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REVIEW

Fentanyl in cancer pain management: avoiding hasty judgments and discerning its potential benefits

Arturo Cuomo[1]

[1]Istituto Nazionale dei Tumori, IRCCS Fondazione G. Pascale, Naples, Italy

Abstract

Cancer pain is an important challenge in treatment and requires a rapid onset of action for its control. In particular, breakthrough cancer pain (BTcP) should be adequately controlled with a stable dose of a short-acting oral opioid. Fentanyl is a synthetic, highly selective opioid with many advantageous chemical properties, including high lipophilicity and distinct pharmacokinetic properties. It is recommended for pain management in a variety of settings, including acute pain, chronic pain and BTcP. To date, its variously designed formulations allow non-invasive administration; amongst others, sublingual fentanyl has proven useful in the management of BTcP and in improving the quality of life of patients with cancer. This review provides an update on the management of BTcP with fentanyl, with consideration of safety, as it remains an important tool in the treatment of cancer pain.

Keywords: breakthrough pain, cancer pain, fentanyl, opioids, quality of life.

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Introduction

Cancer is often associated with chronic and persistent pain syndromes[1–4] depending on the type of cancer,[4] tumour stage, therapies,[5–7] disease course and performance status.[3,8,9] Cancer-related pain is a multidimensional symptom that includes physical, psychosocial, emotional and spiritual components.[10,11] Poor cancer pain management contributes to worsening quality of life (QOL),[12–16] can influence adherence to antitumor treatment,[17] has a significant impact on the psychological aspects of life and emotional well-being,[18,19] and worsens fatigue, sleep disorders, nutritional status, anxiety, depression and social withdrawal.[20–25] Many patients with cancer require emergency department consultation for acute oncological pain, and a high percentage are admitted to hospital to manage pain, thus increasing healthcare costs.[26,27] Therefore, patient characteristics and cancer pain patterns (precipitating factors, intensity, duration, frequency and types of pain)[7,28–30] should be carefully assessed through a detailed history and physical examination using a variety of available and validated tools.[31–35]

Despite the detrimental impact of pain on cancer patients, caregivers and healthcare providers, it remains underestimated and undertreated.[36–38] Pain is reported by approximately 50% of patients at any cancer stage, with moderate-to-severe pain reported by over 36.0% of all patients.[36,37] In advanced or metastatic cancer, two-thirds of patients report pain, which tends to worsen.[36,37,39] In addition, approximately 48% of patients with chronic cancer pain that is stable and controlled by proper treatment also complain of acute transient exacerbation of severe pain, defined as breakthrough cancer pain (BTcP).[40,41] BTcP can occur spontaneously[42] or due to a specific trigger,[43–46] with a high impact on daily activities and QOL[4,47–50] and frequent access to the emergency department.[51–54] Proper assessment of BTcP is required by clinicians to ensure suitable, tailored therapy.[50,55,56]

Cancer pain management

Proper management of cancer-related pain has gained significant attention in recent years because of the increasing focus on 'value-based' medicine,[57] which is focused on improving the quality of healthcare and the effective and efficient use of healthcare resources, considering the patient-perceived value of an intervention, in line with their preferences and wishes.[57] Assessing and managing cancer-related pain are recognized as an

important measure of the value of cancer care.[58,59] The Alliance for Global Cancer Control calls for concerted action to prevent, treat and improve the QOL of patients and survivors worldwide.[60] However, QOL is a multidimensional concept of the overall state of well-being in relation to the values, environments, and cultural and social contexts in which people live.[61,62]

The updated World Health Organization's analgesic ladder focused on QOL[63] provides precise guidance, based on a correct and comprehensive assessment of the patient, on the choice of tailored treatment that should satisfy the patient, improve their QOL and help reduce healthcare costs.[3,64–67] The most effective treatment for cancer pain is multimodal, including pharmacological, behavioural, physical, complementary and invasive approaches.[55,68,69] To provide optimal relief, access to multidisciplinary teams with expertise in all these treatments is essential.[66,70] Therapies should be individualized based on patient status, comorbidities, drug toxicity profile, prior experience, preferred and indicated route of administration, and formulation.[59,71,72]

