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Palliative Sedation at the End of Life: Practical and Ethical Considerations

--Manuscript Draft--

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Abstract:	Sedation is commonly used at the end of life, however there are several practical and ethical considerations for its use. It is important to identify any treatable causes for agitation prior to initiating medication. The drug, dose and route of administration may vary according to the indication for treatment, and specialist advice or supervision may be required. There are a number of ethical and cultural considerations relevant to the use of palliative sedation which must also be understood to ensure best practice in this area.
Response to Reviewers:	
Additional Information:	
Question	**Response**

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Dear Editor,

Thank you for the opportunity to revise our manuscript, titled *"Palliative Sedation at the End of Life: Key Practical and Ethical Considerations".* We appreciate the thoughtful and constructive comments provided by the reviewers. We have carefully considered each point raised and have revised the manuscript accordingly.

Below, we provide a point-by-point response to all reviewer comments. Reviewer comments are presented in **bold**, followed by our detailed responses. Changes made to the manuscript are highlighted in the revised version.

Reviewer 1 comments:

- **The purpose of the paper is unclear. If this is an opinion piece it should state that. This is not research.**

This is an invited Continuing Medical Education article. The format for Clinical Medicine CME articles appears to be:

CME: Palliative Medicine

[title]

The current title reflects standard Clinical Medicine format for CME articles.

- **Do the authors explain the reason for writing a review article in this field:**
  The area is very important, and I would read this topic, however this piece at present doesn't offer anything new, it is a partial summary with some literature review

As above, this is a CME article therefore it is not the intention to present new information. Due to the limited word limit (1200-1500) for CME articles it is not possible to provide a comprehensive review of the literature.

Additional comments (reviewer 1):

Right from the start, I found myself wondering: what kind of paper is this meant to be? It's not a research paper, nor is it a service specification or guideline, it neither is a complete summary in a literature review. It reads more like a personal exploration of palliative sedation - almost as if the author is thinking

aloud while trying to make sense of the topic. There's value in that, but it needs to be framed clearly as an opinion piece or reflective analysis. As it stands, it falls awkwardly between summary and commentary without committing fully to either.

Author response: The paper is intentionally neither an opinion piece nor a commentary; it is an invited CME article. The fact that it is a CME articles should be evident to the reader when published in line with standard Clinical Medicine formatting (as described above). Due to the limited word count for CME articles, only points have been included that are most relevant to a generalist physician readership, rather than a thorough exploration of the topic intended for palliative medicine specialists.

The paper opens with a definition from the EAPC framework, which is fine, but it doesn't really acknowledge how contentious these definitions are - particularly between European and UK/Irish practice. The EAPC leans towards sedation as an endpoint (making patients unconscious to relieve suffering), whereas in the UK and Ireland, we typically see sedation as a side effect of treating symptoms (the double effect principle). This fundamental difference needs to be addressed upfront, because it explains why there's so much variability in decision-making.

The understanding of the variability in decision making is exactly because of this above point.

Many thanks for raising this interesting point. We agree, that there is much variation in practice internationally and we acknowledge this under “principles of palliative sedation” (page 1, line 17). Similarly, the range of potential indications for palliative sedation (symptom control vs sedation as an endpoint) are reflected in the 4 indications for palliative sedation on page 1, lines 21-28).

Whilst the EAPC framework is considered contentious by some, it is the first consensus-based guidance on palliative sedation, informed by extensive literature review and Delphi procedure, with representation from prominent UK palliative medicine academics. We therefore feel that it is the most appropriate framework on which to base this paper, which has international readership.

We have reviewed OvidMedline for any articles citing the EAPC Framework, that refute or challenge the EAPC Framework and have not identified any. We are therefore unable to cite any papers that identify significant differences in UK practice and the EAPC guidance. For this reason (and given the limited word count) we therefore feel that the acknowledgement of variation of practice and indications

internationally is sufficient for an article of this format.

- **The paper ambiguously straddles both paradigms - as the use of the word sedation is used to both describe any medication which causes drowsiness and those medications that are used to cause sleep. This confusion runs throughout the paper. Take the discussion of midazolam: it's presented both as a drug for anxiety (where sedation is incidental) and for terminal haemorrhage (where unconsciousness is the goal).**

In the definition of palliative sedation we explain that sedation reduces consciousness (p1, line 6). Given that consciousness is a spectrum, we feel that it is therefore appropriate to discuss the range of consciousness altering medications, from calming effects, right though to deep unconsciousness.

We conceptualise the intended effects of these drugs as reducing consciousness at higher doses, rather than as sleep.We state that midazolam is anxiolytic at lower doses (as opposed to sedating), rather than presenting it as a drug for anxiety; making the point that if midazolam is used at lower it does not tend to induce reduced consciousness. We therefore explain that consciousness is normally spared at lower doses, with consciousness reducing as doses increase (page 3, line 7). Whilst sedation might be considered incidental at this stage, the decision to initiate midazolam rather than alternative, oral anxiolytics is often reflective of an end of life situation in which progressive increase in sedation is common. We have amended the text to make clear that this is used in an end of life situation.

- **The same 10mg dose can't realistically serve both purposes - one treats symptoms proportionally, the other aims to render the patient unaware. The paper doesn't adequately distinguish between these very different intentions.**

The range of doses and indications for midazolam (between 10mg – 100mg) are given both on page 3, lines 6- 10 and in table 1. Lines 6-8 on page 3 describe the progressively higher doses that are used, and this has been amended to reference the various indications within table 2.

As per table 2, the 10mg dose for anxiety/terminal agitation is given as a dose over 24 hours (via CSCI). The 10mg dose for major haemorrhage is given as a stat dose, hence these are not equivalent doses.

