Treating an Established Episode of Delirium in Palliative Care: Expert Opinion and Review of the Current Evidence Base With Recommendations for Future Development

Shirley H. Bush, MBBS, MRCGP, FAChPM[#], **Salmaan Kanji, BSc Pharm, PharmD[#]**, **José L. Pereira, MBChB, CCFP, MSc**, **Daniel H.J. Davis, MBChB, MRCP**, **David C. Currow, BMed, MPH, FRACP**, **David Meagher, MD, PhD, MRCPsych**, **Kiran Rabheru, MD, CCFP, FRCP, DABPN**, **David Wright, RN, PhD, CHPCN(C)**, **Eduardo Bruera, MD, Meera Agar, MBBS, FRACP**, **Michael Hartwick, MD, FRCPC**, **Pierre R. Gagnon, MD, FRCPC**, **Bruno Gagnon, MD, MSc**, **William Breitbart, MD, FAPM, FAPA**, **Laura Regnier, BSc, MSc, MD, CCFP**, and **Peter G. Lawlor, MB, FRCPI, MMedSc**

Division of Palliative Care (S.H.B., J.L.P., M.H., P.G.L.) and Division of Critical Care (M.H.), Department of Medicine; Department of Psychiatry (K.R.); Department of Family Medicine (L.R.); Department of Epidemiology and Community Medicine (P.G.L.), University of Ottawa; Bruyère Research Institute (S.H.B., J.L.P., P.G.L.), Bruyère Continuing Care; The Ottawa Hospital Research Institute (S.K., P.G.L.); Department of Pharmacy (S.K.) and Department of Radiation Oncology (L.R.); The Ottawa Hospital (K.R., M.H.), Ottawa, Ontario, Canada; Institute of Public Health (D.H.J.D.), University of Cambridge, Cambridge, United Kingdom; Discipline, Palliative and Supportive Services (D.C.C., M.A.), Flinders University, Adelaide, South Australia, Australia; Graduate Entry Medical School (D.M.), University of Limerick, Limerick, Ireland; McGill University (D.W.), Montreal, Quèbec, Canada; Department of Palliative Care and Rehabilitation Medicine (E.B.), The University of Texas M. D. Anderson Cancer Center, Houston, Texas, USA; South West Sydney Clinical School (M.A.), University of New South Wales; Department of Palliative Care (M.A.), Braeside Hospital, HammondCare, Sydney, New South Wales, Australia; Faculty of Pharmacy et Centre de Recherche en Cancèrologie (P.R.G.) and Dèpartement de Mèdecine Familiale et de Mèdecine d'Urgence (B.G.), Universitè Laval; Department of Psychiatry (P.R.G.), CHU de Quèbec; Centre de Recherche du CHU de Quèbec (B.G.), Quèbec City, Quèbec, Canada; and Department of Psychiatry and Behavioral Sciences (W.B.), Memorial Sloan-Kettering Cancer Center, New York, New York, USA

[#] These authors contributed equally to this work.

Abstract

Context—Delirium is a highly prevalent complication in patients in palliative care settings, especially in the end-of-life context.

Objectives—To review the current evidence base for treating episodes of delirium in palliative care settings and propose a framework for future development.

Methods—We combined multidisciplinary input from delirium researchers and other purposely selected stakeholders at an international delirium study planning meeting. This was supplemented by a literature search of multiple databases and relevant reference lists to identify studies regarding therapeutic interventions for delirium.

Results—The context of delirium management in palliative care is highly variable. The standard management of a delirium episode includes the investigation of precipitating and aggravating factors followed by symptomatic treatment with drug therapy. However, the intensity of this management depends on illness trajectory and goals of care in addition to the local availability of both investigative modalities and therapeutic interventions. Pharmacologically, haloperidol remains the practice standard by consensus for symptomatic control. Dosing schedules are derived from expert opinion and various clinical practice guidelines as evidence-based data from palliative care settings are limited. The commonly used pharmacologic interventions for delirium in this population warrant evaluation in clinical trials to examine dosing and titration regimens, different routes of administration, and safety and efficacy compared with placebo.

Conclusion—Delirium treatment is multidimensional and includes the identification of precipitating and aggravating factors. For symptomatic management, haloperidol remains the practice standard. Further high-quality collaborative research investigating the appropriate treatment of this complex syndrome is needed.

Introduction

Delirium is a common neuropsychiatric complication of medical illness across a wide variety of health care settings. The reported prevalence of delirium in inpatient palliative care settings ranges from 26%–62% during admission to 88% in the last days and hours of life.[1,2] In addition to the high frequency of delirium in the terminal phase of illness, it has been independently associated (negatively) with short-term survival.[3,4] Delirium is characterized by a fluctuating constellation of cognitive and neurobehavioral features, including abnormalities of awareness, attention, perception, psychomotor activity, and sleep.[5] Perhaps unsurprisingly, this complex neuropsychiatric syndrome remains not only underdiagnosed but also undertreated.[6–8]

The multifactorial nature of delirium etiology involves a combination of predisposing baseline risk factors and superimposed precipitating factors, many of which are modifiable. Delirium has an element of reversibility when precipitants are identified and successfully removed or minimized. Consequently, across most settings, the standardized approach to delirium management involves searching for and addressing its underlying precipitants in addition to optimal symptomatic treatment with drug therapy.[9–12] Clinicians sometimes face a therapeutic dilemma as to how aggressively they pursue delirium precipitants, particularly in patients who are transitioning to the terminal phase of illness.

Delirium is disturbing to families in all settings, but especially for those whose family member is near the end of life when communication and comfort needs are paramount.[13,14] Refractory delirium, in which the optimal therapeutic interventions have failed to control its clinical features, is the most common indication for the use of continuous sedation at the end of life.[15]

This article aims to 1) appraise the current evidence base for treatment of clinical delirium in the context of palliative care (referring to any type of health care setting in which palliation of a life-threatening illness is indicated) and 2) propose a framework for the future expansion of this evidence base. Pharmacologic and nonpharmacologic preventive strategies also constitute an integral part of a comprehensive delirium management plan but are not addressed in depth in this article.

Methods

This article is based in part on the combined multidisciplinary input from leading delirium researchers (invitation was based on their publication record); specialist physicians in oncology, intensive care, geriatric medicine and psychiatry, liaison psychiatry, and palliative care; and clinical or organizational administrators. This structured process was conducted through a two day international delirium study planning meeting in June 2012 in Ottawa, Canada, in which 31 attendees gathered to identify knowledge gaps and research priorities in relation to delirium in palliative care. The program addressed the symptomatic management of delirium and included multiple formal presentations in addition to small and large group discussions, which were recorded and transcribed.

The meeting data were supplemented by a systematic literature search of Ovid MEDLINE, EMBASE, and Cochrane databases from the earliest available records of each up to April 2013 to identify trials of pharmacologic treatment of delirium. Search terms included "delirium," "confusion," "treatment," "therapeutics," "antipsychotic agents," "alpha adrenergic agents," and "cholinesterase inhibitors"; results were limited to the English language and human clinical trials and systematic reviews. Reference lists of reviews and included articles also were evaluated for relevant trials. The scope of the search was not limited to palliative care. The search yielded 430 potentially relevant citations, of which 55 were reviewed. Only prospective single-arm or parallel-arm comparative trials were retrieved. Thirty-one trials met these inclusion criteria. Although a systematic approach was used to search the literature, no formal quality review of the selected articles was conducted.

Results

Based on our review objectives, literature search, and deliberations at the international delirium study planning meeting, we categorized the evidence informing treatment of clinical delirium into 1) the unique contextual issues in palliative care, 2) pharmacologic interventions, 3) nonpharmacologic interventions, and 4) recommendations for future studies.

Unique Contextual Issues in Palliative Care Settings

Although a certain degree of commonality may exist in relation to some challenging aspects of delirium management across the many health care settings and populations in which it occurs, the relatively unique contextual issues relating to palliative care warrant specific recognition and consideration. These issues include the vulnerability of the patient population, cognitive status and its implications for care, determining the reversibility of delirium; the frequent use of deliriogenic medications, and the delirium experience in the context of end of life.

Challenges for Conducting Research in a Vulnerable Population—Most patients referred for specialist palliative care have a cancer diagnosis and often have advanced disease.[16,17] Conducting delirium research in the advanced cancer population or in any end-of-life condition is challenging because of patient vulnerability, ethical issues around informed consent, and willingness of patients to participate in research, often resulting in limited patient accrual to studies and high attrition rates.[2,18] Furthermore, recruiting patients for comparative effectiveness drug trials is challenging as many patients require psychotropic medications for other indications, such as nausea, mood disorders, pain, and dementia. These factors likely contribute to the reason why there is a paucity of rigorously designed studies on the treatment of delirium in this population.