Moderate-to-severe background pain should be managed appropriately according to the recommendations of cancer pain guidelines.[3,30,55,67,73] The American Society of Clinical Oncology recommends starting opioids at the lowest dose to achieve acceptable analgesia and patient goals, with frequent titration and early management of opioid-related adverse effects.[74,75] Regular follow-up visits are essential to assess treatment response and adjust treatment if needed, as part of a dynamic process of personalization. Opioid rotation, defined as switching from one opioid to another or changing the route of opioid administration, should optimize pain management.[76–79]

It is imperative to improve background analgesia, which is a prerequisite for the diagnosis of BTcP.[41] Furthermore, optimization of the analgesic regimen for background pain results in a reduction in the number, intensity and duration of BTcP.[80–82] The Davies algorithm[82] is normally useful for BTcP diagnosis in patients with adequately controlled background cancer-related pain in the previous week, described as no pain, or a pain intensity of ≤4/10 on a numerical scale of 0–10.[41,82,83] Careful and continuous assessment should be ensured for all patients to limit the burden of BTcP, as it is related to the patient characteristics, stage of disease and treatment.[46,84] Early, targeted, personalized and multimodal pain control is an important predictor of improved pain relief in patients with BTcP.[85–87]

To provide personalized treatment for BTcP, various fast-acting fentanyl-based formulations (TIRF)[88] have been developed and are recommended by guidelines[4,55,89,90] after titration in patients already receiving maintenance opioid therapy for chronic cancer pain with at least 60 mg of oral morphine equivalent.[50,88,91,92] According to the Summary of Product Characteristics, TIRF should not be prescribed to opioid-naive patients, patients with severe obstructive lung conditions or to those with other indications than breakthrough cancer pain.[88]

Transmucosal fentanyl has been introduced because of its more appropriate pharmacokinetics, ideal for the treatment of breakthrough pain episodes characterized by rapid onset (3–15 min), short duration (15–30 min/episode) and moderate-to-severe intensity.[93–95] TIRF medicines, also called rapid-onset opioids (ROOs), have pharmacodynamics that reflects the sudden onset and short duration of breakthrough pain episodes. Several clinical trials and meta-analyses have documented the efficacy of ROOs in controlling BTcP and superiority over oral morphine that provides a time to pain relief of usually more than 30 minutes.[90,93,96–98]

A full range of transmucosal fentanyl formulations is now available for the treatment of BTcP, including oral lollipop fentanyl citrate, fentanyl buccal tablet, sublingual fentanyl, fentanyl buccal soluble film and nasal transmucosal formulations.[88] During clinical trials, post-marketing and real-life experience, no serious adverse events were reported with the use of transmucosal fentanyl formulations.[99–101] Clinically significant respiratory depression associated with the use of fentanyl can occur in patients with severe chronic obstructive pulmonary disease and caution should be taken in other conditions potentially predisposing to respiratory depression; naloxone[102] rapidly reverses all the effects of fentanyl and is the drug of choice in these cases.

Gastroenteric symptoms (nausea, vomiting and constipation) and nervous system disorders (dizziness, somnolence, confusion, hypotension and headache) were the most recurrent events reported.[88] However, it is difficult to distinguish symptoms caused by the various stages of cancer and related therapies or separate adverse events due to the background opioid therapy from those that could be related to transmucosal fentanyl. Dizziness, nausea and somnolence have been reported to be less frequent when fentanyl is released by the nasal route.[103] Taylor and Gabrail reported a small but significant difference in nose itching, sneezing and taste disturbance 60 minutes after administration of fentanyl pectin nasal spray.[104] Therefore, clinicians may need educational training to select the proper product for the individual patient.[105–111] Family and carers should also be involved in education, training and support from diagnosis through to survivorship and end of life.[112–114] Furthermore, improving knowledge of the nature of cancer pain and supporting proper communication about it

reduces the fear of patients and their families, increases adherence to opioid therapy, and reduces opioid abuse or misuse.[115,116]

