

2014

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This article was originally published as:

Bush, S. H., Leonard, M. M., Agar, M., Spiller, J. A., Hosie, A., Wright, D., Meagher, D. J., Currow, D. C., Bruera, E., & Lawlor, P. G. (2014). End-of-Life Delirium: Issues Regarding Recognition, Optimal Management and the Role of Sedation in the Dying Phase.. *Journal of Pain and Symptom Management, Early View (Online First)*.
<http://doi.org/10.1016/j.jpainsymman.2014.05.009>

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Accepted Manuscript

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PII: S0885-3924(14)00288-7

DOI: [10.1016/j.jpainsymman.2014.05.009](https://doi.org/10.1016/j.jpainsymman.2014.05.009)

Reference: JPS 8688

To appear in: *Journal of Pain and Symptom Management*

Received Date: 3 May 2014

Revised Date: 17 May 2014

Accepted Date: 21 May 2014

Please cite this article as: Bush SH, Leonard MM, Agar M, Spiller JA, Hosie A, Wright D, Meagher DJ, Currow DC, Bruera E, Lawlor PG, End-of-Life Delirium: Issues Regarding Recognition, Optimal Management and the Role of Sedation in the Dying Phase, *Journal of Pain and Symptom Management* (2014), doi: 10.1016/j.jpainsymman.2014.05.009.

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Special Article**14-00217R1****End-of-Life Delirium: Issues Regarding Recognition, Optimal Management and the Role of Sedation in the Dying Phase**

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Abstract

Context. In end-of-life care, delirium is often not recognized and poses unique management challenges, especially in the case of refractory delirium in the terminal phase.

Objectives. To review: delirium in the terminal phase context, specifically in relation to recognition issues; the decision-making processes and management strategies regarding its reversibility; the potential refractoriness of delirium to symptomatic treatment; and the role of sedation in refractory delirium.

Methods. We combined multidisciplinary input from delirium researchers and knowledge users at an international delirium study planning meeting and relevant electronic database literature searches (Ovid Medline, Embase, PsycINFO and CINAHL) to inform this narrative review.

Results. The overall management strategy for delirium at the end of life is directed by the patient's prognosis in association with the patient's goals of care. As symptoms of delirium are often refractory in the terminal phase, especially in the case of agitated delirium, the judicious use of palliative sedation is frequently required. However, there remains a lack of high level evidence for the management of delirium in the terminal phase, including the role of antipsychotics and optimal sedation strategies. For the family and health care staff, clear communication, education and emotional support are vital components to assist with decision making and direct the treatment care plan.

Conclusion. Further research on the effectiveness of delirium management strategies in the terminal phase for patients and their families is required. Further validation of assessment tools for diagnostic screening and severity measurement are needed in this patient population.

Key words: Palliative care, hospice, sedation, delirium, terminal, end of life

Running title: Delirium in the Terminal Phase

Accepted for publication: May 21, 2014.

ACCEPTED MANUSCRIPT

Introduction

Delirium is a distressing and complex neurocognitive syndrome that is recognized as an index of serious illness. This is particularly evident in relation to its occurrence in palliative care settings, wherein patients by definition are faced with life-threatening illnesses, most commonly cancer (1). Given the projected population demographic changes, with a substantive proportional increase in the elderly (2,3), and an associated increase in cancer-related deaths (4), delirium is becoming an increasingly important issue in health care. Studies to date would suggest that many patients in palliative care settings experience some degree of delirium in the dying phase (5). Although delirium prevalence rates of 88% have been reported in the hours and days before death (6), the use of such loosely defined terms as terminal anguish or terminal restlessness suggests that in clinical practice delirium may not always be recognized as such in both end-of-life care and in the more immediate terminal phase (7-9).

Given the frequent and perceived natural accompaniment of delirium with the dying phase, this “terminal delirium” paradigm may become a self-fulfilling prophecy, insofar as it may foster an unduly fatalistic approach that overshadows the lesser appreciated potential for reversal, and thus the delirium episode and terminal phase association becomes a *fait accompli*. Reversibility depends on the etiologic factors and the stage of disease in conjunction with the goals of care (6,10).

The association of delirium with the terminal phase may be strengthened further when a deep level of sedation, in the form of palliative sedation, is used to provide symptomatic treatment for delirium-related distress that is refractory to current clinical interventions. In addition to patient distress, the unresolved symptoms of a refractory agitated delirium can be

very distressing to families and challenging for the health care team, and further compounded at the end of life by impeded communication as a result of the delirium (11,12). A recent systematic review of palliative sedation suggests that delirium is one of the most common indications for palliative sedation (13). Although palliative sedation (sedation in the terminal phase) has been the subject of controversy (14), especially when the indications are not clearly defined, it is a necessary and ethically acceptable intervention (15,16). Thus the management of delirium in palliative care settings is perhaps not surprisingly associated with some clinically challenging dilemmas and potential controversy (17).

