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Opioid-Induced Constipation: A Prospective Observational Study on Bowel Function Assessment and Laxative Use in Advanced Cancer Patients Treated with WHO Step III Oral Opioids

Caterina Magnani[1]*, Diana Giannarelli[2], Alice Calvieri[1], Ana Dardeli[1], Arianna Lombardi[1], Valeria Tomasini[1], and Giuseppe Casale[1]

[1]Palliative care and Pain Relief, Antea Palliative Care Unit, Italy
[2]Department of biostatistics, Regina Elena National CancerInstitute, Italy

*Corresponding author
Caterina Magnani, Palliative care and Pain Relief, Antea Palliative Care Unit, Piazza Santa Maria della Pietà, 5, Pad XXII, 00135, Rome, Italy, Fax: 390630332555; Tel: 3906303321/393484455024; Email: c.magnani@antea.net; ricerca@antea.net

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- Opioid-induced constipation
- Constipation
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Abstract

Objective: Opioids are effective in cancer pain management but their use is frequently complicated by side effects such as constipation. The aim of the study was to assess opioid-induced constipation (OIC) in a sample of palliative care cancer patients under treatment with WHO step III oral opioids. A secondary aim was to describe laxative medication use in the same sample.

Method: This was a prospective, observational study of 14-day duration. Subjects with a documented history of cancer pain in treatment with around-the clock oral strong opioids were eligible to participate in the study.

Results: The analysis included 97 patients (mean age 76.0 ± 10.1): 50 were under treatment with oxycodone/naloxone, 25 with morphine, 20 with oxycodone and 2 with hydromorphone. The mean BFI was 35.67 ± 19.38 at recruitment and there were no significant modifications within the 14 days of study. The percentage of non-constipated patients (BFI <28.8) was higher in the OXN group than in the other groups, at both T1 (7 days after recruitment) and T2 (14 days after recruitment) ($p<0.05$). During the study period 46.4% of patients were under treatment with laxative medications. Patients in treatment with oxycodone and morphine consumed more laxatives than the OXN (chi-square 11.30, p-value 0.0007). 87.4% patients referred laxatives AEs.

Conclusions: The study was limited due to difficult advanced cancer patients' recruitment. However this work reinforces the need of further research in palliative care to pro¬vide evidence-based guidance on OIC management in this population.

ABBREVIATIONS

WHO: World Health Organization; EAPC: European Association of Palliative Care; PR: Prolonged-Release; SR: Slow-Release; OXN: Oxycodone/Naloxone; OIC: Opioid-Induced Constipation; AE: Adverse Effect; BFI: Bowel Function Index; ATC: Around-The-Clock; KPS: Karnofsky Performance Status Score; CRF: Case Report Form; NRS: Numerical Rating Scale; CTCAE: Common Terminology Criteria for Adverse Events

INTRODUCTION

Opioid analgesics have been recommended for the management of moderate-to-severe cancer pain by the WHO since 1990 [1]. For 25 years, oral morphine has been recommended as the first choice for cancer pain treatment [2], due to familiarity, availability, and cost rather than proven superiority [2]. The availability of different opioids has significantly improved and clinical studies on oxycodone, hydromorphone, and fentanyl have been carried out in order to assess their efficacy and tolerability profiles compared with morphine [3]. A systematic review conducted to identify and assess the quality of evidence for the use of oxycodone, morphine, and hydromorphone for cancer pain in adults [4] reported no evidence of a significant difference in analgesia or adverse effects in the cancer palliative care population. EAPC evidence-based recommendations on the use of opioids for cancer pain relief state that morphine, oxycodone, or hydromorphone given by the oral route can be

used as the first-choice step III opioid for moderate-to-severe cancer pain [2].