- **Similarly, the inclusion of "patient-requested deep sedation" feels out of place in a UK context. I've never encountered this in practice here, nor continuous sedation purely for pain. These seem to reflect European approaches using anaesthetic-grade drugs like propofol, which again points to the paper's unresolved tension between two models of care.**

It doesn't seem to fit in either viewpoints as it picks and chooses aspects of both, without bringing them together.

As previously stated, the EAPC approaches are currently the definitive policy documents on palliative sedation, have UK representation and there is no citable alternative approach on which to base a debate between tensions between UK care and European Care. Furthermore, as a CME article, there is limited scope for a detailed debate. It is the clinical experience of the authors that some patients in the UK do request deep sedation when faced with unbearable distress.

- ***The ethical sections raise good points but need development. For instance:***
  **** The discussion of "slow euthanasia" identifies a real concern but doesn't suggest safeguards (e.g. mandatory reviews for prolonged sedation).***
  **** Cultural considerations are mentioned (which is great) but lack practical guidance. How exactlyshould clinicians navigate a patient's refusal of sedation due to religious beliefs?***
  **** The claim that sedation doesn't hasten death relies on a 2009 study - more recent evidence is less definitive, especially given definitional variations.***

We agree that these are important points that could be addressed more fully if the format and/or word count allowed. However, in light of the complexity of the subject matter, and non specialist nature of the readership of Clinical Medicine, we feel that it is more important to highlight the importance of contacting specialist teams for advice, rather than providing a comprehensive "how to" guide for navigating ethical challenges in this area.

I have reviewed the literature and cannot identify any studies since 2009 that suggest the evidence is less definitive than it was. More recent papers that support the notion that sedation does not hasten death include;

- Park SJ, Ahn HK, Ahn HY, Han KT, Hwang IC. Association between continuous deep sedation and survival time in terminally ill cancer patients. Support Care Cancer. 2021 Jan;29(1):525-531. doi: 10.1007/s00520-020-05516-8. Epub 2020 May 15. PMID: 32415383.
- Barathi B, Chandra PS. Palliative Sedation in Advanced Cancer Patients: Does it Shorten Survival Time? - A Systematic Review. Indian J Palliat Care. 2013 Jan;19(1):40-7. doi: 10.4103/0973-1075.110236. PMID: 23766594; PMCID: PMC3680838.

- Maltoni M, Scarpi E, Rosati M, Derni S, Fabbri L, Martini F, et al. Palliative sedation in end-of-life care and survival: A systematic review. J Clin Oncol. 2012. https://doi.org/10.1200/JCO.2011.37.3795.

Although older the Maltoni paper is a prospective, multi-centre study and appears to be of a higher quality than subsequent studies, hence (and given the limit on references) we felt that this was the most appropriate reference. However we also note that the Cochrane review from 2015 found evidence that sedation **did not** hasten death so we have updated the reference to cite the Cochrane review instead, given that it is more recent.

If the reviewer is aware of a high quality, more contemporaneous reference we would be happy to include this.

- ***Suggestions for improvement:***
  1. Clarify the paper's purpose - Is it a UK-focused clinical guide? A comparison of European vs UK practice? An opinion piece? Pick one.

We hope that it will become clear during the editorial process that this is a CME article rather than original research.

2. Resolve the paradigm conflict - Either adopt the EAPC framework fully (and address its implications) or clearly position the paper within UK/Irish practice. Indeed - If you are using the EAPC definition it follows you should use the other 41 statements in which includes many elements which are in direct conflict with the above conclusions the author makes - i.e. sedation can be used for psychological or existential suffering in the EAPC definitions.

We acknowledge in line 20- 23 where UK practices differs from EAPC guidance, in terms of continuous deep sedation. We do not state that sedation cannot be used for psychological/existential suffering, but rather highlight that there are certain circumstances in which cultural factors may render this less acceptable to the individual.

3. Strengthen ethical discussion - Add concrete examples and safeguards, particularly around contested areas like existential distress.

As above- beyond word count/scope of article.

4. Update the evidence base - Replace outdated citations with recent studies that reflect current debates. There's good material and thoughts here, but it needs a much sharper and clearer focus. The author clearly knows their stuff - I'd love to see this rewritten with a clearer sense of audience and

purpose. With these changes, it could make a valuable contribution to the literature.

No additional changes to those explained above.

Reviewer 2 Comments:

I have some minor suggestions for the author to think about:
Page 2 lines 29-32: How widespread is the use of palliative sedation? Your sentence would suggest that it is widespread given midazolam and other drug usage but actually is the usage mostly as an anxiolytic and so Palliative Sedation is rare, or is Palliative Sedation about 1/5 of end of life cases

Many thanks – we agree that the inclusion of prevalence data would strengthen the paper and have amended the text and references accordingly.

Page 3, line 22: is it worth defining what terminal agitation is? Some people might question whether it is simply delirium?

An expanded definition of terminal agitation has been provided on p. 2, lines 2-6.

Page 5 Table 2: line 21: should levomepromazine also have the phrase: "used at lower doses to manage nausea/ vomiting" similar to the notes for midazolam so people differentiate when it is being used for sedation

Agreed – we have amended the table accordingly.

Page 10 Line 12: In asking the question, is the patient dying would it be worth putting a timescale?- eg is the patient dying in the next 24/48hrs or next week or next year etcx

Thank you – we agree that this suggestion is an improvement on the original wording. As a result, the second question in Figure 1 has been reworded to: ‘Is the patient in the final week of their life?’

We trust that these revisions address the reviewers’ concerns. We believe the manuscript is now significantly improved and hope it will be suitable for publication in Clinical Medicine

Thank you for your time and consideration.

Sincerely,
Dr Caroline Barry, on behalf of all authors

Consultant in Palliative Medicine, Norfolk and Norwich University Hospital

Questions

1. A 72-year-old man with metastatic prostate cancer and widespread bone metastases was admitted with abdominal pain. Overnight, he becomes profoundly agitated and distressed.

   What is the most appropriate next step?

