




# Personalizing Cancer Pain Therapy: Insights from the Rational Use of Analgesics (RUA) Group

Giustino Varrassi · Flaminia Coluzzi · Vittorio A. Guardamagna ·

Filomena Puntillo  · Giovanni Sotgiu · Renato Vellucci

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## ABSTRACT

**Introduction:** A previous Delphi survey from the Rational Use of Analgesics (RUA) project involving Italian palliative care specialists revealed some discrepancies between current guidelines and clinical practice with a lack of consensus on items regarding the use of strong opioids in treating cancer pain. Those results represented the basis for a new Delphi study addressing a better approach to pain treatment in patients with cancer.

**Methods:** The study consisted of a two-round multidisciplinary Delphi study. Specialists rated

The members of the Rational Use of Analgesics (RUA) Group are listed in Acknowledgements.

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G. Varrassi  
Paolo Procacci Foundation, Rome, Italy

F. Coluzzi  
Department of Medical and Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy

F. Coluzzi  
Anesthesiology, Intensive Care, and Pain Medicine Unit, Sant'Andrea University Hospital, Rome, Italy

V. A. Guardamagna  
Pain Medicine Unit, Istituto Europeo Oncologico, Milan, Italy

their agreement with a set of 17 statements using a 5-point Likert scale (0 = totally disagree and 4 = totally agree). Consensus on a statement was achieved if the median consensus score (MCS) (expressed as value at which at least 50% of participants agreed) was at least 4 and the interquartile range (IQR) was 3–4.

**Results:** This survey included input from 186 palliative care specialists representing all Italian territory. Consensus was reached on seven statements. More than 70% of participants agreed with the use of low dose of strong opioids in moderate pain treatment and valued transdermal route as an effective option when the oral route is not available. There was strong consensus on the importance of knowing opioid pharmacokinetics for therapy personalization and on identifying immediate-release

F. Puntillo (✉)  
Department of Interdisciplinary Medicine (DIM), University of Bari; Anesthesia, Intensive Care and Pain Unit, Policlinico Hospital, 70124 Bari, Italy  
e-mail: [filomena.puntillo@uniba.it](mailto:filomena.puntillo@uniba.it)

G. Sotgiu  
Clinical Epidemiology and Medical Statistics Unit, Department of Medical, Surgical and Experimental Sciences, University of Sassari, Sassari, Italy

R. Vellucci  
University of Florence, Pain and Palliative Care Clinic, Careggi Hospital, 50139 Florence, Italy

opioids as key for tailoring therapy to patients' needs. Limited agreement was reached on items regarding breakthrough pain and the management of opioid-induced bowel dysfunction.

**Conclusion:** These findings may assist clinicians in applying clinical evidence to routine care settings and call for a reappraisal of current pain treatment recommendations with the final aim of optimizing the clinical use of strong opioids in patients with cancer.

**Keywords:** Breakthrough pain; Cancer pain; Opioids; Opioid-induced bowel dysfunction (OIBD); Opioid-induced constipation (OIC)

### Key Summary Points

#### Why carry out this study?

Cancer pain remains prevalent; however, its undertreatment continues, mostly because of concerns regarding the use of strong opioids and the challenges that physicians may encounter in daily management including opioid titration, choice of mode of administration, and minimization of undesired effects such as opioid-induced bowel dysfunction (OIBD).

Current evidence-based recommendations do not satisfactorily provide guidance on the several debated issues in cancer pain therapy, thus leaving physicians to rely solely on their experience and knowledge.

Our survey aimed at reaching consensus among Italian palliative care specialists on five relevant aspects of cancer pain management, namely strong opioid mode of administration, personalization of cancer pain therapy, multimodal therapy, breakthrough cancer pain, and OIBD.

#### What was learned from the study?

More than 70% of participants agreed with the use of low dose of strong opioids in moderate pain treatment and valued transdermal route as an effective option when the oral route is not available.

