsurgical patients may be different. In the long-term, the guideline will be regularly updated to incorporate future studies. Thus, this guideline will continue to evolve as new evidence emerges.

## METHODS

For this guideline, the AGS employed a well-tested framework for development of clinical practice guidelines.<sup>29–33</sup> There were three components to the framework. First, an interdisciplinary expert panel on delirium was created. Second, a development process that included a systematic literature review and evaluation of the evidence by the expert panel was conducted. Third, the guideline document was written and revised initially through committee subgroups and subsequently achieved full consensus of the panel on all recommendation statements. Following manuscript preparation, external peer review was solicited, and an open public comment period was completed. The work for this guideline started with an initial consultation with an expert on guideline development and an author of the Institute of Medicine's (IOM) report on developing trustworthy guidelines. The IOM's reports on Systematic Reviews<sup>34</sup> and Trustworthy Clinical Guideline<sup>32</sup> provided the standards followed throughout our process and guided the framework. The framework and approach are described in greater detail below.

### Literature Search

The methods for the literature review included a combination of comprehensive searches, targeted searches, and specific, focused searches. The steps of the literature search are further outlined in the flow chart included in the guideline (Diagram 1). Comprehensive searches of articles on the pharmacologic and non-pharmacologic interventions for the prevention or treatment of postoperative delirium in PubMed, Embase, and CINAHL were conducted between August 1, 2013, and October 1, 2013, resulting in a total of 6,504 citations. The following search terms were included: *delirium*, *organic brain syndrome*, and *acute confusion*, in combination with a variety of alternative terms for the prevention and treatment of delirium, including all variations of the words *prevention*, *management*, *treatment*, *intervention*, *therapy*, *therapeutic*, or *drug therapy* (eg, prevent, prevents, preventing, prevention, preventions, preventable). The limits placed on these searches included restricting the searches to adults, English only, and articles published from 1988 to the present.

Two targeted searches using the U.S. Library of National Medicine PubMed Special Queries on Comparative Effectiveness Research and PubMed Clinical Queries were also conducted. The search strategy conducted using the Special Queries on Comparative Effectiveness Research included the terms *delirium*, *acute confusion*, and *organic brain syndrome* and returned a total of 2,173 studies, including 473 randomized clinical trials, 1,154 observational studies, and 546 systematic reviews. An additional 1,288 citations were identified through PubMed Clinical Queries using the term *postoperative delirium*.

There were multiple exclusion criteria, because the scope of this review was limited to pharmacologic and nonpharmacologic interventions for the prevention or treatment of peri-operative delirium. All studies related to topics other than prevention and treatment of delirium were excluded, including the pathophysiology, etiology, biomarkers, risk factors, predisposing factors, predictive models, prognostic methods or tools, and assessment (including screening, detection, recognition, identification, diagnosis, and rating scales). Any articles pertaining to delirium in nonadult populations (ie, infants, children, adolescents) were excluded.

Other exclusion criteria included delirium due to alcohol or substance abuse withdrawal, psychosis (eg, schizophrenia), dementia (eg, Alzheimer's disease), traumatic brain injury, emergence delirium, terminal illness, metabolic encephalopathy, or acute stroke. While many studies included persons with dementia or cognitive impairment, delirium-related studies including only or primarily persons with dementia were excluded. Delirium articles based primarily in settings other than the inpatient setting, including the emergency department, the ambulatory or outpatient setting, the community, postacute or long-term care (nursing homes), or hospice/palliative care settings were excluded. Even though palliative care settings were excluded, studies addressing palliative surgery or including patients undergoing palliative surgical procedures were included. Studies in which delirium occurred in patients having undergone neurologic or brain surgery were excluded. All types of publications other than observational studies or randomized clinical trials, including all nonsystematic reviews, comments, editorials, and letters, were excluded. Systematic reviews were utilized to verify completeness of the literature search.

Finally, to capture information on clinical trials that may have not been published, ClinicalTrials.gov (a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world) was searched. ClinicalTrials.gov searches included each of the following drugs: *quetiapine*, *dexmedetomidine*, *melatonin*, *rivastigmine*, *haloperidol*, *gabapentin*, *olanzapine*, *donepezil*, *risperidone*, as well as the terms *analgesia*, *delirium*, and *confusion*. These searches were restricted to studies that were completed and that had results available; these searches were completed on November 26, 2013, and identified 357 studies.

All of the articles that met the inclusion criterion and that were not excluded for the reasons listed above were reviewed by the two panel co-chairs of this guideline project to determine appropriateness for inclusion in the review.

### Panel Selection

After initial nominations by the AGS and its Geriatrics-for-Specialists Initiative Council, the two panel co-chairs screened prospective panel members with recognized expertise in relevant specialties and geriatrics, and recommended several more for inclusion. Other factors that influenced selection were the desire to have interdisciplinary representation and representation from different parts of the country. In addition to the 23-member panel, a representative from the National Committee for Quality Assurance (NCQA), a quality and measures expert, and a caregiver representative were invited to serve as ex officio members. Represented disciplines on the interdisciplinary panel included the fields of geriatric medicine, general surgery, anesthesiology, critical care medicine, emergency medicine, geriatric surgery, gynecology, hospital medicine, neurology, nursing, orthopedic surgery, ophthalmology, otolaryngology, palliative care, pharmacy, psychiatry, physical medicine and rehabilitation, cardiothoracic surgery, urology, and vascular surgery.

To ensure that potential conflicts of interest were disclosed and addressed appropriately, panelists were asked to identify potential conflicts of interest with the panel before the initiation of guideline development. Each expert panel member completed a disclosure form that was shared with the entire panel before the process began. Potential conflicts of interest were reviewed by AGS and by the panel co-chairs, and panel disclosures were made available to the panel throughout the guideline development process, as well as to potential reviewers during the peer review and open comment period. None of the conflicts were rated as disqualifying. Changes in panelist's conflicts of interest were requested and updated three times during the guideline development process. Panel members who disclosed affiliations or financial interests with commercial entities are listed under the disclosures section of this document.

### **Selection of Clinical Topics**

Specific topics regarding postoperative delirium were selected to focus and guide the literature search. To select the topics, two interdisciplinary conference calls were held with specialists from geriatric medicine, general surgery, gynecology, critical care medicine, emergency medicine, anesthesiology, otolaryngology, ophthalmology, orthopedics, thoracic surgery, urology, and physical medicine and rehabilitation. The specialists provided input as to the most critical deficiencies they perceived for postoperative delirium within their specialties. The comments from these calls were collated and provided the impetus for selection of the specific aims chosen for this guideline.

### **Development Process**

Initial consensus was reached between the panel co-chairs and an independent researcher experienced in systematic literature reviews to define key search terms and to develop the protocol for the systematic review, including the search strategy, databases, and inclusion and exclusion criteria for the initial search. After the initial search, meetings were held to address questions of consistency, refinement of exclusion criteria, strategies for evaluating the evidence, and consolidation or expansion of individual search criterion. Abstracts of all articles captured by the initial search (>4,000) were reviewed by the panel co-chairs and two research associates. Every abstract was reviewed by at least two reviewers for inter-rater consistency in meeting the inclusion and exclusion criteria, and consensus was reached. If there was any doubt about an article meeting criteria, the article was included. Articles meeting guideline inclusion criteria were then sorted by topic and provided to the full panel for consideration of inclusion or exclusion. A given article could be assigned to more than one topic.

The full panel then convened for a 2-day, in-person meeting early in the process, to review the initial results of the literature search and begin drafting recommendations. The panel was divided into five working groups aligned with each topic, each assigned in accordance with their specific area of expertise. Groups reviewed the abstracts assigned to their group and evaluated the following inclusion criteria: relevance to the topic, inclusion of original data (not review article), and exclusion of studies with gross

methodologic limitations (case reports or sample sizes <20, lack of control group, risk factor study only). At least two reviewers were required to assess each abstract for this step; some articles were recategorized to different topic groups. The final abstract listing submitted by each working group provided the articles which were extracted into the evidence tables to be used for the actual recommendations. Based on the initial abstract review as well as expert judgment, the groups were asked to develop a preliminary listing of recommendations. Each group presented the group's preliminary recommendations to the full panel for feedback. After the meeting, each group met either via conference calls or through e-mail dialogue to resolve any questions, to add additional articles to the listing for evidence tables, and to refine the preliminary recommendation language.

Following a rigorous process, a team of four independent researchers prepared evidence tables and quality ratings for each study selected by the panel. The four researchers first underwent intensive training and standardization, each completing five initial ratings accompanied by standardization and retraining. For the entire review process, an expert re-rated all of the articles to assure reliability, and one of the panel co-chairs re-rated a 10% subsample. Questions and discrepancies were resolved through discussion. The evidence tables included a summary of the study, as well as a quality rating and rating of the risk of bias. The quality rating system was based on the Cochrane Risk of Bias<sup>35</sup> and Jadad scoring system.<sup>36</sup> The ratings were based on six key elements: evidence of balanced allocation, allocation concealment, blinded outcome assessment, completeness of outcome data, selective outcome reporting, and other sources of bias. Following the Cochrane approach, each article was assigned a risk of bias rating as follows: low risk of bias indicated by low risk on all 6 domains, unclear risk indicated by high or unclear risk of bias on 1 or more of 6 domains, or high risk of bias indicated by high risk on 2 or more of 6 domains. In addition, each article was rated for the use of a validated delirium measure and sample size of 50 or more in each study arm. The citations for which evidence tables were created are denoted with ET in the text and "(ET)" in the bibliography and can be viewed as an online addendum found on [GeriatricsCareOnline.org](http://GeriatricsCareOnline.org).