To improve adherence to analgesic regimens, patient-related barriers, including cognitive or affective factors, need to be explored and addressed.[11] It is also appropriate to communicate the main side-effects of opioids to the patients and encourage them to report the occurrence of adverse events. For example, in the case of fentanyl use, the timing of transdermal patch replacement and the site of application should be precisely explained, and the prevention and treatment of constipation should be anticipated. In the case of TIRFs, careful titration should be implemented, and patients and caregivers should be alerted to the possible occurrence of previously described most common adverse events.[88,117] Furthermore, patients need to be involved in the decision-making process,[118] and clinicians need to be active listeners and empathizers, improve the prescription of pain medications, when necessary, teach non-pharmacological pain management strategies, and reassess pain to improve patient QOL.[75] Physicians must therefore be aware of QOL measures as part of treatment management.[43]

Outcomes in pain management as reported by patients

It is increasingly recognized that patient-reported outcome measures (PROMs), including health-related QOL (HR-QOL), can be useful complements to traditional biomedical outcomes (e.g. freedom from disease and overall survival), adding relevant information for cancer decision-making.[119,120] Patients with cancer can provide their own input to guide treatment using PROMs related to pain. However, the literature shows that, because of ineffective transfer of information and frequent clinician inertia in acting on this information, interventions based on PROMs have achieved only modest reductions in cancer pain intensity.[117] Most patients rated the quality of their pain management as high if they received appropriate care, had a safety net, had a relationship with their healthcare team and had effective pain management.[121] Furthermore, a high level of satisfaction with care may influence decisions regarding seeking care, changing healthcare providers or medical schedules, and adherence to prescribed treatments.[121] Conversely, higher patient satisfaction is associated with lower treatment costs and patient switching. Patient expectations are critical in assessing satisfaction with care; therefore, an overall understanding and evaluation of expectations regarding pain control may facilitate effective intervention.[121,122]

Patients with the most severe pain in particular need additional research into their needs, and their satisfaction with their level of pain should be further assessed.[123] For patients with advanced cancer, whether their pain was 'under control' was determined by their ability to carry out activities or tasks and maintain relationships with family or friends, which was determined by them as individuals.[124] Therefore, the use of a numerical scale is a simpler and objective method of assessing pain intensity during assessment and follow-up re-evaluations.[41,124,125]

The NRS is an 11-point scale (0 = no pain and 10 = worst possible pain) for self-reporting pain and is the most commonly used unidimensional pain scale for the assessment of pain intensity or other dimensions such as pain distress or pain interference. The NRS scale has a high correlation with the Visual Analogue Scale (VAS), which uses a fixed 10-cm ruler with 'no pain' at the top to 'extreme pain' at the right end.[126,127]

The Brief Pain Inventory (BPI)[128] is a self-administered pain assessment tool developed to evaluate cancer pain by assessing pain severity, location, impact on daily functioning and pain relief. For daily interference, the BPI looks at walking ability, general activity, work, relationships with others, enjoyment of life, mood and sleep.[128] The first version was the Wisconsin Brief Scale,[129] followed by the development of the Short Form (BPI-SF),[128] which requires approximately 5 minutes to complete and, based on the available data, had the most robust evidence for selection in the assessment of cancer pain.[130]

In 1992, the RAND Corporation developed the 36-Item Short-Form Health Survey (SF-36),[131] a set of generic and easily administered QOL measures. The SF-36 version 2 can be used across age, disease and treatment groups to assess the perceptions of adult patients regarding their own health and well-being. The survey consists of 36 items grouped into eight dimensions. It can be self-administered or completed in an interview.[131,132] An abbreviated version (12-item Short-Form Health Survey (SF-12v2)) of the SF-36v2 has been shown to be a reliable measure of HR-QOL in adults with self-reported cancer.[133]

The European Organisation for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (EORTC QLQ-C30)[134] was developed to measure the physical, psychological and social functioning of patients with cancer in order to assess their QOL in clinical trials and multicultural clinical research settings. It includes functional scales (physical, cognitive, emotional, role and social), symptom scales (pain, fatigue, nausea and vomiting), and a global health and QOL

scale.[134–137] The EORTC QLQ-C30 has been validated in several languages and is used worldwide because of its cancer specificity, multidimensional structure and ease of self-administration in many cultural settings.[137] The length of the 30 items and some content that may still be inappropriate for advanced illness are potential drawbacks of the EORTC QLQ-C30 when used in palliative care, so the EORTC QOL Questionnaire Core 15 for Palliative Care (EORTC QLQ-C15-PAL) provides a shorter, validated solution.[138]

