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Midazolam in Palliative Care Practice: Indications, Safety and Role in Palliative Sedation.

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Abstract

Background: Palliative medicine is a field of medical practice focused on improving the quality of life of patients by alleviating pain and other somatic and psychological symptoms in the advanced, incurable stage of disease. In cases of symptoms refractory to standard treatment, palliative sedation may be employed, defined as the controlled reduction or loss of consciousness through the use of sedative medications, most commonly benzodiazepines, including midazolam.

Objectives: The aim of this study was to present the current state of knowledge regarding the use of midazolam in palliative care, with particular emphasis on its role in palliative sedation and the associated ethical controversies.

Methods: This study is a review and was developed based on an analysis of the available literature concerning the pharmacological properties of midazolam, its clinical applications, and its safety profile in palliative care.

Conclusions: Due to its pharmacological properties, midazolam is widely used in palliative care and plays a key role in the relief of symptoms in patients at the end of life. Its use in palliative sedation enables an effective and ethically justified reduction of suffering in patients in the terminal stage of disease.

Keywords: midazolam, palliative sedation, palliative care, ethical aspects

Introduction

Palliative care constitutes a crucial component of the healthcare system, providing comprehensive support to patients suffering from incurable and life-limiting diseases. It is a branch of medicine aimed at improving the quality of life of patients and their families by

preventing and alleviating suffering resulting from disease symptoms and their consequences. The approach used in palliative care is holistic, addressing not only the treatment of somatic symptoms but also the psychological, social, and spiritual needs of the patient. Particular emphasis is placed on preserving patient dignity, ensuring the highest possible comfort, and supporting family members throughout the course of illness and dying. Palliative care primarily encompasses patients with chronic, progressive diseases that are refractory to causative treatment or resistant to available therapeutic methods [1]. These are most commonly individuals in advanced stages of cancer, but also patients with other conditions that progressively impair health and shorten life expectancy [2,3].

Despite significant advances in symptomatic treatment and the development of modern supportive therapies, some patients- especially in the terminal phase of disease- do not achieve satisfactory control of certain symptoms. The most common and burdensome among these include severe pain, dyspnea, psychomotor agitation, and pronounced psychological distress. These symptoms can lead to substantial physical and psychological suffering, significantly deteriorating the patient's quality of life in the final stage of life. In situations where standard symptomatic therapies prove ineffective or insufficient, the care team may consider palliative sedation as a last-resort intervention [4].

Palliative sedation is defined as the controlled administration of medications that reduce, and in some cases completely eliminate, patient consciousness to alleviate intractable suffering from symptoms resistant to treatment [5]. This procedure should be applied proportionally to symptom severity and in accordance with medical ethics, taking into account the patient's wishes, family input, and the recommendations of the medical team. Palliative sedation is a complex intervention, both clinically and ethically, and its use requires proper preparation of healthcare personnel and clear procedural guidelines.

In response to the need to standardize clinical practice, the European Association for Palliative Care (EAPC) developed framework guidelines for palliative sedation in 2009, which have been updated in recent years based on a review of current literature and a Delphi process involving international experts in palliative medicine [6]. According to these guidelines, palliative sedation is recognized as an important and ethically acceptable medical intervention in specific cases for patients in the terminal phase of life when other symptomatic treatments are ineffective.

The frequency of palliative sedation in clinical practice is highly variable. Reported rates in studies range from approximately 1% to 88%, reflecting considerable differences in

definitions and clinical practice across centers and countries. Globally, it is estimated that around 20–30% of patients in the final phase of life receive palliative sedation [7]. The most common indications include uncontrolled pain, dyspnea, delirium, and severe psychological distress.

Among the medications used for palliative sedation, midazolam occupies a particularly prominent role. It is a short-acting benzodiazepine with sedative, anxiolytic, anticonvulsant, and hypnotic properties. Midazolam is widely recognized as a first-choice agent in many palliative sedation protocols due to its rapid onset of action, short half-life, and suitability for continuous subcutaneous or intravenous infusion, allowing flexible dose adjustment according to the patient's clinical condition. The aim of this review article is to present the current state of knowledge regarding the use of midazolam in palliative care, with a particular focus on its pharmacological properties, safety profile, and potential adverse effects. Additionally, selected ethical aspects related to the procedure of palliative sedation will be discussed, which play a significant role in clinical decision-making for patients at the end of life.

