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Consensus Statement | Substance Use and Addiction

Expert Panel Consensus on Management of Advanced Cancer–Related Pain in Individuals With Opioid Use Disorder

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Abstract

IMPORTANCE Opioid use disorder (OUD) is an important comorbidity in individuals with advanced cancer, in whom pain is common. Full-agonist opioid medications are the cornerstone of cancer pain management, but the existing literature does not address how to manage cancer pain in patients with OUD.

OBJECTIVE To conduct an expert panel to develop consensus on the appropriateness of management of cancer pain in individuals with co-occurring advanced cancer and OUD.

EVIDENCE REVIEW A 3-round modified Delphi process was completed from August to October 2020 with 2 cases: patient with advanced cancer, pain, and OUD treated with buprenorphine-naloxone or methadone. Participants rated management strategies in round 1, discussed results in round 2, and provided final responses in round 3. ExpertLens, an online approach to conducting modified Delphi panels, was used. Participants were experts in palliative care, addiction, or both, recruited by email from palliative care and addiction-focused professional groups, lists from prior studies, and snowball sampling. Data analysis was performed from November 2020 to July 2021.

FINDINGS Of 120 experts (median age, 40-49 years), most were White (78 participants [94%]), female (74 participants [62%]), and held MD or DO degrees (115 participants [96%]); 84 (70%) participated in all rounds. For a patient with OUD taking buprenorphine-naloxone, it was deemed appropriate to continue buprenorphine-naloxone with thrice-daily dosing. Continuing buprenorphine-naloxone and adding a full-agonist opioid was deemed to be appropriate for patients with a prognosis of weeks to months and of uncertain appropriateness for patients with a prognosis of months to years. For a patient with OUD taking methadone dispensed at a methadone clinic, it was deemed appropriate to take over prescribing and dose twice or thrice daily. Continuing methadone daily while adding another full-agonist opioid was deemed appropriate for patients with a prognosis of weeks to months and of uncertain appropriateness for those with a prognosis of months to years.

CONCLUSIONS AND RELEVANCE The findings of this qualitative study provide urgently needed, consensus-based guidance for clinicians and highlight critical research and policy gaps needed to facilitate implementation.

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Key Points

Question What is the consensus of experts in palliative care, addiction, or both on the appropriateness of strategies to manage advanced cancer–related pain in individuals with co-occurring opioid use disorder?

Findings In this qualitative study, experts deemed it appropriate to continue medication for opioid use disorder (buprenorphine-naloxone or methadone) and to dose methadone outside the context of a methadone clinic 3 times per day. The appropriateness of adding full agonist opioids to either buprenorphine-naloxone or methadone depended on prognosis.

Meaning This study provides urgently needed, consensus-based guidance for clinicians and highlights critical research and policy gaps needed to facilitate implementation.

+ Invited Commentary

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Introduction

Opioid use disorder (OUD) is an important comorbidity in individuals with advanced cancer. In 2019, the US National Survey on Drug Use and Health estimated that 0.5% of all adults, or 1.7 million people, had OUD.[1] Cancer also is a common disease, with 1.8 million incident cases and 607 000 cancer deaths each year.[2] Given cancer's association with risk factors common among individuals

with OUD, such as tobacco use, OUD is likely at least as common among patients with cancer as the national average.[3] Although no widely accepted estimates of OUD prevalence in individuals with advanced cancer exist, a systematic review[4] found that 21% to 29% of individuals taking long-term opioids developed opioid misuse, and 8% to 12% of individuals taking long-term opioids developed OUD. Studies also suggest that clinicians in palliative care, a discipline that focuses on caring for people with serious illnesses such as cancer, spend a substantial amount of time managing opioid misuse or use disorder in their practices.[5]

