Canadian Coalition for Seniors' Mental Health

Coalition Canadienne pour la Santé Mentale des Personnes Âgées

2014 Guideline Update

The Assessment and Treatment of Delirium

2014 GUIDELINE UPDATE

AIMS OF THE GUIDELINE: The CCSMH is proud to have been able to facilitate the development of these clinical guidelines. These are the first interdisciplinary, national best practices guidelines to specifically address key areas in seniors' mental health. These guidelines were written by and for interdisciplinary teams of health care professionals from across Canada. The aim of these guidelines is to improve the assessment, treatment, management and prevention of key mental health issues for seniors, through the provision of evidence-based recommendations. The recommendations are based on the best available evidence at the time of publication and when necessary, supplemented by the consensus opinion of the guideline development group.

AIMS OF THE GUIDELINE UPDATE: Guideline Updates summarize significant developments in the practice since the publication of the original guidelines in 2006. Guideline Updates are authored and reviewed by experts associated with the original guideline development project. Please refer to the original guideline, found on our website at www.ccsmh.ca, for more detailed information regarding the specific practice recommendations.

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Introduction

Since the publication in 2006 of the Canadian Coalition of Seniors' Mental Health (CCSMH) guidelines on *The Assessment and Treatment of Delirium* (Hogan *et al.* 2006), progress on delirium has been incremental rather than transformative. Work done since then has reinforced the need to be aware that delirium commonly complicates the care of older persons admitted to acute care hospitals and long-term care facilities (Siddiqi, House & Holmes 2006), and can have serious long-term consequences especially for those whose symptoms persist (Cole, Ciampi, Belzile & Zhong 2010; Cole 2010; Wilcox *et al.* 2010; Fong *et al.* 2012; Saczynski *et al.* 2012; Davis *et al*. 2012; Gross *et al*. 2012;). A longer duration of delirium is associated with pre-existing dementia, multiple morbidity, increasing delirium severity, hypoactive symptoms, and hypoxia (Dasgupta & Hillier 2010). As with other psychiatric conditions, delirium has a spectrum of severity (Levkoff, Yang & Liptzin 2004). At the milder end of the continuum, there are patients with one or more of the symptoms of delirium who do not meet DSM-defined criteria for delirium. They are referred to as having subsyndromal delirium (SSD). Clinicians should be aware that SSD may be a prodromal state and, as noted in the 2006 guidelines, has outcomes that lie between those of delirious and non-delirious patients (Ouimet *et al.* 2007; Cole *et al.* 2011). Uncertainty, though, remains about how to diagnose SSD, the utility of this classification given the fluctuating course of delirium, and what to do about it (Blazer & van Nieuwenhuizen 2012).

While the CCSMH guidelines on delirium were adapted for older adults at the end of life (Allard *et al.* 2010), they have not been otherwise reviewed since their publication. In 2011, the CCSMH asked the 2006 co-leads to provide a limited update of the guidelines. It was agreed to provide one on pharmacological interventions to either prevent or treat delirium. This area was felt to have the greatest potential interest and need for an update. Its limited scope meant it could be done in a timely manner with the limited resources available. The decision to review drug therapy for this update in no way detracts from the importance of addressing reversible contributors, reducing psychoactive medications, and utilizing non-pharmacological interventions in efforts to prevent or manage delirium (Inouye, Marcantonio & Metzger 2014).

2014 GUIDELINE UPDATE

Summary of Modified Recommendations

All modified or added recommendations are presented together with the page numbers for the original guideline recommendations at the beginning of this update for easy reference. Subsequently, in each section we present the recommendation with a discussion of the relevant literature since the original publication in 2006. We strongly encourage readers to refer to the original 2006 guidelines and the discussion below, rather than only using the summary of modified recommendations.