Methods

A narrative literature review was conducted to evaluate the use of midazolam in palliative care, with particular emphasis on its role in palliative sedation. A structured search was performed using the PubMed database. Publications from the past sixteen years (2009–2025) were considered. The following keywords and combinations were used: "midazolam", "palliative care", "palliative sedation", and "ethics".

Articles were included if they addressed the clinical use, pharmacology, safety, or ethical aspects of midazolam in palliative care. Both original studies and review articles published in English or Polish were considered. Case reports and non-peer-reviewed sources were excluded. Priority was given to the most recent and clinically relevant publications.

Pharmacological Profile of Midazolam

Midazolam is a short-acting benzodiazepine with pronounced sedative, hypnotic, anxiolytic, and anticonvulsant properties. Its mechanism of action is associated with the modulation of GABAergic transmission in the central nervous system. The substance enhances the effect of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) by interacting with the GABA type A receptor complex [8]. This leads to an increased frequency of chloride channel opening, resulting in neuronal hyperpolarization and

inhibition of electrical activity. Chemically, midazolam belongs to the benzodiazepine derivatives and is characterized by a benzene ring fused to a seven-membered diazepine ring. In benzodiazepine structures, the presence of an electronegative halogen substituent at position 7 of the benzene ring plays a crucial role in mediating the sedative and hypnotic effects of this class of drugs [9].

In addition to its sedative effect, midazolam exhibits anticonvulsant and muscle-relaxant properties, resulting from its inhibitory influence on neuronal conduction in the central nervous system. One important pharmacological feature of midazolam is its relatively high lipophilicity, which allows rapid penetration across the blood–brain barrier. Consequently, the drug has a rapid onset of action- the sedative effect typically appears within approximately 1.5–15 minutes following a single intravenous or intramuscular dose [10]. The elimination half-life of midazolam averages 1.5–3 hours, while the clinical duration of effect is estimated at approximately 60–120 minutes. Benzodiazepines, including midazolam, readily cross the blood–brain barrier and the placenta, and may also be excreted in breast milk. Therefore, their use during pregnancy carries potential fetal risk and has been classified as FDA pregnancy category D [11].

Midazolam can be administered via multiple routes, increasing its utility in clinical practice. Depending on the indication, it may be given as boluses or continuous infusion intravenously, intramuscularly, or subcutaneously. Oral, buccal, intranasal, and rectal administration are also possible, which is particularly relevant when intravenous access is difficult or impossible. The volume of distribution of midazolam is approximately 1–2.5 L/kg and may be increased in elderly patients and those with obesity due to enhanced drug distribution into adipose tissue [9]. Midazolam is primarily metabolized in the liver by cytochrome P450 enzymes, mainly CYP3A4 and CYP3A5 isoenzymes. This process produces the main metabolite, 1-hydroxymidazolam, which is subsequently conjugated with glucuronic acid. Metabolites are mainly excreted in urine, with only a small fraction of the drug (approximately 0.03%) eliminated unchanged. About 63–80% of the administered dose undergoes glucuronidation, and the metabolites are excreted within 24 hours. It is also noteworthy that genetic polymorphisms in CYP3A4 and CYP3A5 enzymes can affect the rate of midazolam metabolism, leading to interindividual variability in treatment response, including the intensity of sedation [12].

Due to its pharmacokinetic and pharmacodynamic properties, midazolam is widely used in palliative medicine as a first-choice agent for palliative sedation. Its rapid onset,

relatively short half-life, and suitability for continuous infusion allow precise titration of sedation according to the patient's needs.

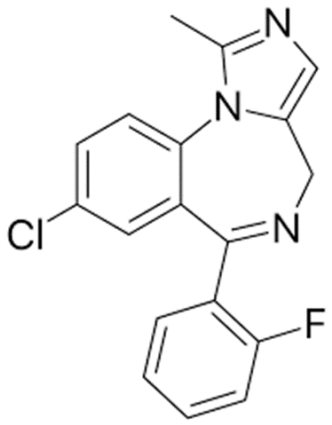

Figure 1. Chemical structure of midazolam (source: PubChem).

