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The Analysis Study of Effectiveness, Safety and Ethical Aspects of End of Life Palliative Sedation : A Comprehensive Systematic Review

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ABSTRACT

Background: Palliative sedation, a clinical practice, has been a topic of debate for over three decades. It involves the use of sedative medications to alleviate intractable symptoms at the end of life. However, the ethical implications of inducing unconsciousness in terminally ill patients remain a concern. This review aims to address these ethical considerations and guide clinical decision-making in the end of life. **Methods:** This systematic review exclusively examined full-text articles published in English between 2014 and 2024, adhering to the PRISMA 2020 guidelines. In order to guarantee the incorporation of high-quality sources, editorial pieces and review articles were excluded unless they were accompanied by a DOI. A exhaustive literature search was conducted using a variety of reputable databases, such as ScienceDirect, PubMed, and SagePub, to collect pertinent studies. **Result:** The study conducted a thorough review of more than 100 publications that were obtained from reputable databases, such as ScienceDirect, SagePub, and PubMed. Eight publications were identified as necessitating a more comprehensive examination subsequent to an initial screening. As a result, a comprehensive review of these selected studies was conducted to guarantee an exhaustive and rigorous assessment. **Conclusion:** Palliative sedation is a controversial intervention used to reduce consciousness in patients suffering at the end of life. It is considered an act of compassion, but ethical debates exist regarding its impact on survival and broader implications. Decision-making involves discussions between healthcare teams, patients, and families, and can be administered in various settings.

Keyword: Palliative sedation, end of life, ethical consideration

INTRODUCTION

Palliative sedation (PS) was first introduced in the early 1990s as a medical practice aimed at providing relief for patients experiencing intractable symptoms at the end of life.[1-3] Despite over three decades of clinical application, there remains considerable debate among medical professionals regarding the precise definition and proper implementation of this procedure.[4-7] The most widely accepted definition of PS involves the use of sedative medications to alleviate symptoms that are deemed unmanageable or refractory, without compromising the patient's dignity and comfort during the dying process.[8] However, establishing a standardized approach to PS has been challenging, largely due to varying interpretations of what constitutes intractable symptoms and differing views on the ethical implications of inducing unconsciousness in terminally ill patients.

Intractable symptoms are defined as those that persist despite multiple treatment attempts, making symptom control impossible without significantly reducing the patient's level of consciousness. These symptoms, often related to severe pain, agitation, or respiratory distress, can severely impact a patient's well-being and disrupt the natural progression toward a peaceful death. The decision to initiate PS raises numerous clinical and ethical questions, including the appropriate timing for sedation, patient selection criteria, and the choice of medications. Additional complexities arise around the need for continued monitoring, hydration, and nutrition during sedation, as well as identifying the most suitable setting for administering this type of care. These uncertainties contribute to the overall complexity of PS, making decision-making challenging for healthcare providers.[1,9,10]

From a bioethical perspective, the practice of PS has sparked significant debate, particularly regarding its distinction from euthanasia.[11] While the goal of PS is to relieve suffering by reducing awareness, concerns arise about the ethical justification of inducing unconsciousness in patients nearing death. This sedation can often hinder communication between patients and their loved ones, adding to the emotional and psychological burdens faced by both families and physicians. The present systematic review aims to address these concerns by examining the effectiveness, safety, and ethical considerations surrounding PS, seeking to develop

a consensus among experts in the field to guide clinical decision-making at the end of life.

METHODS

Protocol

The study was meticulously designed and executed in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, ensuring a high level of methodological rigor. Adherence to these guidelines guaranteed that the review process remained transparent, reproducible, and scientifically robust. Every stage of the review, from the systematic literature search to data extraction and synthesis, was carefully planned to minimize potential bias and enhance the credibility of the findings. By following PRISMA 2020, the study ensures that its conclusions are both reliable and trustworthy, contributing meaningful insights to the field.

Criteria for Eligibility

This study seeks to address key concerns surrounding palliative sedation (PS) by evaluating its effectiveness, safety, and ethical implications. Through a systematic review and synthesis of data from various studies, the research aims to identify emerging trends and provide insights that can inform the development of more effective care strategies for patients undergoing PS. The primary objective is to uncover critical themes in the academic literature that enhance the understanding of PS, offering evidence-based perspectives that can improve clinical outcomes and guide healthcare decision-making.

To ensure precision and analytical rigor, the study applied strict inclusion and exclusion criteria throughout the research process. Only peer-reviewed studies published in English between 2014 and 2024, each verified with a DOI for authenticity, were considered. Non-research articles, such as reviews, editorials, and duplicate entries from the same journals, were excluded to maintain the integrity and focus of the dataset. This selective approach ensures that the findings are derived from high-quality, original research, allowing for more reliable conclusions.

