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Expert consensus-based guidance on approaches to opioid management in individuals with advanced cancer-related pain and nonmedical stimulant use

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

CONFLICT OF INTEREST STATEMENT

The other authors declare no conflicts of interest.

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Abstract

Background: Clinicians treating cancer-related pain with opioids regularly encounter nonmedical stimulant use (i.e., methamphetamine, cocaine), yet there is little evidence-based management guidance. The aim of the study is to identify expert consensus on opioid management strategies for an individual with advanced cancer and cancer-related pain with nonmedical stimulant use according to prognosis.

Methods: The authors conducted two modified Delphi panels with palliative care and addiction experts. In Panel A, the patient's prognosis was weeks to months and in Panel B the prognosis was months to years. Experts reviewed, rated, and commented on the case using a 9-point Likert scale from 1 (very inappropriate) to 9 (very appropriate) and explained their responses. The authors applied the three-step analytical approach outlined in the RAND/UCLA to determine consensus and level of clinical appropriateness of management strategies. To better conceptualize the quantitative results, they thematically analyzed and coded participant comments.

Results: Consensus was achieved for all management strategies. The 120 Experts were mostly women (47 [62%]), White (94 [78%]), and physicians (115 [96%]). For a patient with cancer-related and nonmedical stimulant use, regardless of prognosis, it was deemed appropriate to continue opioids, increase monitoring, and avoid opioid tapering. Buprenorphine/naloxone transition was inappropriate for a patient with a short prognosis and of uncertain appropriateness for a patient with a longer prognosis.

Conclusion: Study findings provide urgently needed consensus-based guidance for clinicians managing cancer-related pain in the context of stimulant use and highlight a critical need to develop management strategies to address stimulant use disorder in people with cancer.

Keywords

cancer; cancer pain; opioids; stimulants; substance use

INTRODUCTION

Building evidence-based approaches for managing co-occurring opioid and nonmedical stimulant use is important in cancer care, given the high rates of stimulant use and ubiquity of prescription opioids.[1,2] Clinicians who treat cancer pain with opioids regularly encounter nonmedical stimulant use (i.e., methamphetamine, cocaine), yet there is little evidence-based management guidance.[3,4] Among people with cancer who receive urine toxicology testing, nonmedical stimulant use is the second most common unexpected substance detected on urine screening after cannabis.[5–7] Non-prescribed stimulant use has been reported in nearly 10% of cancer survivors, three times the reported rate in the US population.[8] People may combine the use of nonmedical stimulants with opioids to ease the rapid "high" that can occur with nonmedical stimulants alone and minimize the sedating effects of opioids.[9,10] Additionally, people with cancer may use nonmedical stimulants to treat common cancer-

related symptoms such as fatigue, enhance the analgesic properties of opioids to treat pain, or treat unaddressed attentional disorders that are made worse by the stresses of cancer and its treatment.[11–14]

The use of opioids and nonmedical stimulants together increases the risk of harm, including overdose and death.[15] Nonmedical stimulant use alone or in combination with opioids can have unpredictable effects because of variations in stimulant purity and contaminated drug supplies.[16] National estimates indicate combined nonmedical stimulants and opioid overdose deaths are increasing sharply. In 2017, between 50.4%–72.7% nonmedical stimulants involved opioids (whether by simultaneous use or because the stimulant drug supply is commonly contaminated with fentanyl).[17–20] For people with cancer, stimulant harms maybe even pronounced because of high rates of noncancer comorbidities, such as cardiac disease or polypharmacy.[21]

Co-occurring nonmedical stimulant use in individuals with cancer pain-prescribed opioids is a significant clinical challenge.[22] Despite this, there are no guidelines or empiric studies (e.g., trial testing or observational studies comparing various management strategies) for how to approach opioid decision-making in this complex situation.[23] To address this gap, we used a Delphi approach to identify expert consensus on opioid management strategies for people with advanced cancer who use methamphetamine or cocaine. To account for potential differences in expected treatment length that could complicate risk/benefit analyses of opioid and stimulant management, we stratified panels based on prognosis.