Midazolam Dosing in Palliative Sedation

The dosing regimen of midazolam in palliative sedation depends on the desired level of sedation and the individual clinical condition of the patient. Therapy typically begins with an initial bolus dose. For light palliative sedation, it is recommended to administer 2.5 mg subcutaneously or 1.25 mg intravenously. When a deeper level of sedation is required, doses of 5–10 mg subcutaneously or 2.5–5 mg intravenously are used [13].

If necessary, a bolus dose equal to half of the initial dose may be repeated after approximately 20 minutes for subcutaneous administration or 5 minutes for intravenous administration. In clinical practice, two to three additional bolus doses are often given during the first few hours of sedation to achieve the desired therapeutic effect.

Once a stable level of sedation is achieved, a maintenance dose is administered via continuous infusion, typically starting at approximately 1 mg/h, either subcutaneously or intravenously. The dose should then be individually adjusted according to the patient's clinical response and the degree of symptom control [13].

In patients with factors that increase the risk of adverse effects- such as age over 60 years, body weight below 60 kg, severe hepatic or renal impairment, significant hypoalbuminemia, or concomitant use of drugs that potentiate sedation- it is recommended to start therapy at half of the standard initial dose. In such cases, extending the interval before potentially increasing the maintenance dose to approximately 6–8 hours is also advisable to reduce the risk of excessive sedation and respiratory depression [13].

Indications for Palliative Sedation

Palliative sedation is a therapeutic intervention used in the care of patients with advanced-stage disease who present with symptoms refractory to standard symptomatic treatment. In clinical practice, several types of palliative sedation are distinguished depending on its duration and the depth of consciousness reduction. One fundamental classification differentiates between temporary (intermittent) sedation and continuous sedation. Temporary sedation, usually lasting up to approximately 48 hours, is applied to provide the patient with short-term relief of consciousness and allow rest in the presence of severe symptoms. It can also serve as a transitional measure, providing time for other concurrently administered symptomatic treatments to take effect. In contrast, continuous sedation is maintained until the end of the patient's life and is used in cases of particularly severe symptoms that do not respond to any other available therapeutic options [6,14]. According to current guidelines, palliative sedation should be considered only in the presence of so-called refractory symptoms, defined as symptoms that cannot be effectively controlled despite the use of optimal and adequate therapeutic methods without imposing excessive burden or adverse effects on the patient. The most common clinical indications for palliative sedation include severe pain, intractable dyspnea, persistent delirium with psychomotor agitation, and seizures resistant to pharmacological treatment [15,16].

In clinical practice, palliative sedation may also be considered in particularly dramatic situations, such as sudden deterioration of the patient's condition or the occurrence of symptoms causing extreme physical or psychological suffering. Such situations include, for example, massive hemorrhages from the respiratory or gastrointestinal tract, which can occur in patients with advanced cancers, such as laryngeal or lung cancer. In these cases, palliative sedation aims not only to alleviate the patient's suffering but also to reduce associated severe anxiety and the sense of imminent threat to life. The decision to initiate palliative sedation should be made with great caution and preceded by a thorough clinical assessment of the patient. It is recommended that the qualification process for this procedure be carried out by a qualified and experienced care team, preferably multidisciplinary. The team should include physicians, nurses, and, whenever possible, psychologists or other specialists involved in palliative care. The involvement of a physician specializing in

palliative medicine, experienced in managing refractory symptoms and conducting palliative sedation, is particularly important [6,14].

When making the decision to initiate sedation, the patient's wishes, prior treatment preferences, and- in cases where communication is not possible- the opinions of family members or caregivers should also be considered. Transparent communication between medical staff and the patient's family plays a key role in ensuring understanding of the therapy's objectives and in minimizing potential ethical concerns associated with the procedure [15].

Use of Midazolam in Palliative Medicine for Other Indications

Due to its broad pharmacological spectrum, midazolam is widely used for symptomatic management in patients receiving palliative care. Beyond its application in palliative sedation, midazolam is employed in the treatment of numerous symptoms that are difficult to control with standard therapies. The most important indications include refractory dyspnea, seizures, agitation associated with acute delirium, insomnia, as well as less common symptoms such as hiccups, pruritus, or muscle spasticity [9,16].