Cognitive Status and its Implications for Care—In a global aging population, dementia presents an increasing health issue, especially in palliative care, in which there is a predominance of elderly patients. Furthermore, dementia is regarded as an end-of-life condition and an indication for palliative care involvement. Regardless of palliative care involvement, mortality rates within six months of a delirium episode superimposed on dementia are high.[19] Dementia is one of the strongest risk factors for the development of delirium in the elderly.[20] When an episode of delirium is superimposed on undiagnosed dementia, challenges may clearly arise in relation to health care decision making. Furthermore, failure of a delirium episode to fully resolve may in itself unmask an evolving dementia and also create challenges for health care decision making, especially when the goals of care have not been clearly established. Patients with cognitive impairment as part of delirium or dementia who require pain management pose unique challenges, in terms of both assessment and the use of opioids and other pharmacologic agents.[21]

Determining the Reversibility of Delirium—Some studies have described the multifactorial etiology of delirium in palliative care settings.[22–24] Up to 50% of delirium episodes in palliative care patients are reversible.[22] Reversibility correlates with the type of identified precipitating factor/s: There is a higher likelihood of reversing an episode of delirium that is precipitated by medications, electrolyte abnormalities, and infection.[23] Patients are less likely to improve if they have had previous episodes of delirium or have a delirium related to hypoxic or global metabolic encephalopathy.[22,23] The ultimate decision to pursue investigation and treatment of delirium precipitants in palliative care settings will depend on the goals of care and the patient's location along the disease trajectory.[25] Given that palliative care is delivered in a variety of settings—from home to standalone inpatient hospice units providing end-of-life care and increasingly through hospital consult teams in

acute care settings[26]—varying access to investigation and treatment of delirium precipitants also may determine the level of therapeutic intervention. Taken together, these factors may influence the spectrum of intensity in relation to therapeutic intervention, marked by polar extremes: one is therapeutic nihilism with potentially reversible episodes neglected and the other is overly aggressive treatment adding burden and morbidity at the end of life. The fundamental principles of palliative care support an individualized approach to the ultimate decision regarding the identification and management of precipitants.

Delirium Experience in the Context of End of Life—A multidisciplinary session at the delirium study planning meeting was devoted to examining aspects of the delirium experience. A high level of distress has been reported by the families and the caregivers of patients with delirium in palliative care settings.[27–31] Palliative care by definition involves multidisciplinary team delivery of care not only for the patient but also for the family.[32] This collaborative input is likely to be particularly useful in the context of delirium: Both support and education for the family are considered essential components of a delirium management plan.[10,14,33–35] Despite the recognition of the value of family involvement and support by published clinical guidelines (low strength of evidence), the effectiveness and impact of this aspect of care has not been studied.

Pharmacologic Interventions

Review of Frequently Used Deliriogenic Medications—As discussed and explored at the delirium study planning meeting, an important component of the initial management of delirium is the identification of reversible causes, including targeted medications. A drug profile review by a pharmacist is invaluable.[36] Medications commonly implicated in precipitating delirium in palliative care include benzodiazepines, corticosteroids, anticholinergics, opioids, and other psychoactive medications.[23,37–40] Opioids are commonly used in palliative care, and their neuropsychiatric side effects, often collectively referred to as opioid-induced neurotoxicity (OIN), commonly occur in patients with advanced disease.[37,41] In addition to delirium, hallucinations (usually visual or tactile) and cognitive impairment, the other features of OIN are severe sedation, myoclonus, seizures, allodynia, and hyperalgesia.[37] Although most often described with high doses of opioids, a twofold increased risk for delirium also has been reported at lower doses.[39] Other factors predisposing to the development of OIN include a rapid escalation in opioid dose, dehydration, renal failure, infection, older age, borderline cognitive impairment, concomitant use of other psychoactive medications, and a prior episode of OIN.[37] OIN is managed by opioid rotation or switching and/or dose reduction.[42,43] Hydration of the patient is also proposed as part of the OIN treatment strategy.[44] The subcutaneous route is frequently used in palliative care settings if necessary. The doses of other contributing drugs (benzodiazepines, corticosteroids, anticholinergics, and psychotropics) should be evaluated for necessity, duplication, drug interactions, administration schedule, and minimally effective dose to minimize the risk for adverse events and impact on cognition and delirium. It has been estimated that approximately 70% of drug-induced delirium episodes resolve with opioid rotation and discontinuation of other drugs.[22] Conversely, undertreated pain also has been shown to be a risk factor for delirium in elderly hip fracture patients.[45]

Antipsychotic Medications for the Symptomatic Treatment of Delirium—Our literature search of delirium treatment yielded 15 prospective cohort studies,[46–60] 15 randomized controlled trials (RCTs), and one post hoc analysis of an RCT.[61–76] Among the 15 prospective cohort studies (Table 1), sample sizes ranged from 10 to 79 patients and evaluated the response to treatment with primarily atypical antipsychotics, with one study of haloperidol and another of rivastigmine.[48,60] Most trials were small in nature and describe the resolution or improvement of symptoms associated with delirium over five to seven days with minimal evidence of serious adverse events. Four of the 15 trials (139 patients) evaluated hospitalized cancer patients.[46,47,58,60] No study specifically sought to evaluate these drugs in the palliative care setting.

Of the 16 RCTs (including the one post hoc analysis of an RCT), sample sizes ranged from 15 to 101 patients (Table 2). Seven trials were placebo controlled, and the remaining eight trials were active comparator controlled. Studies involved typical and atypical antipsychotics, dexmedetomidine, rivastigmine, lorazepam, and one study evaluated ondansetron. Placebo-controlled trials typically allowed rescue therapy (most commonly haloperidol) and were generally found to be associated with faster resolution of symptoms (quetiapine)[63,66,70] or reduce the likelihood of progressing from subsyndromal delirium to active delirium (risperidone).[62] There is no convincing evidence to suggest that any one agent or drug class is superior to another; however, most trials were small in size. The exception is rivastigmine, which was shown to be associated with increased mortality compared with placebo,[65] and thus, all cholinesterase inhibitors should be avoided in the treatment or prevention of delirium. The delirium assessment tools used were highly variable as were the methods used to identify adverse events. Most patients studied were either postoperative patients or critically ill patients. Palliative care patients have not been specifically studied in the RCTs that were identified in our literature search, except for one study of 30 terminally ill AIDS patients, in which both haloperidol and chlorpromazine were independently found to be more effective than lorazepam.[76] At our meeting, the progress of a large Australian multisite placebo RCT of oral risperidone vs. oral haloperidol in palliative care patients was reported as nearing completion.[77]

Our literature search identified few RCTs of treatment interventions for delirium in most settings, particularly in palliative care settings. The generalizability of study findings from other care settings to those of palliative care is often limited, so cautious interpretation is advised in relation to the unique contextual aspects of palliative care. Although the need for collaborative multisite RCTs in palliative care populations is evident,[78,79] it also is important to recognize that uncontrolled open and retrospective studies in palliative care patients may contribute pragmatic evidence that speaks to the contextual issues in this patient population (although not reviewed here).[46,47,58,80]

Despite moderate to low level of evidence for drug treatment in palliative care populations, antipsychotics are frequently used to relieve delirium symptoms, particularly perceptual disturbance or agitation.[81–85] Haloperidol remains the "practice standard" for short-term symptom control and is regularly given to patients with clinical or hyperactive delirium either orally, via feeding tubes, intravenously, subcutaneously, or intramuscularly.[7,86,87] Oral haloperidol undergoes extensive first-pass metabolism, with an average oral

bioavailability of 60% (range, 44%–75%).[88] Thus, the parenteral potency of haloperidol is approximately double that of enteral doses. The time to peak plasma concentration of haloperidol is two to six hours for oral doses, whereas intravenous/intramuscular/ subcutaneous doses have a much faster onset of action, with a time to peak plasma concentration of 10–20 minutes for the subcutaneous route.[89] The half-life of haloperidol ranges from 12 to 35 hours, with an average of 16 hours.[88] Consensus guidelines recommend initial haloperidol doses of 1–2 mg orally every two to four hours as needed and commencing at lower doses (0.25–0.5 mg) in the elderly.[9] The dose should be titrated to the lowest effective dose to minimize adverse events and side effects. If delirium clearly resolves, a trial of discontinuation (of drug therapy for treatment) should be considered. Slower dose titration is often warranted in the elderly to minimize side effects.