MATERIALS AND METHODS

We conducted two online Modified-Delphi on seven common clinical scenarios related to the intersection of substance use and cancer pain management. This analysis focuses on one scenario involving strategies for cancer pain management with cocaine or methamphetamine use and prescribed opioids. Findings from other clinical scenarios explored are published elsewhere.[24,25] The study follows the guidance on conducting and reporting Delphi studies (CREDES) to develop best practice guidance in palliative care.[26]

Participants

We recruited experts by email from a wide range of palliative care and addiction groups who met pre-specified eligibility criteria (Table 1). Interested experts completed a registration survey on demographics, professional training, experience, and expertise (palliative care and/or addiction).

A total of 138 individuals met our eligibility criteria and were invited to participate. We invited 60 experts per panel to adhere to the recommended size of online panels of 40–60 participants. Experts were randomly assigned to either Panel A or B and balanced in terms of expertise (palliative care and addiction) and discipline (physician and advanced practice provider). Experts reporting both addiction and palliative care expertise were included in the addiction category for the purposes of analyses and were identified as having overlapping experience in the illustrative quotes.

Design

Institutional review boards at the University of Pittsburgh (Study 19110301) and the RAND Corporation (Study 2020-0142) approved the data collection protocol. We administered the three-round modified-Delphi process following the principles of the RAND/UCLA Appropriateness Method (RAM) process using ExpertLens, a previously evaluated approach for conducting online modified-Delphi panels allowing experts to rate, comment, and discuss clinical scenarios and management strategies. Experts completed informed consent when first accessing ExpertLens.

Preliminary data suggest that management may differ according to prognosis.[27] Patients expected to live weeks to months rather than years may have less opportunity to experience stimulant harms or engage in treatment for stimulant use disorder. Therefore, Panel A focused on patients with cancer who had a prognosis of "weeks to months" and Panel B focused on a prognosis of "months to years." Otherwise, we used identical procedures for both panels as outlined in our published research protocol.[28]

In Round 1 (August 10–August 25, 2020), experts reviewed, rated, and commented on the case and management strategies presented in Figure 1. We instructed experts to assume they had obtained the previously required waiver to prescribe buprenorphine/naloxone for opioid use disorder (OUD) from the Drug Enforcement Agency and that the patient's insurance covered this treatment.

Experts used 9-point Likert scales (1 = "very inappropriate" and 9 = "very appropriate") to rate the appropriateness of the following potential management strategies: (1) continue full agonist opioid; (2) increase monitoring (more frequent visits, short prescriptions); (3) taper opioids either slowly or rapidly; and (4) transition to buprenorphine/naloxone. These strategies are common opioid management strategies in people with noncancer chronic pain.[29,30] We also asked experts to explain their ratings in free-text boxes.

In Round 2 (September 10–September 17, 2020), experts reviewed bar charts showing their responses and their panel's distribution of Round 1 responses. Color-coded statements described whether the panel reached an agreement and showed the appropriateness of management strategies. Experts reviewed summaries of thematic analyses of Round 1 comments. They used anonymous, asynchronous, moderated discussion boards to discuss Round 1 result with other experts in their panel.

In Round 3 (September 17–October 8, 2020), experts provided final responses that reflected the dialogue in Round 2. We allowed, but did not require, experts to change their initial responses.

Data analysis

We determined expert agreement and/or disagreement on clinical appropriateness from Rounds 1 and 3 (Figure S1) using the analytic approach outlined in the RAM manual and previous ExpertLens panels.[31,32] If agreement existed, the median values were used to determine whether the management strategy was appropriate, uncertain, or inappropriate. We determined the final appropriateness using Round 3 data with the approach outlined in

the online supplement (Figure S2). We followed an identical process for data analysis for each of the two panels.

As in previous ExpertLens panels, we grouped expert comments by numerical ratings, coded them, and analyzed them thematically.[31,33,34] Three trained nonauthors supervised by a Delphi expert/qualitative researcher (D.K.) developed higher-order themes and reviewed them for consistency for all results. The team discussed disagreement until consensus was achieved and confirmed the appropriate clinical interpretation.

RESULTS

Of 129 invited experts, 120 (98%) participated in at least one round and 70% participated in all three rounds. Attrition did not vary among palliative care and addiction experts. Most experts were female, White, and held MD or DO degrees (Table 2).

The quantitative results are provided in Table 3; Figure 2 provides a pictorial of the case and results. Experts from Panels A and B reached the same decision on four of the five management strategies.