There was strong consensus on the importance of knowing opioid pharmacokinetics for therapy personalization and on identifying immediate-release opioids as key for tailoring therapy to patients' needs.

These findings may assist clinicians in applying clinical evidence to routine care settings and call for a reappraisal of current pain treatment recommendations with the final aim of optimizing the clinical use of strong opioids in patients with cancer. The results also highlighted the need to expand current pharmacological knowledge on different analgesics.

## DIGITAL FEATURES

This article is published with digital features, including a summary slide to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.13909973>.

## INTRODUCTION

Pain is one the most disabling and distressing health problems, often feared by patients and healthcare professionals; it affects approximately 66% of patients with cancer [1, 2]. Cancer pain has a substantial impact on patients' quality of life, especially if a neuro-pathic component is present [3, 4] with over one-third of patients describing pain related to cancer as troublesome or even as an intolerable aspect of their cancer. Thus, access to adequate pain relief is a crucial concern for patients with cancer and remains so at all stages of the illness trajectory. In addition, effective management of cancer pain may improve patient-perceived value of cancer treatment, decrease unexpected healthcare utilization, and promote adherence to cancer therapy [5].

Despite a greater understanding of the impact of pain on clinical outcomes and the

wide availability of opioids (the mainstay of moderate to severe cancer pain management), a significant proportion of patients with cancer receive suboptimal analgesia, revealing the need to optimize its management in clinical practice. Common shortcomings in pain management include unstructured assessment, misconceptions about opioid treatment, use of treatment guidelines lacking explicit algorithms and poorly addressing clinicians' concerns about prescribing opioids, lack of systematic monitoring of outcomes, including adverse effects, and of consensus guidance on important obstacles in clinical practice, such as opioid-induced bowel dysfunction (OIBD) [6–10]. As acknowledged by the latest guidelines on cancer pain treatment, the lack of high-quality randomized controlled trials (RCTs) in the setting of cancer-related pain demands an improvement of study designs and a consensus approach to fully support clinical decisions, which are mostly left to the discretion of the clinician [11, 12]. Notwithstanding the proliferation of guidelines addressing pain in patients with cancer [11–13], the resulting recommendations are heterogenous and do not satisfactorily address the complex nature of both baseline and breakthrough pain (BTcP), thus preventing the implementation of an adequate analgesic approach. To achieve optimal outcomes, drug choices should be individualized to guarantee the best match between patients' characteristics and pharmacological features of analgesic medications. While the increasing availability of different opioid formulations should facilitate therapy individualization, the absence of comprehensive comparative trials requires physicians to rely on their understanding and experience when prescribing the medication. In this context, expert consensus recommendations may provide guidance in the absence of objective clinical data.

A previous Delphi survey from the Rational Use of Analgesics (RUA) project investigated the current clinical practices to manage pain in patients with cancer in Italy by gathering the opinion of almost 200 Italian specialists working in the palliative care field [14]. While a strong agreement was reached on the pivotal role of the assessment and control of pain in the

management of patients with cancer, some discrepancies between current guidelines and clinical practice were observed with a lack of consensus on items regarding the use of weak or strong opioids in treating uncontrolled pain [14]. These findings provided the rationale for developing a second Delphi survey to further explore some debated issues in cancer pain therapy in order to achieve consensus on what guides personalized therapy, on how to best approach a major indicator of poor clinical outcome and lower efficacy of opioid therapy, namely BTcP [15], and on how to promote earlier detection and effective treatment of unwanted gastrointestinal effects.

## METHODS

### Study Design

This study was conducted over a 5-month period (October 2019–February 2020) using a two-round Delphi method as previously described [14]. The Delphi method is commonly used to achieve a degree of consensus or agreement on a topic among experts, via an indirect, anonymous, iterative process. Briefly, a four-stage process was developed: (1) constitution of the steering committee in charge of the project; (2) a start-up meeting to identify the main topics; (3) two successive rounds of online surveys to collect the opinion of a panel of experts; and (4) analysis of results and discussion of conclusions by the steering committee. This work is part of the RUA project.

