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Review Article

Palliative sedation in the treatment of existential suffering in end-of-life patients: An integrative review

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Background: Although quality palliative care is available, some people at the end of life suffer from refractory symptoms for which conventional treatments have failed. Palliative sedation (PS) is an option recommended in these cases, including for the treatment of refractory existential suffering (ES) in people at the end of life.
Aim: to analyze the evidence available in the literature on the use of PS to manage ES in people with serious illnesses.
Methods: This is an integrative review based on the steps described by Whittemore and Knalf, and reported in line with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA-2020).
Results: A total of 38 studies published between 2000 and 2024 were included. Themes and sub-themes were identified based on patterns and recurring themes. The two main themes were: 1) PS in the management of ES: challenges for clinical practice, and 2) Definition and assessment of Existential Suffering.
Conclusions: The acceptance of PS for the relief of refractory physical symptoms is widely consolidated, while its use for ES remains controversial. Ethical concerns, especially regarding the distinction between PS, euthanasia, and assisted dying, are common among healthcare professionals. The hesitation regarding the use of PS for ES by these professionals is legitimate, considering the lack of robust evidence showing the efficacy of PS for refractory ES, as well as clear guidelines to support these professionals regarding the definition of refractory ES, how to identify it, and how to use PS in these cases. In addition, the training and experience in PS of healthcare professionals influences decision-making, suggesting that their education and training are essential to ensure the adequate practice of PS.
Registration: Open Science Framework (https://doi.org/10.17605/OSF.IO/XZ3UR).

Keywords: Deep sedation, Palliative sedation, Demoralization, Existential suffering, Systematic review

Background

Despite the availability of quality palliative care (PC), some people with serious illnesses endure severe physical, psychological, or existential suffering at the end of life, for which conventional treatment options fail.[1] In these cases of refractory suffering, intentional reduction of consciousness through palliative sedation (PS) may be recommended.[1] PS consists of the monitored, deliberate, and proportional use of medication for the controlled reduction of a person's level of consciousness, with the aim of relieving suffering, especially when other treatments have proved ineffective.[2] PS can vary in depth and duration, being classified as light or deep sedation, and can be administered intermittently or continuously – the term 'mild sedation' has been replaced by 'light sedation', since 'light' and 'deep' are not extremes of the same scale or pairs of opposites.[2]

The term 'refractory' is used to describe suffering that is both untreatable from the perspective of health and intolerable from the perspective of the person experiencing these conditions, so this duality is crucial to understanding when PS may be suitable.[1]

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Refractory suffering can stem from symptoms, a state of existential distress, or a set of symptoms.[3] In addition, the determination of refractoriness is a joint decision between the medical doctor (and/or multi-professional team) and the patient or their legal representative/significant ones.[3] For Surges et al.,[1] the term suffering encompasses distressing physical and psychological symptoms, as well as existential suffering (ES).

ES represents one of the most complex aspects of symptom management in PC. Yalom suggests that ES results from a lack of resources to face the realities of existence, which include isolation, freedom, death, and the meaning of life.[4–6] This suffering is inherent to the human condition and is intensified in instances of serious illness, when the individual is faced with powerlessness, loneliness, and loss of purpose.[6] Symptoms or a state of existential distress are considered refractory when there is a lack of methods that can provide adequate relief in an acceptable timeframe and without unacceptable adverse effects.[1] In these cases, Surges et al. suggest recognizing ES as a referral for PS.[1]

Despite the above, there are significant gaps in the literature on the theme. The lack of consensus on the definition and criteria that determine ES and refractory ES in clinical practice renders clinical decisions challenging. There is no widely accepted definition of ES nor an agreed term to describe it, thus other terms can be found in the literature to refer to this phenomenon, such as demoralization, demoralization syndrome, total pain,[7] existential distress, psycho-existential suffering, and existential pain.[8] It should be noted that the definitions of 'refractory symptom', 'refractory psychological distress', and 'refractory existential distress' are inconsistent.[9] PS for ES is perceived as a unique situation, as the nature of the symptoms can hinder the determination of their refractoriness, which is often dynamic and varies between patients.[1] Furthermore, clinical guidelines vary widely and often do not clearly address protocols for the use of PS in cases of ES. Therefore, with the aim of analyzing the available evidence in the literature on the use of PS for the management of ES in people with serious diseases, this study aims to fill existing gaps in this field of knowledge, promoting a more solid understanding of best practices and contributing to the development of future guidelines for healthcare professionals on the practice of PS for refractory ES.