- Regardless of prognosis, experts deemed increasing monitoring to be appropriate (Panel A round 3 median value = 9: Panel B round 3 median value = 8).

To improve safety and lessen the risk of accidental overdose, experts across both panels described the importance of patient education on stimulant harms, continued random drug testing to monitor for a pattern of stimulant use, and shorter prescription lengths. Experts further explained that close follow-up enables them to establish trust, develop rapport that can help them understand the patient's motivation to use nonmedical stimulants, and determine if a substance use disorder is present.

- Regardless of prognosis, continuing the patient's opioids was also considered appropriate (Panel A and B round 3 median value = 7).

Experts commented that to avoid compromising the patient's pain control, they would not adjust opioid management unless stimulant use was a persistent issue.

In Panel A, experts weighed cancer and pain control as a more important factor in decision-making than stimulant use. Some experts expressed indifference about stimulant use when the prognosis is short. ExpertA03 (addiction expert) noted "they may have a stimulant use disorder, but they still have terminal cancer" and another addiction expert (A64) said "if prognosis is just weeks to months and pain is well controlled, not sure I really care about other illicit substance use." Other experts (A34, palliative and addiction expert) worried less about polysubstance use with nonmedical stimulants than other substances such as nonmedical opioids, alcohol, and benzodiazepines. For example, expert A14 (palliative care expert) said "short prognosis, good pain control, and no increased [risk for] respiratory depression with the combination use of cocaine/methamphetamine and opioids makes me less worried."

In Panel B, experts said it was appropriate to continue opioids so long as stimulant use was not an ongoing issue. Expert noted that stimulant use would not change opioid management

if it “was the first occurrence” (B15, palliative care expert), “a one-off” (B24, palliative and addiction expert) or there was an “explanation” (B31, addiction clinician). For example, experts wondered if stimulant use was motivated by side effects: “am I giving too many opioids is that why they need a stimulant” (B50, addiction expert). If stimulant use persisted or there were signs of a stimulant use disorder, some palliative care experts (B40, B41, B57) were less comfortable and “struggle with the right decision” as to whether to continue opioids long-term. In instances of a longer prognosis, palliative care experts (B15 and 26) said they would refer to an addiction specialist.

- Regardless of the prognosis, experts agreed that it was inappropriate to taper the patient’s opioids slowly (Panel A and B round 3 median value = 3) or rapidly (Panel A and B median value = 1)

Palliative and addiction experts in both panels reported that tapering opioids was “punitive” (A55, B11, B28, B39, B16), “cruel” (B22), “disruptive” (A62), “not indicated” (A09, A11, A23, A42, B36, B33), and “create more problems” (A36, B60) including “undue suffering” (A04) or “opioid withdrawal” (A20). Moreover, experts highlighted that opioid tapering would not address the underlying issues of stimulant use and rapid tapering was almost “never the right thing” (A01, palliative and addiction expert).

Transition the patient to buprenorphine/naloxone was deemed inappropriate in patients with a shorter prognosis but of uncertain appropriateness for a patient with a longer prognosis (Panel A round 3 median value = 3: Panel B round 3 median value = 4).

In Panel A, experts emphasized that buprenorphine/naloxone is not indicated because the person has cocaine use, not an OUD. Addiction experts (A03, A32, A40, A42, A54, and A57) would not start buprenorphine/naloxone until after reviewing diagnostic criteria and making a diagnosis of OUD. A palliative care expert (A53) said “I would refer to addiction medicine guidance and try to coordinate management.”

In Panel B, experts from addiction and palliative care noted rotation to buprenorphine/naloxone is typically reserved for people with OUD because buprenorphine/naloxone does not address stimulant use. However, several palliative care experts said they would “consider it” (B01, B11, B15, B40).

Across both panels, palliative care experts had variable comfort with buprenorphine, and some commented on wanting co-management with an addiction expert (A53, A47). One palliative expert (A47) commented “I’ll admit that I have limited experience with this approach” (A47); another (B16) said “this [rotation] is very difficult in a patient on an opioid with tolerance; “ whereas another palliative expert (B07) said they “tend to do this if it’s been a recurrent safety concern.” However, addiction experts (A23, A32, A42, B33, B48, and B51) stated that there is no evidence of an OUD diagnosis or indication to switch if the current opioid regimen is working for pain and function.