Ethics committee approval was not required for this study. In Italy and in many other parts of the world, this type of study is not among those that require the approval or written consent of research ethics committees (RECs), because it is observational and does not directly involve patients or healthy human subjects. All participants were aware of the study objectives and that the study results would be presented for this publication; all eligible participants are listed in the Acknowledgements. Participants agreed to participate and independently take part in the survey. No personal data was collected and all data were anonymized. For this reason, the privacy of the participants has been

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protected throughout, as per Italian Privacy Authority regulation on the protection of personal data, according to Italian law, as per Legislative Decree no. 196 of 30 June 2003, amended by Legislative Decree No. 101 of 10 August 2018, and Regulation (EU) 2016/679. Data were stored in a secure database protected by username and password.

### **Governance, Designation, and Identification of Experts**

The steering committee comprised a coordinator, responsible for the project, and five members randomly extracted from a list of professionals with renowned expertise in cancer pain management and palliative care. The steering committee was responsible for developing the statements for the Delphi study, performing the analysis, and interpreting the results. The steering committee identified the survey items by both reviewing the most recent publications and guidelines on cancer pain and analyzing the findings of the previous Delphi survey from the RUA Group with regard to the most debated and consensus-lacking statements on cancer pain management [14]. An initial list of 200 experts were invited on the basis of their documented expertise (authorship of research paper and/or at least 5 years of clinical experience in cancer or palliative treatment). A final board of 191 experts participated in the study.

### **Consensus Process**

Based on the findings of the literature review and of the previous Delphi survey from the RUA Group [14], a preliminary set of statements was drafted covering five relevant aspects of cancer pain management, namely strong opioid mode of administration, personalization of cancer pain therapy, multimodal therapy, BTcP, and OIBD. The consensus process was developed as previously described [14]. Briefly, gaps in the literature on key topics as well as the clinical issues for which consensus had not been achieved were identified by the members of the steering committee who decided which statements were to be included and how they were rephrased in the

final version of the questionnaire. The survey eventually had 17 statements. Supplemental Table 1 lists these statements and the related references from which they were derived.

The first-round questionnaire was delivered at RUA meetings held between October 28 and November 5, 2019, during which experts received a brief overview of the project. Each expert was then asked to complete the Delphi survey anonymously by logging onto an e-platform specifically developed for the RUA project. Participants were asked to rate their agreement to each statement from 0 to 4 (0, complete disagreement; 4, complete agreement) in a 5-point Likert-type scale. The median consensus score (MCS) and the interquartile range (IQR) were calculated for each statement. Consensus on a statement was achieved if the MCS (expressed as value at which at least 50% of participants agreed) was 4 and the IQR was 3–4.

In the second-round questionnaire, the first-round MCS and IQR values for each statement were enclosed and statements were rescored and re-rated. Eight statements were modified in the second round. Experts had the option to explain their choices in a comments section. The second-round questionnaire was also completed online. Finally, participants provided feedback on their interest in the RUA project.

### **Statistical Analysis**

Qualitative variables were summarized with absolute and relative (percentages) frequencies, whereas quantitative variables were described using means (standard deviations) or medians (interquartile ranges) based on their parametric and non-parametric distribution, respectively, as previously described in [14]. Chi-squared or Fisher exact tests were used to compare groups in relation to qualitative variables. A two-tailed *p* value of less than 0.05 was considered statistically significant. Analyses were performed using STATA version 15 (StataCorp, Texas, USA).