   A. Best interests meeting
   B. Chest X Ray
   C. Midazolam 5mg over 24 hours via continuous subcutaneous infusion
   D. Physical examination
   E. Urgent blood tests

Answer D: It is important to exclude reversible causes for agitation before starting pharmacological treatment. In this situation, it would be important to exclude urinary retention as a cause of agitation as an initial step.

2. An 88 year old woman is admitted to hospital with end stage heart failure. It is her fourth admission in the past 12 months. A decision is made to transfer her to a hospice for end of life care. Whilst still in hospital overnight she becomes agitated, attempting to climb out of bed to use the toilet, despite being catheterised.

   On examination, she does not respond to questions and appears highly distressed. Her blood pressure is 90/60 with poor peripheral perfusion. Her saturations are 96% on room air. Her catheter is draining normally.

   She has no known spiritual beliefs. What is the most appropriate management?

   A. intravenous furosemide
   B. oral lorazepam
   C. phenobarbital infusion over 24 hours
   D. rectal diazepam
   E. stat dose subcutaneous midazolam

Answer E: Midazolam is often used first line for the treatment of terminal agitation. In the first instance a single subcutaneous dose is indicated to address the agitation. A subcutaneous infusion of midazolam may be required but this can take several hours to become effective.

3. A 56 year woman with progressive supranuclear palsy had previously declined any form of pain relief or sedation due to her spiritual beliefs. She is dying of pneumonia and has developed terminal agitation. She is still lucid enough to consent to and refuse medical treatment. The ward team feel that she would benefit from a midazolam infusion to help with her agitation.

What is the most appropriate approach to managing this situation?

A. Her family should be asked to consent to sedation on her behalf
B. Her views about the use of sedation should be explored and respected
C. Hospital legal teams should be consulted
D. Sedation should be given in her best interests
E. Spiritual views must not influence medical decisions about sedation

Answer B: The decision to start pharmacological treatment should be an individualised one, based on a patient's wishes, values and preferences for treatment.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Palliative Sedation at the End of Life: Practical and Ethical Considerations

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Author Contributor Statement:

CB wrote the initial draft of the paper with input from RB, GG and IP. All authors reviewed and edited subsequent versions. All authors have approved the final version. CB is the guarantor.

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Key Points

- The aim of palliative sedation is to relieve refractory suffering with the use of medications to reduce consciousness.
- Where palliative sedation is being used to treat agitation at the end of life, it is important to exclude and/or address reversible causes prior to starting medication.
- The drug, dose and route of administration of palliative sedation may vary according to the indication for treatment.
- Appropriate and proportionate use of palliative sedation does not hasten death.
- Suffering may have different meanings for people depending on their backgrounds and life experiences. These should be explored prior to starting palliative sedation.

Abstract:

Sedation is commonly used at the end of life, however there are several practical and ethical considerations for its use. It is important to identify any treatable causes for agitation prior to initiating medication. The drug, dose and route of administration may vary according to the indication for treatment, and specialist advice or supervision may be required. There are a number of ethical and cultural considerations relevant to the use of palliative sedation which must also be understood to ensure best practice in this area.

Palliative Sedation at the End of Life: Practical and Ethical Considerations

Introduction

The aim of palliative sedation is *"to relieve refractory suffering through the monitored, proportionate use of medications intended to reduce consciousness in patients with life-limiting disease"* [1].

In this paper we describe the clinical practice of palliative sedation, explore what is meant by "refractory suffering" in this context, and consider circumstances in which it may, or may not, be considered ethically acceptable to do so.

Principles of Palliative Sedation

The suffering associated with life-limiting disease can be severe and challenging to alleviate. When other options for relieving such distress have been exhausted, it is common practice for doctors to intentionally reduce a patient's level of consciousness. The prevalence of palliative sedation described in the literature ranges from 12-67% [2,3], and midazolam is one of the three most administered drugs in palliative care [4].

There is considerable variation in decision making for palliative sedation [5]. There is little evidence based on high quality, prospective data [6]. Before starting palliative sedation, clinicians must be confident and adept in their assessment of refractory symptoms, and the ability to differentiate between somatic, psychological, and existential suffering [1].

Indications

Palliative sedation may be used in the following circumstances [1]:

1. For the management of refractory suffering
2. In emergency situations where death is both imminent and anticipated to be distressing without sedation
3. Withdrawal of life sustaining interventions where symptoms are likely
4. As temporary respite when other symptom-focused treatment cannot achieve sufficient relief in an acceptable time frame

Common examples are provided in Table 1.

Table 1: Indications for Palliative Sedation	
Symptom Control	• Terminal agitation • Management of terminal haemorrhage • Management of irreversible airway obstruction • Patient request for continuous deep sedation (specialist use only) • Adjunctive treatment of intractable pain (specialist use only)
Withdrawal of Treatment	• Withdrawal of ventilatory support • Withdrawal of clinically assisted hydration & nutrition

Table 1: Indications for Palliative Sedation

The most common use for sedation in palliative care is for terminal agitation (sometimes referred to as terminal restlessness or agitation in the imminently dying).. . It is characterised by distress, anxiety and restlessness in the final days of life. In contrast to standard delirium treatment, pharmacological measures are often considered first line as shown in Figure 1, after the exclusion of reversible causes.

[Figure 1]

Where the possibility of major haemorrhage is foreseen, the patient is normally counselled regarding this possibility. An “anticipatory” bolus dose of sedative medication may be prescribed to achieve rapid unconsciousness (see table 2). In cases of catastrophic arterial bleeding, where death is anticipated within seconds or minutes, there is usually not sufficient time to achieve palliative sedation. Priority should instead be given to remaining calm and staying with the patient.

Palliative sedation for the withdrawal of life-sustaining treatment must be considered in the context of a wider clinical plan. This normally requires MDT decision making, meticulous documentation and discussion with those important to the patient. Consensus national guidance exists to support clinicians in specific scenarios, such as the withdrawal of non-invasive ventilation and of clinically assisted hydration and nutrition [6,7].