DISCUSSION

Our findings address a critical gap previously identified by the Centers for Disease Control and Prevention, National Cancer Comprehensive Network, American Society of Clinical

Oncology, and others: the need for evidence for appropriate opioid management strategies in people with comorbid substance use including individuals with cancer.[35,36] This study also amplifies the need to address gaps in treating stimulant use and stimulant use disorders within cancer care.

Experts approached stimulant use in individuals with cancer with an eye toward monitoring the patient while prioritizing analgesia by continuing opioids. Based on their responses, experts seemed to correctly identify that isolated stimulant use is not necessarily indicative of a substance use disorder.[37] Monitoring strategies offered by experts included more frequent follow-up, regular drug testing, patient education, and short prescriptions to determine if a pattern of use was present. A prior Delphi study identifying management approaches to cocaine use in individuals with opioid misuse in primary care settings supports the importance of re-education about opioid safety and frequent monitoring as a first step.[30] Experts in the present study also often expressed a desire to explore whether nonmedical stimulants were used to address opioid or cancer-related side effects such as sedation. However, regardless of the reason for stimulant use and prognosis, analgesia was seen as a priority, and stopping opioids was considered inappropriate. This is consistent with our prior work in people with cancer and noncancer chronic pain, in which we found that tapering or stopping opioids was nearly never the initial step in addressing any opioid misuse behavior and was only considered if a substance use disorder was present or if there was a pattern of stimulant use.[25,30,38]

Strategies to directly address stimulant use in patients with cancer were less clear in our expert panel. In patients with a longer prognosis, experts mentioned referring the patient to addiction medicine. However, it was unclear what participants hoped addiction medicine would specifically do, and many people with cancer do not have access to an addiction specialist. Additionally, there are no Food and Drug Administration-approved pharmacologic therapies to treat stimulant use disorder treatment and nonpharmacologic therapies such as contingency management and behavioral interventions may be difficult to access.[39] It is also unknown whether these approaches are feasible, acceptable, or effective in individuals with serious illness. In our other work, we have also found that isolated care models that purely focus on substance use disorder, such as opioid treatment programs, appear less optimal for people with cancer because of the burdens of additional appointments, declining functional status, and lack of attention to cancer-related pain.[24,25] Our study and related literature suggest an urgency for integrated care and a research agenda focused on the unique needs of people with cancer and co-occurring substance use.[40–42]

Many experts embodied the spirit of harm reduction, an approach that avoids punishment (i.e., not abruptly stopping opioids and prioritizing pain control),[43] but some experts were not overly concerned by stimulant use in a person with cancer. Surprisingly, some experts had a nihilistic stance questioning whether interventions to improve safety are worthwhile in the context of cancer.[44] This finding suggests in the context of cancer clinicians may miss harm reduction opportunities. Simply harm reduction interventions may include providing naloxone, educating people on stimulant supply, or providing fentanyl drug testing because patients may not be aware stimulant supply can contain additional opioids.[45] When stimulant use was a regular occurrence in people with a longer prognosis, experts considered

switching to buprenorphine. We would interpret this finding to mean that buprenorphine rotation is reasonable to consider as a harm reduction approach, presumably to reduce the risk associated with a full agonist and stimulant combination. This is certainly something we see in clinical practice and implemented in noncancer chronic pain populations,[46] although to our knowledge there is no evidence as to its effectiveness to reduce opioid harms in people with cancer. In sum, although there is increased recognition that harm reduction is an important intervention for people with cancer[47,48] and punitive approaches to substance use are not effective,[49] our results underscore an opportunity to refine the implementation of harm reduction strategies in people with cancer and stimulant use.