The main findings of this review point to significant challenges for clinical practice. The included studies show that the use of PS is widely accepted for physical symptoms such as pain and dyspnea, but that its application for ES can lead to controversy, mainly due to ethical concerns and the lack of clear guidelines. In addition, there is no consensus on an operational definition of ES or refractory ES, as well as a lack of specific criteria for its identification. Such gaps highlight the need for more research, with varying methodological approaches, to explore effective forms of assessment and management for refractory ES. This review therefore suggests the creation of more robust clinical guidelines, as well as increased training and support for healthcare professionals in the management of refractory ES, with the aim of improving PS practices and increasing safety and consistency in the provision of care to people at the end of life.

Methods

Study design

This integrative review (IR) was developed in line with the method proposed by Whittemore and Knafl,[10] based on the following steps: Problem identification, Literature search, Data evaluation, Data analysis, and Presentation.

Protocol and registration

This study is registered in the Open Science Framework Registries (https://doi.org/10.17605/OSF.IO/XZ3UR). The protocol for this review[11] was developed in line with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P).[12] This report has been developed complying with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA-2020).[13]

Problem identification

The guiding question, developed using the PICo (Population, Interest and Context) strategy,[14] is the following: 'What is the available evidence in the literature on the use of palliative sedation to (I) manage existential suffering (Co) in people with serious end-of-life diseases (P)?'.

Literature search

To start the literature search process, a search was carried out in the PubMed database (US National Library of Medicine) to identify the descriptors, alternative terms/synonyms, and keywords most commonly used to index studies related to the topics of interest in this review (palliative sedation and demoralization). Thus, those that recurred most frequently during this preliminary research were selected to compose the search strategies for each database used in this IR. Emtree, MeSH, and CINAHL headings were also selected to complement the search strategies. The selected terms were combined using the Boolean operators AND and OR to create the search strategies used in this review, which are presented in detail in Supplementary Material – Table 2. The databases

consulted were: Medline/PubMed, Scopus, Web of Science, CINAHL, Cochrane Library, and EMBASE (Supplementary Material – Table 1). The development process of the search strategies for the studies in these databases was guided by a librarian. The search for studies in these databases was carried out jointly by two of the authors (GMI and EMCP) on July 18, 2023.

In line with Whittemore and Knafl's (2005) guidelines for the use of at least two study retrieval strategies in integrative reviews, with the aim of ensuring a comprehensive search that identifies as many eligible primary sources as possible, in addition to the database search, a manual search was also carried out on the reference lists of the studies included in this review.[15] The search was updated in November 24, 2024.

The eligibility criteria were: a) regarding the type of study: primary studies, regardless of the design type; b) regarding the participants: people facing serious illnesses/conditions at the end of life, diagnosed with ES, undergoing PS. There were no limitations regarding age, sex, or ethnic origin. There were also no limitations regarding the publication year or language. No gray literature was consulted, since this strategy for study retrieval is not covered by the methodological framework used.[10]

The results retrieved from the databases were exported to EndNote (EndNote Web, Clarivate, Philadelphia – https://www.myendnoteweb.com) and duplicate studies were removed. Subsequently, the remaining studies were loaded into the Rayyan software[16] for the selection stage of the studies to compose the final sample of this IR.

First, study selection was performed by manually screening titles and abstracts according to the aforementioned eligibility criteria. Next, the relevant studies were read in full and those that failed to meet the eligibility criteria were excluded. It should be noted that the study selection process in these two stages was carried out independently by two reviewers (GMI and EMCP). In the event of inconsistencies, these were discussed and resolved and, when necessary, a third reviewer was involved so that an agreement could be reached.

Data extraction was carried out using an instrument prepared by the authors, which covered the following variables: country where the study was carried out, study objective, design, population, and sample, method of ES diagnosis, definition of ES presented, information on the medication/dosage/route of administration used to carry out PS, main PS-ES results, study conclusions and limitations. In order to extract the data for this review, the authors (GMI and EMCP) received prior training in order to retain similarity when extracting data from the studies included in the final sample. Thus, study analysis was divided equally between the authors and, at the end, another author (ACMG) reviewed the final version of the data extraction table in order to standardize the presentation of these data and identify possible missing or incomplete information, as well as any discrepancies.