These evidence tables and quality worksheets were then used by the panelist to independently rate the quality of evidence and strength of recommendation for each recommendation statement using the American College of Physicians' Guideline Grading System<sup>37</sup> (Table 1), which is based on Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) scheme developed previously.<sup>38</sup> Panelist ratings were compiled for each group and returned to that group, who then reached consensus via conference calls. All panelists were trained on the GRADE system using standard methods including print and online materials.

For some criteria (See Table 1 for full description), the panel provided a "strong" recommendation, even though the quality of evidence was low or moderate. In such cases, the strength of recommendation was based on balancing the benefits of treatment against the potential harms and required agreement by the entire panel. Strong recommendations were made when the benefit clearly outweighed

harms (such as with nonpharmacologic interventions) or when the potential harms clearly outweighed the benefits (such as with benzodiazepine treatment). Weak recommendations were made when the panel judged the evidence to be in favor of these interventions, but the current level of evidence or potential risks of the treatment did not support a strong recommendation. The strength of recommendation was “insufficient” when the panel deemed that a recommendation statement should be made but weighed the evidence as being insufficient to determine the net risks and benefits.<sup>37,39</sup>

The strength of recommendation was “not applicable” when no recommendation could be made, that is, the panel did not deem the evidence to weigh either for or against a clinical practice. The approach and detailed descriptions of rating of the quality of evidence are provided in Table 1. The wording of each recommendation followed IOM recommendations. An additional one-day, in-person meeting was held to further discuss each recommendation’s language and its quality of evidence, strength of recommendation, and potential harms. Following this meeting, feedback and edits were incorporated, and a final draft of the recommendations was reviewed and approved by the entire panel via conference call.

The draft statement was sent for peer-review at multiple organizations (listed below), and edits were incorporated by the panel co-chairs. The statement also underwent a period of public commentary (3 weeks), as well as review by lay organizations representing older adults.

## RECOMMENDATIONS

A complete list of all recommendations is included in Table 2. The table lists the recommendations by descending order of strength of recommendation. In these recommendations, “healthcare professionals” refer to all professionals who are members of the interdisciplinary team, including but not limited to physicians, advanced practice clinicians, nurses, pharmacists, social workers and others.

### Nonpharmacologic Interventions for the Prevention and/or Treatment of Postoperative Delirium in Older Surgical Patients

Nonpharmacologic interventions were defined as including behavioral interventions, monitoring devices, rehabilitation, environmental adaptations, psychological and social supports, medication reductions, complementary and alternative medicine, and system and process changes. While considered labor-intensive by many, the benefits of nonpharmacologic interventions to prevent delirium need to be stressed because of the potential gains to the patient and hospital in terms of improved outcomes and overall cost savings.

For prevention of delirium, the goal of the recommendations is to implement intervention strategies for the primary prevention of postoperative delirium, ie, to prevent delirium before delirium develops. To achieve this goal, the prevention recommendations are made for all older adult surgical patients *at risk* of postoperative delirium. At-risk older patients are identified as moderate-to-high risk based on previous risk-stratification models, such as those from the NICE guidelines (at risk defined as having one or more of the following characteristics: age 65 years and older, any cognitive impairment [past or present] and/or dementia, current hip fracture, or severe illness).<sup>19</sup>

For management of delirium, the goals of the recommendations are to decrease delirium severity and duration, to ensure patient safety, and to improve health outcomes in patients with delirium. To achieve these goals, the following recommendations are made for *all delirious patients*.

These recommendations are made based on studies that included both surgical and nonsurgical patient cohorts.

#### I. Education Targeted to Health Care Professionals About Delirium

**Recommendation:** Healthcare systems and hospitals should implement formal educational programs with ongoing formal and/or informal refresher sessions for healthcare professionals on delirium in at-risk older surgical adults to improve understanding of its epidemiology, assessment, prevention, and treatment (strength of recommendation: strong; quality of evidence: low).

**A. Evidence for Recommendation:** The content and frequency of educational programs will need to be tailored to local needs. Educational programs have been found to consistently reduce hospitalized

delirium by three studies rated as having high risk of bias. Lundstrom et al<sup>40ET</sup> performed a randomized trial comparing an educational intervention (a 2-day course on delirium for hospital staff) to usual care and found the benefits of the educational intervention included reduced persistent delirium on hospital day 7 (30% vs. 60%;  $P=0.001$ ) and decreased length of hospital stay ( $9.4\pm 8.2$  vs.  $13.4\pm 12.3$  days;  $P=0.001$ ). Tabet et al<sup>41ET</sup> performed a case-control study of hospitalized patients aged 70 years and older evaluating a delirium educational intervention for ward staff (a 1-hour interactive presentation, written delirium management guidelines, and follow-up sessions) and found that the intervention reduced rates of delirium (9.8% vs. 19.5%;  $P<0.05$ ). Robinson et al<sup>42ET</sup> performed a study on hospitalized older adults with risk factors for delirium and found that a prevention protocol targeting delirium risk factors reduced delirium incidence (13.8% vs. 37.5%;  $P<0.001$ ). Although the nature of the educational interventions in each study varied, the common components were: (1) initial (ranging in length from 1 hour to several half-day sessions) education and ongoing “refresher” sessions, (2) both written and oral content, and (3) opportunities for ongoing one-on-one training and support. It is important to note that the educational interventions may have improved the implementation of effective multicomponent strategies for delirium, and thus, the impact of the educational interventions per se cannot be separately evaluated. Education for delirium prevention is effective when it is interactive, engages leadership, and uses peer support or unit champions.<sup>42ET</sup> All interdisciplinary healthcare team members should receive education, and strategies should also include nurse’s aides and other ancillary staff. Areas targeted for education should include, at a minimum, definitions and epidemiology of delirium, features and symptoms of delirium, outcomes and measurement of delirium, risk factors and high-risk groups, and management and prevention of delirium with a focus on the modifiable causes of delirium and the use of nonpharmacologic approaches as first-line targets for prevention of delirium. At-risk older adults are identified as moderate-to-high risk based on previous risk-stratification models, such as those from the NICE guidelines (age 65 years and older, any cognitive impairment [past or present] and/or dementia, current hip fracture, or severe illness).<sup>22</sup> Given the low harm of education, the potential benefit found in the included studies and the relatively low costs (offset by the high cost of delirium), the strength of the recommendation was rated as strong.

**B. Potential Harms of All Nonpharmacologic Recommendations:** No harmful effects of nonpharmacologic approaches to delirium prevention or management have been reported. The major “harms” of these approaches to delirium management are the costs of program resources (eg, special equipment, specialized units, educational materials, computer expenses, expert trainers) and staff time (eg, personnel costs, training time, and coordination expenses). Previous studies have demonstrated the cost-effectiveness of multicomponent delirium intervention strategies even after consideration of these costs across different settings (general medical, geriatric, hip fracture, surgical, and ICU settings).<sup>43–45, 46ET, 47–48, 49ET</sup> The cost-effectiveness of educational interventions and specialized hospital units has not been evaluated previously. The costs of nonpharmacologic interventions may be offset by the considerable costs of delirium, estimated to exceed \$164 billion per year (2011 USD) in the United States.<sup>5, 13, 50–52</sup> Taken together, the evidence lends support that the benefits of nonpharmacologic approaches to delirium intervention outweigh the potential “harms.”

## II. Multicomponent Nonpharmacologic Interventions Performed by an Interdisciplinary Team for Prevention of Delirium

**Recommendation:** Healthcare systems and hospitals should implement multicomponent nonpharmacologic intervention programs delivered by an interdisciplinary team (including physicians, nurses, and possibly other healthcare professionals) for the entire hospitalization in at-risk older adults undergoing surgery to prevent delirium (strength of recommendation: strong; quality of evidence: moderate).

**A. Evidence for Recommendation:** All older adults admitted for surgery (elective and emergent) who are at risk (defined in introduction of this section) for development of postoperative delirium will benefit from a proactive multicomponent intervention delivered by an interdisciplinary team, including physicians, and nurses (at a minimum), before surgery to prevent postoperative delirium. Interventions to prevent postoperative delirium<sup>22</sup> may include the following elements: cognitive reorientation, sleep enhancement (ie, nonpharmacologic sleep protocol and sleep hygiene), early mobility and/or physical rehabilitation, adaptations for visual and hearing impairment, nutrition and fluid repletion, pain management, appropriate medication usage, adequate oxygenation, and prevention of constipation. This team should perform daily rounding providing both general and specific recommendations. Adherence is an important consideration for these interventions and impacts on outcome.