By adhering to this meticulous methodology, the study guarantees that the data used are both relevant and trustworthy, providing a solid foundation for actionable insights. These conclusions are expected to contribute to advancements in clinical practice, ultimately enhancing the management and ethical application of palliative sedation for patients at the end of life.

Search Strategy

We used "effectiveness OR safety OR ethical OR palliative sedation" as keywords. The search for studies to be included in the systematic review was carried out using the PubMed, SagePub, and Sciencedirect databases.

Table 1. Search Strategy

Database	**Search Strategy**	***Hits***
Pubmed	*("effectiveness" OR "safety" AND "ethical" AND "palliative sedation")*	7
Science Direct	*("effectiveness" OR "safety" AND "ethical" AND "palliative sedation")*	158
Sagepub	*("effectiveness" AND "safety" AND "ethical" AND "palliative sedation")*	41

Data retrieval

The authors conducted a meticulous initial screening of each article by carefully reviewing titles and abstracts to assess their relevance to the study's objectives. Only those studies that met the predetermined inclusion criteria and aligned with the research goals were selected for further, more detailed analysis. This systematic approach allowed for the identification of consistent and meaningful patterns within the literature, ensuring that the final set of studies provided valuable insights.

To maintain uniformity and quality, only full-text articles published in English were considered for inclusion, ensuring consistency in language and eliminating potential translation biases. A rigorous screening process was

implemented to confirm that all selected content directly addressed the study's focus and adhered to the inclusion criteria. Any studies that did not meet these standards were systematically excluded from further consideration and were not included in the final analysis, ensuring a clear and focused dataset.

The evaluation process also took into account a wide range of factors, such as study titles, authors, publication dates, research settings, and methodologies. This comprehensive approach ensured that only the most relevant and high-quality studies were incorporated, thereby enhancing the reliability and robustness of the study's conclusions. By thoroughly vetting each study, the authors were able to ensure the integrity and rigor of the final analysis, leading to more credible and actionable findings.

Quality Assessment and Data Synthesis

The authors carried out a meticulous initial screening by thoroughly reviewing the abstracts and titles of each article to determine their relevance to the study. Articles that met the initial criteria were flagged for further consideration. Following this preliminary assessment, the studies deemed relevant underwent a comprehensive, in-depth evaluation. This rigorous examination allowed for a more thorough understanding of the research, ensuring that only the most pertinent and high-quality studies were selected for detailed analysis.

By adopting this methodical approach, the selection process was refined to exclude irrelevant or lower-quality studies, thereby enhancing the focus and precision of the review. This careful process ensured that the most significant research was advanced for further scrutiny, improving the overall depth and relevance of the analysis. Consequently, the selected studies provided a more nuanced and contextual understanding of the topic, allowing for meaningful insights to emerge from the literature.

Through this rigorous evaluation process, the study was able to concentrate on high-impact findings, offering a well-rounded and detailed assessment of the research landscape. This ensured that the final analysis was both comprehensive and reflective of the most critical trends and themes within the existing body of literature..