It should be explained, to both the patient and those important to them, that palliative sedation is used to address refractory and intolerable suffering, not hasten death. There is no evidence that the appropriate use of sedation shortens prognosis in any context [2]].

Key Management steps

Medications

Benzodiazepines

Midazolam is the benzodiazepine of choice for palliative sedation due to its high parenteral bioavailability, widespread compatibility with other commonly used palliative medications, and low cost. Lower doses (5 to 10mg/24hrs via CSCI) are predominantly anxiolytic and are often consciousness sparing. Midazolam is used first line for patients with anxiety (where the oral route is not appropriate) and cognitive agitation. Higher doses (up to 100mg/24hrs via CSCI) cause progressively deeper levels of sedation where indicated (table 2).

Antipsychotics

Levomepromazine and haloperidol are used in palliative care for both terminal agitation and the management of nausea and vomiting. Higher doses are required when used for sedation. Antipsychotics are often used first line when patients experience psychomotor agitation or distressing hallucinations. The choice of antipsychotic may be influenced by the likelihood of additional beneficial or adverse effects. Levomepromazine is more sedating than haloperidol and works synergistically with midazolam. In the UK it is the preferred antipsychotic for severe terminal agitation. It is added when midazolam alone is insufficiently sedating and a reduction of conscious level is intended. Internationally, some centres use olanzapine or chlorpromazine as alternatives.

Barbiturates

Phenobarbital can be used when antipsychotic medication is either relatively contra-indicated (e.g. Parkinson's Disease) and/or in the presence of agitation refractory to high dose midazolam and levomepromazine. As higher doses are associated with respiratory depression it should only be initiated under specialist supervision.

Other medications

Propofol is a short acting, intravenous anaesthetic conventionally used for the induction and maintenance of anaesthesia, or for sedation in intensive care. Use of propofol is rare in UK palliative care practice but is more common in continental Europe [1]. Administration under the supervision of an anaesthetist is strongly advisable. The alpha$_2$-adrenoreceptor agonist dexmedetomidine may be effective at reducing terminal agitation with less sedation than traditional sedatives [8,9].

Indications for Palliative Sedation: Medications, Doses and Route

Deeper levels of sedation are associated with loss of the oral route. Subcutaneous injection, intravenous injection, rectal and buccal routes produce rapid effects of relatively short duration. When prolonged sedation is required, continuous subcutaneous infusion (CSCI) provides consistent medication administration over 24 hours regardless of conscious level. When the patient has already developed symptoms of terminal agitation, it is appropriate to give a bolus subcutaneous injection, before starting a CSCI which may take three to four hours to reach full effect.

Indication	Medications	Typical Doses	Notes
Terminal agitation [10]	Midazolam	2.5mg – 5mg SC hourly p.r.n . 10mg – 100mg / 24 hours via CSCI	Often used first line. Used at lower doses to reduce anxiety or cognitive agitation.
	Levomepromazine	12.5 – 25mg SC hourly p.r.n. 25mg - 200mg /24 hours via CSCI	Used when reduction of consciousness is intended. Causes postural hypotension. Lowers seizure threshold. Used at lower doses to manage nausea/vomiting
	Haloperidol	1.5 – 2.5mg SC hourly SC p.r.n. 2.5 – 10mg / 24 hours via CSCI	Used when either distressing hallucinations or psychomotor agitation is present. Less sedating than levomepromazine but higher risk of extrapyramidal side effects.
	Phenobarbital	200mg IV or IM loading dose and then hourly p.r.n. 800 – 1,600mg / 24 hours via CSCI	Avoid SC p.r.n. use due to risk of tissue necrosis. Specialist use only.
Major haemorrhage and irreversible airway obstruction [10]	Midazolam	5mg – 10mg buccal / IV / IM / PR p.r.n. every 30 minutes	Priority should be to stay calm and present with the patient. The subcutaneous route should be avoided in haemorrhage due to risk of reduced perfusion and delayed absorption.
NIV withdrawal [6]	Midazolam	2.5 – 5mg IV boluses or 5 - 10mg SC boluses Repeated every 5 mins (IV) or 20 mins (SC) until unconscious	Usually co-prescribed with a SC/IV opioid. CSCI started if survival is prolonged. Seek specialist guidance.

Elective withdrawal of clinically assisted hydration and nutrition [5]	1st line: Midazolam	10mg – 100mg / 24 hours via CSCI	Only under specialist supervision following established clinical guidelines.
	2nd line Levomepromazine	25mg - 200mg /24 hours via CSCI	
Patient request for continuous deep sedation	Midazolam	2.5mg – 5mg SC hourly p.r.n. 10mg – 100mg / 24 hours via CSCI	Ethically and legally contentious, depending on the specific context. Specialist use only.
	Levomepromazine	12.5 – 25mg SC hourly p.r.n. 25mg - 200mg /24 hours via CSCI	
	Phenobarbital	200mg IV or IM loading dose and then hourly p.r.n. 800 – 1,600mg / 24 hours via CSCI	

Table 2: Commonly used medication, doses and route of administration. mg; milligrams. SC; subcutaneous. IV; intravenous. IM; intramuscular. CSCI; continuous subcutaneous infusion.

The Nature of Suffering: Cultural Considerations

A patient's relationship to their suffering must be considered before deliberately reducing their conscious experience.

Suffering can be described as the a posteriori struggle a person goes through in their life when met with physical, psychological, spiritual and/or social challenges [11]. If a person believes that their suffering has an a priori purpose, it is often experienced as more bearable, and may even be perceived as valuable [12].

The purpose of suffering is a major theme in many religious and philosophical traditions. For example, the Qur'an, Torah, Bible, Bhagavad Gita, and Pali Canon all emphasise that suffering in life is temporary. Such suffering is often contrasted with an enduring state of ease or bliss after death as well as self-realisation [14]. Palliative sedation, even for severe suffering at the end of life, may be undesirable for some patients; for example if they believe that it is not congruent with their values or that it may jeopardise their experience of an afterlife.