For the ten delirium prevention studies, patients were assessed at baseline to exclude the presence of delirium and to assess risk factors for delirium.<sup>14ET, 53ET, 54ET, 55ET, 56ET, 57ET, 58ET, 59ET, 60ET, 61ET</sup> A strong level of recommendation is given based on the moderate to high quality level of most of the papers that outline their interventions in a robust fashion.<sup>14ET, 54ET, 55ET, 56ET, 57ET, 58ET, 59ET, 60ET, 61ET</sup> The strength of the recommendation is further supported by the “dose-response” evidence for effectiveness of the interventions provided by several papers that examined level of adherence with outcome rates.<sup>14ET, 53ET, 54ET, 58ET, 62ET</sup>

With regard to the interdisciplinary team component, interdisciplinary interventions have been shown to be effective for sensory enhancement (ensuring glasses and hearing aids or amplifiers are used), mobility enhancement (ambulating at least twice per day if possible), pain control with scheduled acetaminophen, cognitive stimulation and communication standards, and tips to prevent escalating behaviors in persons with delirium. Daily rounding by an interdisciplinary team with an advanced practice nurse or delirium resource nurse is recommended to reinforce the interventions and provide support to staff performing the interventions, but an advanced practice nurse intervening alone has not been shown to be beneficial.

**B. Potential Harms of Recommendation:** See harms statement for nonpharmacologic interventions in the above section titled “I. B. Education Targeted to Health Care Professionals About Delirium, Potential Harms of All Nonpharmacologic Recommendations”.

### III. Multicomponent Nonpharmacologic Interventions Performed by an Interdisciplinary Team for Management of Delirium

**Recommendation:** Healthcare professionals should consider multicomponent interventions implemented by an interdisciplinary team in older adults diagnosed with postoperative delirium to improve clinical outcomes (strength of recommendation: weak; quality of evidence: low).

**A. Evidence/Rationale for Recommendation:** Based on existing studies, multicomponent interventions have included mobility/exercise/physical therapy, reorientation, therapeutic activities/cognitive stimulation, maintenance of nutrition and hydration, sleep enhancement (ie, nonpharmacologic sleep protocol, sleep hygiene), vision and hearing adaptation, nursing education and interventions, and geriatric consultation. The interdisciplinary team involved in the multicomponent interventions should include physicians and nurses and at least one team member with training in delirium management. Communication among the primary surgeon, the patient care team, the patient, and the family/caregivers about delirium-related issues are essential to optimize the management plan. The intervention should address patient safety and should include prevention of documented delirium-related complications, such as falls,<sup>63</sup> functional decline,<sup>6,9,64</sup> pressure ulcers,<sup>65</sup> deep venous thrombosis,<sup>66</sup> aspiration pneumonia,<sup>66–67</sup> and death.<sup>11, 68–70</sup>

Thirteen studies evaluated multicomponent interventions aimed to treat delirium in medical, surgical, orthopedic, and ICU patients.<sup>40ET, 49ET, 56ET, 59ET, 60ET, 71ET, 72ET, 73ET, 74ET, 75ET, 76ET, 77ET, 78ET</sup> Studies were excluded for retrospective designs, lack of control group, and lack of inclusion of delirious patients at baseline. Of the 13 studies, 7 were randomized controlled trials, 2 were prospective cohorts, and 4 had pre/post designs; 8 were rated as low quality with high risk of bias, 4 unclear risk, and 1 low risk. Seven of the studies suggested benefits for at least one of the following outcomes: decreased delirium rate or duration, decreased cognitive or functional decline, decreased length of stay, or decreased costs.<sup>49ET, 56ET, 59ET, 61ET, 71ET, 72ET, 78ET</sup> However, results were inconsistent with 6 studies showing equivocal (nonsignificant) or no benefit.<sup>40ET, 73ET, 74ET, 75ET, 76ET, 77ET</sup>

**B. Potential Harms of Nonpharmacologic Recommendation:** See harms statement for nonpharmacologic interventions in the above section titled “I. B. Education Targeted to Health Care Professionals About Delirium, Potential Harms of All Nonpharmacologic Recommendations”.

### IV. Identify and Manage Causes of Delirium

**Recommendation:** The healthcare professional should perform a medical evaluation, make medication and/or environmental adjustments, and order appropriate diagnostic tests and clinical consultations after an older adult has been diagnosed with postoperative delirium to identify and manage underlying contributors to delirium (strength of recommendation: strong; quality of evidence: low).

**A. Evidence/Rationale for Recommendation:** Early delirium diagnosis and treatment of the underlying cause(s) of delirium, including evaluation for infection, metabolic derangements, environmental contributors, and/or psychoactive medications, are critical to decreasing the duration of delirium. Delays

to initiation of treatment may result in prolonged duration of delirium, which is associated with worse cognitive and functional recovery<sup>79</sup> and may result in higher inpatient morbidity and mortality.<sup>80ET</sup> Interventions that have included identification and treatment of the underlying causes of delirium are associated with decreased delirium duration and severity, reduced length of stay, better cognitive function after discharge, and potential decreases in mortality.<sup>71ET, 77ET, 81ET, 82ET</sup>

There were 4 studies in which the intervention included an evaluation and treatment of the underlying cause(s) of delirium,<sup>71ET, 77ET, 81ET, 82ET</sup> all of which involved multicomponent interventions. Two studies were pre/post designs:<sup>71ET, 82ET</sup> one evaluated a nurse-led interdisciplinary intervention program,<sup>71ET</sup> and the other evaluated the implementation of delirium guidelines using varying levels of feedback.<sup>82ET</sup> One study was a randomized controlled trial evaluating a comprehensive geriatric assessment,<sup>77ET</sup> and another study used a concurrent control-ward design<sup>81ET</sup> to evaluate the implementation of delirium guidelines. Interventions were reported to significantly decrease delirium duration<sup>71ET, 77ET</sup> and severity,<sup>71ET</sup> improve Mini-Mental State Examination scores postoperatively<sup>71ET</sup> and at 6-month follow up,<sup>77ET</sup> decrease acute care length of stay,<sup>81ET</sup> and decrease persistent delirium at hospital discharge.<sup>81ET</sup> Furthermore, trends toward decreased length of stay<sup>82ET</sup> and decreased mortality<sup>81ET</sup> that did not achieve statistical significance were also reported. These findings were not consistent across all studies, however, and 3 studies were rated as low quality with a high risk of bias. Additionally, because of the multifactorial nature of these interventions, it is not possible to determine which component(s) of these dissimilar interventions might be responsible for these favorable outcomes. No studies were identified in which the intervention solely consisted of identifying and treating the underlying cause(s) of the patient's delirium, as it would be considered unethical to randomize participants to a control group that did not receive this care. Although the overall quality of evidence is low, the clinical importance of identifying and treating the underlying cause of delirium warrants a strong recommendation.

**B. Potential Harms of Recommendation:** This recommendation balances the risks of delay in treatment for delirium or its underlying cause(s) with the risks and costs of diagnostic tests and procedures. To identify the cause of a patient's delirium, the patient may be subject to a variety of tests and procedures which, in turn, may be associated with harm. Commonly, this may include obtaining blood and urine samples; the main risks associated with these procedures include pain and infection. More advanced testing may include computed tomography (CT), magnetic resonance imaging (MRI), or lumbar puncture. Overuse of neuroimaging (CT/MRI) is a potential risk, and patients should be selected based on recent falls or head trauma, use of anticoagulation, focal neurologic signs, or fever without other explanation.<sup>5</sup> For agitated patients, sedation and/or restraints may be required to obtain these studies; however, both sedating medications and restraints may exacerbate delirium. The American Geriatrics Society recommends avoiding physical restraints to manage behavioral symptoms of hospitalized older adults with delirium.<sup>83</sup> Additional risks for imaging studies include risks associated with intravenous contrast mediums, including contrast-induced nephropathy, which has an overall risk of 0.6%–2.3% (although risk increases markedly—up to 50%—in patients with risk factors for contrast-induced nephropathy),<sup>84–86</sup> a rare risk of irreversible nephrogenic systemic fibrosis in patients with pre-

existing kidney disease;<sup>87</sup> and the potential carcinogenic effect of ionizing radiation from CT scans.<sup>88</sup> The most common complication of lumbar puncture is headache after the procedure, which occurs in 9%–25% of patients.<sup>89</sup> Rarer complications include infection and bleeding (<0.01%) and, rarely, brainstem herniation. Overall, the potential seriousness of delirium and its attendant complications warrant careful consideration in the risk-benefit decision about performing these invasive procedures in individual patients.

## V. Specialized Hospital Units

**Recommendation:** There is insufficient evidence to recommend for or against hospitals creating, and healthcare professionals using, specialized hospital units for the inpatient care of older adults with post-operative delirium to improve clinical outcomes (strength of recommendation: not applicable; quality of evidence: low).

**A. Evidence for Recommendation:** Six publications evaluated specialized hospital units for older adults with delirium.<sup>90ET, 91ET, 92ET, 93ET, 94ET</sup> Although the nature of interventions in each unit varied across the publications, interventions commonly included trained physician, nurse, and/or rehabilitation staff; environmental adaptations (eg, wall clocks, enhanced lighting, and noise reduction); and multifaceted delirium treatment interventions (eg, avoiding restraints, encouraging mobilization, and providing reorientation). Clinical outcomes evaluated across the studies included use of restraints, duration of delirium, cognitive and physical functioning, mortality, length of stay, and discharge to home. This body of publications had a high risk of bias and was predominantly composed of nonrandomized, single-site studies. Given the quality of existing evidence, the potential for publication bias (ie, failure to publish studies that demonstrate no findings of benefit) and the potential harms (discussed below), there was insufficient evidence to recommend for or against creation or use of specialized hospital units.