Data evaluation

The methodological quality and evidence level of the studies included in this review will be assessed using the Evidence Level and Quality Guide – Johns Hopkins Nursing Evidence-Based Practice.[17]

Data analysis

According to the methodological framework adopted for this review,[10] the analysis process proposed by Miles and Huberman[18] was used consisting of data reduction, display, and comparison, as well as conclusion and verification. The reduction stage consisted of organizing the data from the primary sources into subgroups by similarity. In the display stage, the data was compiled in order to start the interpretation process.[10] Following this, the stage of comparing the primary sources and identifying patterns, themes, and relationships between the data was carried out.[10] At the end of the analysis, the data was compiled into a synthesis with the main conclusions, thus concluding the verification process.[10]

ChatGPT-4 was used as a data management tool to assist with data reduction, display, and comparison, with the aim of supporting the identification of patterns and recurring themes in the studies included in this IR. For this purpose, the file containing the data extraction tables (Supplementary material, Tables 3, 4, and 5) was uploaded to ChatGPT-4 using its file analysis feature, and specific prompts were designed to facilitate content organization and synthesis. The generated outputs were critically reviewed, interpreted, and adapted by the researchers (ACMG and GMI) to ensure the rigor and integrity of the analysis process, as presented in the results. While the use of ChatGPT-4 was not part of the original protocol for this review,[11] its application was considered a practical approach to enhance workflow efficiency by automating certain organizational tasks.[19] It is important to clarify that ChatGPT-4 did not independently conduct the analysis or synthesis of evidence; these tasks were entirely performed by the researchers, with ChatGPT acting solely as a tool for managing and organizing the data.

Results

A total of 38 studies published between 2000 and 2024 were included. The identification and screening process for these studies is described in Fig. 1.

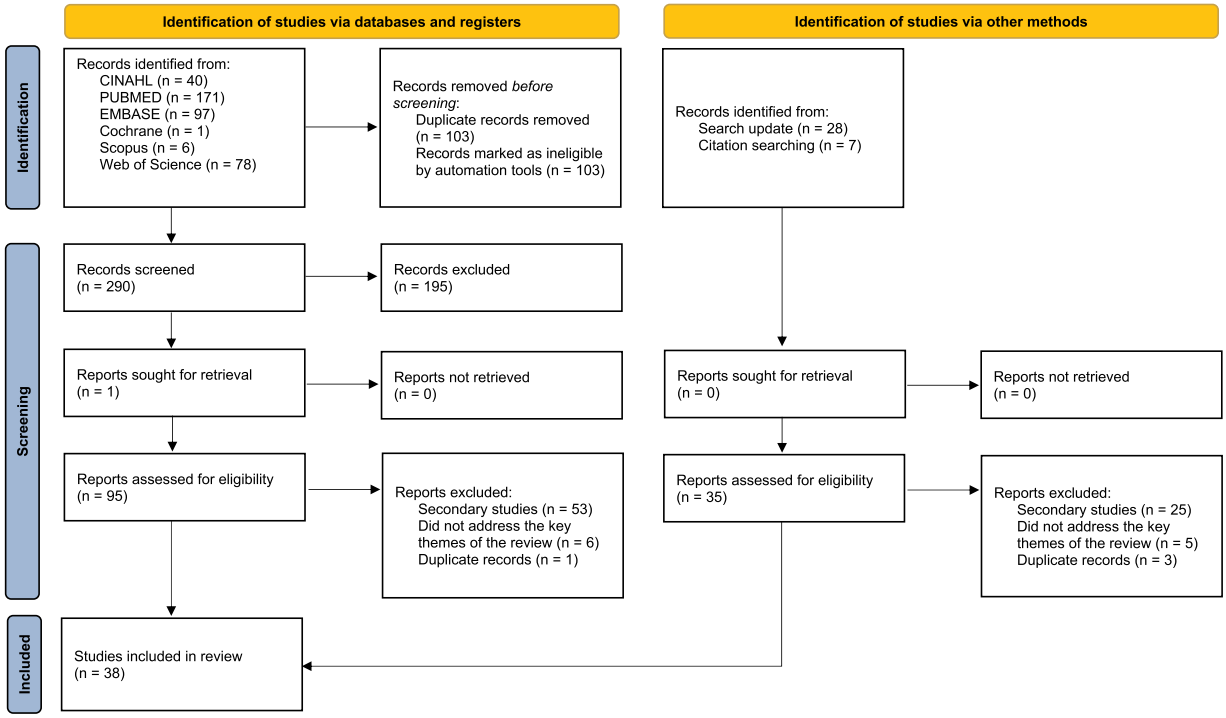

Figure 1 PRISMA Flow diagram. Source: Page et al. (2021)[13]

Based on the data extracted from the included studies (Supplementary material, Tables 3, 4, and 5), themes and subthemes were identified, according to patterns and recurring themes in these studies, as shown in Chart 1.