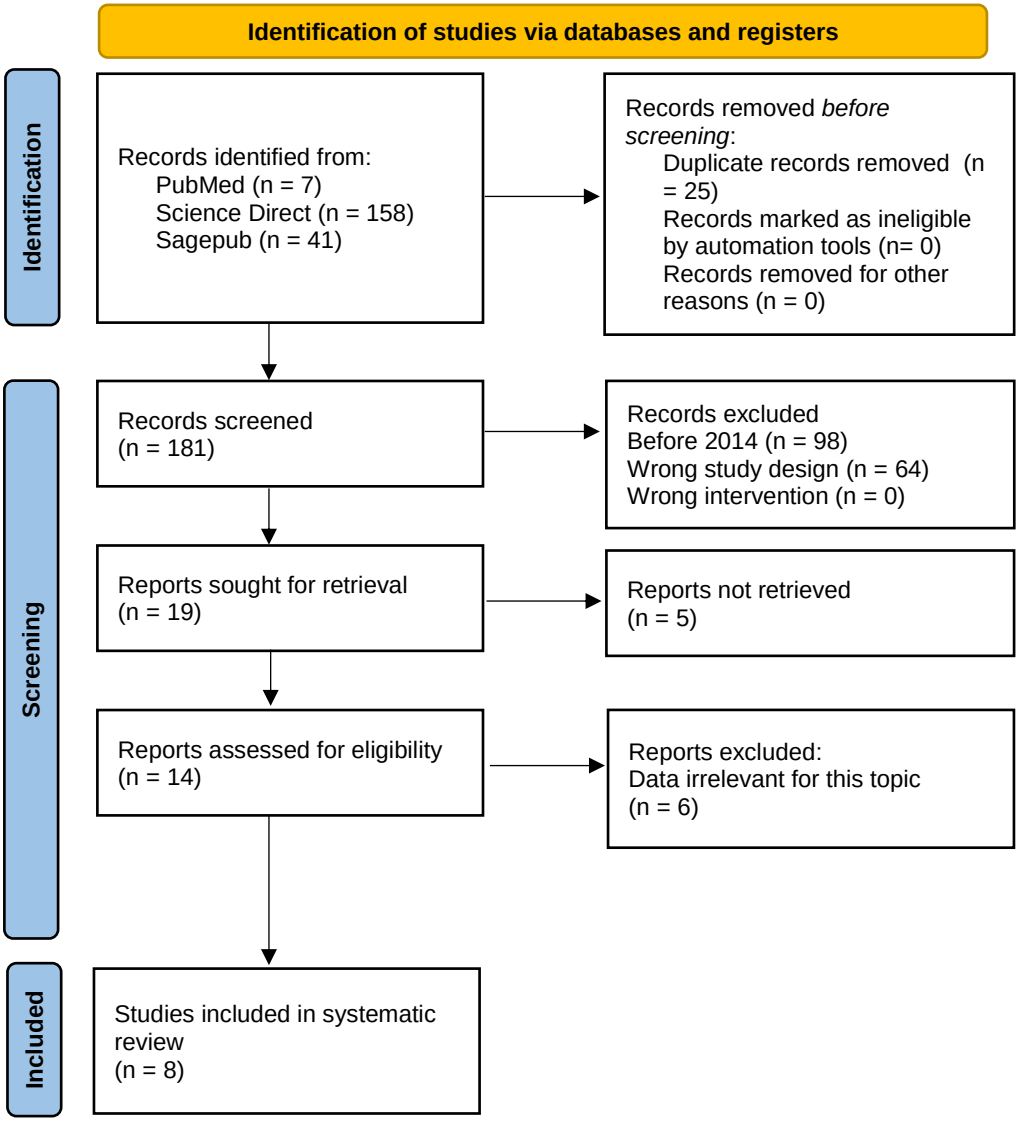

Figure 1. Article search flow chart

Table 2. Critical appraisal of Study

Parameters	(Maltoni et al., 2014)	(Seale et al., 2015)	(Raus et al., 2016)	(Badarau et al., 2019)	(Menezes et al., 2019)	(Akdeniz et al., 2021)	(Tomczyk et al., 2022 a)	(Tomczyk et al., 2022 b)
1. Bias related to temporal precedence Is it clear in the study what is the "cause" and what is the "effect" (ie, there is no confusion about which variable comes first)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Bias related to								

selection and allocation								
Was there a control group?	No	No	No	No	No	No	No	No
3. Bias related to confounding factors								
Were participants included in any comparisons similar?	No	No	No	No	No	No	Yes	Yes
4. Bias related to administration of intervention/exposure								
Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	No.	No.	No.	No.	No.	No.	Yes.	Yes.
5. Bias related to assessment, detection, and measurement of the outcome								
Were there multiple measurements of the outcome, both pre and post the intervention/exposure?	No	No	No	No	No	No	No	No
Were the outcomes of participants included in any comparisons measured in the same way?	No	Yes	No	No	No	No	Yes	Yes
Were outcomes measured in a reliable way?	No	Yes	No	No	No	No	Yes	Yes
6. Bias related to participant retention								
Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	No	No	No	No	No	No	No	No
7. Statistical conclusion validity								
Was appropriate statistical analysis used?	No	No	No	No	No	No	Yes	Yes

RESULT

Our investigation commenced with a systematic collection of research papers from reputable databases, including ScienceDirect, PubMed, and SagePub. We employed a rigorous three-stage screening process to ensure the selection of the most relevant studies for our systematic review. Through this process, eight key studies were identified as being highly pertinent to the research objectives.

These selected studies were subsequently subjected to an in-depth analysis, allowing us to explore the central themes and findings in greater detail. Key topics from these studies were carefully chosen for further examination to provide a nuanced understanding of the subject matter.

To enhance the clarity and structure of our findings, we have compiled a concise summary of the analyzed data in Table 3. This streamlined presentation facilitates a clear and organized interpretation of the results, contributing to a more focused discussion of the study's outcomes.