The Palliative Outcome Scale has emerged as another useful outcome measurement tool for the assessment of QOL and quality of care provided by palliative care service organizations.[138–140]

Finally, the EuroQOL five dimensions questionnaire (EQ-5D 5L) is a self-assessed, short questionnaire developed to complement other QOL measures and to facilitate the collection of a common data set for reference purposes. The scale measures QOL on a 5-component scale including mobility, self-care, usual activities, pain/discomfort and anxiety/depression.[141,142]

Results from recent studies show that both patients in cancer departments[44,143] and patients with advanced cancer in palliative care[144,145] have statistically significant improvements in QOL following tailored BTcP with transmucosal fentanyl formulations. More specific tools are available to help assess the impact of cancer-related pain and BTcP on QOL. The Pain Disability Index (PDI)[146] is a brief instrument designed to assess chronic pain-related disability, providing information that supplements the assessment of physical impairment.

The Alberta Breakthrough Pain Assessment Tool (ABPAT) was developed by Hagen et al.[147] to specifically assess BTcP in the research setting and is often used in conjunction with the BPI or the EORTC QLQ-C30.

Finally, the Hospital Anxiety and Depression Scale (HADS) is useful and accurate in detecting anxiety and depressive states in patients with cancer and may therefore be applicable in clinical practice to assess pain burden.[148,149]

In this article, the management of BTcP is reviewed with a focus on its impact on QOL.

Methods

A narrative review was conducted using PubMed, identifying articles between 2013 and 2023 with the search terms: "breakthrough cancer pain" and "quality of life". Restricting the search to English and human subjects, 82 articles were identified; we then analysed all articles and selected only those relevant to our research, as shown in Table 1. A manual search of the final reference lists was also performed.

Discussion

As previously reported, impairments in sleep, activities of daily living, pleasure in life, ability to work and social interactions have been reported in patients with moderate or severe chronic pain. In recent years, there has been increasing attention on the impact of BTcP on QOL.[12–25] Furthermore, the terms "health", "health-related quality of life" and "quality of life" are used synonymously, and different and incomparable measures are used in the examined studies.[167,168]

Guitart et al.[150] showed pain reduction and significant improvement in SF-12 and HADS scores on both the depression (p=0.005) and anxiety (p<0.001) sub-scales at the end of follow-up in 69 patients treated with sublingual fentanyl tablets for BTcP. Additionally, HADS scores decreased, particularly in younger patients.[169] An updated study was published by Guitart[155] in 2018 showing that sublingual fentanyl tablets have good efficacy and safety regardless of the cancer stage and opioid regimen for background pain. Significant improvements in HADS scores were observed in this subgroup analyses of patients with locally advanced cancer or metastatic cancer treated with transdermal fentanyl for background pain whilst, in the same subgroups defined by cancer stage, no significant improvements in SF-12v2 scores were observed.[155]

Positive results were found by Ueberall et al.[151] in patients treated with fentanyl pectin nasal spray, with significant improvements in BTcP-related limitations in activities of daily living and QOL. SF-12v2 Health Survey scores were significantly higher in patients with severe QOL disability than in those with moderate QOL disability. For BTcP-related disability, the greatest improvements were reported in the modified version of the Pain Disability Index overall QOL and sleep dimensions.

Baek et al.[152] also showed that South Korean patients with BTcP were more likely to complain of sleep disturbance, which was defined as waking up two or more times during sleep, compared with patients without BTcP. A subset analysis of this Korean survey conducted by Kang et al.[49] showed that patients with moderate-to-severe BTcP had significantly greater interference in daily functioning than those with mild BTcP, and impairment was proportionally greater with increasing BTcP intensity (p<0.001).

Hjermstad et al.,[153] in their observational study of patients with advanced cancer in eight countries, highlighted

Table 1. Main studies considered in the review with a focus on impact of breakthrough cancer pain (BTcP) on quality of life.