Pain occurs in 75% to 90% of patients with advanced cancer and often approaches moderate-to-severe levels, which requires intervention to maintain quality of life.[6-8] Full-agonist opioid medications, such as morphine and oxycodone, are the cornerstone of cancer pain management[9] and are widely recommended by oncology guidelines.[10,11] A recent study from the National Survey on Drug Use and Health found that approximately one-half of patients with a past-year cancer diagnosis were prescribed an opioid during that year.[12] Given this reliance on prescription opioids, safe and effective pain management may be particularly difficult to achieve for patients with OUD and advanced cancer.[13]

Two evidence-based, Food and Drug Administration–approved opioid agonist medications for OUD, buprenorphine and methadone,[14] are also approved to manage pain.[15,16] For OUD treatment, they are dosed daily, and buprenorphine is combined with naloxone as a misuse deterrent; for analgesia, they are prescribed at lower doses and higher frequency (multiple times daily). When used to treat OUD, both are highly regulated: methadone must be prescribed in federally licensed methadone treatment programs,[15,17-19] and buprenorphine-naloxone prescribers must have a special Drug Enforcement Agency waiver.[20] Despite their efficacy in managing pain and treating OUD separately, buprenorphine-naloxone and methadone have not been established as dual treatments for co-occurring OUD and cancer pain. Anecdotally, split-dosing these medications into 2 or 3 daily doses may help treat comorbid OUD and pain,[21] but this approach has not been formally studied. Full-agonist opioids (eg, morphine and oxycodone) are typically avoided in individuals with OUD. However, their use in patients with both cancer pain and OUD could be appropriate, with or without the continuation of buprenorphine-naloxone or methadone. Moreover, the best approach may differ according to prognosis, as patients with shorter prognoses have less opportunity to experience the benefits of pharmacological OUD treatment and the longer-term harms of full-agonist opioids, although we fully acknowledge that OUD-related harms occur in individuals at the end of life.

We engaged experts using an online modified Delphi approach to develop consensus on the appropriateness of strategies for managing cancer pain in individuals with co-occurring advanced cancer and OUD.[22,23] Expert panels are conducted when no empirical evidence (eg, randomized clinical trials) exists to answer a particular clinical question.[24] Delphi results are considered expert consensus–level evidence and may be used to generate clinical guidance.

Methods

For this qualitative study, the institutional review boards at the University of Pittsburgh and the RAND Corporation approved our data collection protocol. Participants provided informed consent through the survey. This study follows the Standards for Reporting Qualitative Research (SRQR) reporting guideline for qualitative studies.

We conducted 2 online modified Delphi panels that solicited the perspectives of palliative care and addiction clinicians on the appropriateness of different approaches to pharmacological management of pain and OUD in patients with advanced cancer. Focusing on patients with advanced cancer, whose pain treatment often centers on opioids, allowed us to present a homogeneous group of patients. In anticipation of differences in management based on prognosis, 1 panel (panel A) focused on patients with cancer with a prognosis of weeks to months, and another (panel B) focused on patients with prognoses of months to years. Otherwise, both panels were conducted using the same prespecified research protocol and used ExpertLens, a previously evaluated approach for

conducting online modified Delphi panels,[22,23,25,26] to rate, comment on, and discuss clinical scenarios exploring opioid therapy in palliative care patients with different prognoses. We developed scenarios based on strategies highlighted in the existing literature on management of cancer pain and on OUD.

Participants

We used email to recruit experts from a wide range of palliative care and addiction-focused groups. We also approached palliative care clinicians and used personal networks to identify additional experts. Interested clinicians completed a registration survey with questions about demographic variables, professional training, experience, and expertise. Race and ethnicity were self-reported through the survey and were assessed in this study to more fully describe our sample. Inclusion criteria were expertise in palliative care, addiction, or both (see the **Box**).

A total of 138 individuals were eligible to participate. Because a recommended size of online panels is 40 to 60 experts,[23] we invited more than 60 experts per panel to account for attrition, randomly assigned them to a panel, and balanced the panels in terms of expertise in palliative care and addiction medicine and professional identity (physician vs advanced practitioner). Experts who reported having expertise in both palliative care and addiction medicine were assigned to the addiction category.