Although this review is focused on delirium in the context of the dying phase, it will address issues of clinical relevance, particularly regarding the management approach in the broader end-of-life context. More specifically, this review aims to 1) address issues regarding recognition and terminology; 2) outline the decision-making processes as part of optimal management prior to designating an episode of delirium as refractory; and 3) describe the role of palliative sedation in refractory delirium occurring in the dying phase.

Methods

Data Synthesis

We combined multidisciplinary input from delirium researchers and knowledge users at an international delirium study planning meeting and relevant literature searches as our knowledge synthesis strategy in this review. The literature search to inform this narrative review was conducted in four electronic databases (Ovid Medline, Embase, PsycINFO and CINAHL) for publications between 1990 and December 18, 2013 to identify papers on the management of delirium at the end of life, including sedation. The search terms included “palliative care,”

“terminal care,” “hospice care,” “end of life,” “delirium,” “terminal restlessness” and “sedation” and results were limited to the English language and adults.

Working Definitions

Much of the terminology surrounding end-of-life care is ambiguous. Consequently, for purposes of clarity and consistency, we chose to use a set of brief definitions or descriptions specifically for this review (Table 1). We sought to use previously published definitions where possible. Palliative sedation is described in full in the designated part of the following section.

Results and Discussion

Our literature search yielded a total of 6961 citations from Ovid Medline (52), Embase (45), PsycINFO (20) and CINAHL (6844). The first 300 abstracts in CINAHL (ordered according to relevance as determined by the CINAHL database), and the 117 abstracts from the other three databases were reviewed (S.B.). Full articles meeting our search criteria were retrieved and the content used to inform this narrative review.

Exploring the “Terminal Delirium” Paradigm: Recognition Issues and Terminology

In patients with advanced disease, delirium has been described as the “harbinger of death” (25). An agitated delirium frequently occurs in the last week of life (26). In the last hours and days of life, delirium is often a visible manifestation of a culmination of significant multi-organ failure compounded by other irreversible factors. Poor prognostic factors include delirium severity; irreversible precipitating factors; a greater degree of cognitive impairment; the hypoactive subtype; and history of a previous episode of delirium. (6,25,27-29) With the presence of these factors, the health care team will often initiate conversations with families about a delirium episode being a poor prognostic sign (25).

In the terminal phase of illness, it can be challenging to use the currently available validated delirium screening and diagnostic tools, especially for hypoactive delirium and for patients with a reduced level of consciousness and communication because of natural disease progression (30-33). The final item on the observational Nursing Delirium Screening Scale (NuDESC) (34) on psychomotor retardation was designed to detect hypoactive delirium, but may be rated by nurses observing increasing fatigue and patients spending more time in bed as part of the terminal phase. The Memorial Delirium Assessment Scale (MDAS), developed to rate delirium severity, can be prorated if patients are unable to participate in the assessment (35,36). The diagnosis of delirium in the terminal phase is often made following a global clinical assessment by an experienced practitioner using pattern recognition (37,38).

Historically, the term “terminal restlessness” has been used to describe features consistent with an agitated delirium in patients who were in the dying phase (39). The term encompassed a cluster of symptoms (with a variety of different descriptions) including: frequent non-purposeful motor activity, multifocal myoclonus, fluctuating levels of consciousness, cognitive failure, anxiety, sleep-wake cycle disturbance, and agitation (40,41). The word “restless” is not clinically specific, and can mean either physical (“unable to keep still”), or psychic (“worried, uneasy or anxious”) distress (42). Plucking at bed sheets and pulling off clothes are examples of the purposeless repetitive movements that are often seen. Moaning, groaning and facial grimacing often occur, which may be particularly distressing for family members who interpret their loved one to suddenly be in severe physical pain although they previously either had well-controlled pain or no pain. Therefore, families need support and explanatory education (43,44) to avoid misinterpretation of a delirious patient’s disinhibition and apparent increase in expression of pain. For example, in this context, a patient’s agitation is commonly exacerbated by bladder

distention secondary to urinary retention. Other factors causing agitation include fecal impaction, medication-induced akathisia and uncontrolled pain. Patients should be assessed for all these contributory factors and managed accordingly. As delirium challenges the assessment of physical and psychological symptoms, it may be appropriate to trial a single “rescue” dose of an opioid in addition to administration of an antipsychotic if uncontrolled pain cannot be excluded during a period of severe agitation.

In addition to terminal restlessness, a variety of other terms that refer to similar clusters of symptoms also have been used in the literature, both interchangeably and as separate entities. These include “terminal agitation,” “terminal delirium,” and “terminal anguish” (40). The term terminal anguish seemed to suggest an underlying and perhaps causal state of psychospiritual distress. Indeed, surveyed hospice professionals considered spiritual and psychosocial causes as frequently as physical causes for terminal restlessness (45). As a result of this, preventive measures have been recommended for this state: meeting the spiritual and existential needs of the patient, providing an opportunity to resolve conflicts, and completing death preparation work (40,46). Use of the label “terminal” in all the various terms implies a causal relationship between the terminal phase of illness, usually the 48–72 hours before death, and the symptoms of restlessness (42). In turn, this can sometimes lead to a nihilistic approach to management, whereby a potentially reversible cause of delirium may be missed. Similar concerns relate to the associated state called “terminal cognitive failure,” where the cognitive impairments are emphasized more than motor activity changes, but with similar inherent presumptions as to cause and a likely association with delirium. The use of nonspecific terminology and interchangeable clusters of symptoms confuses the important diagnostic challenge of determining whether the clinical presentation is the result of pain or discomfort, delirium, psychological distress, seizures,