Most studies outside the critical care settings report haloperidol dose ranges of 2–10 mg/ day,[90] with higher daily haloperidol doses for hyperactive delirium compared with mixed and hypoactive subtypes.[90] Much higher doses of haloperidol have been used historically in the intensive care settings,[91,92] in which it is still commonly used.[93] However, there is currently no evidence that the duration of delirium is reduced with haloperidol treatment in adult intensive care patients[94] or in other patient populations.

In palliative care patients, hypoactive delirium is the most common subtype reported.[1,95–98] A recently published study in hospital inpatients with cancer reported a higher prevalence of perceptual disturbances and delusions in hypoactive delirium than previously reported.[99] Practice varies in the management of hypoactive delirium from "as needed" dosing to regularly scheduled haloperidol (or alternative antipsychotic) dosing regimens.[6,7,100] Algorithms have been proposed for delirium pharmacotherapy in palliative care that stratify dosing according to presenting motor subtype.[101] Antipsychotics should be used with caution in patients with Lewy-body dementia, Parkinson dementia, and Parkinson disease because of the risk of extrapyramidal side effects (EPS).

Our literature search confirmed that there remains a relative lack of comparative trials of atypical antipsychotics with conventionally accepted therapies such as haloperidol in the management of delirium[85] (Table 2). Atypical antipsychotics, such as risperidone, olanzapine, quetiapine, and aripiprazole, tend to be used second-line if there are contraindications or side effects, such as acute drug-induced extrapyramidal symptoms, with typical antipsychotics,[7,102,103] although the trials identified were not powered to show this.

Adverse Effects of Antipsychotics—From our literature search, all trials evaluated adverse events in some form but were also underpowered to confidently compare adverse events between treatments. EPS are the most commonly reported adverse event and are reported for both typical and atypical agents without any strong signal of greater incidence or prevalence for one agent over another. This is in contrast to the notion that atypical antipsychotics have a lower propensity to cause EPS as D_2 receptor blockade is mitigated because of their antagonism at both the 5-HT_{2A} and the muscarinic M_1 receptors.[103] Larger trials will be needed to adequately address the comparative safety of these agents in palliative care settings.

EPS have been reported commonly in the psychiatric population taking conventional antipsychotics. Palliative care patients are usually treated with lower antipsychotic doses for shorter periods compared with psychiatric populations. Clinically, acute EPS are often missed or misdiagnosed,[104] and the prevalence in the palliative care population is not clear. However, a low frequency of EPS has been reported in delirium treatment studies even when a specific EPS instrument is used.[81,101] Most instruments for the assessment of acute EPS were developed for acutely psychotic or schizophrenic patients and are lengthy to administer. The development and validation of standardized EPS instruments in palliative care patients is required.

There is a large interindividual variation in propensity to develop EPS. Risk factors include age (older patients and less than 30 years old), neuroleptic potency, and a high rapidly increasing neuroleptic dose on treatment initiation and in slow metabolizers of CYP2D6 substrates. Older patients have a further increased risk if they also have dementia.[88] For haloperidol, a lower incidence of EPS with parenteral (intravenous or intramuscular) route administration compared with other routes has been described.[105] As a temporary solution to alleviate EPS, an oral anticholinergic, such as benzatropine, may be administered. If discontinuation of the antipsychotic medication is not possible, then it can be switched to one with a lower risk of EPS.

Typical and atypical antipsychotics are associated with a prolonged QTc interval. The risk of wide complex ventricular tachyarrhythmias and sudden death is potentiated by combinations of medications often used in palliative care and oncology care that also prolong the QTc interval[106,107] (See www.azcert.org for a list of QT prolonging drugs and drug interactions.). Assessment of risk factors (congenital long QT syndrome, hypokalemia, hypomagnesemia, hypocalcemia, >65 years of age, female gender, conductive cardiac abnormalities, and hypothyroidism) is advisable before initiating therapy.[108,109] The haloperidol (or other antipsychotic drug) dose may need to be reduced or discontinued (along with other contributory medications) if the QTc interval is >450 ms for males and >470 ms for females[110] or increases more than 25% from baseline.[9] Pharmacy and cardiology consultations should be considered.

An U.S. Food and Drug Administration alert was issued in September 2007 recommending electrocardiogram (ECG) monitoring if haloperidol is given by the intravenous route.[111] Baseline ECG and ECG monitoring also have been recommended independent of the route of antipsychotic administration, especially with high doses,[7,102] but this resource may be a challenge in some settings, especially in the community and at the end of life when the goals of care are focused on patient comfort. Evidence from cohorts of palliative care and hospital inpatients treated with haloperidol suggests that severely prolonged QTc intervals (>500 ms) are rare, occurring in less than 1% of patients.[106,112] Future studies of antipsychotic drug treatment and prophylaxis should incorporate ECG monitoring for QTc prolongation.[102]

The use of both atypical and typical antipsychotics in the elderly has been associated with an increased risk of cerebrovascular events and mortality, especially in patients with dementia taking antipsychotics for a median of 60–110 days.[113,114] In contrast, antipsychotic treatment for delirium tends to be short term, and a recent nested case-control analysis found

no significant increase in mortality in elderly delirious patients who received antipsychotics compared with a group who did not.[115]

Other Medications in the Pharmacologic Treatment of Delirium—Psychostimulants, such as methylphenidate, have been used in the management of patients with hypoactive delirium,[116] but the level of evidence is currently limited.[102] Psychostimulants may exacerbate or cause agitation. Other possible adverse effects include hallucinations, restlessness, insomnia, and cardiovascular effects. As benzodiazepines may precipitate or exacerbate delirium in this patient population, they are not routinely used unless the delirium is caused by benzodiazepine or alcohol withdrawal or is related to seizures. In patients with uncontrolled agitation, benzodiazepines may have a limited role in combination with an antipsychotic but not as single agents.[7,9]

Emerging Drugs—A role for other drugs in delirium management has been reported, including melatonin in the postoperative setting,[117] modafinil,[102] valproate,[118] ondansetron,[61,119] and gabapentin as an adjuvant treatment.[120] The use of acetylcholinesterase inhibitors has been reported in case reports and postoperative studies.[121–124] In addition, a recent placebo-controlled randomized trial of rivastigmine add-on therapy for delirium treatment in intensive care patients was discontinued because of safety concerns.[65] A role for statins in both the treatment and the prevention of delirium in critically ill patients has been postulated.[125,126] With proinflammatory cytokines involved in the pathophysiology of delirium, future studies may examine the role of anti-inflammatory medications as adjuvant agents in combination with other medications.

Continuous Sedation at the End of Life—Refractory agitated delirium at the end of life will often necessitate the use of more sedating medications to ensure patient symptomatic relief and comfort when other interventions have failed.[127,128] The most common medications used to effect sedation for refractory delirium at the end of life are methotrimeprazine, chlorpromazine, midazolam, and phenobarbital.[129] Methotrimeprazine (levomepromazine), a phenothiazine, is often used in agitated delirium at the end of life, in which its sedative properties and subcutaneous route of administration are advantageous.[87,130,131] However, it is not available worldwide including in the United States.

Nonpharmacologic Management of Delirium

As discussed at our international delirium study planning meeting, much of the literature on nonpharmacologic strategies is derived from management approaches with older general medical patients and in the intensive care setting. Using a multidisciplinary team is thought to be beneficial, but results are not consistent.[132,133]

Simple environmental strategies are often underutilized.[102,134–136] Noise, excessive light, excessive darkness, and frequent staff and room changes should be minimized. The family can assist in the frequent reorientation of the delirious patient. An orientation board that is updated daily and a visible clock should be made available in patients' rooms. Communication should be clear and simple, and special attention made to the importance of

glasses for vision correction, hearing aids, and dentures. The environment needs to be physically safe for the patient, as well as staff and family, and physical restraints avoided. Patients' hydration and nutrition should be monitored. Specially setup delirium rooms may have a role but need further evaluation.[137] Utilization of a brief psychoeducational leaflet on delirium may benefit family members.[33] Emotional support should be provided for family distress, and debriefing may be necessary for patients who have recovered from an episode of delirium.[13] It is essential that pain is controlled[45] and the sleep-wake cycle is normalized, with blinds opened during the day, background noise at night minimized, and excessive daytime napping discouraged where possible.[6]

Research Agenda for Delirium Management in Palliative Care

To strengthen the evidence base for current delirium practice, further good quality multisite studies are needed.[78,138,139] Most of the delirium research to date has focused on describing the epidemiology and associated harms of delirium in a variety of affected patients, although it has rarely focused on palliative care. There also has been a considerable amount of literature published on the diagnosis of delirium and its subtypes and the "real-world" implementation of standardized screening programs. Despite this impressive volume of literature, the paucity of research investigating the prevention and treatment of delirium in palliative care populations is of concern. To further complicate matters, as highlighted in discussions among our meeting participants, the etiology of delirium appears to differ enough between different populations (i.e., palliative care vs. intensive care unit vs. hospitalized medical patients) to question the appropriateness of extrapolating research findings from other populations to palliative care patients.

