INTRODUCTION

Delirium is defined as an acute and fluctuating confusional state characterized by disturbance in attention, perception, and awareness; abnormalities in cognition; and psychomotor aberrations. It is one of the most common neuropsychiatric complications in hospitalized patients, occurring in up to 85 percent of them in the last weeks and days of life (1-3). Delirium often heralds the presence of serious medical conditions, and it is associated with increased mortality, morbidity, rapid functional decline, loss of independence, institutionalization, and significant distress in patients and caregivers (4-6).

In this review, we will discuss the impact of delirium on patients receiving palliative care, particularly in the last weeks of life; knowledge gaps related to the pathophysiology and management of delirium; and future research directions.

IMPACT ON CARE OF THE DYING

Delirium has an impact on every aspect of patient care, including symptom expression, communication, and decision making. Patients may have altered symptom expression as a result of confusion and disinhibition. Underrecognition of delirium may lead to inappropriate use of treatment modalities as well as aggressive and invasive diagnostic and therapeutic procedures (2, 7, 8). For example, misinterpreting the severity of pain in a delirious patient can result in opioid dose escalation and worsen symptoms related to opioid-induced neurotoxicity. For a patient with hypoactive delirium, fatigue and depression may become the primary considerations, delaying appropriate treatment of the underlying medical causes of delirium.

Delirium interferes with patients’ ability to communicate their needs and goals to their families and the healthcare team (9). Families and caregivers who are not aware of the diagnosis of delirium may feel helpless and distressed when faced with unresolved symptoms and agitation (10, 11). When delirium occurs at the end of life, patients’ inability to have meaningful interaction with their loved ones can result in further distress for caregivers.

In addition to impaired communication, the patient’s ability to make medical decisions is often diminished or lacking, depending on the severity of the delirium and the complexity of the decisions to be made (12). In the last weeks of life, many complex decisions — related to factors such as discharge planning, treatment discontinuation, and personal affairs — need to be addressed. Because patients with delirium often have compromised capacity and autonomy, surrogate decision makers must make many of these decisions. Further research is needed to characterize patients’ decision-making ability in the final weeks of life, which is often decision-specific and which fluctuates with time.

LACK OF UNDERSTANDING OF THE PATHOPHYSIOLOGY OF DELIRIUM

The exact pathophysiology of delirium has not been fully elucidated. According to the cholinergic hypothesis, there is a deficiency in acetylcholine and an excess of dopamine in the central nervous system (13). Other neurotransmitters such as serotonin, glutamate, cortisol, and endogenous opioids have also been implicated in delirium (14). Still other research has focused on the role of cytokines, particularly: interleukin (IL)-1, IL-6, and IL-8; tumour necrosis factor; and interferon (15-17). A systematic review of neuroimaging studies of delirium identified only 12 studies that provided preliminary evidence supporting the role of cortical atrophy and impaired cerebral blood flow in
delirium (18). In any case, findings from these studies may not be generalizable to patients in the last weeks of life.

Clinically, there are three basic types of delirium, which are defined according to their predominant psychomotor presentation: hypoactive, hyperactive, and mixed (19, 20). Hypoactive delirium is characterized by low activity and somnolence; patients may be inappropriately described as being depressed, sedated, or fatigued. Those with hyperactive delirium may be described as experiencing restlessness, agitation, hallucinations, and insomnia; they may even be described as displaying aggressive behaviour. This type of delirium is most often treated with neuroleptics (21). Mixed delirium, the most common type, has features of both hypoactive and hyperactive delirium, and it tends to fluctuate throughout the day. Further studies are needed to characterize the course of delirium in patients in the last days of life in different healthcare settings.

Terminal delirium is defined as irreversible delirium that occurs during the last days of life and continues until death. In a recent study of patients with advanced cancer admitted to an acute palliative care unit (APCU), the proportion of patients with a Richmond Agitation Sedation Scale (RASS) score of -2 or less (that is, an impaired level of consciousness) increased from 45 percent one week before death to 90 percent on the day of death (22, 23). Despite the high prevalence and impact of delirium in the palliative care setting (22, 24), few studies to date have specifically examined the clinical course of delirium in the last days of life. A prospective observational study examined the reversibility of delirium among 71 patients with advanced cancer admitted to an APCU (1). A total of 48/94 delirium episodes (51 percent) were irreversible, and 46/52 deaths (88 percent) were of patients with terminal delirium. In multivariate analysis, factors associated with irreversibility were hypoxic encephalopathy, presence of nonrespiratory infections, and lack of reversible causes (such as psychoactive medications and dehydration). It remains unclear whether terminal delirium differs from reversible delirium in terms of its pathophysiology and presentation.