Ultimately, that which seems purposeless to clinicians may hold profound significance to patients. If a patient's values and beliefs are not explored, the prospect of palliative sedation may increase their suffering, rather than reduce it.

Ethical Considerations

For palliative sedation to be practiced ethically, prescribers must understand its legitimate indications, justifications and aims.

Historically there has been wide variability in terminology and sedation practice [1]. For example, a recent European-wide systematic review of palliative sedation practice found that most studies did not define “refractory” [15]. There is currently no standard tool for refractory symptom assessment.

When palliative sedation is considered for the management of terminal agitation, the dying person will commonly have impaired capacity to consent to treatment. The best interests of the individual should therefore be the guiding ethico-legal principle. Ambiguity as to the aims and justifications of such treatment may lead to medication administration based on other reasons, for example to relieve carer distress.

Mistrust of clinicians may complicate discussions around palliative sedation. For example, individuals from minoritised communities may doubt the compassionate intentions of clinicians offering palliative sedation. Use of restrictive practices such as sedation, restraint and detention of people of black, asian and minority ethnic backgrounds in other medical contexts have been known to be disproportionate and unethical [16,17,18]. Acknowledging this is crucial to ensuring transparency and maintaining trust.

When sedation is prescribed for patients that are not imminently dying, it is important that the level and duration of sedation does not compromise their nutrition and hydration status. Either the level of consciousness achieved must permit sufficient oral nutrition and hydration to sustain life or arrangements must be put in place to provide clinically assisted hydration and nutrition. In the UK, deep sedation of a patient with a prognosis of greater than one to two weeks without maintenance of nutrition and hydration is both poor practice and legally problematic. Such an approach, sometimes termed ‘slow euthanasia’, undermines public trust in the legitimate use of palliative sedation [19].

Conclusion

The use of sedation with the aim of reducing suffering in palliative care is widespread. Indications and practices vary between settings, although clinical guidelines and formularies exist to support practice. Palliative sedation poses several practical and ethical challenges. Clinicians should aim to provide an individualised approach to patient assessment, working closely with specialist palliative care colleagues and the wider MDT.

Key Points

- The aim of palliative sedation is to relieve refractory suffering with the use of medications to reduce consciousness.

- Where palliative sedation is being used to treat agitation at the end of life, it is important to exclude and/or address reversible causes prior to starting medication.
- The drug, dose and route of administration of palliative sedation may vary according to the indication for treatment.
- Appropriate and proportionate use of palliative sedation does not hasten death.
- Suffering may have different meanings for people depending on their backgrounds and life experiences. These should be explored prior to starting palliative sedation.

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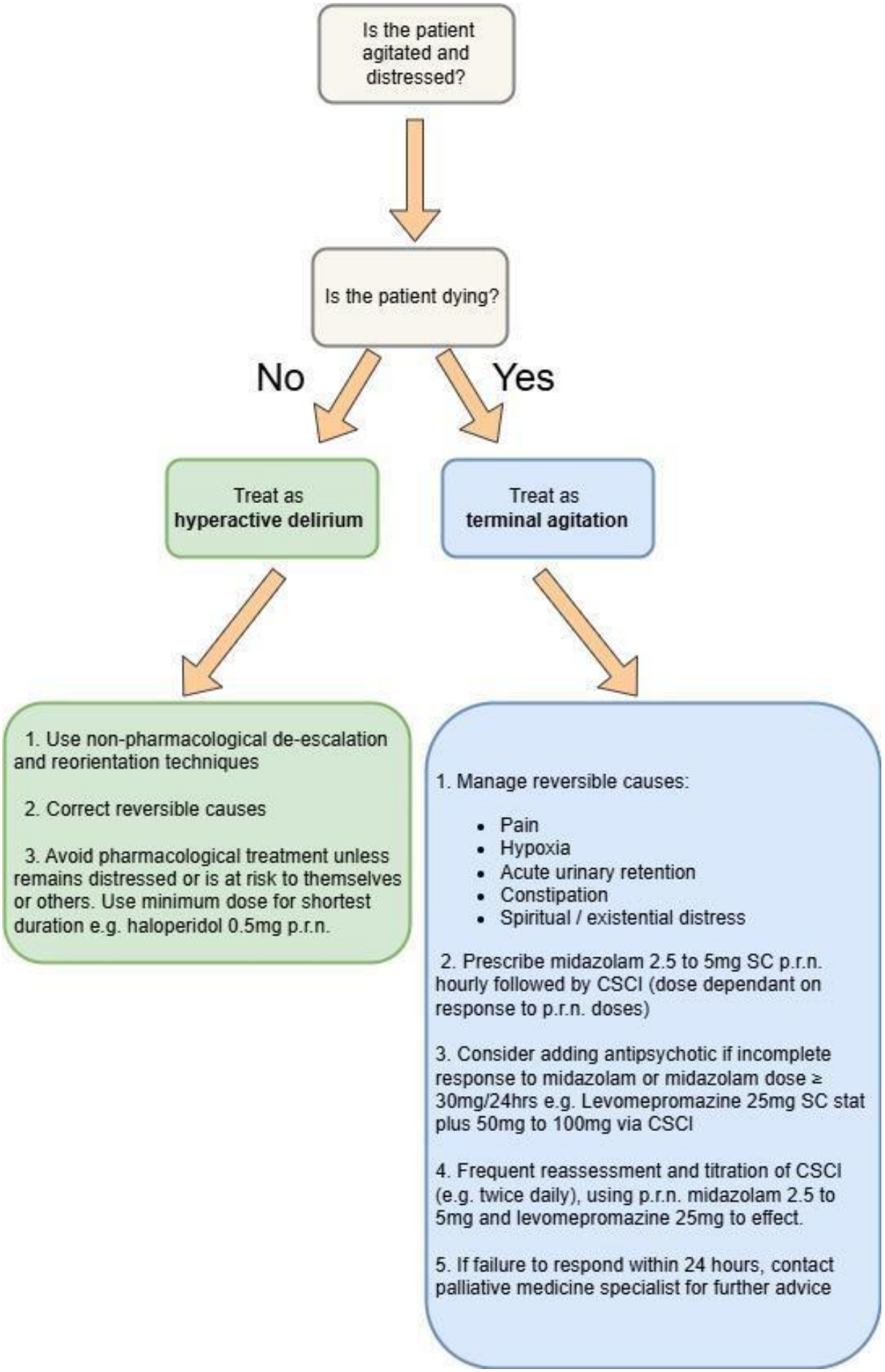
Is the patient agitated and distressed?
Is the patient dying?
No
Yes
Treat as hyperactive delirium
Treat as terminal agitation
1. Use non-pharmacological de-escalation and reorientation techniques
2. Correct reversible causes
3. Avoid pharmacological treatment unless remains distressed or is at risk to themselves or others. Use minimum dose for shortest duration e.g. haloperidol 0.5mg p.r.n.
1. Manage reversible causes:
Pain
Hypoxia
Acute urinary retention
Constipation
Spiritual / existential distress
2. Prescribe midazolam 2.5 to 5mg SC p.r.n. hourly followed by CSCI (dose dependant on response to p.r.n. doses)
3. Consider adding antipsychotic if incomplete response to midazolam or midazolam dose ≥ 30mg/24hrs e.g. Levomepromazine 25mg SC stat plus 50mg to 100mg via CSCI
4. Frequent reassessment and titration of CSCI (e.g. twice daily), using p.r.n. midazolam 2.5 to 5mg and levomepromazine 25mg to effect.
5. If failure to respond within 24 hours, contact palliative medicine specialist for further advice