Future research programs should focus on the treatment and prevention of delirium in palliative care settings. Prospective comparative RCTs are needed to evaluate drug and nondrug therapies for treatment and prevention of delirium and its subtypes.[140] These studies must incorporate longitudinal assessment and need to be powered to address meaningful clinical outcomes, such as quality of life, health economics, mortality, and morbidity, not just rescue medication use and duration/severity/resolution of delirium.[141] Although haloperidol is regarded as the practice standard therapy by consensus for delirium treatment, it has never been validated in clinical trials and thus does not even have an U.S. Food and Drug Administration indication for the treatment of delirium. This notion needs to be challenged in a well-designed placebo-controlled trial.[142] Because of a substantial number of participant study withdrawals (as a result of clinical deterioration or death) in palliative care populations, a palliative-modified intention-to-treat analysis should be considered in the evaluation of RCTs.[143] Drug therapy trials need to address dosing and titration regimens (including variations in regimens according to motor subtype), different routes of administration, and adverse events (including EPS), in addition to efficacy.[140]

Further epidemiologic research may be warranted to develop tools for the identification of palliative care patients at "high risk" for developing delirium. Such tools should be validated and used to determine eligibility for future studies of delirium prevention. Commonality in the use of assessment tools may facilitate audits of delirium management and thus help to establish some comparative benchmarking. Cluster randomized trials might be appropriate

to address real-world barriers to implementation of a standardized approach to screening, prevention, and treatment of delirium.[144] Although not exhaustive, Tables 3 and 4 suggest major themes for future research that would address critically important clinical questions that would further guide the management of delirium and inform clinical practice in palliative care.

Conclusion

In palliative care settings, research is challenging and literature data limited owing to patient vulnerability close to the end of life, difficulty in patient accrual, and high attrition rates. Overall, the evidence base for the management of delirium is limited by the lack of good quality RCTs and practitioners' practice often guided by expert opinion and clinical guidelines. There is, therefore, an outstanding need for more collaborative research, especially double-blind, randomized, placebo-controlled trials, to evaluate efficacious and safe antipsychotic dosing schedules according to the different delirium subtypes and etiologies in the management of delirium in palliative care patients. Comprehensive multifaceted evidence-based interventions in the domains of prevention and environment, combined with effective and safe pharmacologic regimens, are required, along with support strategies for patients, families, and health care providers to reduce the impact of this distressing complication for patients in palliative care settings. Both pragmatic and rigorous study trial designs are essential to further our knowledge synthesis and support its subsequent translation into clinical practice through evidence-based practice policy and guideline development.

Acknowledgments

References

1. Hosie A, Davidson PM, Agar M, Sanderson CR, Phillips J. Delirium prevalence, incidence, and implications for screening in specialist palliative care inpatient settings: a systematic review. Palliat Med. 2013; 27:486–498. [PubMed: 22988044]

2. Agar M, Lawlor P. Delirium in cancer patients: a focus on treatment-induced psychopathology. Curr Opin Oncol. 2008; 20:360–366. [PubMed: 18525328]

3. Caraceni A, Nanni O, Maltoni M, et al. Impact of delirium on the short term prognosis of advanced cancer patients. Italian Multicenter Study Group on Palliative Care. Cancer. 2000; 89:1145–1149. [PubMed: 10964345]

4. Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. Age Ageing. 2006; 35:350–364. [PubMed: 16648149]

5. Meagher DJ. Delirium: optimising management. BMJ. 2001; 322:144–149. [PubMed: 11159573]

6. Inouye SK. Delirium in older persons. N Engl J Med. 2006; 354:1157–1165. [PubMed: 16540616]

7. Michaud L, Bula C, Berney A, et al. Delirium: guidelines for general hospitals. J Psychosom Res. 2007; 62:371–383. [PubMed: 17324689]

8. MacLullich AM, Hall RJ. Who understands delirium? Age Ageing. 2011; 40:412–414. [PubMed: 21636556]

9. American Psychiatric Association. Practice guideline for the treatment of patients with delirium. Am J Psychiatry. 1999; 156:1–20.

10. National Institute for Health and Clinical Excellence (NICE). [Accessed May 19, 2013] Delirium: diagnosis, prevention and management. 2010. http://www.nice.org.uk/cg103http://www.nice.org.uk/cg103Clinical guidelines, CG103

11. Royal College of Physicians and British Geriatrics Society. The prevention, diagnosis and management of delirium in older people: National guidelines. Royal College of Physicians; Salisbury, UK: 2006.

12. Canadian Coalition for Seniors' Mental Health. Guideline on the assessment and treatment of delirium in older adults at the end of life. Adapted from the CCSMH national guidelines for seniors' mental health. The assessment and treatment of delirium. CCSMH; Toronto: 2010.

13. O'Malley G, Leonard M, Meagher D, O'Keeffe ST. The delirium experience: a review. J Psychosom Res. 2008; 65:223–228. [PubMed: 18707944]

14. Partridge JS, Martin FC, Harari D, Dhesi JK. The delirium experience: what is the effect on patients, relatives and staff and what can be done to modify this? Int J Geriatr Psychiatry. 2013; 28:804–812. [PubMed: 23112139]

15. Maltoni M, Scarpi E, Rosati M, et al. Palliative sedation in end-of-life care and survival: a systematic review. J Clin Oncol. 2012; 30:1378–1383. [PubMed: 22412129]

16. Napolskikh J, Selby D, Bennett M, et al. Demographic profile and utilization statistics of a Canadian inpatient palliative care unit within a tertiary care setting. Curr Oncol. 2009; 16:49–54. [PubMed: 19229370]

17. Kaasa S, Torvik K, Cherny N, Hanks G, de Conno F. Patient demographics and centre description in European palliative care units. Palliat Med. 2007; 21:15–22. [PubMed: 17169955]

18. Hui D, Glitza I, Chisholm G, Yennu S, Bruera E. Attrition rates, reasons, and predictive factors in supportive care and palliative oncology clinical trials. Cancer. 2013; 119:1098–1105. [PubMed: 23132290]

19. Whittamore KH, Goldberg SE, Gladman JR, et al. The diagnosis, prevalence and outcome of delirium in a cohort of older people with mental health problems on general hospital wards. Int J Geriatr Psychiatry. 2014; 29:32–40. [PubMed: 23606365]

20. Fong TG, Tulebaev SR, Inouye SK. Delirium in elderly adults: diagnosis, prevention and treatment. Nat Rev Neurol. 2009; 5:210–220. [PubMed: 19347026]

21. Buffum MD, Hutt E, Chang VT, Craine MH, Snow AL. Cognitive impairment and pain management: review of issues and challenges. J Rehabil Res Dev. 2007; 44:315–330. [PubMed: 17551882]

22. Lawlor PG, Gagnon B, Mancini IL, et al. Occurrence causes, and outcome of delirium in patients with advanced cancer: a prospective study. Arch Intern Med. 2000; 160:786–794. [PubMed: 10737278]

23. Morita T, Tei Y, Tsunoda J, Inoue S, Chihara S. Underlying pathologies and their associations with clinical features in terminal delirium of cancer patients. J Pain Symptom Manage. 2001; 22:997–1006. [PubMed: 11738162]

24. Leonard M, Raju B, Conroy M, et al. Reversibility of delirium in terminally ill patients and predictors of mortality. Palliat Med. 2008; 22:848–854. [PubMed: 18755829]

25. Irwin SA, Pirrello RD, Hirst JM, Buckholz GT, Ferris FD. Clarifying delirium management: practical, evidenced-based, expert recommendations for clinical practice. J Palliat Med. 2013; 16:423–435. [PubMed: 23480299]

26. Higginson IJ, Evans CJ. What is the evidence that palliative care teams improve outcomes for cancer patients and their families? Cancer J. 2010; 16:423–435. [PubMed: 20890138]