Our lack of understanding of the pathophysiologic changes of delirium limits our ability to develop new treatments and prevention strategies. Further research is needed to characterize the delirium subtypes and identify individuals at risk of developing terminal delirium.

### LACK OF STANDARD TREATMENT OPTIONS

The current management of delirium involves: identifying and removing any reversible causes (such as psychotropic medications) and managing comorbid conditions (pain, electrolyte abnormalities, and infections); undertaking nonpharmacologic interventions; educating patients and families about the impact of delirium; and using pharmacologic measures such as neuroleptics (haloperidol, chlorpromazine, olanzapine, and quetiapine) and benzodiazepines (25, 26).

Nonpharmacologic interventions for the prevention and treatment of delirium include: orientation aids (for example, family members, family photographs, a clock, hearing/visual aids, and clear communication); environmental control (quiet room, low-level lighting, and adequate space); sleep hygiene (discouraging naps); early mobilization; and relaxation therapy, music therapy, and massage therapy (26, 27).

Importantly, randomized controlled trials supporting these interventions were mostly conducted with patients in the geriatric and general medical/surgical settings instead of patients with only days-to-weeks of life expectancy. Thus, it is still unclear whether these nonpharmacologic measures are effective in the palliative care setting. The National Institute for Health and Clinical Excellence has published a guideline on delirium that describes several pharmacologic and nonpharmacologic interventions; however, the guideline specifically states that it does not cover "people receiving end-of-life care," due to the paucity of evidence (28).

Table 1 provides an overview of randomized controlled trials on delirium. Six of the studies were conducted in medical/surgical units and five were conducted in intensive care units. A Cochrane systematic review identified only one study on drug therapy for delirium in terminally ill patients (29). This landmark randomized controlled trial compared haloperidol (n=11), chlorpromazine (n=13), and lorazepam (n=6) for the management of delirium in human immunodeficiency virus patients (30).

Despite the prevalence of delirium in the palliative care setting, we have not identified any published studies on delirium in the APCU, where terminal delirium is common. The pathophysiology and management strategies used for patients with terminal delirium may be different from those used for patients with reversible delirium. Furthermore, no randomized controlled trials have specifically focused on cancer patients, who are often younger and do not have underlying...
dementia. We also have not identified any randomized trials examining second-line treatment options for delirium.

Because of the scant literature supporting an evidence-based practice in delirium, there is a lack of standardized treatment options for delirium in the palliative care setting. Breitbart et al. reported that chlorpromazine is as efficacious as haloperidol (30). Other studies in the non-palliative-care setting found that olanzapine and risperidone had similar effects in the first-line setting. The National Comprehensive Cancer Network palliative care guidelines suggest that the first-line treatment option is haloperidol; however, the optimal therapeutic dose remains unclear (31). In a prospective study of 99 APCU patients who recovered from their delirium, the haloperidol equivalent daily dose was 2.5 mg (interquartile range: 1 to 4.7 mg). We also found that neuroleptic doses did not correlate with delirium recall, recalled symptom frequency, or distress in patients or family caregivers. However, neuroleptic doses increased with nurses’ and palliative care specialists’ distress related to patients’ symptoms (24). Our findings suggest that neuroleptics, as administered, are ineffective in reducing delirium recall and related distress in patients and caregivers, and that better treatments are needed to manage delirium recall and related distress.

For both clinicians and researchers, there remain many important questions about delirium management in the palliative care setting: What is the best first-line treatment option for delirium? What doses should be used? Should medications be titrated rapidly or scheduled? What is the best second-line treatment option for delirium? By rotating the neuroleptic or additional medications? Should neuroleptics be prescribed based on the different delirium subtypes (hyperactive, hypoactive, and mixed; terminal versus reversible)? What nonpharmacologic treatment options are feasible and effective in the palliative care setting?