2006 Recommendation: Prevention (page 27)
Based on current evidence, psychopharmacologic interventions for unselected older persons to prevent the development of delirium are not recommended **[D]**.
Modified Recommendations: Prevention
There is suggestive evidence that general anesthesia compared to other forms of anesthesia is associated with an increased risk of developing post-operative cognitive dysfunction (POCD) but not post-operative delirium (POD). Further research to confirm the increased risk for POCD and its consequences is required **[B]**.
There is suggestive evidence that short-term, low-dose melatonin reduces the incidence of delirium in older patients admitted to an acute medical unit, but further research is required before it can be recommended for routine use **[B]**.
There is suggestive evidence that short-term, low-dose haloperidol reduces the incidence and/or severity of POD in high risk older patients without contraindications to its use, but further research is needed before it can be recommended for routine use **[B]**.
There is suggestive evidence that risperidone after cardiac surgery reduces the risk of POD in patients without contraindications to its use, but further research is needed before it can be recommended for routine use **[B]**.
There is suggestive evidence that short-term, low-dose olanzapine reduces the risk of POD, but if delirium occurs it might be more severe and of a longer duration. The use of olanzapine for the prevention of POD cannot be recommended at this time **[B]**.
The use of cholinesterase inhibitors solely for the prevention or treatment of delirium is not recommended **[A]**.
To decrease the risk of delirium in mechanically ventilated patients, dexmedetomidine should be considered as a sedative alternative to benzodiazepines and propofol **[A]**.

There is insufficient evidence to support the routine use of any other form of pharmacological intervention for the prevention of delirium **[B]**.

2006 Recommendation: Antipsychotics (page 41-44)

High potency antipsychotic medications are preferred over low potency antipsychotics **[B]**.

Haloperidol is suggested as the antipsychotic of choice based on the best available evidence to date **[B]**.

Atypical antipsychotics may be considered as alternative agents as they have lower rates of extra-pyramidal signs.**[B]**

Modified Recommendations: Antipsychotics

In older persons with a delirium where pharmacotherapy is indicated, low dose, short-term therapy with haloperidol or an atypical antipsychotic (e.g., olanzapine, quetiapine, risperidone) can be considered. Haloperidol is not recommended if there is pre-existing Parkinson disease or Lewy body dementia **[B].**

Methods

The search terms used were the same as for the 2006 Guidelines (Hogan *et al.* 2006), though on this occasion the database search was limited to Medline and restricted to English papers published between July 2005 and June 2011.

A total of 411 papers were identified. Both authors reviewed the titles and abstracts of these papers in order to select which should undergo a full-text review. Controlled trials (especially randomized), meta-analyses, reviews (especially systematic), and practice guidelines potentially relevant to the subject area were chosen. Eighty-nine of the 411 papers identified in the literature search were selected for full-text review. Both authors evaluated each paper. Agreement was reached on all changes or additions to the 2006 recommendations. In the fall of 2012, a draft of the revised recommendations was presented at the annual meeting of the CCSMH. Valuable feedback was obtained, which led to minor modifications.

Because of the length of time between the systematic literature review and the publication of the update, one of the authors (DH) identified additional relevant papers by purposeful non-exhaustive Medline searches, using text terms, to cover the period between July 2011 and September 2014. After this updated examination of the literature, a few further modifications were made to the revised recommendations.

Part 2: Prevention Discussion and Recommendations

Based on the updated review, we recommend that the following 2006 recommendation be replaced by the nine new recommendations summarized below.

2006 Recommendation: Prevention (page 27)
Based on current evidence, psychopharmacologic interventions for unselected older persons to prevent the development of delirium are not recommended **[D].**
Modified Recommendations: Prevention
Intraoperative monitoring of the depth of sedation in order to titrate anesthetic drugs is a promising approach to decreasing the risk of postoperative delirium but further study is required **[B].**