Theme: PS in ES management: challenges for clinical practice

PS referral: influence of the type of suffering

The influence of the type of suffering was used as a criterion for critical selection in the decision to apply PS, so that the use of PS for the management of physical symptoms was more widely accepted than for the management of ES.[20–22] In the study by Papavasiliou et al.,[23] where one of the objectives was to explore ethical questions surrounding sedation practices at the end of life, the researchers concluded that from a medical point of view, it was clear that psycho-existential suffering is not considered a sufficient reason for applying sedation at the end of life. In the study by Cripe et al.,[24] resident physicians rarely refused PS for physical pain, however, 14.3% of residents stated that they would refuse a request for sedation for ES. In some cases, the choice to perform PS for ES relied on the presence of physical symptoms that were considered refractory.[25,26] For Morita et al.,[27] sedation was mainly performed to relieve severe physical distress, such as dyspnea and agitation, and ES alone was rarely considered a reason for sedation. Beauverd et al.[28] concluded in their study that there is a general discomfort among physicians towards prescribing PS for ES.

The use of PS was prevalent for the management of physical symptoms, as noted in the studies carried out by Morita et al.,[27,29] Blondeau et al.,[20] Rietjens et al.,[30] van Deijck et al.,[31] Beauverd et al.,[28] Heijltjes et al.,[21] among others. The main physical symptoms that required the use of PS were pain,[24,27,31–35] dyspnea,[27,31,34,35–38] and delirium,[34–38] with the referral of PS for ES being less common and more controversial. The use of PS for ES has been recurrently reported only in refractory cases, in short-term scenarios, when there are multiple intractable symptoms and/or after other interventions have failed.[24,25,29,31,33,35,37–46]

In the case of the use of PS for ES, healthcare professionals have generally expressed reluctance towards it,[47,48] so that before resorting to PS, these professionals have preferred other alternatives, such as

Chart 1 Themes and subthemes identified in the studies included in the IR.

Themes	Subthemes
PS in ES management: challenges for clinical practice	PS referral: influence of the type of suffering
	Ethical concerns: sedation, euthanasia, assisted dying, and autonomy
	The influence of professionals' training and experience
	Need for education and guidelines for professionals
Definition and assessment of Existential Suffering	Lack of consensus: concept of Existential Suffering
	Common constructs
	Lack of criteria and guidelines for identifying ES and referring PS for ES

psychological, psychiatric, and spiritual care.[20,37,39,40,49] In the study carried out by Morita,[39] for instance, the general frequency of continuous deep sedation for ES was only 1% (90 cases/8.661 total patient deaths), always followed by previous attempts at interventions considered to be less invasive. The use of intermittent sedation[20,27,29,39,43,45,50] or anxiolytics[45] has also been adopted as an initial strategy.

Ethical concerns: sedation, euthanasia, assisted dying, and autonomy

Important ethical concerns remain regarding PS, especially in relation to its use for ES. According to the study by Foley et al.,[51] most medical doctors would refuse to use deep PS for ES cases. These authors suggest that this reluctance may be due, among other reasons, to the fact that they consider PS to be a way of hastening death. In another included study, the healthcare professionals interviewed expressed concern regarding the fact that sedation at the end of life is morally equivalent to euthanasia.[23] The authors of this same study concluded that certain aspects of sedation, including the intent of the practice, are still in question, drawing parallels between sedation at the end of life and euthanasia. In the study by Foley et al.,[51] respondents distinguished PS from euthanasia and assisted dying, refusing to practice assisted dying. In their study, Dumont et al.[48] concluded that in a setting where assisted dying is authorized, it is possible that medical doctors are more inclined to favor assisted dying over PS when patients experience ES. Belgian medical doctors, who participated in the study by Rodrigues et al.,[52] expressed mixed opinions regarding the use of PS for ES and employed a wide range of ethical arguments for and against it, which are primarily related to the four principles of biomedical ethics.

In some of the studies included in this IR, PS was considered as an alternative to euthanasia. Medical doctors interviewed in the study carried out by Rietjens et al.[30] stated that continuous deep sedation is a better alternative to euthanasia, as it can provide comfort to some patients when their thoughts of possible future suffering become unbearable. Respondents also contemplated the use of continuous deep sedation for patients requesting euthanasia.[30] In addition, some considered continuous deep sedation to be less costly or uncomfortable to administer.[30] In the study by Maeda et al.,[50] the use of continuous deep sedation in cases of psycho-existential suffering associated with physical symptoms was also associated with a higher prevalence of patients wishing or requesting hastened dying. In the study by Foley et al.,[51] medical doctors interviewed on how they integrate PS into their practice in cases of ES stated that PS was a better alternative when compared to euthanasia, since it respects the natural timing of death.