**B. Potential Harms of Recommendation:** See harms statement for nonpharmacologic interventions in the above section titled “I. B. Education Targeted to Health Care Professionals About Delirium, Potential Harms of All Nonpharmacologic Recommendations”.

## Pharmacologic Treatments/Interventions used Perioperatively to Prevent Postoperative Delirium in Older Surgical Patients

### VI. Anesthesia Depth

**Recommendation:** The anesthesia practitioner may use processed electroencephalographic (EEG) monitors of anesthetic depth during intravenous sedation or general anesthesia of older patients to reduce postoperative delirium (strength of recommendation: insufficient evidence; quality of evidence: low).

**A. Evidence for Recommendation:** The relationship of depth of anesthesia and the development of postoperative delirium has insufficient evidence to determine the net benefits or risks. Depth of anesthesia is measured by processed EEG monitors, and currently, there is no gold standard. Several studies compared processed EEG monitoring and the occurrence of postoperative delirium. In one small, randomized controlled trial in hip fracture patients receiving a spinal anesthetic as their primary anesthetic technique, deeper levels of adjunctive intravenous sedation with propofol, as measured by the Bispectral Index™ (Covidien; BIS™), were associated with increased rates of postoperative delirium.<sup>95ET</sup> This finding is consistent with nonrandomized, retrospective observations.<sup>96ET</sup> In two trials of Bispectral Index Monitoring vs. standard of care regulation of anesthetic depth (monitoring of heart rate, blood pressure), patients receiving general anesthesia had lower rates of postoperative delirium.<sup>97ET,98ET</sup> However, these two studies did not randomize patients to receive a specific depth of anesthesia. The single randomized trial of depth of anesthesia had many confounding factors, including the use of anesthetic agents that are not measured by the BIS proprietary algorithm.<sup>99</sup> To date, there is equipoise regarding the long-term cognitive effects of intraoperative depth of anesthesia.<sup>97ET,98ET,99</sup>

The major limitation against recommending the routine use of a processed EEG monitor is the lack of adequately powered studies randomizing patients to different depths of general anesthesia. The cited trials include a pilot randomized controlled trial, three studies with high risk of bias, and one randomized controlled trial of spinal anesthesia.<sup>95ET,96ET,97ET,98ET</sup> Therefore, the best level or depth of anesthesia to prevent postoperative delirium is not known.

**B. Potential Harms of Recommendation:** The safety of conducting “light anesthesia” in patients who require general anesthesia has not been demonstrated. Lighter anesthesia may lead to several adverse events, including intraoperative recall; intraoperative movement that may be detrimental to certain types of surgery; and sympathetic stimulation and adverse hemodynamic changes, particularly in older patients or in those with vascular disease. Processed EEG monitors may have the unintended consequence of causing the anesthesia practitioner to over-focus on a single clinical parameter. An additional potential harm is that routine use of processed EEG monitors may increase cost.

## VII. Regional Anesthesia

**Recommendation:** A healthcare professional trained in regional anesthetic injection may consider providing regional anesthetic at the time of surgery and postoperatively to improve pain control and prevent delirium in older adults (strength of recommendation: weak; quality of evidence: low).

**A. Evidence for Recommendation:** Regional anesthesia used to reduce postoperative delirium was found beneficial by two low-quality randomized clinical trials with high risk of bias. Mouzopoulos et al<sup>100ET</sup> randomized hip fracture patients to regional anesthesia (fascia iliaca block) or placebo and found that patients at intermediate risk of delirium receiving regional anesthesia had lower rates of delirium (RR 0.13, 95% CI 0.03–0.53). Kinjo et al<sup>101ET</sup> randomized patients undergoing total knee replacement to receive either femoral nerve block in addition to patient-controlled analgesia or patient-controlled analgesia alone, and found a lower incidence of delirium in the femoral nerve block group (25% vs. 61%;  $P=0.002$ ). Both studies included only patients undergoing lower extremity orthopedic operations, potentially limiting the generalizability of this recommendation. It is important to note that this recommendation is only relevant to procedures for which regional anesthesia is a viable option.

**B. Potential Harms of Recommendation:** Complications of regional anesthesia are uncommon. Peripheral nerve blocks lead to nerve injury in 1%–2% of cases, with permanent nerve injury in 0.2% of cases.<sup>102–103</sup> Other complications of local anesthetic injection include hematoma and intravascular injection. Toxicity of local anesthetics includes neurotoxicity (ranging from lightheadedness to agitation) and cardiac toxicity (arrhythmias and bradycardia).<sup>104</sup>

## VIII. Anesthesia

**Recommendation:** Healthcare professionals should optimize postoperative pain control, preferably with nonopioid pain medications, to minimize pain in older adults to prevent delirium (strength of recommendation: strong; quality of evidence: low).

**A. Evidence for Recommendation:** Adequate postoperative analgesia is associated with decreased delirium. Vaurio et al<sup>105ET</sup> studied patients 65 years and older after noncardiac operations and found that increased levels of pain were independently associated with a greater risk of postoperative delirium (OR 1.1; 95% CI 1.01–4.0). Lynch et al<sup>106ET</sup> studied patients 50 years and older undergoing elective noncardiac operations and found that increased pain at rest was associated with increased risk of postoperative delirium in the first 3 postoperative days (adjusted risk ratio 1.20,  $P=0.04$ ). Additional research has found an association between undertreated pain and the occurrence of delirium.<sup>107ET</sup>

The evidence for prescribing nonopioid alternatives to manage postoperative pain to reduce delirium is less compelling than the evidence that adequate pain control reduces delirium. Leung et al<sup>108ET</sup> performed a randomized controlled trial in 21 patients having spine surgery that compared prophylactic gabapentin administration to placebo and found that gabapentin reduced delirium (0/9 vs. 5/12;  $P=0.045$ ). Krenk et al<sup>109ET</sup> studied a fast track surgery model and found minimal delirium when the nonopioid medications gabapentin, paracetamol (acetaminophen), and celecoxib were used for pain management.

**B. Potential Harms of Recommendation:** Opioid analgesics have risks of constipation, nausea, vomiting, respiratory depression, sedation, impaired judgment, altered psychomotor function, rash, pruritus, and anaphylactoid allergic reactions.<sup>110–111</sup> Long-term opioid use can lead to dependence. Opioid dosing needs to be properly monitored, and patients must be properly managed for potential of respiratory depression. Health care professionals should assess for pain and provide adequate analgesia appropriate to the situation. Nonopioid medications used to treat and prevent postoperative pain can have potential harms specific to the individual medications. Gabapentin has adverse effects, including central nervous system depression, dizziness, double vision, increased risk of falls, pruritus, nausea/vomiting, weight gain, dystonia, and the need for significant dosage adjustment in renal dysfunction. Adverse effects for paracetamol or acetaminophen are rare and are most notable for hepatotoxicity in patients with compromised liver function. Care should be taken not to overdose with acetaminophen in the hospitalized patient, particularly when combination or multiple products are used. Nonsteroidal anti-inflammatory agents are associated with gastrointestinal bleeding, renal toxicity, elevated blood pressure, and anaphylactoid reactions in older adults.

## IX. Avoidance of Inappropriate Medications

**Recommendation:** The prescribing practitioner should avoid medications that induce delirium postoperatively in older adults to prevent delirium (strength of recommendation: strong; quality of evidence: low).

**A. Evidence for Recommendation:** Medications or medication classes associated with delirium that are relevant to the postoperative setting include benzodiazepines, anticholinergics (eg, cyclobenzaprine, oxybutynin, prochlorperazine, promethazine, tricyclic antidepressants, paroxetine and drugs with high anticholinergic properties), diphenhydramine, hydroxyzine, histamine<sub>2</sub>-receptor antagonists (eg, cimetidine), sedative-hypnotics, and meperidine.<sup>33</sup> The studies regarding specific medications or medication classes causing delirium are generally low level evidence. The current recommendation relied on the 2012 AGS Beers Criteria<sup>33</sup> for potentially inappropriate medication use for older adults and focused on the medications commonly prescribed in the perioperative setting. Current evidence most strongly associates use of anticholinergic drugs, meperidine and benzodiazepines with increased postoperative delirium. Agostini et al<sup>112ET</sup> performed a prospective cohort study of hospitalized medical patients examining the effect of diphenhydramine on delirium and found that diphenhydramine was associated with delirium (OR 2.3; 95% CI 1.4–3.6). Marcantonio et al<sup>2ET</sup> performed a nested case control study in patients 50 years and older after major elective noncardiac surgery and found a significant association between meperidine use and delirium (OR 2.7; CI 1.3–5.5). Benzodiazepines were also associated with increased delirium in a dose-response fashion (OR 3.0; CI 1.3–6.8). Taipale et al<sup>113ET</sup> conducted an observational study in patients undergoing cardiac operations and found that patients receiving higher than median midazolam doses were more likely to develop delirium (OR 2.23; CI 1.06–4.70). Luukkanen et al<sup>114ET</sup> performed a cross-sectional study of geriatric ward and nursing home patients 70 years and older and found that patients who took anticholinergic medications were more likely to develop delirium than patients not taking these drugs (27% vs. 17%;  $P=0.050$ ). Drugs that contribute to serotonin syndrome (selective serotonin reuptake inhibitors, linezolid, tramadol, and amphetamines) can lead to delirium. The use of multiple medications (five or greater) has been associated with an increased risk of delirium, likely due to the psychoactive properties of one or more of the agents in the patient's regimen.<sup>115</sup>

**B. Potential Harms of Recommendation:** Avoidance of these medications cannot be recommended for all clinical scenarios, because specific conditions may warrant their use. For example, a patient with a history of alcohol abuse or chronic benzodiazepine usage may require treatment with a benzodiazepine to prevent withdrawal complications, or a patient may require treatment with diphenhydramine for an acute severe allergic or transfusion reaction.