Authors	Year	Development method	Country / Region	Number of patients with BTcP	QOL assessment tools	Setting
Guitart et al.[150]	2015	Multicentre, prospective observation post-authorization, open-label study	Spain	69	SF-12v2 Health Survey HADS	
Ueberall et al.[151]	2016	Prospective, open-label, non-interventional study	Germany	220	Modified version of the Pain Disability Index	Pain and palliative care centres
Baek et al.[152]	2016	Multicentre nationwide study	Korea	177	Sleep disorder defined as the frequency of unexpected awakening from sleep	Inpatient setting
Hjermstad et al.[153]	2016	Observational cross-sectional multicentre study	European Palliative Care Research Collaborative	289	Brief Pain Inventory ABPAT EORTC QLQ-C30	Advanced cancer care centres
Katz et al.[154]	2017	Cross-sectional observational survey	USA	112	Brief Pain Inventory SF-12v2 Health Survey Sheehan Disability Scale, Work Performance Questionnaire Generalized Anxiety Disorder-7 Screener Patient Health Questionnaire-2	Community-dwelling patients with cancer
Guitart et al.[155]	2018	Subgroup analyses on data from Guitart et al.[150]	Spain	69	SF-12v2 Health Survey HADS	Locally advanced cancer and metastatic cancer
Ferrer Albiach et al.[43]	2019	Real-world data collection	Spain	74	EORTC QLQ-C30 SF-12v2 Health Survey	Bone metastases in every setting
Gonella et al.[156]	2019	Secondary analysis of a multicentre, longitudinal, observational study[157]	Italy	92	ABPAT Palliative Outcome Scale	Palliative care
Yang et al.[158]	2019	Randomized controlled double-arm study	China	58	EORTC QLQ-C30	
de Lucas et al.[159]	2020	Observational, prospective, multicentre study	Spain	49?	SF-12v2 Health Survey MOS-SS[160]	Radiation oncology departments
Pointreau et al.[161]	2020	Non-interventional, prospective study	France	92	SF-12v2 Health Survey EORTC QLQ-C30	Patients with head and neck cancer radiation oncology departments

(*Continued*)

Table 1. (Continued)

Authors	Year	Development method	Country / Region	Number of patients with BTcP	QOL assessment tools	Setting
Kang et al.[49]	2020	Subset analysis of a multicentre, non-interventional, cross-sectional, nationwide survey[152]	South Korea	438	SF-12v2 Health Survey	Oncology
Cuomo et al.[44]	2020	Observational, multicentre, cohort study	Italy	154	EORTC QLQ-C15-PAL Pittsburgh Sleep Quality Index[162]	Palliative care units, oncology departments, pain clinics
Matsumura et al.[163]	2021		Japan	40	EORTC QLQ-C15-PAL	Palliative care (outpatients)
Rodríguez et al.[144]	2021	Prospective, observational, multicentre study	Spain	99	EORTC QLQ-C30	Palliative care (inpatients and outpatients)
Rodríguez et al.[145]	2022	Sub-analysis of a prospective, observational, multicentre study[144]	Spain	95	EORTC QLQ-C30	Palliative care (inpatients and outpatients)
Villarroel et al.[143]	2022	Observational, prospective, multicentre study	Spain	104	EORTC 5-level EQ-5D version (EQ-5D-5L) Patient Global Impression of Improvement (PGI-I) scale[164] MOS-SS Goldberg Anxiety and Depression Scale[165] Gijón Social-Familial Evaluation Scale[166]	Oncology departments

ABPAT, Alberta Breakthrough Pain Assessment Tool; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire 30-item; EORTC QLQ-C15-PAL, EORTC for Palliative Care 15 item; HADS, Hospital Anxiety and Depression Scale; MOS-SS, Medical Outcomes Study-Sleep Scale; SF-12v2, 12-item Short-Form Health Survey.

that episodes of BTcP were correlated with significantly worse mean scores on 10 of the 15 functional and symptom scales of the EORTC QLQ-C30.

High interference with activity, mood, ability to walk and work, social relations, sleep and enjoyment of life were also described by Katz et al.[154] amongst community-dwelling patients with cancer pain and BTcP.