or metabolic causes of myoclonus, all of which have different approaches to management. The role of neuroexcitatory opioid metabolites was historically suspected as contributing to the development of myoclonus (41,42). In the past, benzodiazepines alone were used to provide symptomatic relief for agitation in this context (47), whereas adopting the practice of opioid switching as a therapeutic strategy occurred more recently.

The use of parenteral (subcutaneous or intravenous) hydration to reverse the delirium associated with opioid toxicity is well established in palliative care practice but in the context of the patient who is actively dying, the use of parenteral hydration is a hugely contentious and emotive issue. A recent review suggested that reversal of delirium was the only aspect of terminal symptom control and comfort care where the actively dying patient might derive benefit from parenteral hydration (48). There is an urgent need for more research to clarify the potential benefits and harms of parenteral hydration at the end of life (49). Meanwhile, the use of parenteral fluid as a delirium symptom control measure for a patient clearly in the final days of life must be accompanied by very clear and sensitive explanation of its role at the end of life; support for families and carers; and consensus that parenteral fluids will be frequently reviewed, and discontinued if side effects such as worsening respiratory secretions or edema outweigh the symptomatic benefit for the patient.

Delirium Reversibility in End-of-Life Care

At the end of life, the patient's goals of care should be confirmed or established in the first instance. In practice, this is often clarified with the substitute decision maker (SDM), as the patient may not be able to participate in decision making. Some patients' and families' wishes delineate a clear focus solely on patient comfort, so that only delirium symptoms will be managed (with no attempts at reversal) in keeping with patient and family values. However,

efforts focused on comfort and delirium reversal need not be mutually exclusive. Underlying causes for the delirium episode should be sought if consistent with the patient's goals of care, especially if the delirium precipitants can be easily identified. Furthermore effective treatments should be accessible and amenable to administration with minimal burden, thus ensuring no increased distress to the patient. A medication profile review and an increase in the Anticholinergic Risk Scale will assist in identifying potential deliriogenic medications that can be dose-reduced or discontinued (50,51). Apart from the imminently dying context (last hours of life), an opioid switch (with a reduction in opioid equianalgesic dose by 30-50%) also may be appropriate if signs of opioid-induced neurotoxicity are present, although there remains a lack of high level evidence for this strategy in delirious patients (52,53). Although complete or partial reversal of the delirium may be possible, approximately 50% of delirium episodes in palliative care patients cannot be reversed, based on a study conducted in a tertiary palliative care unit in an acute care hospital (6). An episode of delirium is more likely to be irreversible if patients have experienced previous episodes of delirium or if the delirium is a result of a hypoxic or metabolic encephalopathy (6,28).

By its inherent nature, delirium may be manifested by fluctuating symptoms, which may challenge the clinician's estimation of prognosis. The patient's estimated prognosis may influence the intensity of investigations and corrective interventions as recommended by the health care team in accordance with the agreed goals of care. As a health care professional, a significant challenge may be ascertaining that the terminal stage in the patient's illness has indeed been reached. There will often be other accompanying clinical features to indicate that the patient's prognosis is rapidly shortening, such as reduced performance status, anorexia, reduced oral intake, a reduced ability to swallow, weight loss (especially in the temples) as well as a rapid

trajectory of decline and other features of imminent death (such as changes in respiratory pattern, temperature and skin mottling) (54,55). If a patient's prognosis is not clear and such treatment is consistent with their wishes, a time-limited trial of treatment of potential delirium precipitants may be appropriate, such as a trial of antibiotics for suspected infection. An optimal approach to delirium management with the aim of controlling distressing delirium symptoms in the terminal phase is summarized in a stepwise manner in Fig. 1.

Symptomatic Treatment of Delirium in the Terminal Phase

Patients who have recovered from an episode of delirium report significant distress, for both hyperactive and hypoactive clinical subtypes (11,12). In contrast to aged care and intensive care populations, there is currently insufficient evidence to support non-pharmacological approaches in the management of delirium at the end of life (32,56). Potential contributors to agitation in the dying patient, such as pain, urinary retention, and fecal impaction, also should be assessed and managed accordingly. Distressing delirium symptoms such as hallucinations or delusions as well as patient safety concerns may require pharmacological management, regardless of whether the underlying causes are being pursued or not.

Currently there is limited research evidence, with no placebo controlled trial to support the use of antipsychotics in palliative care patients with delirium (57-60). Published in 1996, a randomized double-blind trial in 30 terminally ill AIDS patients compared haloperidol, chlorpromazine and lorazepam (61). Low-dose haloperidol and chlorpromazine were found to be clinically effective, but lorazepam used as a single agent worsened symptoms of delirium. The results of a phase III study in palliative care patients, comparing orally administered haloperidol, risperidone and placebo, are awaited (62).