27. Breitbart W, Gibson C, Tremblay A. The delirium experience: delirium recall and delirium-related distress in hospitalized patients with cancer, their spouses/caregivers, and their nurses. Psychosomatics. 2002; 43:183–194. [PubMed: 12075033]

28. Morita T, Hirai K, Sakaguchi Y, Tsuneto S, Shima Y. Family-perceived distress from delirium-related symptoms of terminally ill cancer patients. Psychosomatics. 2004; 45:107–113. [PubMed: 15016923]

29. Buss MK, Vanderwerker LC, Inouye SK, et al. Associations between caregiver-perceived delirium in patients with cancer and generalized anxiety in their caregivers. J Palliat Med. 2007; 10:1083–1092. [PubMed: 17985965]

30. Namba M, Morita T, Imura C, et al. Terminal delirium: families' experience. Palliat Med. 2007; 21:587–594. [PubMed: 17942497]

31. Bruera E, Bush SH, Willey J, et al. Impact of delirium and recall on the level of distress in patients with advanced cancer and their family caregivers. Cancer. 2009; 115:2004–2012. [PubMed: 19241420]

32. World Health Organization. [Accessed May 19, 2013] WHO definition of palliative care. 2013. http://www.who.int/cancer/palliative/definition/en/http://www.who.int/cancer/palliative/definition/en/

33. Gagnon P, Charbonneau C, Allard P, et al. Delirium in advanced cancer: a psychoeducational intervention for family caregivers. J Palliat Care. 2002; 18:253–261. [PubMed: 12611315]

34. Otani H, Morita T, Uno S, et al. Usefulness of the leaflet-based intervention for family members of terminally ill cancer patients with delirium. J Palliat Med. 2013; 16:419–422. [PubMed: 23477302]

35. Morita T, Akechi T, Ikenaga M, et al. Terminal delirium: recommendations from bereaved families' experiences. J Pain Symptom Manage. 2007; 34:579–589. [PubMed: 17662572]

36. Lapane KL, Hughes CM, Daiello LA, Cameron KA, Feinberg J. Effect of a pharmacistled multicomponent intervention focusing on the medication monitoring phase to prevent potential adverse drug events in nursing homes. J Am Geriatr Soc. 2011; 59:1238–1245. [PubMed: 21649623]

37. Bush SH, Bruera E. The assessment and management of delirium in cancer patients. Oncologist. 2009; 14:1039–1049. [PubMed: 19808772]

38. Jackson N, Doherty J, Coulter S. Neuropsychiatric complications of commonly used palliative care drugs. Postgrad Med J. 2008; 84:121–126. [PubMed: 18372482]

39. Gaudreau JD, Gagnon P, Harel F, Roy MA, Tremblay A. Psychoactive medications and risk of delirium in hospitalized cancer patients. J Clin Oncol. 2005; 23:6712–6718. [PubMed: 16170179]

40. Agar M, Currow D, Plummer J, et al. Changes in anticholinergic load from regular prescribed medications in palliative care as death approaches. Palliat Med. 2009; 23:257–265. [PubMed: 19318461]

41. Daeninck PJ, Bruera E. Opioid use in cancer pain. Is a more liberal approach enhancing toxicity? Acta Anaesthesiol Scand. 1999; 43:924–938. [PubMed: 10522740]

42. Mercadante S, Bruera E. Opioid switching: a systematic and critical review. Cancer Treat Rev. 2006; 32:304–315. [PubMed: 16624490]

43. de Stoutz ND, Bruera E, Suarez-Almazor M. Opioid rotation for toxicity reduction in terminal cancer patients. J Pain Symptom Manage. 1995; 10:378–384. [PubMed: 7673770]

44. Bruera E, Franco JJ, Maltoni M, Watanabe S, Suarez-Almazor M. Changing pattern of agitated impaired mental status in patients with advanced cancer: association with cognitive monitoring, hydration, and opioid rotation. J Pain Symptom Manage. 1995; 10:287–291. [PubMed: 7602179]

45. Morrison RS, Magaziner J, Gilbert M, et al. Relationship between pain and opioid analgesics on the development of delirium following hip fracture. J Gerontol A Biol Sci Med Sci. 2003; 58:76–81. [PubMed: 12560416]

46. Kishi Y, Kato M, Okuyama T, Thurber S. Treatment of delirium with risperidone in cancer patients. Psychiatry Clin Neurosci. 2012; 66:411–417. [PubMed: 22834659]

47. Boettger S, Breitbart W. An open trial of aripiprazole for the treatment of delirium in hospitalized cancer patients. Palliat Support Care. 2011; 9:351–357. [PubMed: 22104410]

48. Oldenbeuving AW, de Kort PL, Jansen BP, Kappelle LJ, Roks G. A pilot study of rivastigmine in the treatment of delirium after stroke: a safe alternative. BMC Neurol. 2008; 8:34. [PubMed: 18803862]

49. Maneeton B, Maneeton N, Srisurapanont M. An open-label study of quetiapine for delirium. J Med Assoc Thai. 2007; 90:2158–2163. [PubMed: 18041437]

50. Takeuchi T, Furuta K, Hirasawa T, et al. Perospirone in the treatment of patients with delirium. Psychiatry Clin Neurosci. 2007; 61:67–70. [PubMed: 17239041]

51. Straker DA, Shapiro PA, Muskin PR. Aripiprazole in the treatment of delirium. Psychosomatics. 2006; 47:385–391. [PubMed: 16959926]

52. Mittal D, Jimerson NA, Neely EP, et al. Risperidone in the treatment of delirium: results from a prospective open-label trial. J Clin Psychiatry. 2004; 65:662–667. [PubMed: 15163252]

53. Parellada E, Baeza I, de Pablo J, Martinez G. Risperidone in the treatment of patients with delirium. J Clin Psychiatry. 2004; 65:348–353. [PubMed: 15096074]

54. Pae CU, Lee SJ, Lee CU, Lee C, Paik IH. A pilot trial of quetiapine for the treatment of patients with delirium. Hum Psychopharmacol. 2004; 19:125–127. [PubMed: 14994323]

55. Sasaki Y, Matsuyama T, Inoue S, et al. A prospective, open-label, flexible-dose study of quetiapine in the treatment of delirium. J Clin Psychiatry. 2003; 64:1316–1321. [PubMed: 14658945]

56. Horikawa N, Yamazaki T, Miyamoto K, et al. Treatment for delirium with risperidone: results of a prospective open trial with 10 patients. Gen Hosp Psychiatry. 2003; 25:289–292. [PubMed: 12850662]

57. Kim KY, Bader GM, Kotlyar V, Gropper D. Treatment of delirium in older adults with quetiapine. J Geriatr Psychiatry Neurol. 2003; 16:29–31. [PubMed: 12641370]

58. Breitbart W, Tremblay A, Gibson C. An open trial of olanzapine for the treatment of delirium in hospitalized cancer patients. Psychosomatics. 2002; 43:175–182. [PubMed: 12075032]

59. Kim KS, Pae CU, Chae JH, Bahk WM, Jun T. An open pilot trial of olanzapine for delirium in the Korean population. Psychiatry Clin Neurosci. 2001; 55:515–519. [PubMed: 11555348]

60. Akechi T, Uchitomi Y, Okamura H, et al. Usage of haloperidol for delirium in cancer patients. Support Care Cancer. 1996; 4:390–392. [PubMed: 8883234]

61. Tagarakis GI, Voucharas C, Tsolaki F, et al. Ondasetron versus haloperidol for the treatment of postcardiotomy delirium: a prospective, randomized, double-blinded study. J Cardiothorac Surg. 2012; 7:25. [PubMed: 22436170]

62. Hakim SM, Othman AI, Naoum DO. Early treatment with risperidone for subsyndromal delirium after on-pump cardiac surgery in the elderly: a randomized trial. Anesthesiology. 2012; 116:987–997. [PubMed: 22436797]

63. Devlin JW, Skrobik Y, Riker RR, et al. Impact of quetiapine on resolution of individual delirium symptoms in critically ill patients with delirium: a post-hoc analysis of a double-blind, randomized, placebo-controlled study. Crit Care. 2011; 15:R215. [PubMed: 21923923]

64. Grover S, Kumar V, Chakrabarti S. Comparative efficacy study of haloperidol, olanzapine and risperidone in delirium. J Psychosom Res. 2011; 71:277–281. [PubMed: 21911107]

65. van Eijk MM, Roes KC, Honing ML, et al. Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial. Lancet. 2010; 376:1829–1837. [PubMed: 21056464]