Another relevant ethical aspect raised in the studies included in the IR sample is the respect for patients' autonomy. Gamblin et al.[53] reported that all the cases of sedation evaluated, for psychological or existential suffering, included a discussion with patients, their consent, as well as the disclosure of information to family members. In his study on the characteristics of patients who received PS therapy for psycho-existential suffering, Morita[39] reported that sedation was carried out on the basis of patient and family consent. Medical doctors interviewed in the study carried out by Rietjens et al.[30] stated that they would consider continuous deep sedation for patients with predominantly emotional/existential suffering, so that their decision-making is characterized by a balance between the patient's wishes, the clinical picture, and their own feelings regarding the situation. Rodrigues et al.[52] emphasize the importance of the participation of all stakeholders (patient, family, and professionals) to avoid inadequate decisions from being made.

Influence of professional training and experience

PC professionals, especially those with specialized training, are inclined to be more supportive of PS in a range of clinical settings. Medical doctors with experience in PC are often referred to when their colleagues lack the necessary knowledge or experience in applying PS. These specialized teams have an important role in supporting medical doctors, helping to explore PC options for patients facing complex dilemmas regarding euthanasia, existential suffering (ES), and PS itself.[36] Resident medical doctors, for instance, state that, for both physical pain and ES, they would refer patients to a PC team, reflecting the importance of specialist support in these decisions.[24] Medical doctors with training in PC are more likely to approve and use PS in patients with complex conditions, such as amyotrophic lateral sclerosis, and are more receptive to the use of this intervention than their peers who lack such experience.[22] In addition, Spanish palliative care medical doctors are inclined to support continuous PS as a proportionate treatment for terminally ill patients, especially when they face refractory dyspnea, agitated delirium, or ES in critical clinical conditions.[37] The adequate use of PS in terminally ill patients has also expanded in countries with developing PC systems, where the practice is considered efficient for the management of untreatable symptoms, such as in the case of intense ES.[35] However, in contrast, in the study carried out by Morita et al.,[29] medical doctors who were less

engaged in the care of terminally ill patients and less specialized in palliative medicine were also significantly less likely to choose psychiatric treatment compared to sedation. Morita et al.[29] highlight the potential risk of the inadequate use of sedation for patients with potentially treatable psychiatric disorders. Less than 40% of the medical doctors who participated in the study considered psychiatric interventions to be a strong possibility for patients with depression and delirium determined by experienced psychiatrists to be intrinsically treatable, yet approximately half of the medical doctors interviewed considered sedation to be a possibility. On the other hand, palliative care specialists or doctors with more experience in providing end-of-life care were more likely to choose psychiatric treatment for such patients, compared to PS. Thus, medical doctors who are less confident in managing ES are inclined to select continuous deep PS.[29]

Younger medical doctors are likely to be more receptive to the use of PS, especially in cases of ES, compared to their more experienced peers. According to the study by Cripe et al.,[24] medical doctors at the beginning of their careers are more likely to contemplate PS for ES, while more experienced medical doctors often resort to alternative approaches before resorting to sedation.

Need for education and guidelines for professionals

Studies suggest that there is a pressing need to provide more robust education and training to healthcare professionals in the management of ES and the adequate use of PS. Morita et al.[29] stress the importance of adequate training and education in end-of-life care, pointing out that clear and valid guidelines are essential for PS therapy. Despite the existing recommendations, Rietjens et al.[30] note that guidelines on continuous deep sedation often fail to correspond to the practical reality of medical doctors, which adds to the difficulty in consistently applying these guidelines. Among Canadian PC physicians, there is no clear consensus on the use of continuous PS for ES, and the difficulty in reaching this consensus is amplified by the lack of universally accepted definitions of key terms related to continuous PS, which hinders the development of adequate guidelines for this practice.[54] This lack of consensus was also found in another international study, which failed to define guidelines on sedation levels for patients with refractory symptoms, especially in cases of ES.[37] While there is widespread agreement on the use of PS for physical symptoms such as refractory dyspnea and delirium in the last days of life, specialists diverge on the application of PS in cases of ES.[37] The lack of consensus has also been found among Belgian PC physicians, as noted by Rodrigues et al.,[52] so these authors suggest that more research is needed to clarify the stances of these professionals and thus further the development of clear guidelines for PS in cases of ES. Cripe et al.[24] points out that the definition of PS used by residents lacked information on the intended level of consciousness, the duration of sedation, or whether the patient would receive hydration or nutrition while sedated.

In the home environment, this need to adapt is particularly more critical. Meesters et al.[55] point out that guidelines such as continuous monitoring, psychological assessment in cases of ES, and dosage adjustment for reassessment of symptom burden are not applicable in home care. Finally, Beauverd et al.[28] conclude that more research and training are essential to clarify the ethical and clinical aspects of PS practice, ensuring that medical doctors can make informed and responsible decisions, especially when dealing with ES cases. Maeda et al.[50] emphasize the need for more studies and discussion in order to develop effective treatment strategies for psycho-existential suffering. For these authors, such research is vital to clarify the recommendations and procedures for continuous deep sedation in cases of ES, both internationally and in specific cultural contexts.[50]

In addition, there are persistent misconceptions surrounding the use of opioids as intervention for continuous palliative sedation, also found by Voeuk et al.,[54] suggesting the need for more robust educational programs to clarify clinical practices.