Delirium clinical practice guidelines (CPGs) encompassing the dying patient also are limited (63), with the National Institute for Health and Clinical Excellence (NICE) guidelines specifically excluding “people receiving end-of-life care” (defined by NICE as the “last few days of life”) (64). It should be noted that clinicians in other specialties, such as geriatrics, internal medicine and oncology, vary in their management of delirium, including in patients in the terminal phase (65,66). We have arbitrarily designated three different approaches to symptomatic treatment, based mainly on the goals of care and increasing levels of sedation. We acknowledge that these approaches are based on current palliative care clinical opinion, as there is a lack of high level evidence at this time (Fig. 1).

Pharmacological Intervention With Minimal Sedation Approach. A minimal sedation approach to management consists of administering appropriately titrated doses of a non-sedating typical (e.g., haloperidol) or atypical antipsychotic (59). Although the aim is not primarily to sedate the patient, it must be acknowledged that some of the newer or atypical antipsychotics such as olanzapine or risperidone are more likely (in a dose-dependent manner) to cause sedation than haloperidol. Patients with hypoactive delirium have been shown to have a poorer response to olanzapine (67). Patients with hypoactive delirium are often lethargic and somnolent and thus may require non-sedating antipsychotics for distressing symptoms, but not necessarily sedating medications. Further research is needed to determine the optimal management of refractory hypoactive delirium, and indeed of all motoric subtypes, at the end of life.

Pharmacological Intervention With a More Sedating Approach or Intermittent Sedation. This approach involves changing from a non-sedating to a more sedating antipsychotic (e.g., methotrimeprazine [levomepromazine] or chlorpromazine), and is indicated if the patient remains agitated despite appropriate doses of minimally sedating antipsychotics. The more

sedating approach also may include intermittent sedation for agitated delirium. This specific practice may involve the addition of low “rescue” doses of a short-acting benzodiazepine (e.g., midazolam or lorazepam) to the treatment regimen. Anecdotally, the strategy of combining a short-acting benzodiazepine with an antipsychotic is frequently used in the acute management of severe agitation in a delirious patient (68-70), as use of a benzodiazepine alone may worsen delirium (61). Short-term sedation with a benzodiazepine also may be warranted in patients who are exhausted because of a lack of sleep. Sleep deprivation is well-documented as a precipitating factor for delirium (3). If there is uncertainty regarding a patient’s condition and the determination of delirium irreversibility, a trial of “respite” sedation for a short predetermined time period may be warranted. This may successfully control the patient’s symptoms, allow an opportunity for reassessment and eliminate the need for pursuing continuous palliative sedation in this instance (71).

Designation of Refractory Delirium at the End of Life. If a dying patient has a non-reversible delirium with persistent and distressing agitated symptoms, then palliative sedation should be considered. An outline of the process in determining the potential need for palliative sedation is shown in Fig. 1. There is an imperative need to control ongoing symptoms of an irreversible agitated delirium for patient comfort, to reduce the level of distress for both the patient and their family, and consequently facilitate a more “peaceful” death (72). Communication among the interprofessional health care team members and with the patient and family, or other SDM, to discuss the role of sedation in an individual patient’s treatment plan is essential. Sedation may be intermittent or continuous, as in continuous palliative sedation. Families may have ambivalent feelings towards the use of sedating medications and reducing the capacity for communication with their loved one (73,74). Conflict may be reduced by positive communication between the family and the health care team, recognizing that family members may have different individual concerns that need to be addressed (75). Information should be provided according to the specific elicited needs of family members. This communication and information-giving can be facilitated by a scheduled meeting involving the interprofessional team (with as many different disciplines in attendance as resources and time permit) and the SDM and core family members. Regular follow-up involving less formal “check in” meetings with family members provides an opportunity to further meet their informational and emotional needs and actively provide ongoing education and support (Fig. 1). Further studies exploring the effectiveness and optimal delivery of these strategies are required (44,76).

The presence of delirium itself has been identified as a factor causing increased difficulty in the decision-making process for family members (77). Delirium increases distress for family members (11,12), especially at the end of life where communication is impaired (73,74,78). In

addition to agitated delirium, family member distress is increased by the presence of cognitive impairment in the patient (79). Families vary in their comfort level of witnessing delirious behavior and express both positive and negative emotions (78). Some families may prefer the patient to be minimally sedated although remaining confused and intermittently agitated, whereas other families may be much more at ease if the patient is more deeply sedated, sleeping peacefully and felt not to be aware of distress. Family members also may feel burdened in making proxy decisions at this time (74). Ideally, a patient will have had an opportunity to clarify his or her values for end-of-life care to their family or SDM as well as the care team before communication becomes impaired, although clearly this is not always the case. The need for emotional support should be assessed in all family members and provided as necessary.