Dyspnea

Dyspnea is a subjective experience of breathing discomfort and represents one of the most common and burdensome symptoms in palliative care. It occurs in approximately 10–70% of patients with cancer, 60–95% of patients with chronic obstructive pulmonary disease (COPD) or heart failure, and nearly 100% of patients with amyotrophic lateral sclerosis (ALS) in the terminal phase. Dyspnea causes significant discomfort, severe anxiety, fatigue, and exacerbates patients' psychological and spiritual suffering. The primary pharmacological therapy for dyspnea in palliative care remains opioids, particularly morphine, which effectively alleviates the perception of breathlessness by modulating central respiratory drive and the anxiety component. Clinical studies have shown that adding midazolam to standard morphine therapy improves symptom control in patients whose dyspnea is refractory to morphine alone. This effect is likely related to midazolam's sedative properties, anxiety reduction, and influence on central perception of respiratory discomfort [16,19].

Seizures

Midazolam is also the most frequently used drug for the acute termination of seizures, both in terminally ill cancer patients and in individuals with other neurological conditions. Its advantages include rapid onset of action, multiple routes of administration (intravenous, subcutaneous, buccal, intranasal, and rectal), and a short half-life, allowing flexible adjustment of therapy according to the patient's clinical status [16].

Agitation and Delirium

Agitation associated with acute delirium is another indication for midazolam in palliative care. Delirium can occur in advanced stages of cancer, organ failure, or as a side effect of medications. Midazolam, due to its sedative and anxiolytic properties, enables rapid reduction of psychomotor agitation, improving patient comfort and safety of care [16,19].

Other Indications

The literature also describes the effectiveness of midazolam in alleviating symptoms such as refractory hiccups, pruritus, and muscle spasticity. Although evidence mainly comes from case reports and observational studies, clinical observations suggest that midazolam can provide valuable support in managing less common symptoms, particularly in patients for whom other interventions have failed [18].

In summary, midazolam is a versatile drug in palliative care. Its pharmacological profile and flexible routes of administration allow its use across a wide range of difficult-to-treat symptoms, contributing to improved patient comfort and overall quality of palliative care.

Safety and Adverse Effects of Midazolam

Midazolam is a relatively safe drug, and most adverse effects occur infrequently, particularly when used short-term at standard doses. The most commonly observed side effect is drowsiness, which in the context of palliative care often coincides with the intended

sedative effect. Nevertheless, administration of midazolam carries the risk of other adverse effects, especially in patients at higher risk, such as older adults, those with chronic hepatic or renal impairment, and patients with cardiovascular disorders, in whom drug accumulation may occur [9,19]. The risk of adverse effects is also increased when midazolam is combined with other central nervous system depressants, including other benzodiazepines, opioids, or sedative medications. In such cases, excessive sedation may occur, and in extreme situations, respiratory depression is possible [20]. Therefore, particular caution is advised, especially during intravenous administration or continuous subcutaneous infusion.

In palliative care, the benefits of midazolam- such as alleviation of pain, anxiety, dyspnea, or psychomotor agitation- generally outweigh the potential risks of adverse effects. Nevertheless, each case should be considered individually, and doses should be adjusted according to the patient's age, body weight, organ function, and concomitant medications [9,19]. The main adverse effects of midazolam include:

- excessive drowsiness and sedation
- disorientation and difficulties with concentration
- dizziness, increased risk of falls and injuries, including fractures
- speech and visual disturbances (e.g., diplopia)
- nausea and vomiting
- memory impairment, including retrograde amnesia and difficulties in forming new memories [20]

Adverse effects are usually reversible upon dose reduction or discontinuation of the drug. In clinical practice, patient monitoring includes assessment of sedation level, respiratory parameters, hemodynamic status, and renal and hepatic function. Careful observation is particularly important during the first hours following a bolus dose or initiation of continuous infusion, when the risk of excessive sedation and respiratory depression is greatest.

In summary, midazolam has a relatively favorable safety profile in palliative care, and its use in controlled doses with appropriate monitoring is effective and well-tolerated. Awareness of potential adverse effects and risk factors allows optimization of therapy and minimization of complications while maintaining high-quality patient care.