A systematic review of general and regional anesthesia on the incidence of postoperative cognitive dysfunction (POCD) and postoperative delirium (POD) found that general anesthesia, compared to other forms of anesthesia, was not associated with a higher risk for POD (odds ratio 0.88, 0.51-1.51 95% confidence interval). However, there was a marginal increase in the risk for POCD (odds ratio 1.34, 0.93-1.95 95% confidence interval) (Mason, Noel-Storr & Ritchie 2010). Another systematic review concluded that the likelihood of POD was equivalent for neuraxial (i.e., a type of regional anesthesia that involves the injection of anesthetic agents around the nerves of the central nervous system, such as spinal and epidural anesthesia) and general anesthesia (pooled incidences were 17.1% for both) (Zhang, Lu, Zou, Wang, Xu & Shi 2013). A third review reported no difference between general and regional anesthesia in rates of POD (Friedman, Soleimani, McGonigle, Egol & Silverstein 2014). Titrating the depth of intraoperative sedation by neuromonitoring has attracted increasing interest as a potential approach to preventing POD. A randomized study of older patients undergoing hip fracture repair under spinal anesthesia with propofol sedation that was titrated by the bispectral index (BIS) found a significantly increased incidence of POD [40.4% vs. 19.3%, p = 0.014] lasting about a day longer with deep compared to light sedation (Sieber *et al*. 2010). Two randomized studies of BIS-guided anesthesia for elective surgery in older patients reported lower rates of POD (15.6% vs. 24.1%, p =0.01 in the first study and 16.7% vs. 21.4%, p = 0.036 in the second), compared to routine care (Chan, Cheng, Lee, Gin & the CODA Trial Group 2013; Radtke *et al.* 2013). Potential mechanisms include avoiding extremely low BIS values and/or reducing anesthetic drug exposure. The specific drugs used for general anesthesia have also been

examined. A small [58 male patients] randomized controlled study of ketamine for the induction of anesthesia in patients undergoing elective cardiac surgery with cardiopulmonary bypass found its use was associated with a significantly lower incidence of POD [3% vs. 31%, p = 0.01]) (Hudetz *et al*. 2009). However this study has not been replicated. Regional nerve blocks for hip fractures are another promising perioperative procedure that will be discussed in a following section. We made a qualified recommendation and assigned a strength grade of "B" as we feel further work is required to confirm and broaden the observations made to date to other patient populations.

Modified Recommendations: Prevention

Short-term melatonin or ramelteon therapy in order to reduce the incidence of POD or delirium in older patients admitted to intensive care or acute medical units requires further study and cannot be recommended at this time **[B].**

Melatonin (a naturally occurring compound produced by the pineal gland in humans, known chemically as N-acetyl-5-methoxytryptamine) is important in sleep/wake regulation. It has been suggested that melatonin supplementation might be helpful in preventing and treating delirium (Lewis & Barnett 2004; Bourne & Mills 2006; Hanania & Kitain 2002). In a study of older patients undergoing a hip arthroplasty, the use of melatonin was associated with a significantly lower incidence of POD compared to those receiving either nothing, midazolam or clonidine (9.4% vs. 32.7%, 44.0%, and 37.3% respectfully, $p < 0.05$) (Sultan 2010). There are a number of methodological concerns about this study, including the exclusion of patients with cognitive impairment (De Jonghe, van de Glind, van Munster & de Rooij 2014). A relatively small (149 patients enrolled), single-site, double-blind, placebo-controlled, block randomized trial of melatonin (0.5 mg given orally every day in the evenings until discharge from hospital, death, or day 14 of the hospital stay) in older (65+) patients admitted to a medical in-patient service found a lower risk of delirium (12% vs. 31%, p = 0.014) with active therapy. The agent was reportedly well-tolerated. No significant benefit was seen on any secondary outcome (i.e., delirium severity, use of sedatives, the use of restraints, mortality, length of stay, sleep). A significant proportion of those enrolled (27 subjects or 18.1%) were excluded from the assessment of overall effectiveness (Al-Aama *et al.* 2011). Finally, a double-blind, randomized controlled trial of 378 analyzed patients found that melatonin (3 mg in the evening for five consecutive days) in older (mean age 84) patients undergoing hip surgery had no

significant effect on the incidence of delirium (29.6% in the melatonin group vs. 25.5% with placebo) (De Jonghe, van Munster *et al.* 2014).

