



The use of methadone in Italian hospices: an updated survey

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Background: Methadone is a valuable drug for pain management but its use in palliative care settings is still challenging. The primary objective of this study was to take an in-depth look at the clinical use of methadone in specialized palliative care settings in Italy.

Methods: A register of all active hospices in Italy at the time of the study was created by consulting the websites of the National Agency for Regional Health Services (Agenas) and the Italian Federation of Palliative Care (Federazione Cure Palliative). A telephone survey composed of an 18-item questionnaire was then carried out with a member of staff of each facility about the period between January and August 2023. A descriptive, non-statistical comparison was made between the results of the present survey and those obtained from a similar survey carried out in 2013.

Results: Of the 275 hospices active at the time of the telephone survey, 160 (58%) responded to the questionnaire and 81 of them (51%) confirmed using methadone in their clinical practice. Questionnaire responses revealed that the perception of operators with regard to methadone has gradually shifted towards a greater appreciation of its strengths compared to the potential difficulties encountered in its use. In fact, the use of methadone increased over a 10-year period from 28% in 2013 to 51% in 2023.

Conclusions: The results of the present study highlighted a considerable variability in the use of methadone in clinical practice, in line with literature data. Its use has substantially increased in recent years, but appropriate training of palliative care professionals is still needed to ensure its safe and effective management.

Keywords: Palliative care; pain medication; methadone; cancer pain; opioids

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Introduction

Methadone is a synthetic opioid with potent agonist activity on mu, delta, and kappa opioid receptors (1-3). Its high affinity for mu receptors, central to supraspinal analgesia,

and delta receptors, important for spinal analgesia, has led to its recommendation as an analgesic for cancer-related pain (2). Additionally, methadone's antagonism of N-methyl-D-aspartate (NMDA) receptors contributes to reducing nociceptive pain, particularly in hyperalgesic

states (1). It also inhibits serotonin and norepinephrine reuptake in the central nervous system.

Methadone's unique properties include high oral bioavailability (>85%), excellent absorption, lack of active metabolites, and incomplete cross-tolerance with other opioids (4). Its lipophilicity and strong binding to plasma proteins, particularly alpha 1-acid glycoprotein, contribute to its pharmacokinetics. It is metabolized in the liver and intestinal wall and eliminated via urine and feces, making it suitable for patients with renal failure (2,5,6). However, its use is generally discouraged in severe acute liver failure due to a lack of specific dosing guidelines (7).

Despite its benefits, methadone's clinical use is limited by its long and unpredictable half-life, significant interindividual pharmacokinetic variations, delayed toxicity, and unclear dosing intervals. Rapid dose increases can lead to respiratory depression, necessitating careful monitoring during initiation and titration. Common side effects include constipation, drowsiness, nausea, vomiting, and sedation, along with potential QT prolongation that may lead to arrhythmias such as torsades de pointes (7,8).

Even if some studies suggest that methadone is more manageable as a first-line analgesic treatment, potentially

improving cancer patients' quality of life (9,10), methadone is primarily employed in opioid rotation to manage poor pain control, toxicity-related side effects from other opioids, hyperalgesia, or refractory pain (11,12). Two main rotation methods are used: the "stop and go" (SAG) approach, which involves an immediate switch to methadone, and the "3-day switch" (3DS), where the previous opioid dose is gradually reduced while methadone is introduced incrementally over three days to minimize toxicity risk (13).

In Italy, hospices are residential palliative care facilities regulated by the National Health Service or non-profit organizations. They are staffed by multidisciplinary teams—including physicians, nurses, psychologists, and social workers—and offer 24/7 care.

To our knowledge, the most recent national survey on methadone use in Italian hospices was conducted by Mercadante *et al.* in 2013 (14), only three years after the implementation of Law 38/2010—a law aimed at guaranteeing access to palliative care and pain management in Italy (15).

The aim of this study is to investigate current methadone use in clinical practice within Italian hospices, with a particular focus on providing an update by comparing the findings with those of the 2013 survey, in order to assess how prescribing practices have evolved, in particular after a decade from Law 38/2010. We present this article in accordance with the STROBE reporting checklist (available at <https://apm.amegroups.com/article/view/10.21037/apm-25-46/rc>).