Design

In round 1 (August 10, 2020, to August 25, 2020), experts reviewed, rated, and commented on 2 clinical scenarios describing a 50-year-old patient with advanced cancer taking active anticancer treatment who has pain related to cancer or its treatment and who has OUD. In the first scenario, the patient is treated with buprenorphine-naloxone. In the second, the patient is treated with methadone (see the **Figure** for a pictorial representation of the cases and eTable 1 in the Supplement for a complete description of both scenarios). The patient's prognosis was weeks to months or months to years, depending on the panel. Experts were instructed to assume they obtained a waiver to prescribe buprenorphine-naloxone for OUD from the Drug Enforcement Agency and that the patient's insurance covers this treatment. Experts rated the appropriateness of 5 to 6 strategies for managing a patient with cancer pain and OUD. Examples included split-dosing buprenorphine-naloxone, adding full-agonist opioids (ie, morphine or oxycodone) to buprenorphine-naloxone or methadone, or switching from 1 opioid agonist to the other. Experts used a 9-point Likert scale, from 1 (very inappropriate) to 9 (very appropriate) and explained their responses in free-text boxes (eFigure 1 in the Supplement).

In round 2 (September 10, 2020, to September 17, 2020), experts reviewed round 1 results. We present bar charts showing how their own responses compared with the group's distribution in eFigure 2 in the Supplement. Below each chart, we show color-coded statements describing whether the panel reached agreement and whether each management approach was deemed appropriate. We analyzed ratings using RAM's approach to analyzing expert panel data.[27] We also display summaries of thematic analyses of round 1 comments. Finally, experts used asynchronous, anonymous, moderated discussion boards to discuss round 1 results with other panelists. In round 3 (September 17, 2020, to October 8, 2020), experts were asked to provide their final response.

Statistical Analysis

To determine the existence of consensus among experts and the level of clinical appropriateness, we applied a 3-step analytical approach outlined in the RAND/UCLA appropriateness method user's manual[27] to the round 3 data in each panel separately (eFigure 3 in the Supplement).[28] To better contextualize our quantitative results, we thematically analyzed all expert comments. As in previous ExpertLens panels,[28,29] we grouped all comments for a given strategy by round 1 and round 3 numerical ratings to which they referred and added their round 2 comments. Data were coded by 3 individuals (not authors of this article) who were trained and supervised by a Delphi expert and a

Box. Recruitment

Participants were recruited from the following groups:
- American Academy of Hospice and Palliative Medicine
- Hospice and Palliative Nurses Association
- Buprenorphine Clinician Support Network
- Society of General Internal Medicine Pain Medicine and Opioid Policy and Advocacy Interest Groups, and
- Palliative Care Research Cooperative Pain and Opioids Special Interest Group.