Limitations to this study must be noted. The first is the potentially low replicability of panel results. We conducted one panel for each case (one longer prognosis and another shorter). We attempted to offset this weakness by increasing the panel size. Our sample is larger than the traditional 9- to 15-person panel, allowing us to engage more experts and increase our validity. Overall, Delphi studies are considered Level V evidence (expert opinion), and further work should test these strategies.[26] We intended to capture the expertise of palliative care clinicians frequently called upon to manage complex cancer pain and opioid misuse and addiction experts who care for people with stimulant use, but this may reduce the generalizability of our findings in other settings where cancer patients receive care or specialty palliative, and addiction care is not accessible.[27,50,51] The management of cancer-related pain and stimulant use is an area of rapidly changing practice; it is possible that consensus on management may change over time, particular with regard to potency and contamination of the existing stimulant supply and as more empiric evidence become available. Moreover, we specifically considered nonprescribed stimulant use, but prescribed stimulant misuse may also yield alternative treatment approaches.

In conclusion, this study provides consensus-based management strategies that can guide clinicians caring for patients with cancer-related pain treated with prescription opioids, alongside nonmedical stimulant use. The findings highlight the need for evidence, education, and an integrated management approach to substance use to better serve people with cancer-related pain and co-occurring stimulant use. Future research should focus on harm reduction, implementation strategies, and a better understanding of management approaches to regular nonmedical stimulant use or stimulant use disorders in people with cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Plain Language Summary

- Among palliative care and addiction experts, regardless of prognosis, it was deemed appropriate to continue opioids, increase monitoring, and avoid opioid tapering in the context of cancer-related pain and nonmedical stimulant use.
- Buprenorphine/naloxone transition as a harm reduction measure was inappropriate for a patient with a short prognosis and of uncertain appropriateness for a patient with a longer prognosis.

Case: 50-year-old patient (unspecified gender) with advanced cancer (defined as cancer that is unlikely to be cured or controlled with treatment), on active anti-cancer treatment, with pain related to their cancer or its treatment.

- The patient does not have a history of an opioid use disorder (OUD).
- They have been prescribed a full agonist opioid (s) (e.g., oxycodone, morphine, hydromorphone, fentanyl, methadone doses three times daily).
- You send appropriate screening and confirmatory urine drug tests. They are positive for the opioid(s) you prescribe and for non-medical cocaine or methamphetamine. Other urine drug testing findings are as expected.
- The patient's pain control and function are acceptable.

You discuss the urine results with the patient, and they acknowledge recent cocaine or methamphetamine use.

FIGURE 1.
Delphi case.