Methods

We consulted the lists and geo-maps of hospices according to region, available on the AGENAS (National Agency for Regional Health Services) website (16), and the register of hospices on the website of the Federazione Cure Palliative (Federation of Palliative Care) to compile a register of all the hospices in Italy (17). A survey was conducted via a structured telephone questionnaire with a designated member of the medical staff at each facility. If the initial call was unanswered or the staff member was unavailable due to urgent commitments, two follow-up attempts were made. Since the study focused exclusively on hospice settings, no stratification by practice type was necessary. The sampling strategy was therefore designed to achieve national coverage within a single, homogeneous care setting. The survey, targeting the period from January to August 2023, comprised 18 items organized into two sections. The

Highlight box

Key findings

- The study shows an increase in the use of methadone in Italian palliative care hospices over the last 10 years (from 28% in 2013 to 51% in 2023). Despite this growth, there remains wide variability in its clinical application, and expert involvement is still considered essential for safe and effective use.

What is known and what is new?

- Methadone is a synthetic opioid with valuable properties in pain management, especially in complex pain and opioid rotation. However, its use in clinical practice has traditionally been limited due to concerns about its pharmacokinetics, risk of accumulation, and the need for specialized knowledge to use it safely.
- This manuscript provides updated, nationwide data on methadone use in Italian hospices, demonstrating an increased acceptance and usage among clinicians. It also shows a shift in perception: operators now express greater confidence in its clinical value, compared to ten years ago.

What is the implication, and what should change now?

- The findings underline the need for standardized guidelines and structured training to support clinicians in the proper use of methadone. The observed variability in practice suggests that further education and expert support are critical to ensuring safe and effective implementation across settings.

questionnaire was adapted from the one used in the 2013 study by Mercadante *et al.* (14), with some modifications to reflect changes in clinical practice and regulations, and to enhance clarity. The first section collected general information about the respondent (e.g., demographic details, professional qualifications, and experience in palliative care) and the facility (e.g., years of activity as a hospice and average annual patient admissions). The second section focused on the utilization of methadone.

Data obtained in this last section of the questionnaire represent estimates provided by hospice staff and are not based on a systematic analysis of patient clinical records; the responses are considered to reflect institutional policies and common practices rather than individual opinions. The questionnaire used for the survey is reported in *Table 1*. For hospices not using methadone, respondents were asked to indicate one main reason for its exclusion from clinical practice. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. Since the research involved only healthcare professionals and not patients, ethical approval was not required. Participation in the survey was voluntary, and all responses were collected anonymously.

Statistical analysis

To explore potential relationships between organizational experience and methadone use, we conducted a set of exploratory analyses. Specifically, we used Spearman's rank correlation to examine monotonic association between years of operation and perceived difficulty, the Mann-Whitney *U* test to compare difficulty scores between users and non-users of methadone, and the Chi-square test of independence to assess the association between years of operation and methadone use.

Statistical analyses were performed using Microsoft Excel 2016 and Python version 3.8, with the SciPy library (version 1.10.1) employed for statistical testing.

During the preparation of this manuscript, the authors used ChatGPT (OpenAI) to assist with language editing and improvement. The authors reviewed and edited the content as needed and take full responsibility for the final text.

Results

Based on the information gathered from Agenas and the Federazione di Cure Palliative websites, 307 hospices were

identified across Italy. Of these, 8 were exclusively pediatric and were therefore excluded from the survey. Additionally, two were listed twice and were therefore counted only once, resulting in a total of 297 adult hospices in Italy.

Of these, excluding the 23 hospices that were no longer operational, the 3 ones closed during the COVID-19 pandemic, the 8 ones misclassified as hospice and the 2 ones with phone numbers not active, the working hospices for adults during the survey period in Italy were 275. Of the 275 hospices 115 did not respond to the telephone survey, information was thus obtained for 160 (58%) facilities. One hundred and thirty-six were medically managed and 7 were nurse-managed. It was not possible to obtain this data for the remaining 17 facilities.