Palliative Sedation: Deep and Continuous Sedation for Relief of Refractory Symptoms in Dying Patients

Table 1 includes a working definition of palliative sedation, and Table 2 provides examples of other published definitions of palliative sedation from CPGs, frameworks and position statements. The degree of reduction in the patient's level of consciousness should be proportionate to the magnitude of the refractory symptom/s in order to relieve the patient's suffering. When applied appropriately, continuous palliative sedation is an ethically justified therapeutic option at the end of life (i.e., last hours, days or one to two weeks of life) when all other available options are exhausted and "when there is a lack of other methods for palliation within an acceptable time frame and without unacceptable adverse effects (refractoriness)" (15,86). The use of proportionate sedation is not associated with hastening death (13).

The term "palliative sedation" started to appear in the literature in 2000 (87,88). Over the years, many other terms have been used to describe sedation for symptomatic relief at the end of

life, including “terminal sedation,” “continuous deep sedation,” and “palliative sedation therapy.” The evolution of the terminology for this type of sedation has been clearly outlined in a recent review paper by Papavasiliou et al. (89). However, this whole issue requires further discussion and consensus. Lack of a clear consensus definition may lead to an underestimation of the frequency of use of palliative sedation in clinical practice. In addition, a standardized worldwide definition is required in order to better compare practices and research internationally.

Indications. Palliative sedation is used in the management of multiple refractory symptoms at the end of life, and delirium is the most common indication (13,24,90,91). Other indications include symptom distress in association with refractory dyspnea, intractable seizures, terminal hemorrhage and uncontrolled pain.

Initiating Continuous Palliative Sedation. The process culminating in the decision to initiate continuous palliative sedation involves the patient, whenever possible, their family and the interprofessional health care team. In the absence of family, a designated SDM or legally appointed power of attorney (POA) should be included in the discussion. The use of a criteria checklist is proposed as a prerequisite to ensure the appropriateness of palliative sedation (92). These criteria include the presence of a progressive, incurable illness with a limited life expectancy, and the informed consent of the patient or SDM. Consultation with a specialist palliative care team is recommended to ensure that the symptom/s are refractory to all treatments and interventions. Family members may need confirmation regarding the refractoriness of the symptom/s and that no other options remain to manage these intractable symptoms and patient distress (93). The anticipated impact of sedation on communication with the patient also should be discussed. Throughout this process, clear documentation is essential.

In addition to published frameworks and position statements (Table 2), a few CPGs on palliative sedation have been developed (21,80,94). Guidelines should specify the nursing responsibilities according to their various roles (e.g., specialist palliative care nurse versus generalist) (95). Further research evaluating the effectiveness and adherence to CPGs is required (96,97).

Medications Used for Palliative Sedation. The level of evidence for the efficacy of medications used for sedation is low and prospective comparative studies are needed to determine the most effective and safest methods (98,99). The choice of medication will vary depending on the indication/s for palliative sedation and also on the care setting (e.g., inpatient versus community) and drug availability. It is paramount that the medication provides *proportional* sedation; thus the aim is to use the lowest possible dose of medication to achieve

the lightest level of sedation that provides symptom relief and comfort. In order to control symptoms of an agitated delirium and relieve suffering in the terminal phase, continuous sedation will often need to be titrated to a level that reduces a patient's level of consciousness, thereby also reducing their capacity for communication.

Midazolam, with a rapid onset of action, is the most commonly used medication for palliative sedation (13). Although it is easy to titrate the dose up or down fairly rapidly, it needs to be administered as a constant infusion to achieve continuous sedation because of its short half-life. Midazolam is occasionally ineffective or can, as with other benzodiazepines, cause a paradoxical increase in agitation (100,101). Other medications reportedly have been used for sedation depending on location of care and drug availability. These include lorazepam, chlorpromazine, levomepromazine (methotrimeprazine) (not available in the U.S.), phenobarbital (phenobarbitone) and propofol (13,83,102,103). Medications for symptom relief, e.g., antipsychotics for delirium, opioids for pain and/or dyspnea, should also be continued.

Monitoring Palliative Sedation. The use of standardized instruments is a critical component of management to ensure best practice in the monitoring of the level of sedation and efficacy of medications, as well as enhancing documentation and ensuring patient safety (15,83,85,104). These tools should assess sedation levels as well as levels of distress in dying patients receiving palliative sedation.