## **RESULTS**

The first-round questionnaire was completed by 97% (186 of 191) of selected experts during the

RUA meetings between October 28 and November 5, 2019. The second-round questionnaire was completed online between January and February 2020 by 163 of the 186 participants of the first round, thus achieving a response rate of 88%. Participants were palliative care experts with clinical experience in cancer pain management and were representative of the entire national territory and population density (75 from Northern Italy, 55 from Central Italy, and 56 from Southern Italy). Moreover, they were specialized physicians (32% oncologists, 22% palliative care experts, 16% specialized in anesthesia, and other specialists including geriatrics, internal medicine, hematology, gastroenterology, psychology, and pathology).

As shown in Table 1, consensus was reached for seven statements. Two statements

concerning strong opioid mode of administration achieved a high level of agreement, with more than 65% of the experts being in complete agreement with them. In particular, about 75% of panelists in the first round of the Delphi survey strongly agreed that the transdermal route of administration should be deemed an effective option when the oral route is not available for therapy with strong opioids and a similar degree of agreement was observed in the second round (68.7%). A similar proportion of participants (71.5% in the first round and 73.6% in the second round) completely agreed with the statement “Low dose of strong opioids can also be used for the treatment of moderate pain”. Three statements concerning personalization of cancer pain therapy achieved the highest level of agreement with percentages of participants agreeing with these statements

**Table 1** Statements with consensus in both the first and second rounds of the Delphi survey

Statement	First round		Second round	
	<i>N</i> (%)	Median (IQR)	<i>N</i> (%)	Median (IQR)
<b>Strong opioids mode of administration</b>				
When the oral route is not available for the therapy with strong opioids, transdermal administration stands as an effective option	139 (74.7)	4 (3–4)	112 (68.7)	4 (3–4)
Low dose of strong opioids can also be used for the treatment of moderate pain	133 (71.5)	4 (3–4)	120 (73.6)	4 (3–4)
<b>Personalization of cancer pain therapy</b>				
Immediate-release opioids are key for tailoring treatment to patients' needs	97 (52.2)	4 (3–4)	106 (65.0)	4 (3–4)
The knowledge of opioid pharmacokinetics is essential for therapy individualization	141 (75.8)	4 (3–4)	137 (84.1)	4 (3–4)
When a patient is poorly responsive to opioids, adjuvants analgesic can widen the therapeutic window and allow therapy continuation or outcome improvement	106 (57.0)	4 (3–4)	104 (63.8)	4 (3–4)
<b>Breakthrough cancer pain (BTcP)</b>				
A full clinical assessment remains the best method to diagnose BTcP	144 (77.4)	4 (3–4)	136 (83.4)	4 (3–4)
In BTcP management the choice of appropriate formulation of fast-onset opioids has to consider patient' characteristics	130 (69.9)	4 (3–4)	128 (78.5)	4 (3–4)

*N* (%) indicates the number (percentage) of clinicians who rated the question as 4 (complete agreement)

ranging from 52% to 75.8% in the first round and from 63.8% to 84.1% in the second round. Overall, there was strong consensus on the importance of knowing opioid pharmacokinetics for therapy personalization and on identifying immediate-release opioids as key for tailoring therapy to patients' needs. Furthermore, most participants agreed on the advantage to include adjuvant analgesics in patients poorly responsive to opioids as this may allow therapy continuation and outcome improvement.

Eight statements did not reach consensus in either round of the Delphi survey, even after being rewritten for the second round (Table 2). Participants disagreed with the use of anticonvulsants or antidepressants in combination with opioids in mixed pain as well as with switching opioid as a means to manage OIBD. Of note, few participants agreed with the statement "Opioid-induced bowel dysfunction is poorly detected and consequently treated later compared to other undesired events related to opioid therapy" [MCS 3, IQR 2–4]. Furthermore, no consensus was reached regarding four additional statements on strong opioid mode of administration with less than 25% of participants agreeing on considering oral morphine as first-line choice for the treatment of moderate-to-severe pain or on taking into account disease prognosis when selecting strong opioid mode of administration. In addition, no more than 1 in 3 participants was in complete agreement with "Transmucosal oral fentanyl formulations are subjected to greater variability in analgesic response compared to nasal ones" and with "Implantable systems for intrathecal drug delivery are able to relieve cancer pain refractory to conventional treatments".