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Palliative Sedation at the End of Life: Practical and Ethical Considerations

Introduction

The aim of palliative sedation is *"to relieve refractory suffering through the monitored, proportionate use of medications intended to reduce consciousness in patients with life-limiting disease"* [1].

In this paper we describe the clinical practice of palliative sedation, explore what is meant by "refractory suffering" in this context, and consider circumstances in which it may, or may not, be considered ethically acceptable to do so.

Principles of Palliative Sedation

The suffering associated with life-limiting disease can be severe and challenging to alleviate. When other options for relieving such distress have been exhausted, it is common practice for doctors to intentionally reduce a patient's level of consciousness. ~~Sedating medications are used in up to a fifth of deaths~~The prevalence of palliative sedation described in the literature ranges from 12-67% [2,3], and midazolam is one of the three most administered drugs in palliative care [4~~2~~].

There is considerable variation in decision making for palliative sedation [5~~3~~]. There is little evidence based on high quality, prospective data [6~~4~~]. Before starting palliative sedation, clinicians must be confident and adept in their assessment of refractory symptoms, and the ability to differentiate between somatic, psychological, and existential suffering [1].

Indications

Palliative sedation may be used in the following circumstances [1]:

1. For the management of refractory suffering
2. In emergency situations where death is both imminent and anticipated to be distressing without sedation
3. Withdrawal of life sustaining interventions where symptoms are likely
4. As temporary respite when other symptom-focused treatment cannot achieve sufficient relief in an acceptable time frame

Common examples are provided in Table 1.

Table 1: Indications for Palliative Sedation	
Symptom Control	• Terminal agitation • Management of terminal haemorrhage • Management of irreversible airway obstruction • Patient request for continuous deep sedation (specialist use only) • Adjunctive treatment of intractable pain (specialist use only)
Withdrawal of Treatment	• Withdrawal of ventilatory support • Withdrawal of clinically assisted hydration & nutrition

Table 1: Indications for Palliative Sedation

The most common use for sedation in palliative care is for ~~for the treatment of agitation in the imminently dying. T~~terminal agitation (sometimes referred to as terminal restlessness or agitation in the imminently dying).~~is . a common feature of the dying process~~. It is characterised by distress, anxiety and restlessness in the final days of life. ~~-~~In contrast to standard delirium treatment, pharmacological measures are often considered first line as shown in Figure 1, after the exclusion of reversible causes.

[Figure 1]

Where the possibility of major haemorrhage is foreseen, the patient is normally counselled regarding this possibility. An "anticipatory" bolus dose of sedative medication may be prescribed to achieve rapid unconsciousness (see table 2). In cases of catastrophic arterial bleeding, where death is anticipated within seconds or minutes, there is usually not sufficient time to achieve palliative sedation. Priority should instead be given to remaining calm and staying with the patient.

Palliative sedation for the withdrawal of life-sustaining treatment must be considered in the context of a wider clinical plan. This normally requires MDT decision making, meticulous documentation and discussion with those important to the patient. Consensus national guidance exists to support clinicians in specific scenarios, such as the withdrawal of non-invasive ventilation and of clinically assisted hydration and nutrition [~~5,~~6,7].

It should be explained, to both the patient and those important to them, that palliative sedation is used to address refractory and intolerable suffering, not hasten death. There is no evidence that the appropriate use of sedation shortens prognosis in any context [2][~~7~~].

Key Management steps

Medications

Benzodiazepines

Midazolam is the benzodiazepine of choice for palliative sedation due to its high parenteral bioavailability, widespread compatibility with other commonly used palliative medications, and low cost. Lower doses (5 to 10mg/24hrs via CSCI) are predominantly anxiolytic and are often consciousness sparing. Midazolam is used first line for patients with anxiety (where the oral route is not appropriate) and cognitive agitation. Higher doses (up to 100mg/24hrs via CSCI) cause progressively deeper levels of sedation where indicated (table 2).