In 97% of cases, the operator interviewed was the Director of the hospice or a doctor delegated by him. The interviewed operator was not a doctor in 5 cases (3%), in particular 4 were nurses and one was an administrative director. The clinical background of the interviewed physicians included palliative care (*n*=51), oncohematology (*n*=40), internal medicine and related subspecialties (*n*=31), anesthesiology (*n*=20), general practice (*n*=5), and other fields (*n*=6).

The average number of years' experience working in hospices was 10.7 (range, 2 months–32 years), while the average age of staff was 57.0 years (range, 30–79 years). Nineteen hospices had been operating for less than 5 years, 27 had been operating >5 years and <10 years, 48 between 10 and 15 years, and 61 hospices >15 years. This information was not available for 5 facilities.

With regard to the average number of admissions per year, 18 hospices admitted <100 patients each year, 48 hospices admitted >100 and <200 patients, 34 hospices reported >200 and <300 admissions, and 13 hospices admitted >300 patients. Data on the average annual patient volume were not available for 47 facilities.

With regard to the perception of difficulty in using methadone for pain management on a scale from 0 (extremely easy) to 10 (extremely difficult) 34 survey responders (21%) gave a 0–3 rating, 61 (38%) gave a 4–6 rating, while 51 (32%) gave a 7–10 rating. Fourteen staff members (9%) did not answer the question (specific rating numbers for each survey responder are shown in *Figure 1*).

With regard to the use of methadone, 81 (51%) of the 160 facilities that answered to the telephone survey reported using the drug in clinical practice, while 79 (49%) did not. Of these 7 nurses-led hospices, only 1 reported using methadone, while 1 did not provide an answer and

Table 1 Survey questions

Question number	Question	Options (if available)	Comments (if needed)
1	Role and job title of operator	Team doctor, nursing coordinator, hospice nurse	–
2	Specialization of interviewee and basic training	Oncologist, anesthetist, geriatrician, etc.	Ward sisters or nurses for the nursing staff
3	Years of experience in a hospice	–	This referred to the total number of years the employee had worked in a palliative care setting
4	Gender	Male/female	–
5	Age	–	–
6	The number of years the facility has been operating as a hospice	–	–
7	Average number of patients hospitalized per year and/or number of beds	–	Estimates have been influenced by clinical and organizational changes related to the Sars-Cov-2 pandemic
8	Do you think methadone is a difficult drug to use?	From 0 to 10	Quantifying the subjective difficulty of administering methadone it on a scale from 0 (very easy to use) to 10 (very difficult)
9	Do you use methadone in pain management?	Yes/no	If no, was requested to answer to question number 17
10	From January 2023 to today (August 2023), have you used methadone? If so, in how many patients?	Yes/no, if yes number of patients	–
11	What percentage of patients treated with opioids for over a year use methadone?	≤1%, >1% but ≤5%, >5% but ≤10%, >10%	–
12	Do you use methadone in vials for parenteral administration?	Yes/no	–
13	Do you use methadone as a first-line opioid? And at what doses?	Yes/no, if yes methadone doses	–
14	What dose conversion formula do you use to switch to methadone?	–	–
15	Is the switch to methadone more common for uncontrolled analgesia or for the appearance of side-effects caused by other drugs?	–	–
16	Is the switch to other analgesics more common for uncontrolled analgesia or for the appearance of side-effects from methadone?	–	–
17	Why don't you use methadone?	–	The question was asked to those who answered 'no' to question no. 9 in order to understand the main reasons behind this choice
18	Does the hospice where you work have medical or nursing management?	–	The question was asked because there are situations where the hospice is mainly managed by nursing staff, with the doctor in charge of the hospice only present for a few hours a day and not every day

The survey questions are supplemented with answer options (where present) and explanation notes.

the remaining 5 did not use it. Regional differences about use of methadone and the difficulty in using it are shown in *Figure 2*, and a table next to the maps indicates the number of hospices per region that participated in the study. Among the former, 27 (34%) reported not having used methadone in the survey period, while the remaining 54 (68%) facilities estimated to have administered the drug to between 1 and 50 patients during this period. For patients who had been receiving opioids for more than 12 months 38 (47%) hospices reported that <1% of patients were on methadone; 28 (35%) facilities estimated to use the drug in >1% and <5% of patients; and 13 (16%) facilities in >5% and <10%. Only 2 (2%) facilities reported administering the drug in >10% of patients.