Ramelteon is an agonist of melatonin approved in the United States and other countries for insomnia characterized by difficulty with falling asleep. A randomized single-blind study of ramelteon 8 mg or placebo administered every night for seven days to a small group (n = 67) of older (65-89 years of age) patients newly admitted to hospital with a serious medical problem reported a significantly lower risk of delirium (3% vs. 32%, p = 0.003) with active treatment (Hatta *et al.* 2014). There are no published studies comparing melatonin to ramelteon in their ability to prevent delirium.

The negative recommendation with a [B] grade was given because of the inconsistency and limitations of the current evidence. Larger confirmatory studies in different populations are required before its use can be advocated. The National Institute for Health and Clinical Excellence (2012) has also made a call for additional research on melatonin.

Modified Recommendations: Prevention

There is inconsistent evidence that short-term, low dose haloperidol reduces the incidence and/or severity of POD in high risk older patients without contraindications to its use. Further research is needed before it can be recommended for routine use **[B].**

By preventing neuroexcitatory potentiation and/or antagonizing sigma-1 receptors, haloperidol may be an effective prophylactic agent for delirium (Caplan 2012). A randomized placebo-controlled trial of haloperidol (0.5 mg three times daily started pre-operatively and then continued for up to three days after surgery) in older (70+) patients at intermediate to high risk for delirium admitted for acute or elective hip surgery showed no statistically significant difference in the primary outcome measure, the incidence of POD (15.1% with haloperidol vs. 16.5% with placebo, relative risk 0.91, 0.6-1.3 95% confidence interval). However, there were significant differences favouring haloperidol in the severity and duration (5.4 vs. 11.8 days, p < 0.001) of delirium, as well as a shorter average length of hospital stay (17.1 vs. 22.6 days, p < 0.001) if POD occurred (Kalisvaart, de Jonghe, Bogaards *et al.* 2005). No haloperidol-related adverse effects were noted. In a prospective cohort study of hip fracture patients, those deemed at high risk for delirium were treated with prophylactic low dose haloperidol. Those identified as high risk did have a higher incidence of delirium, but using a before-after design, prophylactic treatment with haloperidol did not reduce overall delirium incidence (Vochteloo *et al.* 2011). A randomized, double-blind,

placebo-controlled trial of IV haloperidol (0.5 mg IV bolus injection, followed by continuous infusion at a rate of 0.1 mg/hr. for 12 hours) in older (65+) patients admitted to intensive care units after non-cardiac surgery, showed a significantly lower incidence of POD during the first seven postoperative days (15.3% vs. 23.2%, p = 0.031). The treatment was well tolerated (Wang *et al.* 2012). The Hope-ICU was a double-blind, placebo-controlled randomized trial of critically ill adults requiring mechanical ventilation. Patients received haloperidol 2.5 mg or 0.9% saline IV every eight hours irrespective of coma or delirium status for up to 14 days. Haloperidol had no impact on the number of days spent in delirium (Page *et al.* 2013). A randomized, controlled, open-label study of older patients undergoing elective surgery showed no significant difference in the incidence of delirium (POD 42.4% with haloperidol vs. 33.3% in the control group, p = 0.0309) (Fukata *et al*. 2014). Intravenous haloperidol is approved for use in Canada but QT prolongation and torsades de pointes can occur. These rare adverse events almost always arise in patients with additional risk factors and after cumulative dosages of 2 mg or more (Eyer-Massettl, Cheng, Sharpe, Meir & Guglielmo 2010). Australian guidelines for the management of hip fractures in older persons and a Cochrane review of interventions for preventing delirium in hospitalized patients both concluded that prophylactic low dose haloperidol might reduce the severity and duration of POD and shorten length of hospital admission for hip surgery (Mak, Cameron & March 2010; Siddiqi, Holt, Britton & Holmes 2007). The positive studies reviewed targeted high risk older patients (i.e., older patients at intermediate to high delirium risk undergoing orthopedic surgery, older patients admitted to an intensive care unit after non-cardiac surgery) and excluded patients with a variety of contraindications including Parkinsonism and a prolonged corrected QT interval on a baseline ECG. The "B" grade recommendation that additional work is required was made because of the limited and inconsistent results of the research done to date.