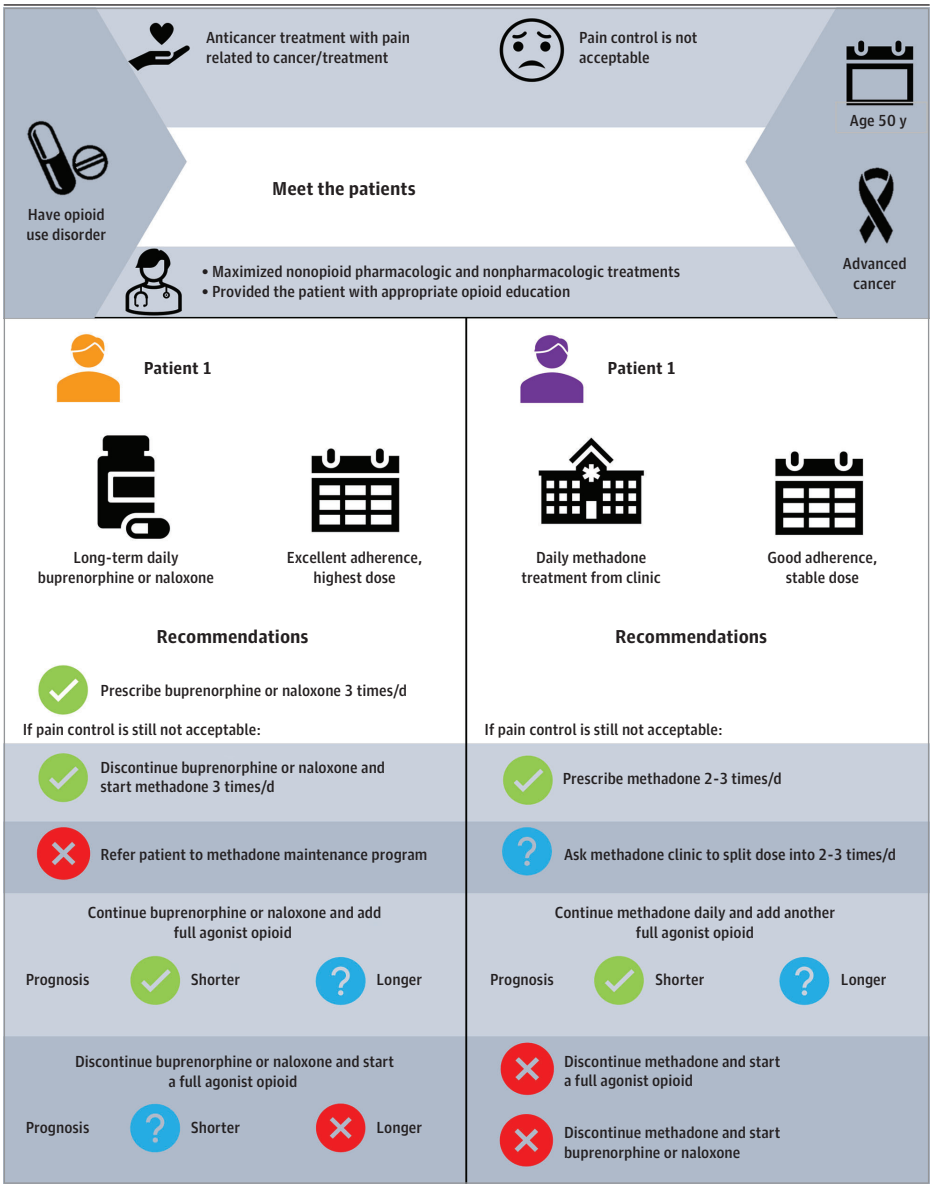
Individuals were eligible to participate if they were aged 18 years or older and
- were board-certified in addiction medicine, palliative care, or both OR
- had trained (in residency or fellowship) in addiction medicine, palliative care or both, OR
- demonstrated other expertise in adult addiction or palliative care (were waivered to prescribe buprenorphine-naloxone for opioid use disorder; prescribe buprenorphine-naloxone, methadone or other opioids in palliative care or addiction settings to manage pain or addiction; conduct research related to opioid prescribing in palliative care settings or outpatient opioid use disorder treatment or have spoken at national conferences about these topics).

qualitative researcher (D.K.), who reviewed results for consistency and developed higher-order themes. The team discussed any disagreement until consensus was reached. The lead author (J.S.M.) reviewed the final themes to ensure correct clinical interpretation. The data were analyzed using Excel software version 16.55 (Microsoft). Data analysis was performed from November 2020 to July 2021.

Results

Of the 129 invited experts, 120 (93%) participated in at least 1 round of either panel A (prognosis of weeks to months) or panel B (prognosis of months to years). Most of the experts were White (78 participants [94%]), female (74 participants [62%]), and held MD or DO degrees (115 participants [96%]), with a median age of 40 to 49 years (**Table 1**). Seventy percent (84 participants) participated in all 3 rounds.

Figure. Summary of Cases and Recommendations



Quantitative results are summarized in **Table 2**. Of 11 strategies considered, the panels reached identical decisions on the appropriateness of 7 strategies. The appropriateness of the remaining 4 differed according to prognosis. The next 2 subsections include detailed descriptions of our rating results for each case separately, adding qualitative results to provide additional context as needed. Key qualitative themes and illustrative quotes are presented in eTable 2 in the Supplement. The Figure summarizes the results. Both cases specified that the patient has cancer-related pain, and their pain and function are not acceptable.