Over the years, several instruments have been developed to monitor sedation and/or agitation levels, mostly in intensive care settings. These include the Ramsey Scale (105), the Rudkin Scale (106), the Riker Sedation-Agitation Scale (SAS) (107), and the Richmond Agitation-Sedation Scale (RASS) (108). The Consciousness Level Scale was specifically developed and validated in the palliative care setting (109). It assesses the level of consciousness

only, and not agitation. Similarly, the modified Rudkin scale, also validated in the palliative care setting, assesses consciousness alone (110). The Communication Capacity Scale has a single item on conscious level, with three other items related to patient communication and one on voluntary movement, whereas the complementary Agitation Distress Scale rates agitation distress (111). These scales were initially studied in terminally ill cancer patients with delirium and later used in palliative care inpatients receiving palliative sedation (98). In 2009, the European Association for Palliative Care's Expert Working Group on Palliative Sedation recommended the use of the RASS or similar instrument in the monitoring of palliative sedation (15). The RASS was originally developed and validated in adult patients in the intensive care setting (108,112). This simple instrument requires brief health care professional observation of the patient in order to provide a quantitative score (range +4 to -5) on the patient's level of agitation or sedation at the time of assessment. It should be noted that the original RASS instrument provides a snapshot measure of "agitation," as opposed to being a formal screening assessment for "agitated delirium." Although the RASS is currently used in many palliative care settings (90,96,113,114), there are few reports examining the reliability of modified versions in patients with advanced cancer (115). A version of the RASS modified for palliative care inpatients, the RASS-PAL, demonstrated high inter-rater reliability in a recent pilot study (116). Further research is needed on the development and validation of sedation and agitation monitoring instruments specific to palliative care populations.

Addressing Ongoing Communication and Other Concerns During Palliative Sedation.

Family members may experience significant distress when their relative is receiving continuous palliative sedation (117). They may need reassurance that the sedated patient is no longer distressed (93). Occasionally, families request sedation to be reduced or discontinued once the

patient appears calm, in the hope of resuming meaningful communication (75). Throughout the process of palliative sedation, ongoing emotional support and frequent information should be provided to both the family and the health care team (118-121).

Conclusion

Uniform terminology is required for delirium in the terminal phase. With the challenges of recognizing delirium in dying patients, further research is needed on validated diagnostic tools that can be reliably used in this patient population. Potentially pivotal decision-making challenges arise at various points in end-of-life delirium management, especially in the terminal phase. The overall management strategy is directed by the patient's prognosis in association with the patient's goals of care, as influenced by patient and family values. As symptoms of agitated delirium are often refractory at this time, the judicious use of palliative sedation is frequently required. For the family and health care staff, clear communication, education and emotional support are vital components to assist with decision making and direct the treatment care plan. The current evidence base to inform practice is lacking and further research (Table 3) on the effectiveness of such management strategies for dying patients with delirium and their families is urgently required.

Disclosures and Acknowledgments

There was no funding source or sponsorship for this article and the authors have no conflicts of interest to disclose. Drs. Shirley Bush and Peter Lawlor receive research awards from the Department of Medicine, University of Ottawa. Dr. Eduardo Bruera is supported in part by National Institutes of Health grants RO1 NR010162-01A1; RO1 CA122292-01; RO1 CA124481-01; and in part by the M. D. Anderson Cancer Center support grant CA 016672. Dr.

David Meagher receives funding from the Health Research Board (Ireland) and the All-Ireland Institute of Palliative Care.

The authors acknowledge input from the participants (listed in the Foreword to this section) at the SUNDIPS Meeting, Ottawa, June 2012. This meeting received administrative support from Bruyère Research Institute and funding support through a joint research grant to Dr. Peter Lawlor from the Gillin Family and Bruyère Foundation.

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Table 1. Working Definitions of Terms Used in This Paper

<p><i>End of life</i>: the presence of progressive life-limiting disease in a patient with a prognosis of months or less. This definition is based on a systematic review of prognostic terminology in palliative care by Hui et al.¹⁸</p>
<p><i>Actively dying (viewed as synonymous with the dying or terminal phase)</i>: “the hours or days preceding imminent death during which time the patient’s physiologic functions wane”.¹⁹ Eagar et al. provided common clinical descriptors of a “terminal care phase” in their definitions of palliative care phases for a case-mix classification.²⁰ We have opted to use the term <i>dying phase</i> in our review and view it as being synonymous with ‘actively dying’.</p>
<p><i>Refractory symptom or refractory delirium</i>: a symptom is defined as refractory if it continues to cause distress despite the use all other possible and tolerable symptomatic treatments that do not compromise consciousness. Furthermore, following careful assessment and communication, there is consensus among patient or substitute decision maker, family members, attending physician, and interprofessional care providers that no other treatments are tolerably acceptable or likely to provide adequate relief within an acceptable time frame.²¹ We use the term <i>refractory delirium or distress related to refractory delirium</i> in the same context as this description of refractory symptom.</p>
<p><i>Goals of care</i>: are the intended purposes of health care interventions and support as recognized by both a Patient or Substitute Decision Maker and the Health Care Team.²²</p>
<p><i>Agitated delirium</i>: based on psychomotor classification of delirium, this refers to a hyperalert episode of delirium in which features of hyperactivity (motor restlessness) are evident.²³</p>
<p><i>Terminal delirium</i>: this refers to an episode of delirium that occurs in the dying phase and thus implies that reversal will not be pursued.</p>
<p><i>Palliative sedation or sedation in the terminal phase</i>: this has been defined as “the intentional</p>

administration of sedative drugs in dosages and combinations required to reduce the consciousness of a terminal patient as much as necessary to adequately relieve one or more refractory symptoms".²⁴