Theme: definition and evaluation of existential suffering

Lack of consensus: the concept of existential suffering

The lack of a clear and consensual definition of ES is one of the main limitations in studies on PS. In approximately 39% of the studies included in this review, it was not possible to find a definition of ES, which shows the lack of consensus on the concept. Papavasiliou et al.[23] consider psycho-existential suffering to be subjective, difficult to define, assess, and manage. For instance, the study by Foley et al.[51] defines ES as feelings of meaninglessness and a desire to control the moment of death, but this is only one of several approaches found in the literature. Van Deijck et al.[43] highlights the lack of a clear operational definition of ES as a significant limitation, noting that the lack of consensus on the concept can lead to inconsistent diagnoses, negatively impacting the validity of the results. Schur et al.[34] found a high prevalence of ES among patients with a referral for PS, but noted that the participating PC centers lacked a clear definition of 'existential distress,' which could have contributed to varying diagnoses. Similarly, Picco et al.[44] argue that refractory ES is

an entity that urgently requires an operational definition to facilitate consensus among professionals. Furthermore, Benitez-Rosario et al.[37] suggest that different interpretations of ES may be at stake, as the concept remains undefined, hindering the adequate assessment of this type of suffering.

Common constructs

Based on the definitions of ES presented in the studies included in this IR, the following most recurrent constructs were identified: lack of meaning,[26,27,34,37,52,54] hopelessness,[27,30,39–41,43,54] anxiety/fear of death,[30,39,40,51–54] loss of dignity and autonomy,[25,28,31,43,54] loneliness and isolation,[34,39,49,52,54] and feeling as a burden to others.[27,39,43,51,52,54]

Scarcity of criteria and guidelines for identifying ES and referring PS for ES

The lack of clear criteria and validated guidelines for the identification and referral, especially of refractory ES – which could require PS – is a significant limitation in clinical practice and for research. The difficulty in adequately assessing ES was a recurring theme in several studies in this IR, including those by Papavasiliou et al.,[23] Voeuk et al.,[54] and Suzzoni et al.,[46] which highlight the complexity of identifying and treating ES uniformly and effectively. In 94% of the studies included in this review, there were no clear statements on how ES was diagnosed. Studies such as the one by Picco et al.[44] emphasize that refractory ES is an entity that requires an operational definition and assessment methods that can contribute to establishing a consensus among healthcare professionals. Medical doctors have reported difficulty in classifying ES, as highlighted in the studies by Rodrigues et al.,[26,52] highlighting the need for clinical guidelines to direct this assessment. Morita et al.[27] also encourage further research with the aim of developing validated assessment methods and establishing a standard therapy for the treatment of ES in terminally ill patients.

Midazolam was the most commonly used medication for PS, being cited in several of the included studies, with varying dosages and administration routes, including subcutaneous and intravenous.

The main limitations presented by the studies included in the review reflect methodological issues. One of the most recurrent limitations was the low response rate of the participants. For instance, in the Dumont et al.[48] study, response rates ranged from 36% to 42%. In addition, the small sample size was another frequent limitation, found in the studies by Suzzoni et al.[46] and Gaignard et al.[49] Another challenge faced in retrospective studies, such as the one by Voeuk et al.,[54] was the memory bias of professionals, who may not accurately recall previous events or clinical decisions. In general, in the studies included in this IR, the reports on the medications used to perform PS, and other related information (e.g. administration routes used, etc.), were flawed and scarce, with the presentation of superficial information or even no information on these topics.

Regarding the level of evidence, 79% of the included studies were classified as level III (non-experimental studies with a quantitative or qualitative design). In terms of the quality of the evidence, only one study[52] was classified as A (high quality), all the others were classified as B (good quality) or C (low quality) (Supplementary material, Chart 4).

Discussion

Two core themes were identified in line with the aim of this review: the first is related to the challenges of applying PS to manage ES in clinical practice, and the second to the lack of consensus on the definition of ES and the referral of PS for ES. In the first theme, clinical challenges involving the referral of PS were highlighted, which were mainly influenced by the type of suffering presented by the patients. Ethical issues, such as the distinction between sedation, euthanasia, and assisted dying, as well as respect for patient autonomy, emerged as recurring concerns. In addition, professionals' training and experience influenced their behavior towards PS, highlighting the urgent need for education and clearer guidelines for the professionals. In the second theme, the lack of consensus on the concept of ES (as well as what refractory ES would be) was evident, with common constructs emerging from the definitions found in the included studies. However, the scarcity of criteria and guidelines for the identification and referral of PS for ES was pointed out as a critical limitation in clinical practice.