Case 1: Patient With OUD Taking Buprenorphine-Naloxone

Regardless of prognosis, it was deemed appropriate to continue buprenorphine-naloxone with thrice-daily dosing (preferred to twice-daily dosing, the appropriateness of which depended on prognosis) (Table 2). If pain control was still not acceptable, the panel deemed appropriate discontinuing buprenorphine-naloxone and starting methadone with thrice-daily dosing (assuming the patient's corrected QT interval was normal). Although this strategy was deemed appropriate, experts noted legal concerns with prescribing methadone outside of an opioid treatment program. Methadone was viewed by some as a superior analgesic to buprenorphine-naloxone (although 1

Table 1. Expert Characteristics

Characteristic	Participants, No. (%)		
	Overall (N = 120)	Panel A (n = 57)	Panel B (n = 63)
Age, y			
30-39	34 (28)	15 (26)	19 (30)
40-49	40 (33)	21 (37)	19 (30)
50-59	25 (21)	13 (23)	12 (19)
60-69	20 (17)	8 (14)	12 (19)
≥70	1 (1)	0	1 (2)
Race			
Asian	18 (15)	4 (7)	14 (22)
Black	3 (3)	2 (4)	1 (2)
White	94 (78)	51 (89)	43 (68)
Other[a]	5 (4)	1 (2)	4 (6)
Prefer not to answer	1 (1)	0	1 (2)
Hispanic ethnicity	7 (6)	4 (7)	3 (5)
Gender			
Female	74 (62)	35 (61)	39 (62)
Male	46 (38)	22 (39)	24 (38)
Clinical role			
MD	115 (96)	56 (98)	59 (94)
Nurse practitioner	5 (4)	1 (2)	4 (6)
Time since completion of last postgraduate degree, y			
<5	28 (23)	10 (18)	18 (29)
5-9	20 (17)	11 (19)	9 (14)
10-14	20 (17)	13 (23)	7 (11)
≥15	51 (43)	23 (40)	28 (44)
Prescribing opioids for pain in ambulatory palliative care	72 (60)	32 (56)	40 (63)
Having a buprenorphine waiver	81 (68)	43 (75)	38 (60)
Prescribing buprenorphine-naloxone for substance use disorder in ambulatory palliative care	26 (22)	11 (19)	15 (24)
Prescribing buprenorphine-naloxone for substance use disorder in a different setting (eg, opioid treatment program, primary care)	47 (39)	25 (44)	22 (35)
Prescribing methadone in a methadone treatment program	14 (12)	6 (11)	8 (13)
Conducting research or presenting at a national conference on opioid prescribing in individuals with serious illness	44 (34)	24 (42)	20 (32)

[a] Other race included Native Hawaiian and American Indian.

expert noted a lack of head-to-head trials) with the ability to address both pain and OUD. However, it was deemed inappropriate to refer the patient to a methadone maintenance program because of concerns about the hardship of daily methadone clinic visits in someone with a serious illness, fragmentation of care by adding a new team of clinicians, and clinics' ability to address pain.

Continuing buprenorphine-naloxone and adding a full-agonist opioid (eg, oxycodone, morphine, hydromorphone, or fentanyl) to the buprenorphine-naloxone was deemed to be appropriate for patients with a prognosis of weeks to months, as a way to provide additional analgesia while continuing to treat OUD. Experts also noted concerns about the efficacy of full-agonist opioids in the presence of buprenorphine. One expert stated, "If the pain is not resolvable and prognosis is poor, it may be easier to discontinue the buprenorphine and switch to [full-agonist] opioids for pain." Continuing buprenorphine-naloxone and adding a full-agonist opioid was deemed to be of uncertain appropriateness for patients with a prognosis of months to years, depending on whether there was a good long-term relationship between the patient and practitioner, close monitoring was possible, and the plan for full agonist was only short term (eg, to address an acute pain management need). Discontinuing the buprenorphine-naloxone and starting a full-agonist opioid other than methadone was deemed to be of uncertain appropriateness for patients with a prognosis of weeks to months but inappropriate for patients with a prognosis of months to years. Hesitations were the same, including concerns about relapse with a full agonist, especially without buprenorphine-naloxone for OUD treatment.