Antipsychotics

Levomepromazine and haloperidol are used in palliative care for both terminal agitation and the management of nausea and vomiting. Higher doses are required when used for sedation. Antipsychotics are often used first line when patients experience psychomotor agitation or distressing hallucinations. The choice of antipsychotic may be influenced by the likelihood of additional beneficial or adverse effects. Levomepromazine is more sedating than haloperidol and works synergistically with midazolam. In the UK it is the preferred antipsychotic for severe terminal agitation. It is added when midazolam alone is insufficiently sedating and a reduction of conscious level is intended. Internationally, some centres use olanzapine or chlorpromazine as alternatives.

Barbiturates

Phenobarbital can be used when antipsychotic medication is either relatively contra-indicated (e.g. Parkinson's Disease) and/or in the presence of agitation refractory to high dose midazolam and levomepromazine. As higher doses are associated with respiratory depression it should only be initiated under specialist supervision.

Other medications

Propofol is a short acting, intravenous anaesthetic conventionally used for the induction and maintenance of anaesthesia, or for sedation in intensive care. Use of propofol is rare in UK palliative care practice but is more common in continental Europe [1]. Administration under the supervision of an anaesthetist is strongly advisable. The alpha$_2$-adrenoreceptor agonist dexmedetomidine may be effective at reducing terminal agitation with less sedation than traditional sedatives [8,9].

Indications for Palliative Sedation: Medications, Doses and Route

Deeper levels of sedation are associated with loss of the oral route. Subcutaneous injection, intravenous injection, rectal and buccal routes produce rapid effects of relatively short duration. When prolonged sedation is required, continuous subcutaneous infusion (CSCI) provides consistent medication administration over 24 hours regardless of conscious level. When the patient has already developed symptoms of terminal agitation, it is appropriate to give a bolus subcutaneous injection, before starting a CSCI which may take three to four hours to reach full effect.

Indication	Medications	Typical Doses	Notes
Terminal agitation [10]	Midazolam	2.5mg – 5mg SC hourly p.r.n . 10mg – 100mg / 24 hours via CSCI	Often used first line. Used at lower doses to reduce anxiety or cognitive agitation.
	Levomepromazine	12.5 – 25mg SC hourly p.r.n. 25mg - 200mg /24 hours via CSCI	Used when reduction of consciousness is intended. Causes postural hypotension. Lowers seizure threshold. Used at lower doses to manage nausea/vomiting
	Haloperidol	1.5 – 2.5mg SC hourly SC p.r.n. 2.5 – 10mg / 24 hours via CSCI	Used when either distressing hallucinations or psychomotor agitation is present. Less sedating than levomepromazine but higher risk of extrapyramidal side effects.
	Phenobarbital	200mg IV or IM loading dose and then hourly p.r.n. 800 – 1,600mg / 24 hours via CSCI	Avoid SC p.r.n. use due to risk of tissue necrosis. Specialist use only.
Major haemorrhage and irreversible airway obstruction [10]	Midazolam	5mg – 10mg buccal / IV / IM / PR p.r.n. every 30 minutes	Priority should be to stay calm and present with the patient. The subcutaneous route should be avoided in haemorrhage due to risk of reduced perfusion and delayed absorption.
NIV withdrawal [6]	Midazolam	2.5 – 5mg IV boluses or 5 - 10mg SC boluses Repeated every 5 mins (IV) or 20 mins (SC) until unconscious	Usually co-prescribed with a SC/IV opioid. CSCI started if survival is prolonged. Seek specialist guidance.

Elective withdrawal of clinically assisted hydration and nutrition [5]	1st line: Midazolam	10mg – 100mg / 24 hours via CSCI	Only under specialist supervision following established clinical guidelines.
	2nd line Levomepromazine	25mg - 200mg /24 hours via CSCI	
Patient request for continuous deep sedation	Midazolam	2.5mg – 5mg SC hourly p.r.n. 10mg – 100mg / 24 hours via CSCI	Ethically and legally contentious, depending on the specific context. Specialist use only.
	Levomepromazine	12.5 – 25mg SC hourly p.r.n. 25mg - 200mg /24 hours via CSCI	
	Phenobarbital	200mg IV or IM loading dose and then hourly p.r.n. 800 – 1,600mg / 24 hours via CSCI	

Table 2: Commonly used medication, doses and route of administration. mg; milligrams. SC; subcutaneous. IV; intravenous. IM; intramuscular. CSCI; continuous subcutaneous infusion.

The Nature of Suffering: Cultural Considerations

A patient's relationship to their suffering must be considered before deliberately reducing their conscious experience.

Suffering can be described as the a posteriori struggle a person goes through in their life when met with physical, psychological, spiritual and/or social challenges [11]. If a person believes that their suffering has an a priori purpose, it is often experienced as more bearable, and may even be perceived as valuable [12].

The purpose of suffering is a major theme in many religious and philosophical traditions. For example, the Qur'an, Torah, Bible, Bhagavad Gita, and Pali Canon all emphasise that suffering in life is temporary. Such suffering is often contrasted with an enduring state of ease or bliss after death as well as self-realisation [14]. Palliative sedation, even for severe suffering at the end of life, may be undesirable for some patients; for example if they believe that it is not congruent with their values or that it may jeopardise their experience of an afterlife.

Ultimately, that which seems purposeless to clinicians may hold profound significance to patients. If a patient's values and beliefs are not explored, the prospect of palliative sedation may increase their suffering, rather than reduce it.

Ethical Considerations

For palliative sedation to be practiced ethically, prescribers must understand its legitimate indications, justifications and aims.

Historically there has been wide variability in terminology and sedation practice [1]. For example, a recent European-wide systematic review of palliative sedation practice found that most studies did not define “refractory” [15]. There is currently no standard tool for refractory symptom assessment.