Ethical Considerations in Palliative Sedation

The use of palliative sedation is associated with numerous ethical controversies that arise among patients and their families, as well as within the medical community. One of the most frequently raised issues is the need to clearly distinguish this procedure from euthanasia, as well as concerns regarding the potential impact of palliative sedation on patient survival [18,19]. Available scientific data on the effect of palliative sedation on patient survival remain inconclusive. Some studies suggest the possibility of life-shortening effects, while others indicate no impact or even potential prolongation of life. However, it should be emphasized that most available analyses are subject to significant methodological limitations, such as heterogeneity of study populations, lack of randomization, and difficulties in controlling confounding factors. Conducting a randomized, double-blind trial in this context would be ethically unacceptable, further limiting the acquisition of definitive scientific evidence [19,20].

In the context of potential effects on life expectancy, particular reference should be made to the classical ethical principle of double effect. According to this principle, an action undertaken to achieve a morally good outcome- in this case, alleviation of patient suffering- can be considered ethically permissible even if it carries a possible, unintended side effect, such as potential shortening of life. The condition, however, is that the action is not aimed at producing the negative effect and that there is proportionality between the intended therapeutic goal and the risk of adverse outcomes [21].

A key issue in the ethical discussion is also the distinction between palliative sedation and euthanasia. These procedures differ in both their purpose and the means employed. The aim of palliative sedation is to relieve suffering through controlled reduction of patient consciousness while maintaining proportionality and individualized dosing [18]. In clinical practice, sedative medications- primarily benzodiazepines- are titrated gradually according to the patient's clinical response. In contrast, the purpose of euthanasia is the direct termination of life through administration of lethal doses of pharmacological agents, such as muscle relaxants or potassium chloride. Unlike palliative sedation, euthanasia is intentional, and its primary aim is to end life, which constitutes a fundamental ethical difference between the two procedures [19,21].

Respect for patient autonomy is another crucial element in the ethical application of palliative sedation. Decisions regarding its implementation should, whenever possible, incorporate the informed consent of the patient, their values, beliefs, and prior treatment preferences. When the patient is unable to express their wishes, communication with family members or caregivers and acting in the patient's best interest are essential [18,20].

Equally important is proper communication between the healthcare team and the patient's family. Requests for euthanasia should be treated as important signals of suffering and a starting point for a deeper assessment of the patient's needs, including inadequate symptom control, anxiety, or psychosocial issues. The appropriate response from the care team should include intensification of palliative and psychological support, rather than fulfilling a request to end life [18,22]. Despite ongoing controversies, often stemming from misunderstandings of the nature of palliative sedation, the procedure is considered ethically acceptable and constitutes an important component of care for patients in the terminal phase of illness. Its primary goal remains the provision of maximal comfort and respect for patient dignity at the end of life. In this way, palliative sedation aligns with fundamental principles of medical ethics, such as beneficence, non-maleficence, and respect for patient autonomy.

Conclusions

Midazolam plays a key role in palliative care, representing one of the primary drugs used for symptomatic management in patients with advanced, incurable diseases. Its pharmacological properties- such as rapid onset of action, short half-life, multiple routes of administration, and predictable effect profile- make it particularly useful in this patient population.

As the underlying disease progresses, both somatic and psychological symptoms intensify, significantly reducing patients' quality of life and causing substantial physical and existential suffering. In cases refractory to standard symptomatic treatment, palliative sedation with midazolam remains an effective method for alleviating suffering in the terminal phase of life.

The use of palliative sedation should always be considered a last-resort intervention, implemented only after other available therapeutic options have been exhausted. Individualized clinical decision-making is essential, taking into account the patient's condition, preferences, and values, as well as close collaboration with the family and care team. Ensuring therapy safety through appropriate patient monitoring and careful dose titration is also a critical component.

Despite existing controversies, palliative sedation is regarded as an ethically permissible and integral part of modern palliative care. Its overarching goal remains to provide the patient with maximum comfort and to respect their dignity at the end of life.

Disclosure

Author's Contribution

Conceptualization: Maciej Stodulski

Formal analysis: Maciej Stodulski, Marta Zdunek

Investigation: Maciej Stodulski

Writing rough preparation: Maciej Stodulski, Marta Zdunek

Writing review and editing: all authors

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