Modified Recommendations: Prevention

There is suggestive evidence that risperidone after cardiac surgery reduces the risk of POD in patients without contraindications to its use, but further research is needed before it can be recommended for routine use **[B].**

A relatively small (126 subjects) randomized trial of a 1 mg single dose of risperidone sublingual upon awakening after elective cardiac surgery with cardiopulmonary bypass showed a lower incidence of POD (11.1% vs. 31.7%, p = 0.009) (Prakanrattana & Prapaitrakool 2007). Limitations of this study included

poor blinding procedures (the compared treatments had perceptible differences) and the relatively young age of participants (mean age was approximately 61). A small (101 subjects) randomized placebo-controlled trial of risperidone (0.5 mg every 12 hours until 24 hours after disappearance of SSD or until delirium developed) targeted to older (65+) patients with SSD after on-pump cardiac surgery showed a significantly lower likelihood of developing POD with active therapy (13.7% vs. 34%, p = 0.031) (Hakim, Othman & Naoum 2012). Both studies pre-screened participants and excluded those who didn't meet eligibility criteria. Neither study reported beneficial effects on delirium severity, delirium duration, length of ICU stay, or length of hospital stay with risperidone. Larger studies of longer duration in more diverse populations are needed.

Modified Recommendations: Prevention

There is suggestive evidence that short-term, low dose olanzapine reduces the risk of POD, but if delirium occurs it might be more severe and of a longer duration. The use of olanzapine for the prevention of POD cannot be recommended at this time **[B].**

A double-blind, placebo-controlled, single site, randomized trial evaluated the utility of olanzapine (5 mg orally immediately before and after surgery) for the prevention of POD in older patients undergoing elective knee or hip replacement therapy. The incidence of POD was significantly lower if given olanzapine (14.3% vs. 40.2%, p < 0.0001), and the time-to-onset of delirium was greater (p < 0.0001). However, if delirium occurred it was significantly more severe (p = 0.02) and lasted longer (2.2 days vs. 1.6 days, p = 0.02). There were also slightly more postoperative cardiac complications with active therapy. A study limitation was that patients were only followed for four days (Larsen, Kelly, Stern *et al*. 2010). Further research is required to clarify the relative balance of benefit and harm.

Modified Recommendations: Prevention

The use of cholinesterase inhibitors for the prevention or treatment of delirium is not recommended **[A].**

Donepezil (5 mg per day for 14 days prior to and 14 days after surgery) in patients undergoing elective joint replacements did not have a significant impact on the incidence of POD (20.5% in those given donepezil vs. 17.1% assigned to placebo, p = 0.069) (Liptzin, Laki, Garb *et al.* 2005). In another small study of donepezil for the

prevention of POD in patients undergoing elective total hip replacements, there was no significant reduction in the incidence of delirium (Sampson *et al.* 2007). A pilot study of donepezil (5mg daily initiated within 24 hours of surgery) in older hip fracture patients showed no benefit and significantly more side effects (Marcantonio, Palihnich, Appleton & Davis 2011). It was felt the results did not justify any further work on the possible utility of this agent for POD. A Cochrane review concluded there was no evidence from controlled trials that donepezil was an effective agent for delirium (Overshott, Karim & Burn 2008). In a double-blind, randomized, placebo-controlled trial, rivastigmine (three doses of 1.5 mg of oral rivastigmine per day starting the evening before surgery and continuing until the evening of the sixth postoperative day) was examined as a means to prevent delirium in older patients undergoing elective cardiac surgery. Delirium developed in 30% of those treated with rivastigmine and 32% of patients given placebo ($p = 0.8$). There was no treatment effect on Mini-Mental State Examination and clock drawing results ($p = 0.4$ and $p = 0.8$ respectively), nor any significant difference in the number of patients who received haloperidol ($p = 0.9$) (Gamberini *et al*. 2009). A double-blind, placebo-controlled randomized trial examined the effect of rivastigmine (initial dose of 1.5 mg twice daily that was incrementally increased to 6 mg twice daily from day 10 onwards) on the duration of delirium in critically ill patients. The study was terminated early because of a nearly significant higher mortality in the treated group (22% vs. 8%, $p = 0.07$). As well, the median duration of delirium was non-significantly greater in the rivastigmine group (5 days vs. 3 days, $p = 0.06$) (Van Eijk *et al.* 2010). No controlled study of galantamine for delirium has been published. Aside from the lack of any evident efficacy, cholinesterase inhibitors have a number of potential adverse effects that would raise concerns about their use in older patients admitted to hospital with severe medical and surgical conditions. For example, they may increase the effects of succinylcholine (a muscle relaxant that is used as an anesthetic drug) and can be associated with a variety of cardiac problems, such as bradycardia, syncope and pacemaker insertion (Gill *et al.* 2009). Please note that abrupt cessation of a cholinesterase inhibitor in patients on long-term therapy for dementia can be associated with an acute worsening of cognitive abilities and is not recommended if there is no clinical indication to stop the agent quickly (Singh & Dudley 2003; Minett *et al.* 2003; Bidzan & Bidzan 2012).