The influence of the type of suffering on the decision to use PS was evident[56]. The data indicate that the use of PS for managing physical symptoms, such as pain, dyspnea, and delirium, is widely accepted.[20–22] However, ES is often regarded as an insufficient indication for sedation, which may cause discomfort among healthcare professionals.[23,24] This concern is justified by the fact that, as the results of this review also suggest, there is a lack of robust evidence supporting the effectiveness of PS for refractory ES, as well as clear criteria to guide the identification of this type of suffering. The absence of adequate guidelines to assist healthcare professionals in the proper application of PS in these cases may also lead to uncertainty, as highlighted by Rietjens et al.,[30] who notes that the recommendations for continuous deep sedation do not always align with the reality of physicians' experiences and opinions. Furthermore, there is a risk that patients may

experience an uncomfortable death if sedation is not properly managed, raising concerns about the quality of care provided.[57]

The literature points to ethical concerns among healthcare professionals regarding PS, especially in relation to its use for ES[58]. These concerns are due to PS being regarded as a practice equivalent to euthanasia or assisted dying. This same concern was found in a scoping review carried out on PS conducted at home.[59] PS differs from euthanasia in terms of objective, methods, outcome, and timing.[60] Surges et al.[1] states that 'the aim of palliative sedation is to relieve refractory suffering, not to shorten life'. Thus, the expected outcome in PS is reduced consciousness. As for euthanasia and assisted dying, their aim is to interrupt the patient's life and the expected outcome is death. However, even though these are different interventions with different purposes, there are reports of PS being used with the aim of shortening the patient's life – which would be characteristic of euthanasia and assisted dying.[40,61] PS, euthanasia, and assisted dying are ethically intertwined, which can spark a debate over their similarities and differences.[62] In places where euthanasia is illegal, such as the UK, medical doctors are likely to highlight the distinctions between the two practices (for instance, in terms of the expected outcome: lowering of the level of consciousness in the case of PS and death). In contrast, in countries such as Belgium and the Netherlands, where euthanasia is legal, PS is regarded as one of the options in the end-of-life care continuum.[62] Some argue that PS is morally preferable to euthanasia, meeting similar needs without raising the same consent issues. However, others see the two practices as ethically continuous, suggesting that they should be treated similarly, which can lead to skepticism among those opposed to euthanasia.[62] Although related, PS entails its own ethical complexities that should be addressed separately from euthanasia.[62] Another ethical aspect of the use of PS concerns patient autonomy. Autonomy is a key issue in medical ethics, particularly in the context of PS. This raises questions regarding patient choice and informed consent. Factors such as diminished capacity, vulnerability, and asymmetry of knowledge between patients and medical doctors can threaten decision-making voluntariness.[62] PS should only be used if it is in line with the patient's autonomous plans for their life, emphasizing the importance of understanding the patient's long-term values and preferences.[62]

The training and experience of professionals influence their stances on PS. Furthermore, the need for adequate education and guidelines for professionals to practice PS, as well as the lack of consensus on the definition of ES and the criteria for its diagnosis, is recurrent in the literature. Professionals trained in PC are more inclined to use PS in complex cases and to support its application in ES situations. The lack of adequate training for medical doctors in PS favors the underutilization of this practice when it is recommended, and its inadequate use in non-refractory cases. Morita et al.[29] showed that medical doctors who are less specialized in PC are more likely to select sedation instead of exploring more suitable alternatives according to the case, especially in patients with potentially treatable psychiatric conditions, which may raise concerns regarding the inadequate use of PS. On the other hand, the fact that PS is considered by some to be 'slow euthanasia' may lead medical doctors to be 'extremely careful' regarding the underutilization of sedative medication dosages.[56,63] In a Dutch study carried out with nurses, sedation was considered insufficiently effective by 42% of respondents.[64]

In 39% of the studies included in this review, the definition of ES was not found, and in 95%, what criteria were used to identify ES were not found. ES, as a multifaceted construct that encompasses the psychological and spiritual dimensions, entails feelings of death anxiety, loss of meaning and purpose, isolation and loneliness, a sense of loss of control, among others, which are exacerbated by the experience of living with a severe illness.[65] The lack of consensus on the definition of ES, especially refractory ES, and clear criteria for its diagnosis compromises not only the identification of the condition itself, but also the selection of adequate interventions[58]. This lack of consensus can have significant clinical implications for end-of-life care, compromising the effective assessment and management of patients' needs. The creation and implementation of specific clinical guidelines on PS for refractory ES are vital to ensure that professionals can conduct treatment ethically and safely, avoiding controversial practices. In this context, the European Association for Palliative Care (EAPC) initiative stands out, which, through the publication of the Revised EAPC Recommended Framework on Palliative Sedation,[1,66] aims to promote best practices related to PS, including the management of refractory ES. This document offers evidence-based guidelines and consensus for healthcare professionals engaged in the care of adult patients with life-limiting illnesses, in all care settings, as well as guiding medical associations and healthcare policy makers.[1,66]