Case 2: Patient With OUD Taking Methadone Dispensed at a Methadone Clinic

Regardless of prognosis, it was deemed appropriate to split the methadone dose into twice-daily or thrice-daily dosing, taking over the prescribing from the clinic, for reasons similar to those expressed in case 1 (**Table 3**). However, it was deemed inappropriate to discontinue methadone and start a full-agonist opioid, for reasons similar to those expressed in case 1, including transitioning the patient

Table 2. Results of Delphi Process for Case 1, a Patient With Opioid Use Disorder Taking Buprenorphine-Naloxone

Panel and recommendation	Round 3 decision[a]	Median score	Participants, No.
Panel A: prognosis of weeks to months			
A. Continue buprenorphine-naloxone and divide the original dose into twice-daily dosing	Appropriate	7	51
B. Continue buprenorphine-naloxone and divide the original dose into thrice-daily dosing	Appropriate	7	49
C. Continue buprenorphine-naloxone and add full-agonist opioid (eg, oxycodone, morphine, hydromorphone, fentanyl) to the buprenorphine-naloxone	Appropriate	7	47
D. Discontinue the buprenorphine-naloxone and start methadone with thrice-daily dosing (you may assume the patient's corrected QT interval is normal)	Appropriate	7	48
E. Discontinue the buprenorphine-naloxone and start a full-agonist opioid other than methadone (eg, oxycodone, morphine, hydromorphone, fentanyl)	Uncertain	5	45
F. Refer patient to methadone maintenance program	Inappropriate	1	48
Panel B: prognosis >1 y			
A. Continue buprenorphine-naloxone and divide the original dose into twice-daily dosing	Uncertain	6	53
B. Continue buprenorphine-naloxone and divide the original dose into thrice-daily dosing	Appropriate	7	52
C. Continue buprenorphine-naloxone and add full-agonist opioid (eg, oxycodone, morphine, hydromorphone, fentanyl) to the buprenorphine-naloxone	Uncertain	6	51
D. Discontinue the buprenorphine-naloxone and start methadone with thrice-daily dosing (you may assume the patient's corrected QT interval is normal)	Appropriate	7	49
E. Discontinue the buprenorphine-naloxone and start a full-agonist opioid other than methadone (eg, oxycodone, morphine, hydromorphone, fentanyl)	Inappropriate	3	49
F. Refer patient to methadone maintenance program	Inappropriate	2	48

[a] Experts used a 9-point Likert scale, from 1 (very inappropriate) to 9 (very appropriate). Decisions indicate a lack of disagreement and were considered appropriate if the median score was 6.5 to 9, uncertain if the median score was 3.5 to 6, and inappropriate if the median score was 0 to 3.5.

from methadone to buprenorphine-naloxone because of the patient being stable on methadone, concerns about inferior pain control with buprenorphine-naloxone, and challenges with buprenorphine-naloxone induction given methadone's long half-life.

The appropriateness of asking the patient's methadone clinic to split the dose into twice-daily or thrice-daily dosing was deemed uncertain. Some experts stated that methadone clinics are either not allowed or not willing to do this. Others thought that this approach, if possible, would be useful.

Continuing the methadone daily while adding another full-agonist opioid was deemed to be appropriate for patients with a prognosis of weeks to months to maintain the stability of continuing with the methadone clinic while also achieving additional analgesia. Experts noted that excellent communication with the methadone clinic, patient buy-in, and close monitoring are important. Additionally, experts noted the important role methadone clinics (and their "plethora of support structures") can play in managing OUD.