## X. Antipsychotics Used Prophylactically to Prevent Delirium

**Recommendation:** There is insufficient evidence to recommend for or against the use of antipsychotic medications prophylactically in older surgical patients to prevent delirium (strength of recommendation: not applicable; quality of evidence: low).

**A. Evidence for Recommendation:** Prophylactic use of antipsychotic medications to prevent delirium in postoperative patients has limited, inconsistent, and contradictory support in the literature. Studies describe different regimens prescribed to heterogeneous patient populations with varying results. Most studies are of low quality and often with high risk of bias. Five studies found decreased incidence of delirium,<sup>116ET, 117ET, 118ET, 119ET, 120ET</sup> and three did not.<sup>121ET, 122ET, 123ET</sup> Larsen et al<sup>116ET</sup> performed a randomized controlled trial (rated with a high risk of bias) comparing low-dose olanzapine to placebo in patients 65 years and older undergoing elective orthopedic joint surgery and found a lower incidence of delirium (14.3% vs. 40.2%;  $P < 0.001$ ) in patients receiving olanzapine. However, delirium episodes in the olanzapine group were more severe and lasted longer than those in the placebo group. Another study found nearly the opposite effect. Kalisvaart et al<sup>123ET</sup> performed a randomized controlled trial comparing 0.5 mg haloperidol three times daily to placebo in high-risk older patients undergoing hip operations and found no difference in delirium incidence (15.1% vs. 16.5%). However, in contrast to the previous study, decreased delirium severity and duration was found in the haloperidol group. In an additional study,<sup>122ET</sup> haloperidol prophylaxis did not change delirium rates in high-risk hip fracture patients. The highest quality study investigating prophylactic haloperidol use<sup>121ET</sup> was performed in ventilated ICU patients, which limits its generalizability to postoperative delirium. In this randomized controlled trial of low-dose prophylactic haloperidol compared with placebo in mechanically ventilated ICU patients, some of whom had delirium at enrollment, there was no effect on delirium-free or coma-free days.

**B. Potential Harms of Recommendation:** The potential harms associated with antipsychotic medications are numerous and include, but are not limited to, central nervous system effects (such as somnolence, extrapyramidal effects such as muscle rigidity, tremor, restlessness, swallowing difficulty, decreased seizure threshold, and neuroleptic malignant syndrome), systemic and cardiovascular effects (such as QT prolongation, dysrhythmias, sudden death, hypotension, and tachycardia), pneumonia, urinary retention, postural instability, falls, deep venous thrombosis, anticholinergic effects, syndrome of inappropriate antidiuretic hormone, and metabolic effects (such as weight gain, insulin resistance, and hypertriglyceridemia). Although the harms increase with chronic use, even short-term treatment is associated with increased mortality.<sup>124</sup> Patients with Parkinson disease or Lewy body dementia can develop both cognitive and functional deterioration from antipsychotic medications. The harms of haloperidol were studied prospectively in 119 palliative care patients with delirium in which 12% of patients reported somnolence, rigidity, tremor, and restlessness at 10 days of treatment.<sup>125</sup> In general, the randomized controlled trials examining antipsychotics for treatment of delirium are underpowered to adequately examine the rates of these adverse effects.

The inadvertent chronic administration of antipsychotics, after inpatient initiation during an episode of delirium, is an important harm. A review of 59 patients who received antipsychotics during an episode of delirium while admitted to an ICU demonstrated that 47% continued to receive the drug after discharge from the ICU, and 33% as an outpatient after discharge from the hospital without a clear indication.<sup>126</sup> Long-term exposure to antipsychotic medications is associated with significant adverse effects and increased health care costs and is unwarranted for the acute treatment of agitation due to a delirious episode.

## XI. Cholinesterase Inhibitors

**Recommendation:** In older adults not currently taking cholinesterase inhibitors, the prescribing practitioner should not newly prescribe cholinesterase inhibitors perioperatively to older adults to prevent or treat delirium (strength of recommendation: strong; quality of evidence: low).

**A. Evidence for Recommendation:** Newly prescribing prophylactic cholinesterase inhibitors in the perioperative setting has been found by four randomized controlled trials not to be effective in reducing the incidence of postoperative delirium. Gamberini et al<sup>127ET</sup> compared rivastigmine and placebo started the evening before surgery in patients 65 years and older who were undergoing elective cardiac operations and found no difference in incidence of postoperative delirium (32% vs. 30%;  $P=0.8$ ) or duration of delirium. Liptzin et al<sup>128ET</sup> compared donepezil to placebo started 2 weeks before surgery and continued 2 weeks after joint replacement and found no difference in the incidence of delirium (20.5% vs. 17.1%;  $P=0.69$ ). Two small pilot studies similarly found no difference in the incidence of postoperative delirium with the prophylactic prescription of cholinesterase inhibitors.<sup>129ET, 130ET</sup> Notably, in the trial completed by Marcantonio et al,<sup>129ET</sup> the donepezil group had more adverse effects, and a trend toward more serious adverse events than the placebo group. The risk of bias was high in all of these studies.

Two studies compared use of a cholinesterase inhibitor to placebo for treatment of delirium and found no differences in duration of delirium.<sup>131ET, 132ET</sup> One trial in critically ill medical and surgical patients was halted early based on a trend toward higher mortality in the rivastigmine group (22% vs. 8%;  $P=0.07$ ).<sup>132ET</sup>

**B. Potential Harms of Recommendation:** Adverse effects of cholinesterase inhibitors include diarrhea, anorexia, dyspepsia, bradycardia, and potential to exacerbate peptic ulcer disease, cardiac conduction disorders, seizures, asthma, and benign prostatic hypertrophy. Cholinesterase inhibitors may increase mortality when used to treat delirium in the ICU setting.<sup>132ET</sup> Because there is evidence of worsening symptoms after withholding cholinesterase inhibitors,<sup>133</sup> cholinesterase inhibitors should be continued in patients with Alzheimer disease who have been stabilized on treatment before surgery. However, if agents are held for more than 2 days, a patient's tolerance for gastrointestinal adverse effects may be reduced, causing diarrhea, nausea, and vomiting with reinitiation of higher doses.

## Pharmacologic Treatments/Interventions used to Treat Postoperative Delirium in Older Surgical Patients

### XII. Antipsychotics in the Setting of Severe Agitation

**Recommendation:** The prescribing practitioner may use antipsychotics at the lowest effective dose for the shortest possible duration to treat patients who are severely agitated or distressed, and are threatening substantial harm to self and/or others. In all cases, treatment with antipsychotics should be employed only if behavioral interventions have failed or are not possible, and ongoing use should be evaluated daily with in-person examination of patients (strength of recommendation: weak; quality of evidence: low).

**A. Evidence for Recommendation:** The evidence for pharmacologic treatment of postoperative delirium with antipsychotic medications is difficult to interpret because of the heterogeneity in the drugs studied, dosages administered, patient populations, and outcomes examined. There are no placebo-controlled, randomized clinical trials testing the benefit of antipsychotics in older, postoperative, agitated, delirious patients. All placebo-controlled trials testing the use of antipsychotic agents in treating delirium report using additional open-label haloperidol or other additional antipsychotic medications for agitation in both treatment and placebo groups. Hakim et al<sup>134ET</sup> performed a placebo-controlled randomized trial in older postoperative surgical patients and found that although postoperative randomization to risperidone (1 mg/day) prevented progression to full delirium, it did not decrease the need for haloperidol or risperidone for agitation, or the length of ICU or hospital stay. Girard et al<sup>135ET</sup> conducted a pilot randomized controlled study of antipsychotics in medical and surgical ICU patients that compared groups receiving haloperidol (mean daily dose 4.5 mg), ziprasidone (mean daily dose 113 mg), or placebo, and found no difference between the three arms in the number of delirium-free or coma-free days. Two smaller studies compared the outcomes of the use of quetiapine (mean daily dose 100 mg and 40 mg, respectively) to placebo in patients on a mixed surgical and medical ICU and medical/surgical/orthopedic wards, respectively.<sup>136ET, 137ET</sup> Quetiapine administration was associated with decreased time to resolution of delirium, decreased time spent delirious, less agitation, and possibly increased rate of resolution of non-cognitive symptoms. However, with treatment arms of less than 20 patients, these findings should be confirmed in larger studies.