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Table 2. Examples of Definitions of “Palliative Sedation” from Clinical Practice Guidelines, Frameworks and Position Statements

Origin/ Year		Reference
Sedation Guideline Task Force in Japan: Clinical guideline 2005	<p>“Palliative sedation therapy is defined as (1) the use of sedative medications to relieve suffering by the reduction in patient consciousness level or (2) intentional maintenance of reduction in patient consciousness level resulting from symptomatic treatments.”</p> <p>“Palliative sedation therapy is classified according to duration and degree of sedation, and is described as (<i>sic: a</i>) combinations of these classifications (e.g., continuous-deep sedation, intermittent-mild sedation).”</p>	Morita et al. ^{80, p. 717}
American Academy of Hospice and Palliative Medicine (AAHPM): Position statement 2006	<p>“Palliative sedation (PS): The use of sedative medicine at least in part to reduce patient awareness of distressing symptoms that are insufficiently controlled by symptom-specific therapies. The level of sedation is proportionate to the patient’s level of distress, and alertness is preserved as much as possible.”</p>	<p>http://www.aahpm.org/positions/default/sedation.html</p> <p>September 15, 2006⁸¹</p>

	<p>“Palliative sedation (PS) to unconsciousness: The administration of sedatives to the point of unconsciousness, when less extreme sedation has not achieved sufficient relief of distressing symptoms. This practice is used only for the most severe, intractable suffering at the very end of life.”</p>	
<p>Committee on National Guideline for Palliative Sedation, Royal Dutch Medical Association: Guideline for palliative sedation 2005</p>	<p>“Palliative sedation is ‘the intentional lowering of consciousness of a patient in the last phase of his or her life’.”</p> <p>“The objective of palliative sedation is to relieve suffering.”</p> <p>“It is very important that palliative sedation is given for the right indication, proportionally and adequately.”</p>	<p>Verkerk et al. ⁸², p. 667</p>
<p>Expert panel (international group of palliative care clinicians): Recommendations for standards 2007</p>	<p>“Palliative sedation therapy (PST) is the use of specific sedative medications to relieve intolerable suffering from refractory symptoms by a reduction in patient consciousness.”</p> <p>“Refractory symptoms are symptoms for which all possible treatment has failed, or it is estimated that no methods are available for palliation within</p>	<p>De Graeff and Dean ⁸³, p. 68</p>

	the time frame and the risk-benefit ratio that the patient can tolerate.”	
European Association for Palliative Care (EAPC): Framework 2009	“Therapeutic (or palliative) sedation in the context of palliative medicine is the monitored use of medications intended to induce a state of decreased or absent awareness (unconsciousness) in order to relieve the burden of otherwise intractable suffering in a manner that is ethically acceptable to the patient, family and health-care providers.”	Cherny 2009 ¹⁵ (Page 581)
Palliative Sedation Task Force of the National Hospice and Palliative Care Organization (NHPCO) Ethics Committee: Position statement 2010	“ <i>Palliative sedation</i> is the lowering of patient consciousness using medications for the express purpose of limiting patient awareness of suffering that is <i>intractable</i> and <i>intolerable</i> .” “This statement addresses the use of palliative sedation only for patients who are <i>terminally ill</i> and whose death is imminent.”	Kirk and Mahon ⁸⁴ , pp. 914, 915
Canadian Society of Palliative Care Physicians Taskforce:	“Continuous palliative sedation therapy (CPST) is the use of ongoing sedation continued until the patient’s death.” “CPST is indicated only for refractory and	Dean et al. ⁸⁵ , pp. 870, 871

Framework 2012	intolerable suffering, usually in the last 2 weeks of life.” “Sedation should be carefully titrated to adequately relieve suffering.”	
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Table 3. Questions for the Future Research Agenda in the Management of Delirium in Dying Patients ^a

<p><i>Assessment:</i></p> <ul style="list-style-type: none"> • What are the most appropriate tools for the diagnosis of delirium, including hypoactive subtype, in the dying phase? • What are the most reliable validated tools to monitor treatment efficacy in this population? • What is the reliability of instruments specifically developed for the monitoring of sedation and agitation during palliative sedation?
<p><i>Management of delirium:</i></p> <ul style="list-style-type: none"> • What are the efficacy and harms of non-pharmacological interventions in the dying phase? • What are the comparative efficacies and harms of pharmacological interventions in the dying phase? <ul style="list-style-type: none"> ○ What is the role for antipsychotics and rescue low dose short-acting benzodiazepine? ○ What are appropriate dosing and titration strategies for non-sedating and sedating antipsychotics? • What is the efficacy of multicomponent interventions for management of delirium symptoms? <ul style="list-style-type: none"> ○ Are different interventions required for different delirium subtype, i.e. hyperactive vs. hypoactive?
<p><i>Management of refractory delirium at the end of life:</i></p> <ul style="list-style-type: none"> • What is the optimal management of refractory delirium with an agitated component? • What is the optimal management of refractory delirium that is predominantly hypoactive?
<p><i>Palliative sedation:</i></p> <ul style="list-style-type: none"> • What are the efficacy and harms of different pharmacological interventions? <ul style="list-style-type: none"> ○ What are appropriate dosing and titration strategies?