Modified Recommendations: Prevention

To decrease the risk of delirium in mechanically ventilated patients, dexmedetomidine should be considered as a sedative alternative to benzodiazepines and propofol **[A].**

Dexmedetomidine (a pharmacologically active dextroisomer of medetomidine, this is a centrally acting selective α_2-adrenergic receptor agonist) can be used for sedating mechanically ventilated patients. In a study comparing dexmedetomidine to lorazepam for sedation in medical and surgical ICU patients, its use was associated with more delirium-free and coma-free days (seven versus three days, $p = 0.01$) (Pandharipande *et al.* 2007). Another study comparing dexmedetomidine to midazolam found a lower incidence of delirium with dexmedetomidine (54% vs. 76%, $p < 0.001$) (Riker *et al.* 2009). In a randomized study of postoperative sedation of patients undergoing cardiac valve procedures, dexmedetomidine was associated with a significantly lower incidence of delirium than propofol (short-acting, intravenously administered hypnotic agent) or midazolam (10% vs. 44% vs. 44%, $p < 0.001$) (Maldonado *et al.* 2009). There is suggestive but not conclusive evidence supporting the use of dexmedetomidine in weaning delirious patients off ventilators (Reade *et al.* 2009; Yapici *et al.* 2011; Shehabi *et al.* 2010). A systematic review contrasting benzodiazepine with non-benzodiazepine-based sedation for mechanically ventilated adults concluded that further research is required on the issue of their respective impacts on delirium risk (Fraser *et al.* 2013). However, a recent meta-analysis of the randomized controlled trials that compared dexmedetomidine with other sedating agents concluded that its use was associated with a significant reduction in the incidence of delirium (Pasin *et al.* 2014).

Modified Recommendations: Prevention

There is suggestive evidence that regional nerve blocks for pain management in older patients with a hip fracture are associated with a lower rate of delirium but further research is required to confirm this finding **[B].**

Delirium is a common complication of hip fractures in older patients (Chaudhry, Devereaux & Bhandari 2013). The use of regional nerve blocks (i.e., fascia iliaca, 3-in-1 [femoral, obturator, sciatic nerves], or continuous epidural block) to manage pain was associated with a lower risk of delirium in four small randomized controlled trials (Foss, Kristensen, Kristensen, Jensen & Kehlet 2005; Graham,