Quality of life was assessed using the SF-12v2 in a Spanish study conducted in radiation oncology departments in Spain (CAVIDIOR study).[159] The 79 patients with BTcP who received transmucosal fentanyl (65%) reported an improvement in BTcP control at the end of the evaluation period as well as significant improvements in social functioning, role-emotional status, mental health and vitality, sleep quality, and caregiver burden. The same outcomes are described by Pointreau et al.[161] in a population of patients with head or neck tumours treated with fentanyl pectin nasal spray for BTcP in French radiation oncology departments. Matsumura et al.,[163] using the Japanese version of the EORTC QOL Questionnaire Core 15 for Palliative Care (EORTC QLQ-C15-PAL), also concluded that breakthrough pain relief appears to be an important measure to improve QOL in outpatients with advanced cancer.

The aim of the recent CAVIDIOM study[143] was to comprehensively assess QOL in patients with BTcP treated in medical oncology services. QOL improved significantly ($p<0.001$) in patients receiving ROO therapy at tailored doses (67–800 µg) at the end of the study. In addition,

statistically significant correlations were found between three EQ-5D-5L dimensions (mobility, pain/discomfort and anxiety/depression) and several MOS-SS dimensions, with an overall improvement in sleep quality.

In this study,[143] the overall patient improvement in QOL was rated similarly by patients and physicians: 'much better' was chosen by 36% of patients and 34% of physicians, whilst 'a little better' was chosen by 27% of patients and 30% of physicians. The result was different in the CAVIDIOR study,[159] where more physicians (81.9%) responded positively than patients (43.6%). The CAVIDIOM study authors[143] suggested that patient and clinician perceptions of QOL improvement may vary based on care setting, being more similar in medical oncology units than palliative care and radiation oncology units.[143]

In the CAVIDIOPAL study,[144] including patients with advanced cancer and after 28 days of individualized BTcP therapy mainly with low-dose transmucosal fentanyl, Rodríguez et al. showed very significant improvements ($p<0.001$) in almost all domains of EORTC QLQ-C30. An additional analysis from CAVIDIOPAL[145] showed that low-dose sublingual fentanyl effectively reduced BTcP in patients with advanced cancer in palliative care units, significantly improving QOL. According to patient and physician perspectives, 85.3% and 83.1% of patients, respectively, reported some degree of improvement. The authors therefore concluded that low sublingual doses (67 µg, 100 µg and 133 µg) and careful titration appear to be an appropriate option in elderly or frail patients.[145] Sublingual fentanyl may be a valid and safe option for patients with mucositis because absorption rates from buccal fentanyl are similar in patients with and without mucositis.[170]

The BEST multicentre observational study[44] in palliative care, oncology and pain clinics enrolled 154 Italian patients with BTcP. The individualized treatment of BTcP with transmucosal fentanyl led to a significant improvement in all physical and emotional characteristics of the EORTC QLQ-C15-PAL, except for nausea and vomiting and dyspnoea. In addition, at the end of the study, significant improvements were seen in global health ($p=0.002$) and sleep quality as assessed by the Pittsburgh Sleep Quality Index.[162]

Gonella et al.,[156] pooling all Palliative Outcome Scale items, found no difference in QOL between patients with predictable and spontaneous BTcP, suggesting that patients with predictable BTcP are more likely to report interference with activities of daily living, whereas those with unpredictable BTcP are more affected in the sleep and mood domains.

There is evidence that QOL is rarely included as a treatment outcome for BTcP in patients with metastases. Ferrer Albiach et al.[43] enrolled 386 patients with bone metastases and BTcP in any care setting in Spain. More than 50% of patients reported unpredictable BTcP and 44.3% experienced predictable BTcP episodes. In this study,[43] a ROO was the treatment of choice for bone metastatic BTcP. In the palliative care setting, the overall percentage of sublingual fentanyl prescriptions was higher.

Finally, a recent study conducted in China by Yang et al.[158] to evaluate the effectiveness of pain management using a new app, called Pain Guard, has assessed the feasibility and changes in patient QOL and improvements in the management of BTcP. This innovative real-time pain assessment mechanism and electronic reporting system appears to be more effective in collecting pain data, enhancing medication adherence and optimal BTcP management as well as improving QOL.