Continuing the methadone daily while adding another full-agonist opioid was deemed to be of uncertain appropriateness for patients with a prognosis of months to years. Experts raised concerns about having multiple prescribers. Split-dosing the methadone and taking over the prescribing by the clinic was thought by some experts to be a better approach for achieving analgesia, albeit for short-term pain in someone who is doing well and is in close communication with a methadone clinic.

Discussion

In this qualitative study, experts generally favored continuing treatment with methadone or buprenorphine-naloxone in patients with OUD, advanced cancer, and pain. However, this study raised important questions about the choice between buprenorphine-naloxone and methadone, how methadone should be prescribed for these individuals, and when it is appropriate to prescribe a full agonist.

The choice between buprenorphine-naloxone and methadone in individuals with OUD, advanced cancer, and pain is complex. Although there is some evidence as to the efficacy of buprenorphine-naloxone and methadone for cancer pain,[30] little is known about their comparative effectiveness with regard to pain or addiction outcomes in this patient population. For patients

Table 3. Results of Delphi Process for Case 2, a Patient With Opioid Use Disorder Taking Methadone

Panel and recommendation	Round 3 decision[a]	Median score	Participants, No.
Panel A: prognosis of weeks to months			
A. Continue the methadone daily (prescribed by the methadone clinic) and with the methadone clinic's agreement, add another full-agonist opioid (eg, oxycodone, morphine, hydromorphone, fentanyl) to the methadone	Appropriate	7.5	48
B. Ask the methadone clinic to switch the patient to split-dose methadone (2 or 3 times daily)	Uncertain	4	48
C. Switch the patient to split-dose methadone (2 or 3 times daily) prescribed by you	Appropriate	7	46
D. Discontinue methadone and start a different full-agonist opioid (eg, oxycodone, morphine, hydromorphone, fentanyl)	Inappropriate	3	45
E. Transition the patient to buprenorphine-naloxone	Inappropriate	3	45
Panel B: prognosis >1 y			
A. Continue the methadone daily (prescribed by the methadone clinic) and with the methadone clinic's agreement, add another full-agonist opioid (eg, oxycodone, morphine, hydromorphone, fentanyl) to the methadone	Uncertain	6	54
B. Ask the methadone clinic to switch the patient to split-dose methadone (2 or 3 times daily)	Uncertain	5	50
C. Switch the patient to split-dose methadone (2 or 3 times daily) prescribed by you	Appropriate	7	52
D. Discontinue methadone and start a different full-agonist opioid (eg, oxycodone, morphine, hydromorphone, fentanyl)	Inappropriate	2	51
E. Transition the patient to buprenorphine-naloxone	Inappropriate	3	52

[a] Experts used a 9-point Likert scale, from 1 (very inappropriate) to 9 (very appropriate), Decisions mean there was lack of disagreement and were considered appropriate if the median score was 6.5 to 9, uncertain if the median score was 3.5 to 6, and inappropriate if the score was 0 to 3.5.

taking buprenorphine-naloxone, experts generally thought it was appropriate to switch to split-dosed methadone if pain was not controlled. However, for patients already taking methadone, experts expressed reluctance to switch to buprenorphine-naloxone because of perceptions about inferior pain control and the challenges that methadone's long and unpredictable half-life poses to this transition. These findings underscore the importance of additional research to investigate how to optimally dose buprenorphine-naloxone and methadone in patients with advanced cancer pain and OUD and factors influencing the preferred choice.

In situations where methadone is preferred, our results underscored current challenges and opportunities related to methadone prescribing. Methadone for OUD is administered by opioid treatment programs licensed to dispense methadone, a system that exists in parallel to the rest of the medical system.[31] Although methadone prescribing outside these programs is legal for pain, it is illegal for OUD; the implications for treating pain in individuals with OUD are uncertain. This is troubling because patients with OUD can have complex medical challenges, and substance use is a factor associated with the risk of many serious medical illnesses, including cancer. This raises major challenges to treating OUD with methadone in patients who have a serious medical illness. In our study, experts noted that attending methadone clinics may be burdensome and, for a seriously ill patient, even inappropriate. Along these lines, the addiction literature includes perspectives from leaders in the field who have suggested that expanded access to methadone is appropriate in individuals regardless of medical comorbidity. As long as methadone licensure remains as it is today, some experts were comfortable with work-arounds, such as communicating with methadone clinics to ask for help with split-dosing the methadone, whereas others were not. Some experts worried that dosing methadone in this way does not adequately treat OUD. Interestingly, many experts were comfortable split-dosing the methadone themselves to circumvent the methadone clinic system entirely.