Randomized controlled studies comparing antipsychotics in the absence of a placebo comparison arm do not demonstrate a difference in treatment benefit or adverse events between various antipsychotic agents.<sup>138ET, 139ET, 140ET, 141ET, 142ET, 143ET, 144ET</sup> The most frequently studied medication is haloperidol (evaluated in 6 of 7 studies), followed by risperidone and olanzapine (used in 4 of 7), and quetiapine (2 of 7). None of these studies included a homogenous postoperative sample of patients, and many do not represent patients in the geriatric age group. Secondary data analysis of two studies suggested that patients of older age (>75 years) were less likely to respond to antipsychotics than younger patients, particularly for olanzapine.<sup>141ET, 143ET</sup>

**B. Potential Harms of Recommendation:** See harms statement for pharmacologic interventions to prevent delirium in the above section titled “X. B. Antipsychotics”.

### XIII. Benzodiazepines

**Recommendation:** The prescribing practitioner should not use benzodiazepines as a first line treatment of the agitated post-operative delirious patient who is threatening substantial harm to self and/or others to treat postoperative delirium except when benzodiazepines are specifically indicated (including but not limited to treatment of alcohol or benzodiazepine withdrawal). Treatment with benzodiazepines should be at the lowest effective dose for the shortest possible duration, and should be employed only if behavioral measures have failed or are not possible and ongoing use should be evaluated daily with in-person examination of the patient (strength of recommendation: strong; quality of evidence: low).

**A. Evidence for Recommendation:** There is no evidence supporting the routine use of benzodiazepines in the treatment of delirium in hospitalized patients. Breitbart et al<sup>144ET</sup> conducted a prospective randomized clinical trial in delirious, medically hospitalized AIDS patients with an average age of 39 years (N=30) randomly assigned to treatment with haloperidol, chlorpromazine, or lorazepam. Not only did the lorazepam group (n=6) not have improved delirium outcomes, but this arm was also terminated early because of significant adverse effects, including disinhibition, sedation, ataxia, and increased confusion.

There is substantial evidence that benzodiazepines may promote delirium. Marcantonio et al<sup>12ET</sup> developed a prediction model based on a prospective study of older adults undergoing cardiac surgery and demonstrated that postoperative exposure to benzodiazepines was significantly associated with development of delirium. Additionally, prospective cohort studies of patients in medical intensive care settings suggest that benzodiazepines are associated with a longer duration of delirium<sup>145ET</sup> and that lorazepam is an independent risk factor for transitioning to delirium in ICU patients.<sup>146ET</sup>

**B. Potential Harms of Recommendation:** The potential harms of this recommendation include withholding treatment for conditions in which benzodiazepines are indicated. These include, but are not limited to, alcohol and benzodiazepine withdrawal. Amato<sup>147</sup> conducted a review of 64 randomized controlled trials that evaluated the effectiveness and safety of benzodiazepine treatment for alcohol withdrawal. This review suggests a protective benefit against alcohol withdrawal symptoms and seizures in particular when compared to placebo.

## XIV. Pharmacologic Treatment of Hypoactive Delirium

**Recommendation:** The prescribing practitioner should not prescribe antipsychotic or benzodiazepine medications for the treatment of older adults with postoperative delirium who are not agitated and threatening substantial harm to self or others (strength of recommendation: strong; quality of evidence: low).

**A. Evidence for Recommendation:** Based on the current evidence, pharmacologic treatment has not been consistently shown to modify the duration or severity of postoperative delirium. The clinical trials reviewed<sup>134ET, 135ET, 144ET</sup> in the prior two recommendations (above sections XII. and XIII.) do not support the hypothesis that medications improve care of the delirious patients. Thus, there is no evidence of benefit from treatment of antipsychotics in patients without agitation. In addition, the harms of both antipsychotics and benzodiazepines are substantial and well documented, with the potential for increased morbidity and mortality. Weighing the lack of benefits against the substantial potential risks, the strong recommendation was made that health care providers should not prescribe these classes of drugs for treatment of delirium in patients without significant agitation that threatens the patient's safety or the safety of others. The use of antipsychotics should be reserved for short-term management of acute agitation in the setting of possible substantial harm as outlined in the section (above) for treatment of postoperative delirium in older surgical patients with behavior (ie, agitation) that substantially threatens the patient's safety or the safety of others. These uses may be more frequent in settings such as postoperative recovery rooms and ICUs. This recommendation addresses the treatment of nonagitated delirium, which is distinct from delirium prophylaxis.

**B. Potential Harms of Recommendation:** A theoretical harm of this recommendation is that patients with hypoactive delirium who may be experiencing hallucinations and delusions might get symptomatic relief from their experiences, even if these medications do not resolve the delirious episode. Hallucinatory and delusional experiences might be difficult to elicit from a hypoactive patient during the delirious episode, and withholding antipsychotic medications in this situation might be associated with increased suffering. However, there are no objective data on this potential harm in the literature. This recommendation is not intended to discourage future research on antipsychotics and delirium.

## CONCLUSIONS

Successful postoperative management of delirium for older adults requires knowledge of both nonpharmacologic and pharmacologic interventions aimed to prevent and treat delirium. The recommendation statements provide a framework to allow hospital systems and health care professionals to implement actionable, evidence-based measures to improve delirium prevention and treatment.

### Box 1. Clinical Practice Guideline Summary

#### **This clinical practice guideline provides eight strong recommendation statements.**

For these recommendations, the panel weighed the evidence for each intervention and determined either that the benefits clearly outweighed the risks or that the risks clearly outweighed the benefits.

- Multicomponent nonpharmacologic interventions delivered by an interdisciplinary team should be administered to at-risk older adults to prevent delirium.
- Ongoing educational programs regarding delirium should be provided for health care professionals.
- A medical evaluation should be performed to identify and manage underlying contributors to delirium.
- Pain management (preferably with nonopioid medications) should be optimized to prevent postoperative delirium.
- Medications with high risk for precipitating delirium should be avoided.
- Cholinesterase inhibitors should not be newly prescribed to prevent or treat postoperative delirium.
- Benzodiazepines should not be used as first-line treatment of agitation associated with delirium.
- Antipsychotics and benzodiazepines should be avoided for treatment of hypoactive delirium.

#### **This clinical practice guideline provides an additional 3 weak recommendation statements.**

The panel judged the evidence to be in favor of these interventions, but the current level of evidence or potential risks of the treatment did not support a strong recommendation.

- Multicomponent nonpharmacologic interventions implemented by an interdisciplinary team may be considered when an older adult is diagnosed with postoperative delirium to improve clinical outcomes.
- The injection of regional anesthetic at the time of surgery and postoperatively to improve pain control with the goal of preventing delirium may be considered.
- The use of antipsychotics (eg, haloperidol, risperidone, olanzapine, quetiapine, or ziprasidone) at the lowest effective dose for the shortest possible duration may be considered to treat delirious patients who are severely agitated or distressed or who are threatening substantial harm to self and/or others.

**This clinical practice guideline also provides one “insufficient evidence” recommendation statement.** The panel deemed that a recommendation statement should be provided for this intervention to be considered, but the current level of evidence or potential risks of the treatment did not support either a strong or weak recommendation.

- Use of processed electroencephalographic (EEG) monitors of anesthetic depth during intravenous sedation or general anesthesia may be used to prevent delirium.

**Finally, the panel concluded there was insufficient evidence to recommend either for or against the following recommendations:**

- Prophylactic use of antipsychotic medications to prevent delirium
- Specialized hospital units for the inpatient care of older adults with postoperative delirium

This guideline has some important limitations that are worthy of mention. First, the recommendations were limited by the available evidence, which was often not extensive and frequently of low quality. Second, the search strategies may have missed some studies, and importantly, studies published in languages other than English were excluded. Third, many of the studies were not specific to the postoperative setting, and the panel applied their findings to the surgical setting. In spite of the origins of the evidence, however, because the expert panel focused on applying the findings to the peri- and postoperative setting, thus the specific recommendations must be extrapolated with caution to other settings. Particularly, our systematic review of the literature excluded studies related to sedation in the ICU, and studies related to palliative care and nursing home care settings. In all cases, these guidelines are not intended to supersede clinical judgment or individual patient choices or values. Ultimately, clinical decision-making must always be customized to the individual situation.

Despite these limitations, this guideline has many strengths. We used an evidence-based approach guided by IOM standards for the systematic review and guideline development. All of the evidence underwent rigorous review for quality and risk of bias through a carefully standardized process. The guideline panel, which included broad and appropriate interdisciplinary expertise relevant to the recommendations, carefully considered the evidence and achieved full consensus. Additionally, the guideline panel was supported by quality measure experts who helped guide the language used in the recommendation statements to be optimal for translation into clinical quality measures. The guideline has been revised based on peer review and public commentary, including extensive input from the target audience of healthcare professionals, as well as from lay audiences, family caregivers, and senior advocacy organizations. Finally, regular updates of the guidelines are planned.