Among the 81 hospices using methadone in clinical practice, 20 (25%) also reported using methadone intravenously, and 9 (11%) administered methadone as a first-line treatment. Although there was variability in the starting dosage, the initial dose never exceeded 10 mg during the first 24 hours.

A high variability was found in the response to the question about the conversion dose when switching from other analgesic medications to methadone. All interviewed staff reported rotating patients to methadone based on the equivalent oral morphine dose (DEMO) and then proceeding with a dose conversion following different proportions depending on the reference formula used. With regard to the main reasons for rotation to methadone, 57 (70%) of the 81 facilities switched to methadone therapy primarily for uncontrolled pain management; 6 (7%) for the onset of side-effects caused by previous therapies; and 9 (11%) reported both uncontrolled pain and opioid-related side effects as reasons for the switch. Nine (11%) facilities did not perform rotation because methadone treatment had already been established prior to hospice admission.

We also investigated the reasons for rotating patients off methadone therapy. Among the 81 hospices using methadone, 40 centers (49%) reported having to switch patients to other opioids for various reasons. The most frequently cited cause for rotation was the onset of dysphagia combined with a decline in the patient's performance status and level of consciousness, reported by 24 facilities (30%). Side-effects attributed to methadone were indicated as the main reason for switching in 8 cases (10%), while uncontrolled pain was identified as the primary cause in 6 hospices (6%). A small number of centers, 2 in total (2%), reported that both uncontrolled pain and side-effects were equally relevant factors influencing the decision

to rotate to a different opioid.

Hospices that did not use methadone (n=79) were asked to indicate the reasons for its exclusion from clinical practice. The most frequently reported reason (28%) was a preference for alternative medications, which were perceived as more effective either based on personal beliefs or institutional guidelines. Difficulties in obtaining methadone, mainly due to issues related to controlled substance registers or pharmacy logistics, were cited by 23% of the facilities. A lack of staff experience in methadone administration was reported by 16% of respondents. Additionally, 10% of interviewees described methadone as a complex drug, primarily due to challenges in dose conversion and concerns about drug accumulation and related adverse effects. Nine percent indicated that they had not encountered clinical situations requiring methadone use. Furthermore, 3% of hospices highlighted the advanced condition of patients as a limiting factor, particularly in relation to the oral formulation, which was often considered unsuitable in end-of-life care. Finally, 11% of facilities did not report any specific reason for not using methadone.

No statistically significant associations were found in any of the comparisons investigated. Specifically, there was no monotonic correlation between years of hospice operation and perceived difficulty in using methadone (Spearman $\rho=0.05$, $P=0.576$). Operators who reported using methadone did not differ significantly in their perceived difficulty compared to non-users (Mann-Whitney $U=2177.00$, $P=0.149$) (see *Figure 1B,1C*). Finally, there was no association between years of operation and methadone use (Chi-squared =3.22, $P=0.359$).

Discussion

Methadone use in palliative care is increasingly recognized for its unique pharmacological properties and efficacy in managing complex cancer pain, especially in cases of opioid tolerance or refractory symptoms (18-20). International guidelines, such as those from the European Association for Palliative Care (EAPC) (21) and the National Comprehensive Cancer Network (NCCN) (22), provide evidence-based recommendations for methadone prescribing and opioid rotation strategies to optimize safety and effectiveness.

Recent systematic reviews have highlighted methadone's favorable safety profile and the benefits of careful dose conversion protocols, which are crucial to minimizing