Of note, two statements achieved consensus only in the second round of the Delphi survey (Table 3). Over 50% of participants concurred that, when treating BTcP, the dosing of rapid-onset opioids should be titrated in order to minimize the risk of adverse events [MCS 4, IQR (3–4)]. Similarly, almost 55% of panelists considered advisable the administration of specific  $\mu$ -opioid receptor antagonists with a peripheral activity in OIBD management.

Difference of opinion was observed when geographical distribution of participants was considered with a higher number of participants from Southern Italy being more in favor of the use of implantable intrathecal drug delivery systems in refractory cancer pain compared to those from Northern Italy (53.6% vs. 17.3%). Of note, more participants from Southern Italy disagreed with the statement about oral morphine as first-line choice in moderate-to-severe pain than those from Northern Italy (30.4% vs. 26.7%). Overall, the RUA project was strongly appreciated by the participants and was scored to be productive and fruitful by 90.9% and 87.1% of the participants at the end of the first and second rounds, respectively.

## DISCUSSION

Cancer pain remains prevalent; however, its undertreatment continues, mostly because of concerns regarding the use of strong opioids and the challenges that physicians may encounter in daily management including opioid titration, choice of mode of administration, and minimization of undesired effects such as OIBD. While clinicians are striving to fully address the goals of pain control in any patient with cancer, i.e., optimization of the patient's comfort and function while avoiding unnecessary adverse effects from medications, current evidence-based recommendations do not satisfactorily provide them with guidance on the several debated issues in cancer pain therapy, thus leaving them to rely solely on their experience and knowledge [11, 12]. In such a challenging scenario, consensus methods such as the Delphi survey technique can help enhance effective decision-making in clinical practice and provide guidance to improve appropriateness of analgesic therapy in patients with cancer. Based on the current guidelines and the emerging evidence on the management of some of the most burdensome aspects of cancer pain care, our survey aimed at reaching consensus among Italian palliative care specialists on five relevant aspects of cancer pain management, namely strong opioid mode of administration,

**Table 2** Statements without consensus in either the first or second round of the Delphi survey

Statement	First round		Second round	
	<i>N</i> (%)	Median (IQR)	<i>N</i> (%)	Median (IQR)
<b>Strong opioids mode of administration</b>				
The choice of strong opioid mode of administration should consider the disease prognosis (first-round statement)	43 (23.1)	2 (0–3)		
The disease prognosis does not impact on the choice of strong opioid mode of administration (revised statement)			34 (20.9)	2 (1–3)
Oral morphine represents the first choice for the treatment of moderate-severe pain (first-round statement)	46 (24.7)	3 (2–3)		
Oral morphine does not represent anymore the first choice in moderate-severe pain treatment (revised statement)			32 (19.6)	2 (1–3)
Transmucosal oral fentanyl formulations are subjected to greater variability in analgesic response compared to nasal ones (first-round statement)	63 (33.9)	3 (2–4)		
Transmucosal buccal fentanyl formulations are subjected to greater variability in analgesic response compared to nasal ones (revised statement)			59 (36.2)	3 (2–4)
Implantable systems for intrathecal drug delivery can relieve cancer pain refractory to conventional treatments (first-round statement)	60 (32.3)	3 (2–4)		
Implantable systems for intrathecal drug delivery are components of the armamentarium employed to relieve cancer pain refractory to conventional treatments (revised statement)			56 (34.4)	3 (2–4)
<b>Multimodal therapy</b>				
In mixed pain treatment anticonvulsants are the most useful drugs in combination with opioids (first-round statement)	65 (35.0)	3 (2–4)		
In the therapy of pain with a prevalent neuropathic component, anticonvulsants are the most useful drugs in combination with opioids (revised statement)			71 (43.6)	3 (3–4)
In mixed pain treatment antidepressants are the most useful drugs in combination with opioids (first-round statement)	25 (13.4)	2 (2–3)		
In the therapy of pain with a prevalent neuropathic component, antidepressants are the most useful drugs in combination with opioids (revised statement)			25 (15.3)	2 (2–3)
<b>Opioid-induced bowel dysfunction (OIBD)</b>				
Opioid-induced bowel dysfunction (OIBD) is poorly detected and consequently treated later compared to other unfavorable events related to opioid therapy (first-round statement)	64 (34.4)	3 (2–4)		
Opioid-induced bowel dysfunction (OIBD) is often poorly detected by palliative care specialists (revised statement)			23 (14.1)	2 (1–3)