CHALLENGES OF RESEARCH IN DELIRIUM

There are multiple challenges related to conducting research with patients in the palliative care setting who have delirium. Barriers to research include patient frailty, perceived difficulties in obtaining consent, lack of validated outcome assessments, and lack of therapeutic innovations.

Patients affected by delirium are a vulnerable population. They often have a short survival and a poor performance status. A majority experience distress related to their delirium, and some may be agitated. Safeguards need to be in place to ensure that studies are conducted in an ethical and safe manner (32). At the same time, participation in research studies, even in the last days of life, can be meaningful for patients and their families. Furthermore, therapeutic trials offer the possibility of immediate benefits building on the highest standards of care.

Obtaining informed consent from delirious patients would be a challenge. By definition, patients’ decision-making capacity is compromised when they are delirious, making it impossible for them to understand the study and consent to participate (33). Breitbart et al. obtained consent from patients prior to the development of delirium (30); however, this approach involves screening and following a large number of individuals to identify the few who will eventually become delirious. Surrogate consent is now obtained for most studies. In some cases, if and when patients are well enough to make decisions during the course of the study, they have been asked to provide their consent to continue with the clinical trial (34, 35).

Assessment of outcomes in delirious patients presents another challenge. The Delirium Rating Scale (DRS) (36), Memorial Delirium Assessment Scale (MDAS) (37), and RASS (38, 39) are highly validated and reliable instruments to assess the severity of delirium. However, other novel outcome measures for delirium — such as communication capacity, delirium distress, delirium recall, and caregiver distress — have only been examined in a few observational studies and require further validation (40-42).

As discussed earlier, because there is a lack of understanding of the pathophysiology of delirium, particularly in the palliative care setting, few novel therapeutic options are available. Furthermore, few companies have invested in developing medications for delirium.

NEWEST DEVELOPMENTS

We are conducting a parallel, double-blind, randomized controlled trial comparing a single dose of lorazepam plus haloperidol versus placebo plus haloperidol for a single episode of agitation in cancer patients with mixed and/or hyperactive delirium admitted to our APCU (43). Patients were eligible if: they had a diagnosis of advanced cancer; had a diagnosis of delirium based on Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) criteria; and had an RASS score of 2 or higher in the past 24 hours, despite being on a scheduled haloperidol...
dol dose of 1-8 mg. We excluded patients already on scheduled chlorpromazine or benzodiazepine and those who had contraindications to neuroleptic or benzodiazepine use.

The primary outcome was RASS intensity over the eight hours after medication administration, and the secondary outcomes included neuroleptic use, delirium-related distress in nurses and caregivers (the Delirium Experience Questionnaire), symptom expression (Edmonton Symptom Assessment Scale), need for neuroleptics, delirium recall (Delirium Recall Questionnaire), adverse effects, discharge outcomes, and survival.

Because agitation can occur at any time of the day, it was essential for us to have the resources to administer study treatments and conduct study assessments at all hours. The bedside nurses played a critical role in the study design, enrollment, and assessments; several nursing champions provided training and support for APCU nurses. We were able to successfully enroll patients in this trial. These preliminary data suggest that: it is feasible to enroll patients with agitated delirium; caregivers are willing to provide surrogate consent and complete study assessments; and highly trained bedside nurses in the APCU can play a significant role in study enrollment.

An Australian-led randomized controlled trial comparing the use of oral risperidone, oral haloperidol, and placebo for patients admitted to palliative care has recently completed enrollment. The primary objective was to compare oral risperidone and oral placebo in the management of targeted delirium symptoms at 72 hours from treatment commencement. Results are pending.

WHAT MUST BE DONE TO OBTAIN RELIABLE ANSWERS?

Delirium is one of the most common and distressing syndromes seen in palliative care patients. However, the lack of research on delirium in the palliative care setting jeopardizes clinicians’ ability to provide patient care effectively. We highlight 10 approaches for future research.

1. Epidemiologic studies can help to characterize the prevalence, subtypes, and impact of delirium in various palliative care settings, particularly APCUs and hospices. Such studies could also help us to identify risk factors for developing delirium. It is important to consider that the epidemiology, pathophysiology, and outcomes of delirium may differ among patient populations (such as cancer patients and dementia patients).