## FUTURE DIRECTIONS

Delirium remains one of the most common and under-recognized postoperative complications in older adults. Future work needs to prioritize both health care quality and research initiatives. Given the relative lack of high-quality studies on such a common and deleterious complication in surgical patients, health care policy makers and funding agencies are strongly encouraged to allocate funding to support future work on delirium. From a health care quality perspective, the recommendation statements from this guideline are prime candidates for developing into quality measures to incentivize system-wide adoption of optimal prevention and treatment of postoperative delirium. Next steps to facilitate widespread adoption would include standardized protocols and implementation tools, process monitoring and auditing criteria, and on-line materials and staff to assist with addressing barriers and challenges to implementation of these guidelines. Other health care quality priorities include public education to minimize risk factors for delirium (eg, limit alcohol use, enhance cognition), policy incentives to improve recognition and management, and bridging the knowledge gap of health care professionals regarding delirium care.<sup>5</sup>

To address other topics related to postoperative delirium not covered in this guideline, the AGS postoperative delirium panel developed a Best Practices statement to be co-published with this clinical practice guideline manuscript. The purpose of the postoperative delirium Best Practices statement was to provide a more comprehensive statement with information listed in a reader-friendly format to guide clinicians in the care of their older patients with regard to delirium, covering topics already well covered in previous guideline statements and systematic reviews (such as screening, diagnosis, and risk factors for delirium) that were not covered in the present guideline.

Research priorities regarding the prevention and treatment of delirium include assessing the long-term benefits of nonpharmacologic prevention, trials of drug reduction (intra- and postoperatively) to prevent delirium, trials of nonopioid pain regimens to prevent delirium, and combined approaches of nonpharmacologic and pharmacologic delirium management. Larger and more rigorous clinical trials of treatment strategies are greatly needed in areas that address pathophysiologic contributors to delirium. Other delirium research priorities include improving delirium measurement, particularly for hypoactive delirium; developing a cost-effective delirium evaluation; and improving delirium risk stratification.<sup>5</sup> Findings of future research may result in changes to guideline recommendations, which will be regularly updated (ideally every 3-5 years) through a guideline panel process. Ultimately, it is hoped that the diligent work of the panel to provide this clinical guideline and best practices recommendations will help to improve clinical care, advance research, and lay the groundwork for critical discoveries in this important area that will improve quality of life for older adults and their families.

## ACKNOWLEDGMENTS

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The following individuals were members of the AGS Expert Panel on Postoperative Delirium: Sharon K. Inouye, MD, MPH, Harvard Medical School and Aging Brain Center, Institute for Aging Research, Hebrew Senior Life, Boston, MA (co-chair); Tom Robinson, MD, MS, University of Colorado School of Medicine, Aurora, CO (co-chair); Caroline Blaum, MD, MS, New York University School of Medicine, New York, NY; Jan Busby-Whitehead, MD, CMD, AGSF, Center for Aging and Health, University of North Carolina School of Medicine, Chapel Hill, NC; Malaz Boustani, MD, MPH, Indiana University School of Medicine, Indianapolis, IN; Ara Chalian, MD, Hospitals of University of Pennsylvania, Philadelphia, PA; Stacie Deiner, MD, Mount Sinai Hospital, New York, NY; Donna Fick, PhD, RN, FGSA, FAAN, College of Nursing and Medicine, The Pennsylvania State University, University Park, PA; Lisa Hutchison, PharmD, University of Arkansas for Medical Sciences, Little Rock, AR; Jason Johanning, MD, University of Nebraska Medical Center, Omaha, NE; Mark Katlic, MD, Sinai Hospital, Baltimore, MD; James Kempton, Yale University and West Haven VA, New Haven, CT; Maura Kennedy, MD, MPH, Beth Israel Deaconess Medical Center, Boston, MA; Eyal Kimchi, MD, PhD, Massachusetts General Hospital, Boston, MA; Cliff Ko, MD, University of California Los Angeles, Los Angeles, CA; Jacqueline Leung, MD, MPH, University of California San Francisco, San Francisco, CA; Nancy E. Lundebjerg, American Geriatrics Society (ex-officio, caregiver rep); Melissa Mattison, MD, Harvard University and Beth Israel Deaconess Medical School, Boston, MA; Sanjay Mohanty, MD, American College of Surgeons, Chicago, IL; Arvind Nana, MD, JPS Health, Fort Worth, TX; Dale Needham, MD, PhD, Johns Hopkins University, Baltimore, MD; Karin Neufeld, MD, MPH, Johns Hopkins Hospital, Baltimore, MD; and Holly E. Richter, PhD, MD, University of Alabama at Birmingham, Birmingham, AL.

Sue Radcliff, Independent Researcher, Denver, CO, and Christine Weston, Independent Researcher, Baltimore, MD, led the literature review efforts of the panel. Additional research assistance was provided by Sneeha Patil, Gina Rocco, and Jirong Yue. Susan E. Aiello, DVM, ELS, provided editorial services. Marianna Drootin, MPA, Elvy Ickowicz, MPH, and Mary Jordan Samuel provided additional research and administrative support. The development of this paper was supported in part by the American Geriatrics Society Geriatrics-for-Specialists Initiative (AGS-GSI) through an unrestricted grant from the John A. Hartford Foundation. The funding source played no role in the design, conduct, reporting or content of this guideline. The following organizations with special interest and expertise in the treatment and prevention of postoperative delirium provided peer review of a preliminary draft of this guideline: American Academy of Hospice and Palliative Medicine, Academy of Geriatric Emergency Medicine, Alzheimer's Association, American Academy of Family Physicians, American Academy of Neurology, American Academy of Physical Medicine and Rehabilitation, American Association of Critical Care Nurses, American Case Management Association, American College of Chest Physicians, American College of Emergency Physicians, American College of Physicians, American Delirium Society, American Medical Directors Association, American Physical Therapy Association (APTA), American Society of Colon and Rectal Surgeons, American Society of Consultant Pharmacists, American Society of Health System Pharmacists, American Thoracic Society, American Urogynecologic Society, Association of

Academic Psychiatrists, Gerontological Advance Practice Nursing Association, National Association of Social Workers, Society for Advancement of Geriatric Anesthesia, Society for Social Work Leadership in Health Care, Society of Critical Care Medicine, Society of Gynecologic Surgeons, and Society of Hospital Medicine.

**Conflict of Interest:** Drs. Blaum, Boustani, Chalian, Inouye, Katlic, Kempton, Kennedy, Kimchi, Ko, Mohanty, and Nana indicated no conflicts of interest. Dr. Busby-Whitehead indicated her spouse is a paid consultant for Ironwood Pharma, Ono Pharma: Fecal Incontinence and Irritable Bowel Syndrome, and her spouse has received a grant from Salix Pharma, Ono Pharma: Fecal Incontinence and Irritable Bowel Syndrome. Dr. Deiner has received grants from the NIH, ADRC, and AGS Foundation for Anesthesia Education and Research, and Dr. Deiner's spouse has received grants from NIH, ADRC, AGS Foundation for Anesthesia Education and Research, and Brookdale. Dr. Deiner's spouse is also on the speaker's panel for Baxter. Both Dr. Deiner and spouse receive product support from Covidien and Aspect. Dr. Fick is a paid consultant for SLACK Inc. as Editor of the Journal of Gerontological Nursing. Dr. Fick has current R01 funding from the NIH and from the National Institute of Nursing Research. Ms. Giovannetti is employed by the National Committee for Quality Assurance (NCQA) which conducts health care quality research, develops health care quality measures, publishes health care quality data, and distributes health care quality products (eg, Accreditation, Certification). Dr. Hutchison received grants from MedEd Portal/Josiah Macy Foundation IPE Award, and Dr. Hutchison and spouse hold shares in Cardinal Health and Care Fusion. Dr. Johanning received a royalty on Isolation Station from Harloff Corporation. Dr. Mattison is a paid contributor for Practical Reviews in Hospital Medicine, is an UpToDate Contributor, and has consulted for Imprivata. Dr. Leung and her husband receive funding from the NIH. Dr. Leung's husband is the co-founder of Mynosys Inc. Dr. Needham is Chair of the Early Mobility Committee for the upcoming Society of Critical Care Medicine Clinical Practice Guideline for pain, agitation, delirium, early mobility, and sleep. Dr. Neufeld is participating on a grant from ORNIM medical manufacturing that is funding a portion of her salary. Dr. Richter is a paid consultant for and has received a research grant from Pelvalon. She also has received royalties from UpToDate. Dr. Robinson has received research grants from Medtronic, Inc., Karl Storz Endoscopy America, and Covidien. Nancy Lundebjerg had no conflicts of interest to disclose. Gina Rocco and Jirong Yue have no conflicts of interest to disclose. Sneha Patil has commercial interest in Oracle.

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\*ET is used to indicate citations for which evidence tables were created. These are denoted with ET in the text and “(ET)” in the bibliography and can be viewed as an online addendum found on [www.GeriatricsCareOnline.org](http://www.GeriatricsCareOnline.org).

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**Table 1. Key to Designations of Quality and Strength of Evidence**

<b>Quality of Evidence</b>	
<b>High</b>	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes ( $\geq 2$ consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodologic flaws showing large effects).
<b>Moderate</b>	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes ( $\geq 1$ higher-quality trial with $> 100$ participants; $\geq 2$ higher-quality trials with some inconsistency; $\geq 2$ consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodologic flaws showing at least moderate effects) limits the strength of the evidence.
<b>Low</b>	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.
<b>Strength of Recommendation</b>	
<b>Strong</b>	Benefits clearly outweigh risks and burden, or risks and burden clearly outweigh benefits. Panel judged the evidence and determined that the benefits clearly outweighed harms or the potential harms clearly outweighed the benefits.
<b>Weak</b>	Benefits finely balanced with risks and burden. Panel judged the evidence to be in favor of these interventions, but the current level of evidence or potential risks of the treatment did not support a strong recommendation.
<b>Insufficient</b>	Insufficient evidence to determine net benefits or risks. Panel judged the evidence as warranting a recommendation statement to be made, but weighed the evidence as being insufficient to determine the net risks and benefits.
<b>Not applicable</b>	No recommendation made. Panel determined that no recommendation could be made, that is, a statement could not be made either for or against a clinical practice.