66. Tahir TA, Eeles E, Karapareddy V, et al. A randomized controlled trial of quetiapine versus placebo in the treatment of delirium. J Psychosom Res. 2010; 69:485–490. [PubMed: 20955868]

67. Overshott R, Vernon M, Morris J, Burns A. Rivastigmine in the treatment of delirium in older people: a pilot study. Int Psychogeriatr. 2010; 22:812–818. [PubMed: 20353624]

68. Kim SW, Yoo JA, Lee SY, et al. Risperidone versus olanzapine for the treatment of delirium. Hum Psychopharmacol. 2010; 25:298–302. [PubMed: 20521319]

69. Girard TD, Pandharipande PP, Carson SS, et al. Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium: the MIND randomized, placebo-controlled trial. Crit Care Med. 2010; 38:428–437. [PubMed: 20095068]

70. Devlin JW, Roberts RJ, Fong JJ, et al. Efficacy and safety of quetiapine in critically ill patients with delirium: a prospective, multicenter, randomized, double-blind, placebo-controlled pilot study. Crit Care Med. 2010; 38:419–427. [PubMed: 19915454]

71. Reade MC, O'Sullivan K, Bates S, et al. Dexmedetomidine vs. haloperidol in delirious, agitated, intubated patients: a randomised open-label trial. Crit Care. 2009; 13:R75. [PubMed: 19454032]

72. Lee KU, Won WY, Lee HK, et al. Amisulpride versus quetiapine for the treatment of delirium: a randomized, open prospective study. Int Clin Psychopharmacol. 2005; 20:311–314. [PubMed: 16192839]

73. Han CS, Kim YK. A double-blind trial of risperidone and haloperidol for the treatment of delirium. Psychosomatics. 2004; 45:297–301. [PubMed: 15232043]

74. Skrobik YK, Bergeron N, Dumont M, Gottfried SB. Olanzapine vs. haloperidol: treating delirium in a critical care setting. Intensive Care Med. 2004; 30:444–449. [PubMed: 14685663]

75. Kim JY, Jung IK, Han C, et al. Antipsychotics and dopamine transporter gene polymorphisms in delirium patients. Psychiatry Clin Neurosci. 2005; 59:183–188. [PubMed: 15823165]

76. Breitbart W, Marotta R, Platt MM, et al. A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. Am J Psychiatry. 1996; 153:231–237. [PubMed: 8561204]

77. Agar, M. [Accessed May 1, 2013] Oral risperidone, oral haloperidol, and oral placebo in the management of delirium in palliative care. 2013. http://apps.who.int/trialsearch/Trial.aspx?TrialID=ACTRN12607000562471http://apps.who.int/trialsearch/Trial.aspx?TrialID=ACTRN12607000562471

78. Currow DC, Agar M, Tieman J, Abernethy AP. Multi-site research allows adequately powered palliative care trials; web-based data management makes it achievable today. Palliat Med. 2008; 22:91–92. [PubMed: 18216083]

79. Shelby-James TM, Hardy J, Agar M, et al. Designing and conducting randomized controlled trials in palliative care: a summary of discussions from the 2010 clinical research forum of the Australian Palliative Care Clinical Studies Collaborative. Palliat Med. 2012; 26:1042–1047. [PubMed: 21844138]

80. Shinno H, Matsuoka T, Yamamoto O, et al. Successful treatment with quetiapine for delirium in terminally ill cancer patients. Psychogeriatrics. 2007; 7:64–68.

81. Meagher DJ, McLoughlin L, Leonard M, et al. What do we really know about the treatment of delirium with antipsychotics? Ten key issues for delirium pharmacotherapy. Am J Geriatr Psychiatry. 2013; 21:1223–1238. [PubMed: 23567421]

82. Leentjens AF, Rundell J, Rummans T, et al. Delirium: an evidence-based medicine (EBM) monograph for psychosomatic medicine practice, commissioned by the Academy of Psychosomatic Medicine (APM) and the European Association of Consultation Liaison Psychiatry and Psychosomatics (EACLPP). J Psychosom Res. 2012; 73:149–152. [PubMed: 22789420]

83. Lonergan E, Britton AM, Luxenberg J, Wyller T. Antipsychotics for delirium. Cochrane Database Syst Rev. 2007 CD005594.

84. Flaherty JH, Gonzales JP, Dong B. Antipsychotics in the treatment of delirium in older hospitalized adults: a systematic review. J Am Geriatr Soc. 2011; 59(Suppl 2):S269–S276. [PubMed: 22091572]

85. Candy B, Jackson KC, Jones L, et al. Drug therapy for delirium in terminally ill adult patients. Cochrane Database Syst Rev. 2012; 11 CD004770.

86. Gagnon P. Treatment of delirium in supportive and palliative care. Curr Opin Support Palliat Care. 2008; 2:60–66. [PubMed: 18685397]

87. Caraceni A, Simonetti F. Palliating delirium in patients with cancer. Lancet Oncol. 2009; 10:164–172. [PubMed: 19185834]

88. Vella-Brincat J, Macleod AD. Haloperidol in palliative care. Palliat Med. 2004; 18:195–201. [PubMed: 15198132]

89. Twycross, R.; Wilcock, A.; Dean, M.; Kennedy, B. PCF: Palliative care formulary. Canadian edition. Nottingham, UK: 2010.

90. Hui D, Bush SH, Gallo LE, et al. Neuroleptic dose in the management of delirium in patients with advanced cancer. J Pain Symptom Manage. 2010; 39:186–196. [PubMed: 20152585]

91. Adams F, Fernandez F, Andersson BS. Emergency pharmacotherapy of delirium in the critically ill cancer patient. Psychosomatics. 1986; 27:33–38. [PubMed: 3952253]

92. Riker RR, Fraser GL, Cox PM. Continuous infusion of haloperidol controls agitation in critically ill patients. Crit Care Med. 1994; 22:433–440. [PubMed: 8124994]

93. Hipp DM, Ely EW. Pharmacological and non-pharmacological management of delirium in critically ill patients. Neurotherapeutics. 2012; 9:158–175. [PubMed: 22270810]

94. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med. 2013; 41:263–306. [PubMed: 23269131]

95. Spiller JA, Keen JC. Hypoactive delirium: assessing the extent of the problem for inpatient specialist palliative care. Palliat Med. 2006; 20:17–23. [PubMed: 16482754]

96. Meagher D. Motor subtypes of delirium: past, present and future. Int Rev Psychiatry. 2009; 21:59–73. [PubMed: 19219713]

97. Meagher DJ, Leonard M, Donnelly S, et al. A longitudinal study of motor subtypes in delirium: relationship with other phenomenology, etiology, medication exposure and prognosis. J Psychosom Res. 2011; 71:395–403. [PubMed: 22118382]

98. Leonard M, Donnelly S, Conroy M, Trzepacz P, Meagher DJ. Phenomenological and neuropsychological profile across motor variants of delirium in a palliative-care unit. J Neuropsychiatry Clin Neurosci. 2011; 23:180–188. [PubMed: 21677247]

99. Boettger S, Breitbart W. Phenomenology of the subtypes of delirium: phenomenological differences between hyperactive and hypoactive delirium. Palliat Support Care. 2011; 9:129–135. [PubMed: 24468480]

100. Platt MM, Breitbart W, Smith M, et al. Efficacy of neuroleptics for hypoactive delirium. J Neuropsychiatry Clin Neurosci. 1994; 6:66–67. [PubMed: 7908548]

101. Meagher D, Leonard M. The active management of delirium: improving detection and treatment. Adv Psychiatr Treat. 2008; 14:292–301.