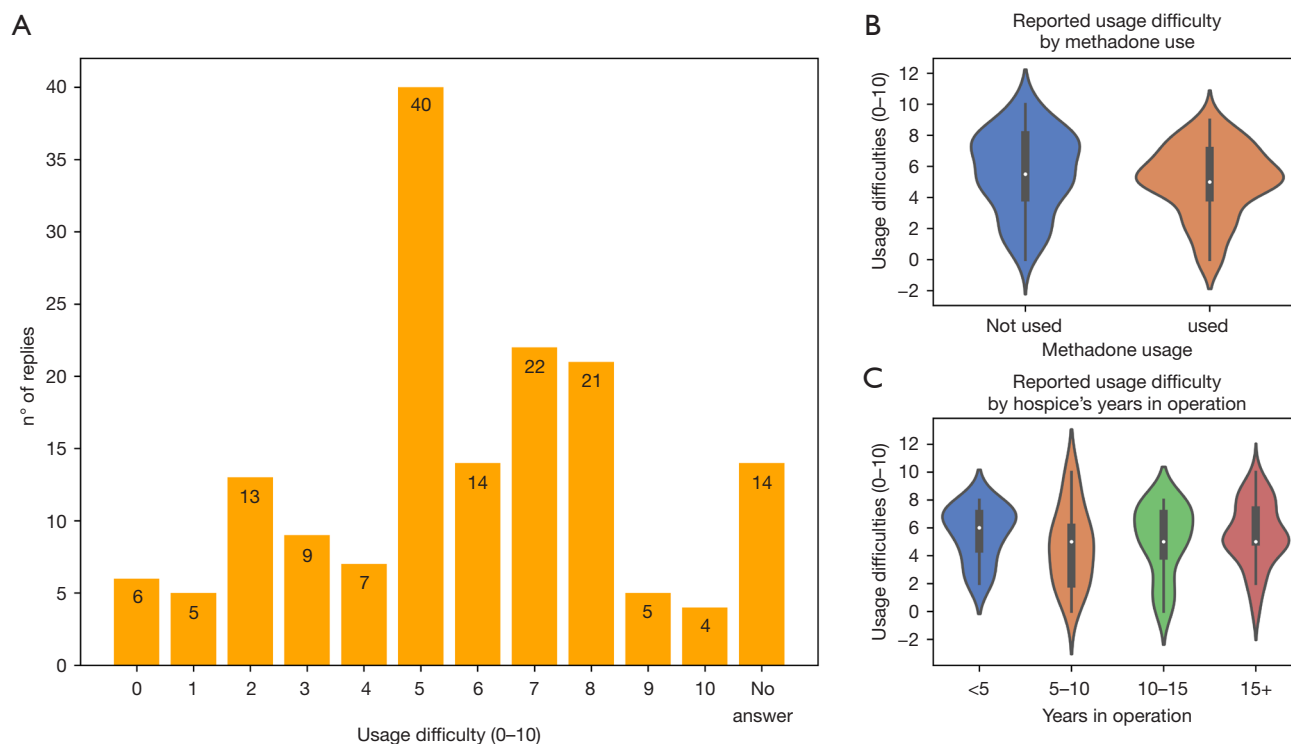


Figure 1 Perceptions of methadone use difficulty among Italian hospice physicians. (A) Distribution of responses to the question assessing perceived difficulty in using methadone, rated on a scale from 0 (very easy) to 10 (very difficult). (B) Violin plot comparing perceived difficulty scores between current methadone users and non-users; statistical analysis performed using the Mann-Whitney *U* test. (C) Violin plot illustrating the association between years of hospice operation and perceived difficulty in methadone use; analysis performed using Spearman's rank correlation coefficient.

adverse effects and improving patient outcomes (2,23).

Our study investigates the use of methadone in Italian hospices compared with the study by Mercadante *et al.* from 2013 (14), over 10 years ago, to examine changes in prevalence, usage patterns and perceived barriers among healthcare professionals. In the present study we conducted a telephone survey targeting 275 adult hospices and using a questionnaire to assess hospice characteristics, methadone utilization practices, and perceived challenges over the period between January and August 2023. However, the comparison with the 2013 data should be interpreted with caution, as it was conducted without a formal statistical approach and was intended for descriptive purposes only.

The response rate in 2023 was 58%, lower than the 84% reported in 2013. However, the use of methadone increased significantly over the 10-year period, with 51% of hospices in 2023 using it compared to 28% in 2013. The response rate of 58% may have introduced selection bias, as hospices more inclined to use methadone may have been more likely

to participate, potentially leading to an overestimation of its actual use in Italy. Interestingly, the number of hospices that had been operating for over 15 years increased from 4 in 2013 to 61 in 2023, and the average annual number of hospice admissions also rose from 189 in 2013 to 208 in 2023.