Adapted from Qaseem A, Snow V, Owens DK, et al 2010.

**Table 2. Summary Table of Guideline (ordered by strength of recommendation)\***

Recommendation Statement	Strength of Recommendation	Quality of Evidence
<b>Strong Recommendations</b>		
<b>II.</b> Healthcare systems and hospitals should implement multicomponent nonpharmacologic intervention programs delivered by an interdisciplinary team (including physicians, nurses, and possibly other healthcare professionals) for the entire hospitalization in at-risk older adults undergoing surgery to prevent delirium.	Strong	Moderate
<b>I.</b> Healthcare systems and hospitals should implement formal educational programs with ongoing formal and/or informal refresher sessions for healthcare professionals on delirium in at-risk older surgical adults to improve understanding of its epidemiology, assessment, prevention, and treatment.	Strong	Low
<b>IV.</b> The healthcare professional should perform a medical evaluation, make medication and/or environmental adjustments, and order appropriate diagnostic tests and clinical consultations after an older adult has been diagnosed with postoperative delirium to identify and manage underlying contributors to delirium.	Strong	Low
<b>VIII.</b> Healthcare professionals should optimize postoperative pain control, preferably with nonopioid pain medications, to minimize pain in older adults to prevent delirium.	Strong	Low
<b>IX.</b> The prescribing practitioner should avoid medications that induce delirium postoperatively in older adults to prevent delirium.	Strong	Low
<b>XI.</b> In older adults not currently taking cholinesterase inhibitors, the prescribing practitioner should not newly prescribe cholinesterase inhibitors perioperatively to older adults to prevent or treat delirium.	Strong	Low
<b>XIII.</b> The prescribing practitioner <u>should not</u> use benzodiazepines as a first line treatment of the agitated post-operative delirious patient who is threatening substantial harm to self and/or others <u>to treat postoperative delirium</u> except when benzodiazepines are specifically indicated (including but not limited to treatment of alcohol or benzodiazepine withdrawal). Treatment with benzodiazepines should be at the lowest effective dose for the shortest possible duration, and should be employed only if behavioral measures have failed or are not possible and ongoing use should be evaluated daily with in-person examination of the patient.	Strong	Low
<b>XIV.</b> The prescribing practitioner <u>should not</u> prescribe antipsychotic or benzodiazepine medications for the treatment of older adults with postoperative delirium who are not agitated and threatening substantial harm to self or others.	Strong	Low

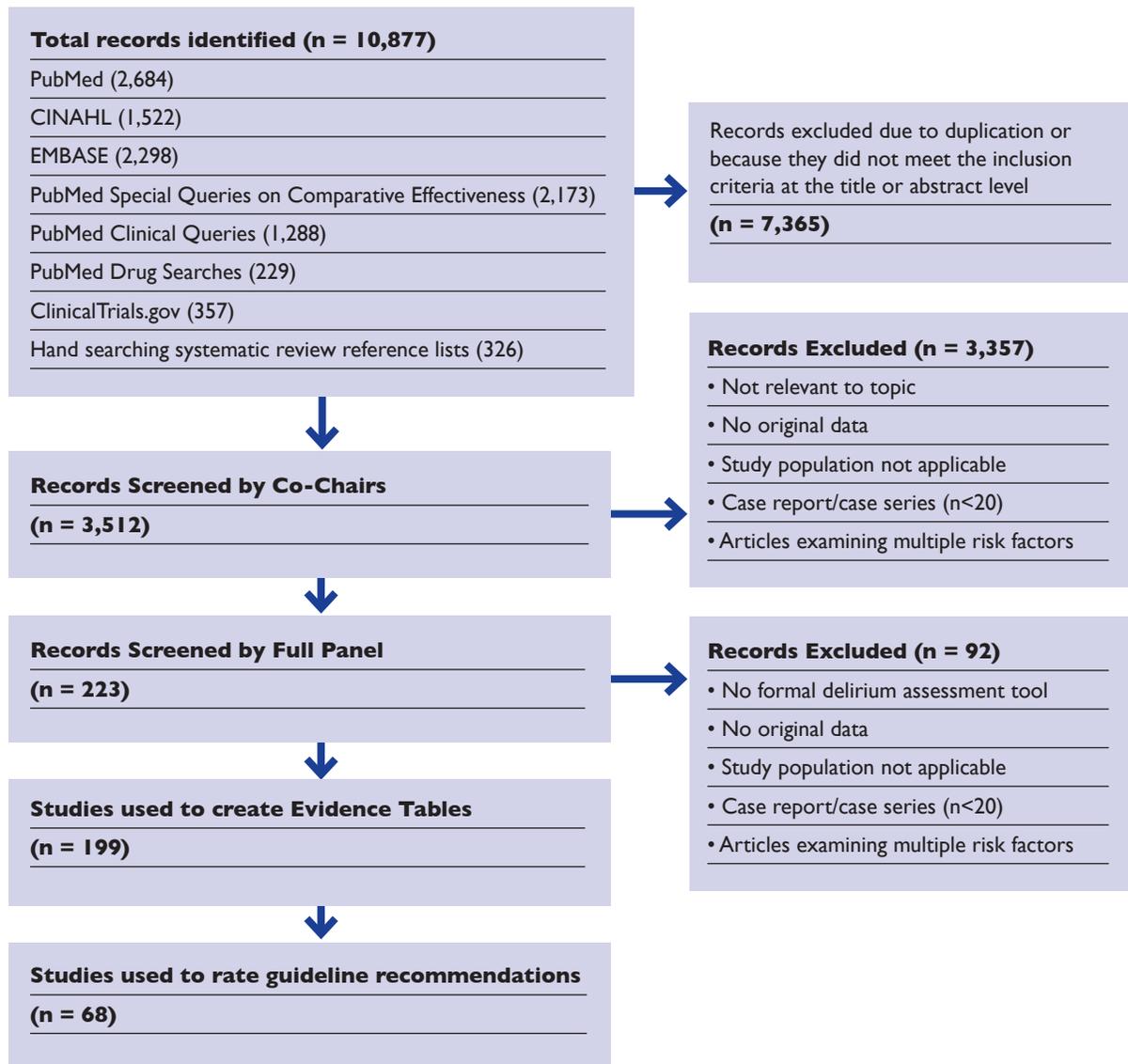
\*Not in numerical order; but ordered by strength of recommendation

**Table 2. Summary Table of Guideline / continued  
(ordered by strength of recommendation)\***

Recommendation Statement	Strength of Recommendation	Quality of Evidence
<b>Weak Recommendations</b>		
<b>III.</b> Healthcare professionals should consider multicomponent interventions implemented by an interdisciplinary team in older adults diagnosed with postoperative delirium to improve clinical outcomes.	Weak	Low
<b>VII.</b> A healthcare professional trained in regional anesthetic injection may consider providing regional anesthetic at the time of surgery and postoperatively to improve pain control and prevent delirium in older adults.	Weak	Low
<b>XII.</b> The prescribing practitioner may use antipsychotics at the lowest effective dose for the shortest possible duration to treat patients who are severely agitated or distressed, and are threatening substantial harm to self and/or others. In all cases, treatment with antipsychotics should be employed only if behavioral interventions have failed or are not possible, and ongoing use should be evaluated daily with in-person examination of patients.	Weak	Low
<b>Recommendations Without Sufficient Evidence</b>		
<b>VI.</b> The anesthesia practitioner may use processed electroencephalographic (EEG) monitors of anesthetic depth during intravenous sedation or general anesthesia of older patients to reduce postoperative delirium.	Insufficient	Low
<b>X.</b> There is insufficient evidence to recommend for or against the use of antipsychotic medications prophylactically in older surgical patients to prevent delirium.	Not Applicable	Low
<b>V.</b> There is insufficient evidence to recommend for or against hospitals creating, and healthcare professionals using, specialized hospital units for the inpatient care of older adults with postoperative delirium to improve clinical outcomes.	Not Applicable	Low

\*Not in numerical order, but ordered by strength of recommendation

**Diagram I – American Geriatrics Society Clinical Practice Guideline for Postoperative Delirium in Older Adults**



**Key words:** “delirium”, “acute confusion”, or “organic brain syndrome” from January 1, 1988 to October 1, 2013

**Inclusions:**

- Prevention, management and treatment studies
- Adult population
- Limit to hospital setting
- Limit to perioperative interventions (end at hospital discharge)
- In ICU, limit to delirium prevention/management (exclude sedation only)

**Exclusions:**

- Non-English language
- Non-systematic reviews, editorials, comments, letters, dissertations
- Populations: pediatric, alcohol/substance withdrawal, schizophrenia, dementia, stroke, brain surgery or trauma, nursing home or post-acute setting, and other non-hospital settings (rehab, hospice, outpatient)