102. Breitbart W, Alici Y. Evidence-based treatment of delirium in patients with cancer. J Clin Oncol. 2012; 30:1206–1214. [PubMed: 22412123]

103. Boettger S, Breitbart W. Atypical antipsychotics in the management of delirium: a review of the empirical literature. Palliat Support Care. 2005; 3:227–237. [PubMed: 16594462]

104. Weiden PJ, Mann JJ, Haas G, Mattson M, Frances A. Clinical nonrecognition of neuroleptic-induced movement disorders: a cautionary study. Am J Psychiatry. 1987; 144:1148–1153. [PubMed: 2888321]

105. Menza MA, Murray GB, Holmes VF, Rafuls WA. Decreased extrapyramidal symptoms with intravenous haloperidol. J Clin Psychiatry. 1987; 48:278–280. [PubMed: 3597329]

106. Walker G, Wilcock A, Carey AM, et al. Prolongation of the QT interval in palliative care patients. J Pain Symptom Manage. 2003; 26:855–859. [PubMed: 12967735]

107. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical antipsychotic drugs and the risk of sudden cardiac death. N Engl J Med. 2009; 360:225–235. [PubMed: 19144938]

108. Roden DM. Drug-induced prolongation of the QT interval. N Engl J Med. 2004; 350:1013–1022. [PubMed: 14999113]

109. Pickham D, Helfenbein E, Shinn JA, et al. High prevalence of corrected QT interval prolongation in acutely ill patients is associated with mortality: results of the QT in Practice (QTIP) Study. Crit Care Med. 2012; 40:394–399. [PubMed: 22001585]

110. U.S.Food and Drug Administration. [Accessed March 26, 2013] TdP–low risk drugs (<0.1%). 2013. http://www.fda.gov/ohrms/dockets/ac/01/slides/3746s_01_Ruskin/sld027.htmhttp://www.fda.gov/ohrms/dockets/ac/01/slides/3746s_01_Ruskin/sld027.htm

111. U.S.Food and Drug Administration. [Accessed March 26, 2013] Information for healthcare professionals: Haloperidol (marketed as Haldo, Haldol Decanoate and Haldol Lactate). http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm085203.htmhttp://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm085203.htm

112. Blom MT, Bardai A, van Munster BC, et al. Differential changes in QTc duration during in-hospital haloperidol use. PLoS One. 2011; 6:e23728. [PubMed: 21961030]

113. Schneider LS, Dagerman K, Insel PS. Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. Am J Geriatr Psychiatry. 2006; 14:191–210. [PubMed: 16505124]

114. Kales HC, Kim HM, Zivin K, et al. Risk of mortality among individual antipsychotics in patients with dementia. Am J Psychiatry. 2012; 169:71–79. [PubMed: 22193526]

115. Elie M, Boss K, Cole MG, et al. A retrospective, exploratory, secondary analysis of the association between antipsychotic use and mortality in elderly patients with delirium. Int Psychogeriatr. 2009; 21:588–592. [PubMed: 19368755]

116. Gagnon B, Low G, Schreier G. Methylphenidate hydrochloride improves cognitive function in patients with advanced cancer and hypoactive delirium: a prospective clinical study. J Psychiatry Neurosci. 2005; 30:100–107. [PubMed: 15798785]

117. Hanania M, Kitain E. Melatonin for treatment and prevention of postoperative delirium. Anesth Analg. 2002; 94:338–339. [PubMed: 11812694]

118. Bourgeois JA, Koike AK, Simmons JE, Telles S, Eggleston C. Adjunctive valproic acid for delirium and/or agitation on a consultation-liaison service: a report of six cases. J Neuropsychiatry Clin Neurosci. 2005; 17:232–238. [PubMed: 15939979]

119. Bayindir O, Guden M, Akpinar B, Sanisoglu I, Sagbas E. Ondansetron hydrochloride for the treatment of delirium after coronary artery surgery. J Thorac Cardiovasc Surg. 2001; 121:176–177. [PubMed: 11135174]

120. Leung JM, Sands LP, Rico M, et al. Pilot clinical trial of gabapentin to decrease postoperative delirium in older patients. Neurology. 2006; 67:1251–1253. [PubMed: 16914695]

121. Slatkin N, Rhiner M. Treatment of opioid-induced delirium with acetylcholinesterase inhibitors: a case report. J Pain Symptom Manage. 2004; 27:268–273. [PubMed: 15038335]

122. Liptzin B, Laki A, Garb JL, Fingeroth R, Krushell R. Donepezil in the prevention and treatment of post-surgical delirium. Am J Geriatr Psychiatry. 2005; 13:1100–1106. [PubMed: 16319303]

123. Sampson EL, Raven PR, Ndhlovu PN, et al. A randomized, double-blind, placebo-controlled trial of donepezil hydrochloride (Aricept) for reducing the incidence of postoperative delirium after elective total hip replacement. Int J Geriatr Psychiatry. 2007; 22:343–349. [PubMed: 17006875]

124. Marcantonio ER, Palihnich K, Appleton P, Davis RB. Pilot randomized trial of donepezil hydrochloride for delirium after hip fracture. J Am Geriatr Soc. 2011; 59(Suppl 2):S282–S288. [PubMed: 22091574]

125. Morandi A, Hughes CG, Girard TD, et al. Statins and brain dysfunction: a hypothesis to reduce the burden of cognitive impairment in patients who are critically ill. Chest. 2011; 140:580–585. [PubMed: 21896517]

126. Katznelson R, Djaiani GN, Borger MA, et al. Preoperative use of statins is associated with reduced early delirium rates after cardiac surgery. Anesthesiology. 2009; 110:67–73. [PubMed: 19104172]

127. Cherny NI, Radbruch L. European Association for Palliative Care (EAPC) recommended framework for the use of sedation in palliative care. Palliat Med. 2009; 23:581–593. [PubMed: 19858355]

128. Dean MM, Cellarius V, Henry B, et al. Framework for continuous palliative sedation therapy in Canada. J Palliat Med. 2012; 15:870–879. [PubMed: 22747192]

129. de Graeff A, Dean M. Palliative sedation therapy in the last weeks of life: a literature review and recommendations for standards. J Palliat Med. 2007; 10:67–85. [PubMed: 17298256]

130. Prommer E. The use of levomepromazine in palliative care. Eur J Palliat Care. 2005; 12:8–10.

131. Dietz I, Schmitz A, Lampey I, Schulz C. Evidence for the use of levomepromazine for symptom control in the palliative care setting: a systematic review. BMC Palliat Care. 2013; 12:2. [PubMed: 23331515]

132. Cole MG, McCusker J, Bellavance F, et al. Systematic detection and multidisciplinary care of delirium in older medical inpatients: a randomized trial. CMAJ. 2002; 167:753–759. [PubMed: 12389836]

133. Mudge AM, Maussen C, Duncan J, Denaro CP. Improving quality of delirium care in a general medical service with established interdisciplinary care: a controlled trial. Intern Med J. 2013; 43:270–277. [PubMed: 22646754]

134. Meagher DJ, O'Hanlon D, O'Mahony E, Casey PR. The use of environmental strategies and psychotropic medication in the management of delirium. Br J Psychiatry. 1996; 168:512–515. [PubMed: 8730950]

135. Zimberg M, Berenson S. Delirium in patients with cancer: nursing assessment and intervention. Oncol Nurs Forum. 1990; 17:529–538. [PubMed: 2399166]

136. McCusker J, Cole M, Abrahamowicz M, et al. Environmental risk factors for delirium in hospitalized older people. J Am Geriatr Soc. 2001; 49:1327–1334. [PubMed: 11890491]

137. Flaherty JH, Little MO. Matching the environment to patients with delirium: lessons learned from the delirium room, a restraint-free environment for older hospitalized adults with delirium. J Am Geriatr Soc. 2011; 59(Suppl 2):S295–S300. [PubMed: 22091576]

138. Seitz DP, Gill SS, van Zyl LT. Antipsychotics in the treatment of delirium: a systematic review. J Clin Psychiatry. 2007; 68:11–21. [PubMed: 17284125]

139. Lacasse H, Perreault MM, Williamson DR. Systematic review of antipsychotics for the treatment of hospital-associated delirium in medically or surgically ill patients. Ann Pharmacother. 2006; 40:1966–1973. [PubMed: 17047137]

140. Bourne RS, Tahir TA, Borthwick M, Sampson EL. Drug treatment of delirium: past, present and future. J Psychosom Res. 2008; 65:273–282. [PubMed: 18707951]

141. Hughes CG, Brummel NE, Vasilevskis EE, Girard TD, Pandharipande PP. Future directions of delirium research and management. Best Pract Res Clin Anaesthesiol. 2012; 26:395–405. [PubMed: 23040289]

142. Trzepacz PT, Bourne R, Zhang S. Designing clinical trials for the treatment of delirium. J Psychosom Res. 2008; 65:299–307. [PubMed: 18707954]

143. Currow DC, Plummer JL, Kutner JS, Samsa GP, Abernethy AP. Analyzing phase III studies in hospice/palliative care. A solution that sits between intention-to-treat and per protocol analyses: the palliative-modified ITT analysis. J Pain Symptom Manage. 2012; 44:595–603. [PubMed: 22819439]