- What is the comparative reliability of instruments to monitor sedation and agitation in the context of palliative sedation that have been developed specifically in palliative care populations?

Protocol-guided treatment:

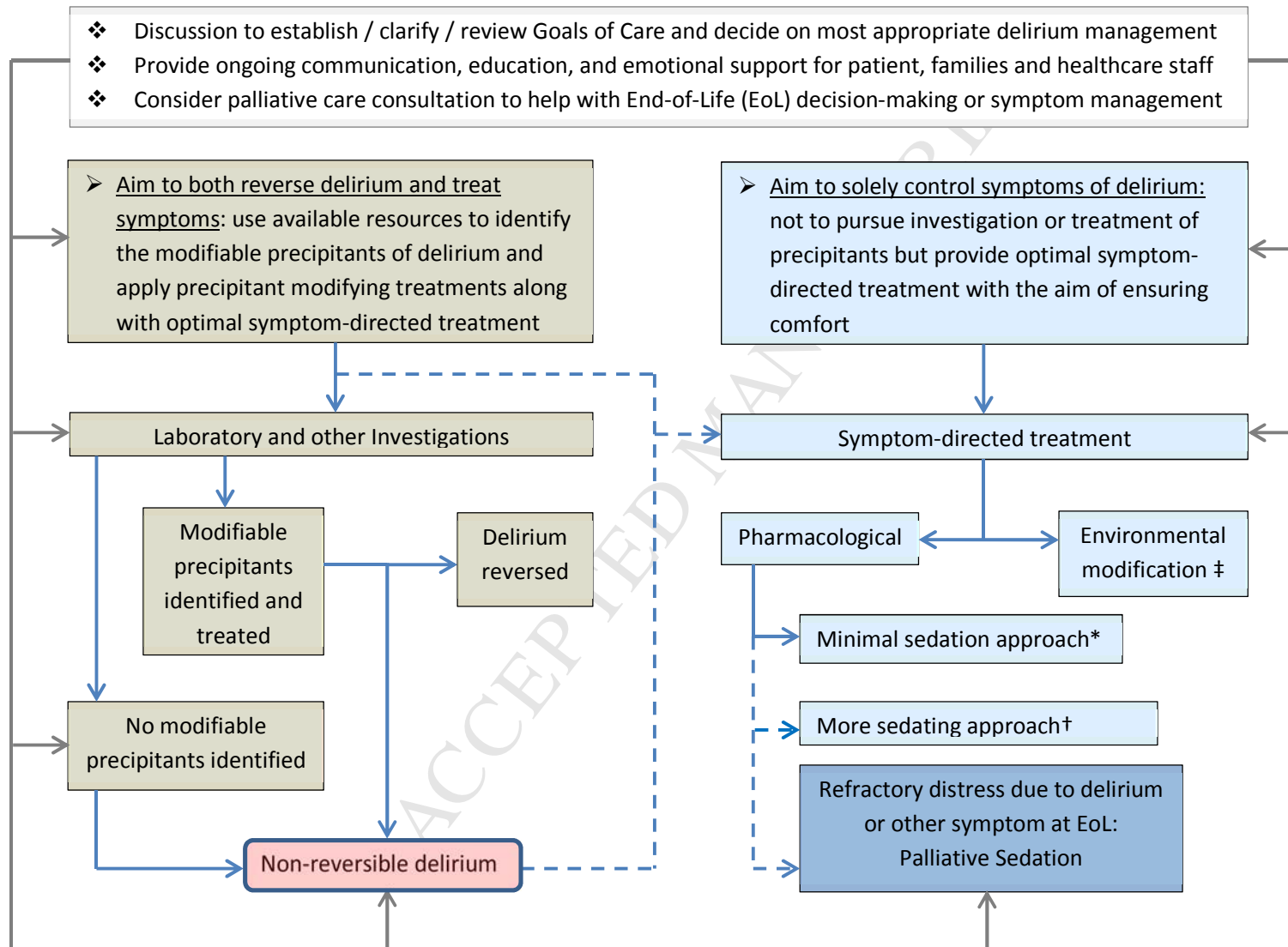
- What are the outcomes of expert consensus protocol-guided treatment in the management of delirium in the dying phase and palliative sedation?

Families/carers:

What are the optimal education and support strategies for families and carers with a loved one experiencing refractory delirium or receiving palliative sedation?

^a See also “An Analytical Framework for Delirium Research in Palliative Care Settings,”¹⁷ in this Special Section.

Figure 1. End-of-Life delirium: framework for clinical decision-making and designation of non-reversible and refractory delirium outcomes



*Non-sedating typical or atypical antipsychotic; †Add rescue dose of benzodiazepine or change to sedating antipsychotic to specifically achieve mild to moderate levels of sedation as a goal; ‡Includes other non-pharmacological approaches.