The perceived difficulty of using methadone shifted slightly, with “very difficult” responses decreasing from 43% in 2013 to 32% in 2023 and “moderately difficult” responses increasing from 32% to 38% in the same period. With regard to administration routes, the use of parenteral methadone increased slightly in 2023 (25%) compared to 2013 (18%). Notably, the use of first-line methadone decreased from 21% in 2013 to 11% in 2023, and initial dosing remained consistent, not exceeding 10 mg/day in both surveys. Due to the exploratory nature of this study, detailed data on methadone dose conversion formulas were not systematically collected. Although a specific question was included, responses were too limited to allow

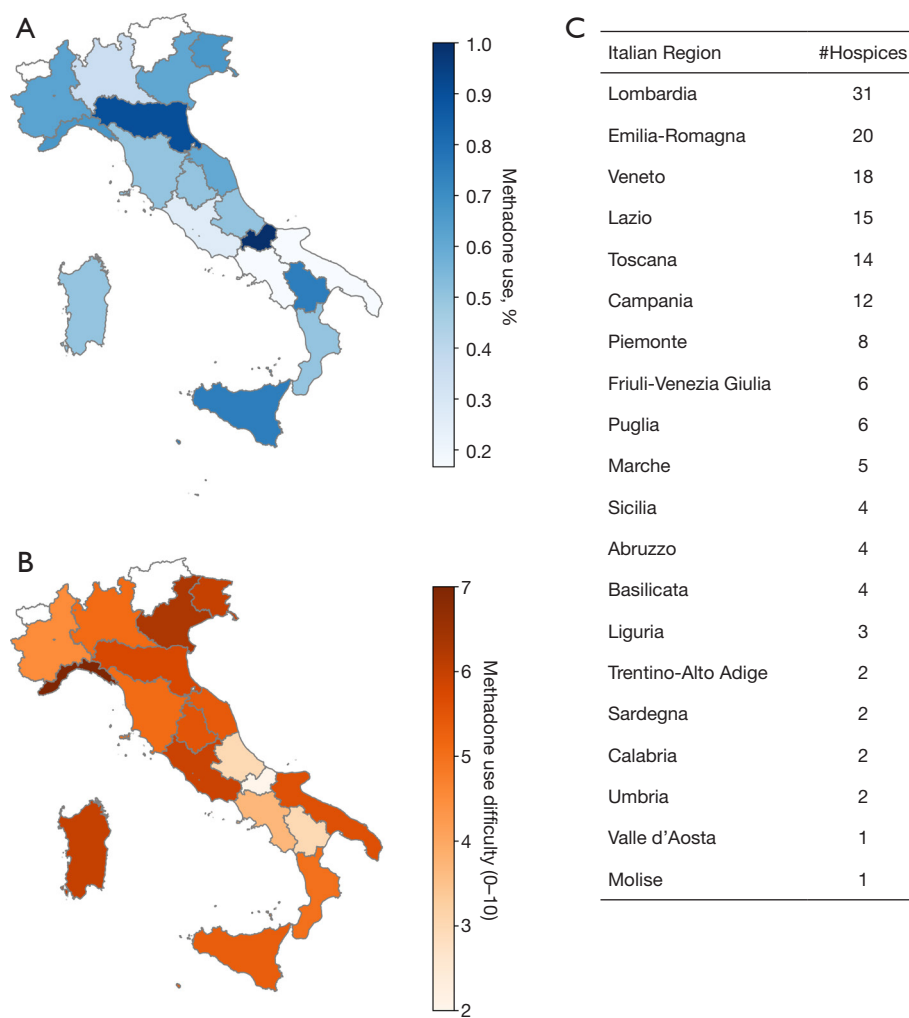


Figure 2 Regional distribution of methadone use and perceived difficulty in Italian hospices. (A) Map of Italy showing the average frequency of methadone use per region, represented on a blue color scale (lighter shades indicate lower usage; darker shades indicate higher usage). (B) Map of Italy showing the average perceived difficulty of methadone use per region, represented on an orange color scale (lighter shades indicate lower perceived difficulty; darker shades indicate higher perceived difficulty). (C) Table summarizing the number of hospices that participated in the study in each region.

meaningful analysis. Nevertheless, clinicians generally reported following established methods from the literature, such as the SAG and 3DS protocols. Only a small number of interviewed hospices were predominantly nurse-led, and although most had regular physician availability, methadone use in these settings was rare. Due to the limited sample size, no statistically meaningful conclusions can be drawn regarding potential associations between organizational models and methadone prescribing.