Multidisciplinary approaches may also be useful to tailor the management of BTcP episodes to individual characteristics and to ensure close follow-up, reorganizing interdisciplinary tasks around patient-centred care and outcomes.[66,70,143,171]

The integration of early palliative care interventions has a positive impact on the QOL of patients, survivors and carers, and a systemic model of early supportive care should be implemented.[172–175] In the same way, improvements in QOL have been reported in patients with cancer receiving palliative care, particularly in symptoms such as pain, nausea and fatigue as well as in physical and psychological functioning.[176]

In addition, patients were often in doubt about the use of prescribed long-acting opioids to treat cancer pain due to their perception of the risks and benefits, and they defined their own parameters for opioid use. Therefore, education and counselling are needed to optimize the use of opioids as part of cancer pain management.[116,177] For patients in palliative care treated with strong opioids who fear adverse effects and death or dying, better awareness of patient preconceptions about opioids can alleviate suffering by improving pain management and reducing opiophobia.[178] The opioid crisis and the unprecedented rise in opioid abuse in the United States have heightened public fears about the risks associated with opioid treatment and created stigma around opioid users.[179–182] This can be a complicating factor in cancer pain management, as clinicians must strike a balance between satisfying the patient's need for pain relief and minimizing the risk of abuse and misuse.[183–185]

However, the opioid epidemic is mainly confined to the United States and geographical areas with specific legislation and where the healthcare system is predominantly based on private healthcare providers.[185,186] Indeed,

the European Pain Federation Task Force study of trends in opioid prescriptions, substance use disorders and deaths as a proxy for opioid-related harm over the last 20 years shows that Europe is not facing an opioid crisis.[187] Furthermore, the European Drug Survey concluded, in 2017, that there is no evidence to suggest that opioids prescribed to patients with pain are problematic in Europe, and that the increase in opioid prescriptions may represent the satisfaction of an unmet need in cancer pain management and palliative care.[187,188] In 2019, the Organisation for Economic Co-operation and Development stated that the appropriate use and regulatory environment for prescription opioids can be compatible with increased access to these drugs for medical use.[189] Of note, the American Society of Clinical Oncology supports public health efforts to reduce opiate abuse through government regulation whilst ensuring efficient and compassionate access to analgesics for patients with cancer.[190] Conversely, in Italy, efforts are still being made to ensure access to treatment for all patients suffering from pain, as provided for in Law 38/2010.[191] The Italian health system regulates opioid prescribing and pain specialists carefully counsel patients and caregivers. [111,191–193] However, in the wake of the opioid crisis in the USA, the national regulatory authority has added an 'addictive' warning to opioid packaging,[194] which may exacerbate the under-prescription of opioids for cancer pain, despite Italy having one of the lowest levels of opioid consumption in Europe.[195]

Fentanyl and its derivatives, either diverted from medical use or illicitly manufactured, play a comparatively small role in deaths and acute poisonings that occur in Europe.[196] The number of fentanyl-related fatal overdoses appears to be significantly lower in Europe than in the USA, with only 0.5% of people registering with drug treatment services citing fentanyl and its derivatives as their primary drug.[197,198] Furthermore, most cases of abuse, dependence or withdrawal in Europe are related to non-cancer pain indications and mostly to transdermal formulations.[196] Approximately 60% of patients using intranasal fentanyl and almost 75% of those using transmucosal fentanyl were not diagnosed with cancer, and more than 70% of both groups used no opioids for background pain.[196]

Collaborative efforts should still be intensified globally to find solutions that balance our responsibility to reduce deaths and overdoses with the ethical imperative to make opioids widely available to patients who need them to effectively manage chronic cancer pain without arbitrary restrictions on prescribing, dosing or access. Again, more nationwide educational programmes and training for clinicians involved in cancer pain management are needed to improve early diagnosis, appropriate treatment and adequate knowledge of the risks of overdose or misuse of analgesics.[110,199,200] Additional efforts should be directed at early identification of patients at risk of addiction[201] and at raising patient awareness of the need to avoid sharing medicines, to keep opioids under lock and key, and to dispose of expired or unused medicines.[72,111,201–203] To ensure effective knowledge transfer between all healthcare professionals caring for a patient who may be at higher risk of dependence, the diffusion of personal health electronic records could be decisive.[185]