2. Standardized definitions of delirium subtypes should to be developed. A series of questions should be investigated: When is agitated delirium considered a refractory symptom requiring palliative sedation? What is terminal delirium? How do we differentiate between hyperactive and mixed delirium? The Delphi method offers a consensus-based approach to deriving definitions.

3. We also urgently need to identify which patients have potentially reversible delirium. These individuals would benefit from aggressive measures to treat comorbidities and acute complications. Conversely, it is important for us to identify with confidence which individuals are likely to die with delirium.

4. Molecular biology and neuroimaging studies are essential to gaining a better understanding of the pathophysiology of delirium in palliative care patients. This basic knowledge will facilitate the prompt recognition of patients at risk, the diagnosis of delirium, the development of novel interventions, and the identification of predictive factors for treatment response.

5. Further validation of delirium-related outcomes — such as communication capacity, delirium distress, delirium recall, caregiver distress, and bereavement — are critical.

6. Randomized controlled trials are needed to examine the optimal nonpharmacologic interventions and pharmacologic treatment options for delirium in the palliative care setting. Specifically, the optimal medication doses and ways to start medications need to be determined.

7. In addition to treatment trials, we need to conduct studies examining prevention of delirium.

8. Postmarketing surveillance studies examining the incidence of serious adverse events in the palliative care population associated with neuroleptics, such as QT prolongation and extrapyramidal symptoms, are needed.

9. Therapeutic trials need to focus on homogeneous populations and target specific cohorts based on patient prognosis (days to weeks, weeks to months), setting (palliative care unit, home hospice), and delirium subtype (hypocactive, hyperactive, and mixed).

10. Finally, funding is critical to support high-quality research in delirium.

ACKNOWLEDGEMENTS

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Table 1 / Randomized Controlled Trials of Delirium

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>n</th>
<th>Design</th>
<th>Findingsa</th>
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<tbody>
<tr>
<td>Breitbart et al. 1996 (30)</td>
<td>Medical (HIV)b</td>
<td>30</td>
<td>Double blind RCTb</td>
<td>Haloperidol–chlorpromazine&gt;lorazepam</td>
</tr>
<tr>
<td>Hu et al. 2004 (43)</td>
<td>Medical</td>
<td>175</td>
<td>Open label RCT</td>
<td>Haloperidol–olanzapine&gt;usual care</td>
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<tr>
<td>Han et al. 2004 (44)</td>
<td>Medical</td>
<td>28</td>
<td>Double blind RCT</td>
<td>Haloperidol–risperidone</td>
</tr>
<tr>
<td>Kim et al. 2010 (45)</td>
<td>Medical</td>
<td>32</td>
<td>Double blind RCT</td>
<td>Olanzapine–risperidone</td>
</tr>
<tr>
<td>Tahir et al. 2010 (46)</td>
<td>Medical/surgical</td>
<td>42</td>
<td>Double blind RCT</td>
<td>Quetiapine–placebo</td>
</tr>
<tr>
<td>Skrobik et al. 2004 (48)</td>
<td>ICUd</td>
<td>73</td>
<td>Double blind RCT</td>
<td>Olanzapine–haloperidol</td>
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<tr>
<td>Pandharipande et al. 2007 (34)</td>
<td>ICU</td>
<td>106</td>
<td>Double blind RCT</td>
<td>Dexametomidine–lorazepam</td>
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<tr>
<td>Riker et al. 2009 (35)</td>
<td>ICU</td>
<td>375</td>
<td>Double blind RCT</td>
<td>Dexametomidine–midazolam</td>
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<td>Reade et al. 2009 (49)</td>
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<td>20</td>
<td>Open label RCT</td>
<td>Dexametomidine–haloperidol</td>
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<tr>
<td>Devlin et al. 2010 (50)</td>
<td>ICU</td>
<td>36</td>
<td>Double blind RCT</td>
<td>Quetiapine–placebo</td>
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</table>

a The symbol “~” denotes no significant difference; “>” denotes greater efficacy.

b Human immunodeficiency virus.
c Randomized controlled trial.
d Intensive care unit.