Baird & McGuffie 2008; Mouzopoulos *et al*. 2009; Godoy Monzón, Vazquez, Jauregui & Iserson 2010). In the largest of these studies (Mouzopoulos *et al*. 2009), when delirium did occur, it was less severe and didn't last as long. Based on these reports, as well as two cohort studies, a systematic review concluded there was moderate evidence that regional nerve blocks prevented delirium in this patient population (Abou-Setta *et al.* 2011). Improved pain control and/or reduced opioid requirements were felt to explain these results. These positive results have to be interpreted with caution. In addition to the limited number and small sizes of the studies, a number of them excluded patients with significant preoperative cognitive impairment, didn't provide information on how delirium was diagnosed (Rashiq *et al.* 2013), and in the Mouzopoulos *et al.* study (2009), only the participants were blinded (Inouye, Westendorp & Saczynski 2014). Australian guidelines for the management of hip fractures in older persons concluded that the use of regional anesthesia might reduce the likelihood of postoperative confusion (Mak, Cameron & March 2010). The *Quality-Based Procedures Clinical Handbook for Hip Fracture* for Ontario recommended that regional nerve blocks be considered for pain control especially for patients at high risk for delirium (Health Quality Ontario 2013). However, in the only study that reported on the issue of patient risk level (Mouzopoulos *et al*. 2009), delirium prevention was restricted to those at an intermediate risk for this outcome (i.e., there was no evident benefit for those deemed at high risk). It is generally believed that regional nerve blocks are underutilized in Canada (Haslam, Lansdown, Lee & van der Vyver 2013). While the beneficial effect on pain control would be another reason to advocate for their greater use, we feel further studies are required before we could definitely state that regional nerve blocks are effective in preventing delirium.

Modified Recommendations: Prevention

There is insufficient evidence to support the routine use of any other form of pharmacological intervention for the prevention of delirium **[B].**

There is no consistent high quality evidence showing efficacy, tolerability and/or safety that would support the routine use of other forms of pharmacotherapy for the prevention of delirium (Diaz *et al.* 2001; Aizawa *et al.* 2002; Leung, Sanda, Vaurio & Wang 2006; Leung, Sands, Rico *et al.* 2006; Pesonen *et al.* 2011; Kato *et al.* 2011; Sauër, Slooter, Veldhuijzen, van Eijk & van Dijk 2013; Robinson *et al.* 2014).

Part 4.4 Pharmacological Management Discussion and Modified Recommendation

On review of the recent literature and the 2006 recommendations, we recommend replacing the three 2006 recommendations below with the modified recommendation summarized below.

2006 Recommendation: 4.4.2 Antipsychotics (page 41-44)

High potency antipsychotic medications are preferred over low potency antipsychotics **[B].**

Haloperidol is suggested as the antipsychotic of choice based on the best available evidence to date **[B].**

Atypical antipsychotics may be considered as alternative agents as they have lower rates of extra-pyramidal signs **[B].**

Modified Recommendations: Antipsychotics

In older persons with a delirium where pharmacotherapy is indicated, low dose, short-term therapy with haloperidol or an atypical antipsychotic (e.g., olanzapine, quetiapine, risperidone) can be considered. Haloperidol is not recommended if there is pre-existing Parkinson disease or Lewy body dementia **[B].**

The strength of the recommendation was assigned a [B] grade because of the major methodological limitations with the available studies (Seitz, Gill & van Zyl 2007; Flaherty, Gonzales & Dong 2011) and the increasing concerns about the risks of antipsychotics. There is only limited support for low dose, short-term (usually for one week or less) antipsychotic therapy for delirium in restricted situations (i.e., when there is evidence of significant distress and/or to prevent the older delirious patient from endangering themselves or others AND non-pharmacological approaches are either inappropriate or ineffective). Notwithstanding, antipsychotics are perceived as beneficial by many health care practitioners and are frequently used for the treatment of delirium (Devlin, Bhat, Roberts & Skrobik 2011). An indication for haloperidol (first generation, high potency, typical antipsychotic) for the management of delirium is noted in the 2014 edition of the *Compendium of Pharmaceuticals and Specialties* (CPS) (Canadian Pharmacists Association 2014). This is not a listed indication for any of the atypical (i.e., second generation) antipsychotics, and their use for delirium would have to be viewed as off-label. Systematic reviews have concluded that haloperidol and atypical antipsychotics have similar efficacy in treating the symptoms of