These findings demonstrate that the current methadone laws do not serve patients with serious illnesses well. Methadone has meaningful safety concerns, including unpredictable and long half-life, and has been associated with a disproportionate number of opioid overdose deaths compared with the number of prescriptions dispensed.[32] For some patients, methadone clinics provide structure and safety guardrails. However, the circumstances under which methadone can be safely used for OUD outside of methadone programs remains unclear.[33] What is clear is that some clinicians already prescribe methadone outside of clinics for patients with both pain and OUD, a circumvention of the system that suggests it may be time for a new approach, which could include special licenses and training for clinicians and creation of methadone programs that better attend to patients' pain and complex medical needs.

Even in situations where buprenorphine-naloxone may be preferred, there are substantial barriers to buprenorphine-naloxone access. Although any physician (and in some states advanced practitioners) can get a Drug Enforcement Agency waiver to prescribe buprenorphine-naloxone, uptake of the waiver is low.[34] Even if the waiver requirement is removed, as some experts have urged,[35] clinician adoption of buprenorphine-naloxone prescribing should be studied and addressed.

Finally, experts grappled with how to use full agonists other than methadone in patients with advanced cancer pain and OUD. Experts agreed that for patients with a prognosis of months to years, full-agonist opioids alone are inappropriate but may be appropriate for those with a prognosis of weeks to months. In addition, experts raised concerns about the risks of adding full agonists to methadone or buprenorphine-naloxone. Some experts suggested that continuing buprenorphine-naloxone reduces full agonists' analgesic potential, although the perioperative literature suggests it does not.[36-39] Prospective studies examining these risks would provide much-needed clarity.

Limitations

This study has limitations. Appropriate expert selection is always a threat to Delphi study results. We recruited a large number of clinicians with robust addiction and palliative care expertise, but few advanced practitioners, who represent a substantial amount of the care provided to patients with

advanced cancer in the US. In addition, we restricted experts to palliative care and addiction clinicians, whom we though would have the most relevant expertise. However, this may reduce generalizability of our findings to other settings in which patients with advanced cancer are treated, such as oncology and primary care. Despite being palliative care and addiction experts, a minority of experts prescribed buprenorphine-naloxone in ambulatory palliative care settings, and a minority prescribed methadone in a methadone treatment program. This lack of direct experience may affect their view of appropriateness of some of the approaches queried. Although our expert panels were much larger than in-person panels, not all experts engaged in all 3 rounds. We retained 70% of experts, which is better than in many previously reported online Delphi studies.[40-42] Furthermore, as is common in appropriateness panels,[27] we did not address issues related to policy or cost, which were beyond the scope of this study.

Conclusions

This study provides crucial, urgently needed, evidence-based guidance for clinicians caring for patients with advanced cancer pain and OUD. It brings to light important research questions key to improving care for patients with advanced cancer. Finally, it lays out a policy agenda that highlights gaps in our ability to provide the best quality care for these patients. Leaders at all levels—health systems, insurers, regulators, legislators, and professional organizations—must work collaboratively to address these gaps.

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SUPPLEMENT.

eFigure 1. Round 1 Questions
eFigure 2. Round 2 Feedback and Discussion
eFigure 3. Statistical Approach to Analyzing Data About Appropriateness of Management Strategies From a Modified Delphi Panel
eTable 1. Case Scenarios
eTable 2. Buprenorphine-Naloxone and Methadone Qualitative Summaries