Table 3. The literature included in this study

Author	Origin	Method	Sample	Result
Maltoni et al.[12] (2014)	Italy	Review	-	Palliative sedation is a proportionate, variable procedure used to relieve refractory symptoms in terminally ill patients without the intention of hastening death. It is separate from other end-of-life decisions and has been proven to have no detrimental impact on survival.
Seale et al.[13] (2015)	United Kingdom	Retrospective Study	156 participants	A study of 156 interviews with end-of-life care providers revealed differences in ethical rationales for sedation. In the UK, titration doses proportionately against symptoms is more likely, with potential harms including social and biological death. In Belgium and the Netherlands, rapid inducement of deep

				unconsciousness is more acceptable, often seen as a response to unbearable suffering and pressure to hasten death. Dutch guidelines for sedation align with practices in the Netherlands and Belgium, while the European Association for Palliative Care has a more international framework.
Raus et al.[14] (2016)	France	Review	-	Sedation, a controversial practice at the end of life, is considered both ethical and legal. France has passed an amendment to the Public Health Act, granting certain terminally ill patients the right to continuous deep sedation. However, the proposed bill suggests it should be considered a sui generis practice, requiring withholding of artificial nutrition and hydration, and not unbearable suffering. This raises questions about decriminalizing euthanasia and PAS.
Badarau et al.[15] (2019)	Switzerland	Review	-	The recent amendment in Belgian law allows euthanasia for minors, sparking debates on morally acceptable end-of-life practices in pediatrics. Critics argue that continuous and deep sedation until death (CDS) is a morally preferable alternative to euthanasia, meeting patient needs, and not raising capacity issues. However, the aim is to emphasize ethical issues with both practices.
Menezes et al.[16] (2019)	Brazil	Review	-	Palliative sedation is a decision-making process

				for end-of-life patients with refractory symptoms, such as dyspnea and delirium. It involves discussions and agreement among the team, patient, and family members. Midazolam is the most indicated drug, and neuroleptics may be required. The decision depends on intention and proportionality, distinguishing it from euthanasia or assisted suicide.
Akdeniz et al.[17] (2021)	Turkey	Review	-	Healthcare professionals face ethical challenges in end-of-life care decisions, requiring a deep understanding of biomedical ethics principles. These principles guide decisions regarding resuscitation, mechanical ventilation, artificial nutrition, terminal sedation, withholding treatments, euthanasia, and physician-assisted suicide, ensuring the rights, dignity, and vigor of all parties involved in the clinical ethical decision-making process.
Tomczyk et al.[18] (2022)	Switzerland	Systematic Review	35 studies	The analysis of 35 CPGs from 14 countries and 1 international CPG revealed diverse formal characteristics and thematic scope, making it difficult to compare due to differences in terms and definitions of palliative sedation. Three main situations were identified: fully explicit thematic

				scope, partially explicit thematic scope, and without an explicit thematic scope.
Tomczyk et al.[19] (2022)	Switzerland	Systematic Review	21 studies	This study explores the ethical challenges of palliative sedation in clinical practice guidelines for adults, focusing on whether these guidelines specify ethical issues for patients with cancer and non-cancer. The aim is not to make normative judgments or assess the quality of the guidelines, but to identify the full spectrum of these challenges.

DISCUSSION

The use of palliative sedation (PS) to reduce consciousness in patients experiencing extreme suffering at the end of life first emerged in the late 1980s. Since then, ethical debates have arisen regarding its impact on survival, as well as the broader implications of this intervention. A key development in this area came in 1994, with the definition of refractory symptoms, which continues to guide current practice.[20,21] Refractory symptoms are understood as those where all available treatments have either failed or are deemed futile by a consensus of experts after multiple evaluations. These symptoms cannot be alleviated within a timeframe or cost-benefit level that the patient can tolerate. Among the most challenging symptoms to manage in the final days of life are delirium and dyspnea, followed by nausea and vomiting.[12,22] Research over seven years in palliative care units confirmed that PS is most often indicated for cases of dyspnea, delirium, and anxiety, while physical pain is usually more manageable and less likely to require sedation.[23]

The increasing use of PS for psycho-existential suffering, particularly in patients with advanced cancer, has sparked significant controversy. Studies have shown that patients experiencing profound psycho-existential distress, including

feelings of loss of autonomy, dependency, and a perceived lack of meaning in life, are more likely to seek options such as assisted suicide or euthanasia. Critics of PS for these reasons argue that psycho-existential suffering does not always imply that a patient is nearing death. Therefore, PS should only be considered after all other medical, psychological, and spiritual interventions have been exhausted. Decision-making around PS is highly complex and must involve discussions between healthcare teams, patients, and their families. This dialogue is crucial for ensuring that PS is only pursued when symptoms are truly refractory and death is imminent. It is also essential to communicate that PS neither hastens nor delays death but may limit a patient's ability to communicate verbally with loved ones.[24,25]