delirium (Lonergan, Britton, Luxenberg *et al*. 2007; Lacasse, Perreault & Williamson 2006; Seitz, Gill & van Zyl 2007; Ozbolt, Paniagua & Kaiser 2008; Campbell *et al.* 2009). A small single-blind, randomized trial comparing the efficacy of olanzapine, risperidone, and haloperidol reported similar efficacy and tolerability (Grover, Kumar & Chakrabarti 2011). Another small study showed similar overall efficacy for olanzapine and risperidone, but an exploratory analysis that will require confirmation suggested the response to risperidone was poorer in the older age group (Kim *et al.* 2010). Adding to the body of research supporting the use of atypical antipsychotics, two recent small randomized controlled trials showed faster time to delirium resolution with quetiapine compared with placebo (Devlin *et al.* 2010; Tahir *et al.* 2010). Maneeton *et al.* (2013) reported that quetiapine and haloperidol were equally effective and safe in the treatment of delirium. Yoon *et al.* (2013) in a non-randomized but assessor-blinded study found haloperidol, risperidone, olanzapine, and quetiapine to be equally efficacious and safe in the treatment of delirium, though response rates were lower (especially for olanzapine) in patients 75 or older. At low doses the tolerability of haloperidol is comparable to atypical antipsychotics, but at higher dosages extrapyramidal side effects become more common (Lonergan, Britton, Luxenberg *et al*. 2007; Campbell *et al.* 2009). Advantages for low dose haloperidol compared to the atypical antipsychotics include oral and parenteral preparations, minimal anticholinergic effects, and infrequent development of orthostatic hypotension. Haloperidol is not recommended if there is pre-existing Parkinson disease or Lewy body dementia. Warnings have been issued for atypical antipsychotics such as olanzapine, quetiapine and risperidone, stating that older patients with dementia treated with these agents are at an increased risk of death compared to placebo. Though a warning was not issued, an increase in mortality has also been observed with typical antipsychotics such as haloperidol when used to treat older patients with dementia (Gill *et al.* 2007). There is little data on the impact of short-term antipsychotic use on mortality in older hospitalized patients with a delirium. In an underpowered study, their use was not associated with a statistically significant increased mortality rate (odds ratio 1.53, 95% confidence interval 0.83-2.80) (Elie *et al.* 2009). A prospective observational study of 2,453 delirious older (mean age 73.5 years) in-patients who received antipsychotics reported that, in the opinion of the involved psychiatrist, none of the 386 deaths that occurred was due to antipsychotic side effects (Hatta *et al.* 2014). Controlled trials using more rigorous methodology are needed to clarify this particular issue. The major modification to the 2006 recommendation is to now view haloperidol and the atypical antipsychotics as equivalent options in most patients.

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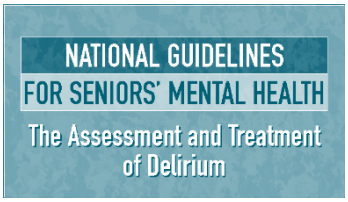
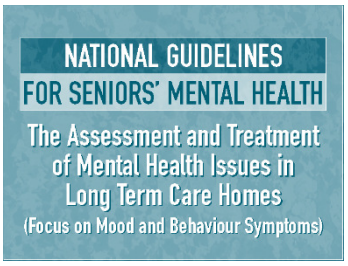
Canadian Coalition for Seniors Mental Health Tools and Resources





These resources and more can be downloaded from our website at www.ccsmh.ca.

Notes:

ABOUT CCSMH

MISSION: To promote the mental health of seniors by connecting people, ideas and resources.

VALUE STATEMENT: Mental illness is not a normal part of aging. All seniors have the right and deserve to receive services and care that promotes their mental health and responds to their mental illness needs.

CCSMH WORKING PRINCIPLES: Our actions and decisions are guided by:

- Collaboration
- Multidisciplinary Inclusiveness
- Integrity
- Accountability
- Effectiveness
- Transparency

STRATEGIC PRIORITY AREAS: The following are current priorities areas for the CCSMH:

- Advocacy and Public Awareness
- Education
- Research
- Promoting Best/Promising Practices
- Caregiving
- Human Resources/Capacity Building

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Canadian Coalition for Seniors' Mental Health

Coalition Canadienne pour la santé mentale des personnes âgées

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