144. O'Hanlon S, O'Regan N, Maclullich AM, et al. Improving delirium care through early intervention: from bench to bedside to boardroom. J Neurol Neurosurg Psychiatry. 2014; 85:207–213. [PubMed: 23355807]

Table 1

Prospective Single-Arm Studies of Pharmacologic Treatment for Delirium

Year	First Author	Study Design	Patient Population	Study Size	Study Intervention	Main Study Finding
2012	Kishi[46]	Cohort study	Hospitalized cancer patients	29	Risperidone	Risperidone was effective in 48% of patients, whereas 79% showed some reduction in delirium severity.
2011	Boettger[47]	Cohort	Hospitalized cancer patients	21	Aripiprazole	Patients exhibited significant improvement and resolution of delirium over seven days of treatment with aripiprazole.
2008	Oldenbeuving[48]	Cohort	Stroke	17	Rivastigmine	Delirium symptoms improved in 16 of 17 patients.
2007	Maneeton[49]	Cohort	Hospitalized medical patients	17	Quetiapine	Quetiapine was associated with an improvement in symptoms over the seven day study period.
2007	Takeuchi[50]	Cohort	Hospitalized patients	38	Perospirone	87% of patients showed improvement in delirium symptoms over a mean of five days. The most common side effects were fatigue (15%) and sleepiness (6%).
2006	Straker[51]	Cohort	Hospitalized medical patients	14	Aripiprazole	12 of 14 patients had a significant reduction in symptoms over the course of the study.
2004	Mittal[52]	Cohort	Hospitalized medical and surgical patients	10	Risperidone	Symptomatic improvement observed over the seven day study period.
2004	Parellada[53]	Cohort	Hospitalized medical patients	64	Risperidone	91% of patients had symptomatic improvement over the course of seven days.
2004	Pae[54]	Cohort	Hospitalized medical patients	22	Quetiapine	Symptomatic improvement observed in 86% of patients over the course of seven days.
2003	Sasaki[55]	Cohort	Hospitalized medical patients	12	Quetiapine	All patients had resolution of symptoms at a mean of five days.
2003	Horikawa[56]	Cohort	Hospitalized medical patients	10	Risperidone	Eight of 10 patients had symptomatic improvement of delirium.
2003	Kim[57]	Cohort	Hospitalized medical patients	12	Quetiapine	Symptomatic improvement was observed over a mean of six days.
2002	Breitbart[58]	Cohort	Hospitalized cancer patients	79	Olanzapine	76% of patients had complete resolution of delirium. Age>70 years was found to be the strongest predictor of suboptimal response to olanzapine.
2001	Kim[59]	Cohort	Hospitalized medical and surgical patients	20	Olanzapine	Symptomatic improvement was observed over an average course of seven days.
1996	Akechi[60]	Cohort	Hospitalized cancer patients	10	Haloperidol	Symptomatic improvement was described for all patients over a median of six days.

Table 2

Prospective Parallel-Arm Comparative Trials of Pharmacologic Treatment for Delirium

Year	First Author	Study Design	Patient Population	Study Size	Study Intervention	Primary Outcome	Main Study Finding
2012	Tagarakis[61]	RCT	Postcardiac surgery	80	Haloperidol vs. ondansetron	Resolution of delirium symptoms assessed 10 minutes after single dose of the study drug	No difference in efficacy between haloperidol and ondansetron but fewer side effects with ondansetron.
2012	Hakim[62]	RCT	Postcardiac surgery with subsyndromal delirium	101	Risperidone vs. placebo	Proportion of patients transitioning from subsyndromal delirium to clinical delirium	Early administration of risperidone was associated with significantly less clinical delirium compared with placebo.
2011	Devlin[63]	Post hoc analysis of RCT	ICU	29	Quetiapine vs. placebo	Time to resolution of delirium symptoms	Quetiapine associated with faster resolution of delirium symptoms compared with placebo despite the use of as needed haloperidol.
2011	Grover[64]	Single blind RCT	Mixed medical/surgical patients	64	Haloperidol vs. olanzapine vs. risperidone	Efficacy (Delirium Rating Scale-Revised-98) and safety.	All patients showed improvement in delirium severity over the six day study period, but no difference between drugs was found.
2010	van Eijk[65]	RCT	ICU	104	Rivastigmine vs. placebo	Efficacy (duration of delirium) and safety	This study, originally planned to enroll 440 patients, was stopped early after 104 patients were enrolled because of increased mortality in the rivastigmine arm compared with placebo (22% vs. 8%, $P = 0.07$).
2010	Tahir[66]	RCT	Mixed medical, surgical, and orthopedic patients	42	Quetiapine vs. placebo	Efficacy (Delirium Rating Scale-Revised-98) and safety.	Quetiapine was associated with faster resolution of some non-noncognitive symptoms of delirium when compared to compared with placebo.
2010	Overshott[67]	RCT	Hospitalized medical patients	15	Rivastigmine vs. placebo	Feasibility of a larger trial	Described as a pilot study. No meaningful inferences about delirium treatment made.
2010	Kim[68]	RCT	Hospitalized patients (72% with malignant cancer)	32	Risperidone vs. olanzapine	Efficacy (Delirium Rating Scale-Revised-98) and safety	Risperidone and olanzapine were both effective in reducing symptoms of delirium, but no difference in efficacy or safety between groups was found. Response to olanzapine was better in patients over 70 years of age.
2010	Girard[69]	RCT	ICU	101	Haloperidol vs. ziprasidone vs. placebo	Feasibility of a larger trial	Described as a pilot study. No difference in clinical outcomes (efficacy or safety).
2010	Devlin[70]	RCT	ICU	36	Quetiapine vs. placebo	Time to resolution of delirium	All patients received haloperidol as needed. Quetiapine was associated with faster resolution and shorter

Year	First Author	Study Design	Study Size	Study Intervention	Patient Population	Primary Outcome	Main Study Finding
							durations of delirium compared with the placebo group.
2009	Reade[71]	RCT	20	Dexmedetomidine vs. haloperidol	ICU	Time to extubation	The α_2 agonist dexmedetomidine was associated with a significantly shorter time to extubation in mechanically ventilated critically ill patients and ICU length of stay compared with haloperidol.
2005	Lee[72]	RCT	31	Quetiapine vs. amisulpride	Hospitalized medical patients	Efficacy (Delirium Rating Scale-Revised-98) and safety	Both agents were shown to improve symptoms of delirium, but no difference between groups was found.
2004	Han[73]	RCT	28	Risperidone vs. haloperidol	Hospitalized medical patients	Efficacy (Memorial Delirium Assessment Scale) and safety	Both agents were shown to improve symptoms of delirium over the seven day study period, but no between-group differences were found.
2004	Skrobik[74]	RCT	73	Olanzapine vs. haloperidol	ICU	Efficacy (Delirium Index) and safety	Clinical improvement over the five day study period in both groups. No differences in efficacy were identified between groups. Extrapyramidal symptoms were noted more frequently among patients randomized to haloperidol.
2004	Kim[75]	RCT	42	Risperidone vs. haloperidol	Hospitalized medical and surgical patients	Describe the relationship between treatment response and dopamine transporter genetic polymorphisms	Both drugs were shown to be effective, but no differences in efficacy between groups were found.
1996	Breitbart[76]	RCT	30	Haloperidol vs. chlorpromazine vs. lorazepam	Hospitalized AIDS patients	Efficacy (Delirium Rating Scale) and safety	Patients randomized to haloperidol or chlorpromazine exhibited symptomatic improvement over the course of the study, whereas the lorazepam arm of the study was terminated prematurely because of treatment-limiting adverse effects.

RCT = randomized controlled trial; ICU = intensive care unit

Table 3

Suggested Prospective Interventional Research Themes for Delirium Prevention and Screening

Population	Among palliative care patients *at risk of*, delirium …		
Intervention	… does delirium prevention with pharmacotherapy …	… does delirium prevention with nonpharmacologic measures …	… does routine and standardized screening for delirium …
Comparator	… compared with placebo …	… compared with usual care …	
Outcome	… improve survival, health economics, palliative morbidity, and quality of life?		

Table 4

Suggested Prospective Interventional Research Themes for Delirium Treatment

Population	Among palliative care patients *with* delirium or a specific delirium subtype …		
Intervention	… does treatment with psychoactive pharmacotherapy …		… what is the incremental benefit of treatment with psychoactive pharmacotherapy …
Comparator	… compared with placebo …	… compared with other active treatments …	… compared with nonpharmacologic measures that address precipitating factors …
Outcome	… improve survival, health economics, palliative morbidity, and quality of life?		