In 2001, PS was formally defined as the use of sedatives to relieve intractable, refractory symptoms by reducing a patient's consciousness, and it was further classified into several categories based on the depth, duration, and indication of sedation. These categories include moderate, deep, intermittent, continuous, primary, and secondary sedation, which provide a more structured framework for clinicians to tailor PS to the specific needs of patients. The authors emphasize that these subcategories aim to enhance the precision of sedation, such as using primary, continuous, deep sedation for delirium in cancer patients, or secondary, continuous, moderate sedation for dyspnea in lung cancer patients. By refining the use of PS in this way, healthcare providers can improve the quality of end-of-life care, ensuring that patients receive the appropriate level of sedation based on their unique clinical situations.[26-28]

Palliative sedation (PS) can be administered in various settings, including hospitals, hospices, and even in the patient's home, depending on their preferences and medical needs. Recent reviews have demonstrated that home-based PS is a viable and safe option for patients with refractory symptoms who wish to die at home, provided that proper patient selection and monitoring are ensured. Midazolam, a benzodiazepine, is the preferred drug for initiating PS due to its ease of titration, rapid onset, short half-life, and availability of a specific antagonist. It can also be combined with other medications for enhanced symptom control. Neuroleptics, such as chlorpromazine, are effective for managing delirium, while opioids may continue to be used for pain relief. However, caution must be exercised

with high-dose opioids, as they can potentially cause adverse effects like delirium, sweating, and agitation. Patient monitoring during PS should focus solely on ensuring comfort and managing any adverse effects, with traditional measures like cardiac and blood pressure monitoring discontinued to avoid unnecessary stress for both the patient and their family. Psychological and spiritual support for both the healthcare team and the patient's relatives is also crucial during this process.[12,27,29]

One of the most intricate ethical debates surrounding palliative sedation (PS) centers on distinguishing it from euthanasia and assisted suicide. From a bioethical perspective, PS is justified by three key principles: double effect, proportionality, and autonomy. The principle of double effect, crucial to understanding the ethical basis of PS, allows for actions that have both good and harmful outcomes, provided that the harmful effect (e.g., shortening of life) is not the intended goal but rather an unintended side effect of relieving suffering. This principle stipulates that the action itself must be morally good or neutral, the intention must be to achieve a good outcome (relief from suffering), and the negative consequences (such as a potential reduction in lifespan) must not be the direct means of achieving that relief. Proportionality, another bioethical tenet, ensures that the alleviation of suffering outweighs any negative outcomes, further distinguishing PS from euthanasia. Euthanasia's explicit goal is to cause death, whereas PS aims to alleviate intolerable symptoms, with any life-shortening effects being secondary and unintended.[16]

The ethical distinction between PS and euthanasia is also underscored by differences in medical practice and intent. In PS, sedative doses are carefully titrated to relieve symptoms like pain and anxiety without the intention of causing death, whereas euthanasia involves administering lethal doses to deliberately end life. This difference highlights the importance of respecting patient autonomy while adhering to the ethical principle of nonmaleficence, which seeks to not harm. PS is considered an act of compassion, allowing patients and their families relief from continuous suffering, yet it does not seek to hasten death. Recent literature confirms that PS, unlike euthanasia or assisted suicide, does not have a direct impact on survival rates, further reinforcing its ethical permissibility. However, the irreversible nature of PS, especially when it results in unconsciousness, raises

ethical concerns that demand thoughtful deliberation by healthcare teams, patients, and families alike.[11,29]

CONCLUSION

Palliative sedation (PS) is a controversial intervention used to reduce consciousness in patients experiencing extreme suffering at the end of life. It is considered an act of compassion, allowing patients and their families relief from continuous suffering without the intention of hastening death. However, ethical debates have arisen regarding the impact on survival and the broader implications of this intervention. Refractory symptoms, such as delirium, dyspnea, and anxiety, are the most challenging to manage in the final days of life. PS is most often indicated for cases of dyspnea, delirium, and anxiety, while physical pain is usually more manageable and less likely to require sedation. Decision-making around PS is complex and must involve discussions between healthcare teams, patients, and their families. PS can be administered in various settings, including hospitals, hospices, and home settings, depending on the patient's preferences and medical needs.

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