**Table 2** continued

Statement	First round		Second round	
	N (%)	Median (IQR)	N (%)	Median (IQR)
Switching opioid is useful in opioid-induced bowel dysfunction (OIBD) (first-round statement)	33 (17.7)	2 (1–3)		
In case of severe opioid-induced constipation, it is useful to replace it with another opioid (revised statement)			12 (7.4)	2 (1–2)

N (%) indicates the number (percentage) of clinicians who rated the question as 4 (complete agreement)

**Table 3** Statements without consensus in the first round but consensus in the second round of the Delphi survey

Statement	First round		Second round	
	N (%)	Median (IQR)	N (%)	Median (IQR)
<b>BTcP</b>				
In severe BTcP treatment, about all rapid-onset opioids available on the market, the dosage should be titrated for suitable analgesia and to minimize the risk of adverse events	85 (45.7)	3 (3–4)	86 (52.8)	4 (3–4)
<b>Opioid-induced bowel dysfunction (OIBD)</b>				
The opioid effects on gastrointestinal tract are mediated by the mu-receptor, thus the administration of specific antagonists with a peripheral activity is advisable	85 (45.7)	3 (3–4)	89 (54.6)	4 (3–4)

N (%) indicates the number (percentage) of clinicians who rated the question as 4 (complete agreement)

personalization of cancer pain therapy, multi-modal therapy, BTcP, and OIBD.

### Strong Opioid Mode of Administration

Both ESMO (European Society for Medical Oncology) and EAPC (European Association of Palliative Care) guidelines recommend the use of low dose of strong opioids for the treatment of mild to moderate pain, although this indication is not currently part of the World Health Organization (WHO) guidance [11, 12]. In adherence to the aforementioned recommendations, more than 70% of participants agreed on the use of low dose of strong opioids for the

treatment of moderate pain. Although the oral route of administration of analgesic drugs should be advocated as the first choice [11], transdermal, transmucosal, and intranasal routes can be considered in patients with cancer who may have several contraindications to oral administration such as nausea, vomiting, problems with swallowing (dysphagia), impaired gastrointestinal function, and xerostomia (dry mouth syndrome) [8]. About strong opioid mode of administration, discrepancies between current guidelines and clinical practice were also observed. Despite ESMO recommendations that deemed oral morphine as the opioid of first choice for moderate to severe cancer pain, less than 25% of participants agreed with this



statement. Of note, participants seemed to support the notion, stated in the EAPC guidelines [12], that morphine has remained the first choice for reasons of familiarity, availability, and cost rather than proven superiority but no consensus was significantly reached. About 10% of patients with cancer have pain that is difficult to manage with oral or parenteral analgesic drugs [11], thus becoming refractory to all conventional strategies. To this end, intrathecal analgesia may serve as a therapeutic option for patients who have exhausted all other treatment potentialities as well as for patients experiencing side effects from their current treatment options. However, only 1 in 3 participants were in favor of such interventions for the management of refractory pain in line with the concerns related to the complex positioning of the implantable systems as well as their limited use in the presence of infections, coagulopathy, or very short life expectancy as may be seen in advanced cancers [11].