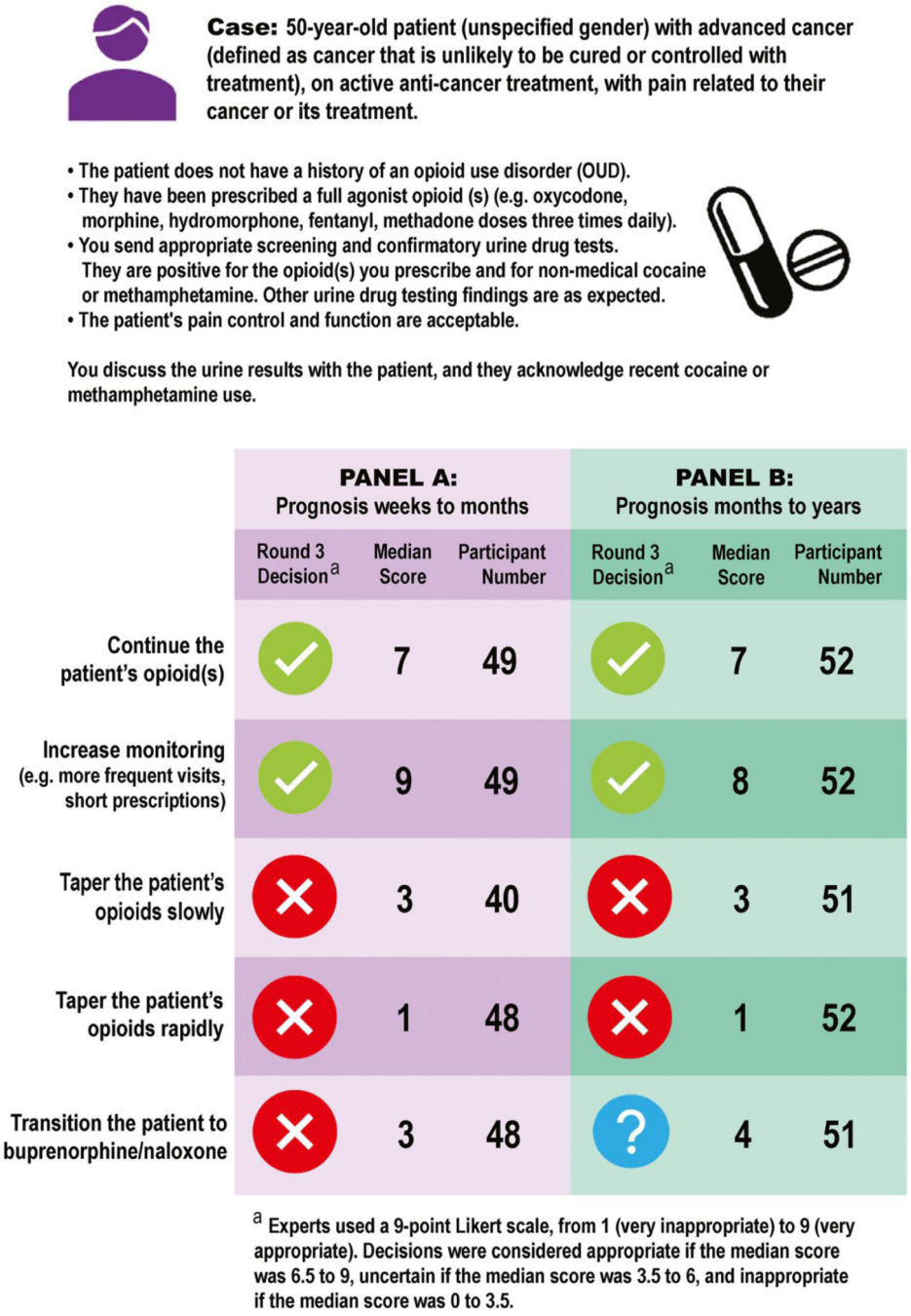

FIGURE 2.
Pictorial of results.

TABLE 1

Recruitment and eligibility.

Groups from which participants were recruited:
• 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
• Palliative Care Research Cooperative Pain and Opioids Special Interest Group
Individuals were eligible to participate if they were >18 years old and
• were board-certified in addiction medicine, palliative care, or both OR
• completed training (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 OUD; 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 OUD treatment or have spoken at national conferences about these topics).

Abbreviation: OUD, opioid use disorder.

TABLE 2

Participant characteristics.

Characteristics	Participant No. (%)		
	Overall *N* = 120	**Panel A *N* = 57**	**Panel B *N* = 63**
Age, years 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 or older	1 (1)	0 (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 (0)	1 (2)
Ethnicity Hispanic	7 (6)	4 (7)	3 (5)
Gender Female	74 (62)	35 (61)	39 (62)
Male	46 (38)	22 (39)	24 (38)
Clinical role Physician	115 (96)	56 (98)	59 (94)
Nurse practitioner	5 (4)	1 (2)	4 (6)
Time since completion of last post-graduate degree Less than 5 years ago	28 (23)	10 (18)	18 (29)
5–9 years ago	20 (17)	11 (19)	9 (14)
10–14 years ago	20 (17)	13 (23)	7 (11)
15 or more years ago,	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 (e.g., opioid treatment program, primary care)	47 (39)	25 (44)	22 (35)
Prescribing methadone in a methadone treatment program	14 (12)	6 (11)	8 (13)

Characteristics	Participant No. (%)		
	Overall *N* = 120	Panel A *N* = 57	Panel B *N* = 63
Conducting research or presenting at a national conference on opioid prescribing in individuals with serious illness	44 (34)	24 (42)	20 (32)

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

TABLE 3

Results.

	Panel A: prognosis weeks–months			Panel B: prognosis months to years		
	Round 3 decision[a]	Median score	Participant no.	Round 3 decision[a]	Median score	Participant No.
A. Continue the patient's opioid (s)	Appropriate	7	49	Appropriate	7	52
B. Increase monitoring (e.g., more frequent visits, short prescriptions)	Appropriate	9	49	Appropriate	8	52
C. Taper the patient's opioids slowly	Inappropriate	3	40	Inappropriate	3	51
D. Taper the patient's opioids rapidly	Inappropriate	1	48	Inappropriate	1	52
E. Transition the patient to buprenorphine/naloxone	Inappropriate	3	48	Uncertain	4	51

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