When palliative sedation is considered for the management of terminal agitation, the dying person will commonly have impaired capacity to consent to treatment. The best interests of the individual should therefore be the guiding ethico-legal principle. Ambiguity as to the aims and justifications of such treatment may lead to medication administration based on other reasons, for example to relieve carer distress.

Mistrust of clinicians may complicate discussions around palliative sedation. For example, individuals from minoritised communities may doubt the compassionate intentions of clinicians offering palliative sedation. Use of restrictive practices such as sedation, restraint and detention of people of black, asian and minority ethnic backgrounds in other medical contexts have been known to be disproportionate and unethical [16,17,18]. Acknowledging this is crucial to ensuring transparency and maintaining trust.

When sedation is prescribed for patients that are not imminently dying, it is important that the level and duration of sedation does not compromise their nutrition and hydration status. Either the level of consciousness achieved must permit sufficient oral nutrition and hydration to sustain life or arrangements must be put in place to provide clinically assisted hydration and nutrition. In the UK, deep sedation of a patient with a prognosis of greater than one to two weeks without maintenance of nutrition and hydration is both poor practice and legally problematic. Such an approach, sometimes termed ‘slow euthanasia’, undermines public trust in the legitimate use of palliative sedation [19].

Conclusion

The use of sedation with the aim of reducing suffering in palliative care is widespread. Indications and practices vary between settings, although clinical guidelines and formularies exist to support practice. Palliative sedation poses several practical and ethical challenges. Clinicians should aim to provide an individualised approach to patient assessment, working closely with specialist palliative care colleagues and the wider MDT.

Key Points

- The aim of palliative sedation is to relieve refractory suffering with the use of medications to reduce consciousness.

- Where palliative sedation is being used to treat agitation at the end of life, it is important to exclude and/or address reversible causes prior to starting medication.
- The drug, dose and route of administration of palliative sedation may vary according to the indication for treatment.
- Appropriate and proportionate use of palliative sedation does not hasten death.
- Suffering may have different meanings for people depending on their backgrounds and life experiences. These should be explored prior to starting palliative sedation.

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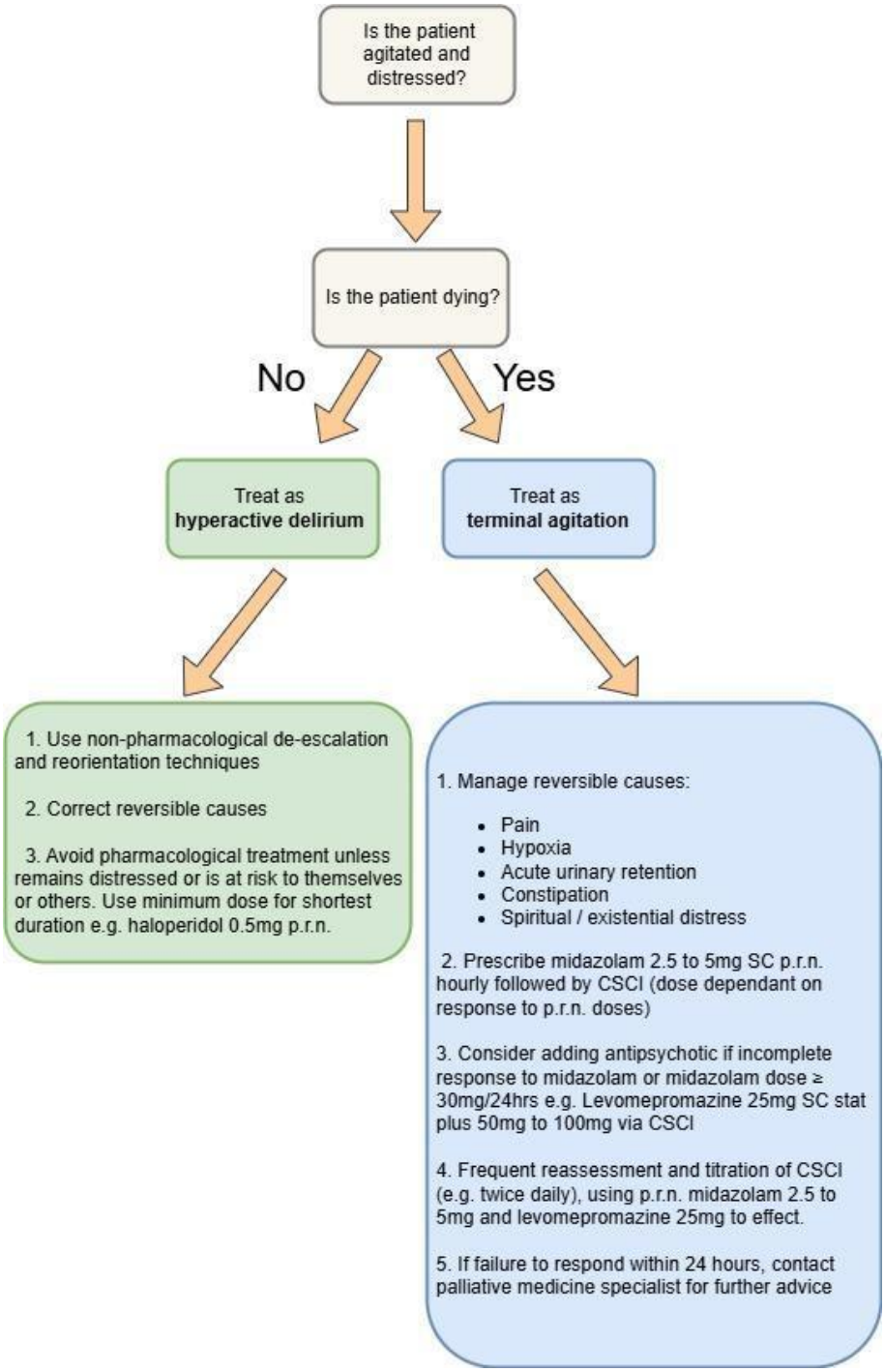
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