### Personalization of Cancer Pain Therapy

The problem in treating chronic pain and cancer pain is not the search for effective drugs but rather the appropriate choice and use of these therapies [16]. In this context, recent insights into the pain expression pathway have led to a paradigm shift in pain management, allowing clinicians to deliver personalized treatments tailored to the individual's needs [17]. Nonetheless, the development of more effective and personalized pharmacological and non-pharmacological pain treatment has been advocated as a useful approach to improve cancer pain treatment [18]. Consensus was gained on all statements concerning personalization of pain therapy with 65% of participants agreeing on the key role of immediate-release opioids in tailoring treatment to patients' needs in view of their recommended use in dose titration and therapy individualization [11, 12]. Of note, immediate-release formulations are much more flexible than long-acting preparations, both in the dose titration period and when the pain is poorly controlled [12]. Furthermore, an in-depth knowledge of opioid

pharmacokinetic profile was valued as relevant for therapy personalization with the highest level of agreement achieved among participants.

### Multimodal Therapy

Cancer pain is mediated by a mixture of nociceptive and neuropathic mechanisms. Adjuvant analgesics are frequently added to opioids to target specific neuropathic pain mechanisms [12] when opioids alone provide inadequate pain relief [11]. No consensus was reached on the use of antidepressants or anticonvulsants in combination with opioids in mixed pain. This finding suggests that there is limited clinical evidence supporting the efficacy and tolerability of this combination therapy with a recent systematic review showing that combining opioid analgesia with gabapentinoids did not significantly improve pain relief in patients with tumor-related cancer pain compared with opioid monotherapy [11, 19]. Thus, clinicians should balance the limited beneficial potential against the greater risk of undesired effects of such combination therapy.

### Breakthrough Cancer Pain

BTcP is reported in about 70% of patients with cancer and it is the main indicator of poor clinical outcome and lower efficacy of opioid therapy; however, mounting evidence suggests that BTcP is often managed suboptimally [15]. Poor BTcP management exposes the patient to a further worsening of conditions and also increases the costs of care for the healthcare system. In line with a greater awareness towards the BTcP-associated burden, participants strongly agreed on the importance of a full clinical assessment to effectively diagnose BTcP and on relevance of considering patients' characteristics when selecting fast-onset opioid formulations. Accordingly, an expert opinion document had provided a practical overview of the actions to take in BTcP diagnosis and recalled that accurate diagnosis demands careful evaluation of the specific characteristics of an individual patient's pain, including time of

onset, duration, peak intensity, relationship to background pain, location, type, and particular features, as well as any triggers and effects on their daily routine and/or quality of life [20].

During the past 10 years, interest in BTcP has been increasing, mostly encouraged by the development of novel pharmaceutical formulations specifically intended for the treatment of BTcP with transmucosal buccal and nasal fentanyl formulations offering advantages over the oral ones [21]. It has been suggested that several factors influence the pharmacokinetic profile of fentanyl, favoring a wide inter- and intra-patient variability [22]; knowledge of the profile is essential for guiding the safe use of opioids in cancer-related pain as well as to facilitate dose titration. The variable binding of serum fentanyl to plasma proteins may contribute to observed variability of pharmacokinetic and pharmacodynamic parameters among patients [23] and there is uncertainty whether differences in variability of analgesic response can be observed among fentanyl formulations. No full consensus was achieved among participants [MCS 3, IQR (2–4)] on the statement “Transmucosal oral fentanyl formulations are subjected to greater variability in analgesic response compared to nasal ones”. Such a finding may mirror the limited evidence explaining the wide intra- and inter-patient variability and demands further prospective research on fentanyl pharmacokinetics in patients with cancer using various fentanyl formulations during the phases of the disease trajectory [22].