Overall, the present study suggests a growing trend of methadone use in Italian hospices, with a preference for

methadone rotation over first-line therapy. The perceptions of healthcare professionals have also shifted towards a greater acknowledgement of the clinical benefits of methadone, despite its potential challenges.

Despite signs of increased methadone adoption, the wide regional and institutional variability observed in this study (see *Figure 2*) highlights deeper systemic issues. In the absence of formal training programs and standardized national protocols, clinicians often rely on personal experience or informal local routines, resulting in inconsistent prescribing practices and unequal patient

access. These disparities are further compounded by logistical and administrative barriers—such as regulatory constraints and lack of institutional policies—as well as by persistent cultural resistance linked to limited professional training and historical caution around methadone use. Although methadone is acknowledged in the 2018 Italian Association of Medical Oncology (AIOM) guidelines as a potential option for cancer pain management in Italy (24), it is not accompanied by structured protocols or official dose-conversion schemes. In contrast, several European countries have adopted more structured approaches. In the United Kingdom, national opioid conversion guidelines developed by the Faculty of Pain Medicine and National Health Service networks promote standardized opioid rotation, including methadone, and are supported by targeted educational programs (18). In France, palliative care is formally recognized as a university-certified specialty, with defined curricula and national recommendations that include methadone for complex pain management (19). These frameworks contribute to more consistent clinical practices and help reduce regional disparities in access and use. This variation in structural support is reflected in real-world methadone prescribing trends. A nationwide survey of German inpatient hospices reported that 95% of facilities used methadone derivatives, suggesting widespread clinical acceptance (20).

In Sweden, registry data from specialized palliative care units showed that 8.6% of patients (410 of 4,780) received low-dose methadone as an add-on to other opioids (25). In contrast, methadone use appears much more limited in North American home-based hospice settings, where only 1.95% of patients (416 of 21,219) on long-acting opioids were prescribed methadone (26). Compared to these figures, our study shows that Italian hospice use of methadone remains modest, though it has slightly increased since 2013. This places Italy in an intermediate position between the higher adoption observed in Germany and the more conservative approaches in North America. These differences underscore the critical role of national policy, clinical training, and structured guidance in shaping opioid prescribing behavior at the end of life.

The present study has some limitations. In particular the heterogeneity of responders, physicians, nurses, and one administrative staff member, may have influenced the responses due to varying perspectives and experiences. However, it is important to note that in the hospice where the administrative member who responded to the survey worked, methadone was not used. Therefore, his answers

should not have affected the clinical validity of the results. Even if the responses are considered to reflect institutional policies and common practices rather than individual opinions, some variability due to respondent profiles cannot be excluded. Moreover, the question regarding the “difficulty” of methadone use posed a risk of subjective interpretation, as participants may have understood and assessed the term “difficult” differently based on their individual experiences. Another limitation is the absence of data triangulation such as verification through institutional protocols, pharmacy records, or patient charts. As a result, the findings reflect reported practices rather than objectively validated behaviors. Finally, the questionnaire was not formally validated or pilot-tested. However, it was based on a previously published survey and developed by a multidisciplinary team with expertise in palliative care and opioid management.

Conclusions

In conclusion, methadone has become a valuable tool in hospice pain management. To enhance the appropriate and safe use of methadone in hospice settings, it may be advisable to develop national clinical protocols for opioid rotation and the inclusion of methadone-specific modules in continuing medical education (CME programs). The establishment of the postgraduate specialization in Palliative Medicine and Care in Italy (DM 28 September 2021, GU n. 301, 20 December 2021) represents a significant milestone and strong opportunity to improve structured training in hospice and palliative care settings. Ultimately, collaboration among healthcare providers and researchers is essential to promote evidence-based methadone use and improve pain management in patients with complex pain conditions.

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Footnote

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