It is worth noting that midazolam was the most commonly used medication for PS, which indicates its preference among professionals to achieve the levels of sedation needed to manage physical and existential suffering. Midazolam is a benzodiazepine widely used in PC and is considered essential for

quality care in terminally ill patients.[67] It acts on the benzodiazepine receptor, intensifying the action of gamma-aminobutyric acid, which confers sedative, anxiolytic, and anticonvulsant properties.[67] With its brief onset of action and short duration, midazolam allows greater dosage flexibility compared to other benzodiazepines.[67] However, Gabl et al.[68] highlight the fact that since ES is a multidimensional experience that is prone to turning into despair and, ultimately, a desire to die due to the perception of hopelessness and meaninglessness, pharmacological treatment, or even sedation, are unable to meet the holistic needs of those suffering from ES.

Finally, the main limitations of the studies reviewed in this IR include the low response rate and the small sample size, which limits the generalizability of the findings. In addition, the retrospective studies suffered recall bias, compromising the accuracy of the data reported. The lack of details on the medications used and the therapeutic regimens applied is another relevant limitation, indicating the need for increased rigor in the collection and, above all, reporting of clinical data. The absence of such data compromises the replication of studies and hinders the full interpretation of interventions. These limitations highlight the need to improve the design of the studies and the quality of the data reported, with the aim of strengthening conclusions on the use of PS to manage refractory ES.

Although robust evidence from meta-analyses and randomized controlled trials is essential for evidence-based practice, which guides decision-making in clinical practice, it is necessary to recognize that carrying out studies with such designs can be challenging in the context of end-of-life patients. Conducting clinical trials on PC patients involves ethical and logistical challenges. Although several patients with advanced diseases wish to participate in studies, it is their decision, whenever possible, to participate. Mild cognitive impairment should not automatically exclude participation, and the use of simplified consent or legal representatives can be an ethical alternative.[69,70] Finally, well-conducted randomized clinical trials remain the preferred approach to answering causal questions.[71] However, considering the advancements in the method for observational studies, Dahabreh et al.[71] argue that causal interpretations of the results of this type of study, when well conducted, may be possible when there are strong assumptions. Maltoni et al.,[72] from the results of their systematic review on the clinical practice of PS to assess the effect of this practice on patient survival, indicate that, even in the absence of direct evidence from randomized clinical trials, PS, when adequately referred and correctly used to relieve unbearable suffering, does not seem to have a detrimental effect on the survival of terminally ill cancer patients.

Limitations

Although the number of studies included in this IR is representative, the review may not have covered all the relevant publications on the subject, especially considering the methodological and cultural variations in the practice of PS for ES. Furthermore, the search strategies used can be interpreted as a limitation, considering the possibility of not including terms/keywords relevant to the theme under study. Another limitation concerns the failure to search for materials in the gray literature, but it should be noted that this did not breach the methodological framework adopted for this review.

Conclusion

The use of PS in the management of refractory ES is still a practice surrounded by clinical and ethical challenges. PS is widely accepted for relieving refractory symptoms such as pain, dyspnea, and delirium, while its use for ES remains controversial. Healthcare professionals are reluctant to apply PS exclusively for ES, preferring to exhaust psychological, spiritual, and psychiatric interventions before resorting to sedation. In addition, ethical concerns, especially regarding the distinction between PS, euthanasia, and assisted dying are common among these professionals. The concerns regarding the use of PS for ES by healthcare professionals are legitimate, considering the lack of robust evidence showing the efficacy of PS for refractory ES, as well as clear guidelines to advise these professionals on the definition of refractory ES, how to identify it, and how to use PS in these cases. In addition, healthcare professionals' training and experience in PC influence decision-making, suggesting that the education and training of these professionals are essential to ensure the adequate practice of PS.

In light of this, we recommend the development of more robust guidelines and carrying out additional studies to clarify the adequate management of refractory ES in end-of-life patients, from diagnosis to the evaluation of the interventions implemented. Studies that provide a better understanding of ES, with the aim of establishing a consensus on the concept, are also necessary.

Declaration on the use of Generative AI

All text in the manuscript was written by the authors, and no sections were copied directly from ChatGPT-generated text.

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