In contrast, consensus was reached during the second round of the Delphi survey on the need, for all rapid-onset opioids, to titrate the dosage in order to minimize the risk of adverse events as also suggested by a previous expert opinion [20]. The rapidity of drug effect onset could make rapid-onset opioids a treatment option with greater risk of serious complications if not adequately prescribed; thus, earlier identification of patients more prone to develop complications because of misuse or risk of addition is of paramount relevance in clinical practice [24].

## Opioid-Induced Bowel Dysfunction

The management of opioid-induced adverse effects is an important aspect of pain management because each adverse effect requires a careful assessment and treatment strategy [11]. OIBD is a frequent complication in opioid users, which significantly limits quality of life and hinders treatment compliance, thus posing a substantial burden on healthcare systems [25–27]. No consensus was reached regarding the prevalent underestimation of this undesired condition by palliative care specialists, although a recent survey reported that nearly 60% of healthcare professionals failed to adequately inform patients on constipation as a highly incident side effect of opioids [27]. A similar finding was also observed when participants were surveyed on the effectiveness of switching opioid in OIBD management. The lack of consensus among participants mirrors the absence of a clear diagnostic definition and a lack of standardization in OIBD treatment, and demands better education of both physicians and patients regarding this distressing condition. In this scenario, an improved awareness about evidence-based treatments such as peripheral  $\mu$ -opioid receptor antagonists which appear to address the underlying pathophysiology of OIBD may inform appropriate therapeutic interventions to help relieve OIBD in patients with cancer [26, 28].

Overall, the present study confirms both the lack of agreement among pain experts in certain fundamental aspects related to opioid mode of administration and OIBD and the discrepancy between current guideline recommendations and palliative care specialists' patterns of clinical practice, thus suggesting that this may profoundly impact cancer pain treatment. Despite such discrepancies, the present study also reveals several important findings relative to clinical practice that are not well addressed in the scientific literature but may be highly relevant.

## Limitations of the Study

We acknowledge that the present study suffers from some limitations. The Delphi technique only provides qualitative results, resulting from the degree of agreement of the panelists, based on the evidence, their clinical practice, and experience. These recommendations must be taken as experts' opinions, acknowledging that this is a convenience sample of palliative care specialists in Italy and may not be generalizable to other populations where patterns of treatment and care as well as availability and therapeutic indications of the evaluated analgesic medications may vary. Furthermore, the potential sample of panelists was large and comprised experienced clinicians from different geographical areas; some panelists were based in Italian regions where the long-lasting use of palliative care has generated concerns regarding the invasive nature of intrathecal administration that would make participants from Northern Italy more reluctant to consider that mode of administration as an option compared to those from Southern Italy, where palliative care has been diffused only in recent years. Thus, such heterogeneity may explain why consensus was not reached on some statements.

## CONCLUSION

The findings of the second Delphi survey within the RUA project may assist clinicians in applying clinical evidence to routine care settings and call for a reappraisal of current pain treatment recommendations with the final aim of optimizing the clinical use of strong opioids in patients with cancer. It is clear that there is still much to do, to achieve an optimal and equalized therapy. The results also showed the necessity to increase the pharmacological knowledge on different analgesics.

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**Compliance with Ethics Guidelines.** Ethics committee approval was not required for this study. In Italy and in many other parts of the world, this type of study is not among those that require the approval or written consent of research ethics committees (RECs), because it is observational and does not directly involve patients or healthy human subjects. All participants were aware of the study objectives and that the study results would be presented for this publication; all eligible participants have been included in the list of collaborators. Participants agreed to participate and independently take part in the survey. No personal data was collected and all data were anonymized. For this reason, the privacy of the participants has been protected throughout, as per Italian Privacy Authority regulation on the protection of personal data, according to Italian law, as per Legislative Decree no. 196 of 30 June 2003,

amended by Legislative Decree No. 101 of 10 August 2018, and Regulation (EU) 2016/679. Data were stored in a secure database protected by username and password.

**Data Availability.** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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