New formulations with 'abuse-deterrent' properties have been developed and commercialized, whilst other formulations are in registration or preclinical trials to ensure high efficacy, good safety and tolerability profiles, and to reduce the risk of abuse, misuse and diversion of opioids prescription.[90,204–208]

Inequalities in the management of chronic cancer pain persist, with major socioeconomic barriers, such as cultural and language barriers, economic status, geographic location, race/ethnicity and lack of time off work being the most common.[209–213] Age, gender and physical and mental health comorbidities were also recorded.[214,215] From a public health and policy perspective, the provision of optimal pain care is paramount because of the potential implications of poorly treated pain and subsequent costs to society. Therefore, close worldwide collaboration between researchers and clinicians and professional organizations is warranted.[216] Initiatives to improve clinician awareness of inequalities in pain management are also recommended. Sensitivity training, culturally and linguistically appropriate interventions, and collaborative cross-cultural education can help to eradicate disparities.[217–219]

Finally, additional challenges in oncology, including cancer pain management, have emerged during the COVID-19 pandemic.[72,220] Fortunately, however, it has also been an opportunity to stimulate the exploration of remote care solutions through telemedicine experiences and emerging technological solutions.[158,221–225] Telemedicine appears to hold promise for the effective management of patients with chronic pain. This approach can provide tailored pain management, improve access to health services and establish and maintain a long-term therapeutic alliance.[226] Telehealth interventions could also be an effective and alternative method of QOL improvement for cancer survivors with persistent pain.[227] A logical next step in improving cancer care and clinical management is the extension of innovative technologies to the management of cancer pain. However, the impact of telehealth therapies on pain and pain-related conditions remains poorly documented and requires further study and common structured pathways.[226]

Outcomes and HR-QOL at the system level can be improved through routine monitoring of patient-reported outcomes using health information technologies.[228–231] Both clinician and patient experience could be improved by a system that provides a better immersive experience combined with real-time consultation.[232–235]

Conclusion

The effective management of cancer-related pain is an important measure of the value of cancer care. Improving overall QOL through adequate pain control also improves compliance with cancer treatment and even survival. Timely pain assessment with frequent reassessment, multimodal and multidisciplinary management strategies, and appropriate analgesic prescribing are the major and mandatory interventions to improve cancer pain management and cancer care outcomes.

There is a need for effective strategies to improve the QOL for all patients with chronic cancer pain and for more policies specifically designed to overcome and eliminate inequalities in pain management. A reorganization of multidisciplinary roles with a vision of patient-centred care should be addressed, considering opportunities to develop and apply PROMs and increase early palliative care provision to improve QOL.

Because the 1960s, fentanyl has been one of the most successful opioid due to its favourable pharmacokinetics, and a range of patients, including in the post-operative, paediatric, pre-hospital and critical care settings, have benefited from the wide range of fentanyl formulations. In cancer care, long-acting transdermal fentanyl could be a good choice for control of moderate-to-severe background pain, whilst sublingual fentanyl tablets are an excellent choice for BTcP treatment. Many clinicians believe that, for daily practice, to simplify the management of opioid side-effects, it is helpful to use the same molecule (fentanyl) to control both background pain and episodes of BTcP.

There are still opportunities for the future development of fentanyl-related products, and new fentanyl formulations with novel safety and abuse-deterrent properties are being investigated, following inspiration and warning by the opioid epidemic affecting the USA.

Finally, it would be useful for clinicians, patients and decision-makers to consider future challenges and opportunities offered by digital health in cancer pain assessment and management or by use of artificial intelligence applications in pain research. All the initiatives and measures mentioned in this article, together with patient, family and clinician educational programmes, are aimed at improving the QOL of patients with cancer, which remains the ethical goal to be pursued.

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Correspondence: Arturo Cuomo, Istituto Nazionale Tumori – IRCCS Fondazione G. Pascale, Naples, Italy. Email: a.cuomo@istitutotumori.na.it

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