In Italy, the following strong opioids are available for oral route: morphine, oxycodone, hydromorphone, and methadone. In clinical practice either morphine, oxycodone, hydromorphoneor the association OXN is used to treat moderate-to-severe cancer pain. Although strong opioids are effective in pain management, their use is frequently complicated by side effects such as dizziness, nausea, sedation, constipation and itching [5]. Tolerance to different secondary opioid effects develops at different rates. While tolerance to central nervous system opioid effects such as sedation, dizziness, nausea and vomiting can occur rapidly, there is minimal development of tolerance to constipation [6]. The prevalence of OIC in cancer patients has recently been estimated in the Dyonisos study [7] as 61.7%. Research on OIC in cancer patients[8] has shown that constipation might create symptom distress and have a negative impact on overall quality of life [9]. Furthermore, patients with OIC are often under treatment with laxatives and they frequently experience the bothersome AEs of these medications. Although OIC is the most frequently reported and persistent side effect in patients receiving opioid analgesia [10], current strategies to manage it are not well defined, frequently lack a good evidence base and may be ineffective [11]. Cancer patients continue to experience OIC despite laxative use in 84.7% of cases [7,12]. A Cochrane review on the effectiveness and differential efficacy of laxatives for the management of constipation in people receiving palliative care was first published in 2006 and then updated in 2010 and 2015 [13]. There are no reported conclusions on the individual effectiveness of different laxatives because of insufficient data from clinical research. No evidence suggests that one laxative agent should be recommended over others [2]. However, use of peripherally acting opioid antagonists has been identified as a promising approach; these agents specifically target gastrointestinal receptors without limiting the central analgesic activity of opioids [14].

The current research is an observational prospective study conducted to assess OIC in a sample of patients with moderate-to-severe cancer pain under treatment with strong opioids given by the oral route. The secondary objectives included the assessment of the analgesic efficacy, the description of laxative medication use and the assessment of laxatives' AEs.

MATERIALS AND METHODS

This was a prospective, observational study of 14-day duration. The study protocol was approved by the local research ethics committee and was conducted in full compliance with applicable Good Clinical Practice and regulations. Patients were given an information sheet, after which they had the opportunity to ask questions about the study. Then, they were asked to sign a consent form.

Advanced cancer patients aged more than 18 years, with a documented history of moderate-to-severe pain requiring ATC opioid therapy were eligible to participate in the study. Subjects were required to be on a stable dose of a WHO step III oral opioid, for at least 7 days prior to recruitment.

Patients were excluded from the study for the following reasons

1) evidence of clinically unstable disease or significant renal, hepatic or psychiatric disease; 2) KPS < 20; 3) clinically significant gastrointestinal disease; 4) cognitive impairment; 5) any condition associated with altered pain perception; 6) significant structural abnormalities of the GI tract or enterostomy drainage bag; 7) chemotherapy or radiotherapy within 2 weeks before recruitment visit that would influence bowel function.

The assessment tools used in the study were

1. BFI [15] for OIC: it is a clinician-administered tool that allows easy measurement of OIC from the patient's perspective and includes three variables: "ease of defecation"; "feeling of incomplete bowel evacuation"; and "personal judgement of constipation". Using a numerical analogue scale of 0–100, patients rate these variables according to their experience during the preceding 7 days, where 0 represents freedom from the symptom and 100 represents maximum difficulty or the most severe symptom. The BFI score is calculated as the mean of the three component scores. The BFI reference range for non-constipated patients with chronic pain can be defined as 0–28.8 [16]. Changes in the BFI scores of ≥ 12 points are likely to be related to clinically meaningful changes in patients' perceptions of their bowel habits [16,17]. BFI is considered to be a reliable and valid measure of OIC in European countries [15].

2. NRS for pain intensity self-assessment: it is a verbally administered 11-point scale, with 0 indicating no pain, 1–3 mild pain, 4–6 moderate pain, and 7–10 severe pain [18].

3. CTCAE [19] for laxative adverse events assessment: this is the standardized method for safety and tolerability assessment in clinical cancer studies. It is routinely updated and used in conjunction with the medical dictionary for regulatory activities by regulatory agencies. Using CTCAE, adverse events are graded on a scale from grade 1 to 5, in which, by convention grades 1–3 represent progressive worsening in severity or frequency of the toxicity, interference with self-care and the performance of daily activities, and the need for clinical intervention. The adverse events related to laxative treatment, registered in the current study were: abdominal swelling, abdominal pain, diarrhoea and bloating.

A flow diagram of the study protocol is reported in Figure (1).

Descriptive statistics were used to summarize the data. Mean and standard deviation were calculated when referring to quantitative variables and absolute counts and percentages when related to qualitative items. The paired Student's t test was used to analyse differences in age while the chi square test was used to measure association among categorical factors. IBM SPSS v.21 statistical software was used for analysis.

RESULTS

Patients were recruited from an Italian palliative care unit that provided assistance to 980 cancer patients during the study period (15 May 2015 to 15 May 2016). Of these patients, a total of 102 participated in the study and data from 97 were usable because the remaining 5 CRFs were incomplete. 52.6% were inpatients and 47.4% outpatients.

Patients' characteristics are reported in Table (1). At the first follow-up visit (T1) 10 patients had dropped out (7 had died and 3 had changed the route of drug administration), at the second follow-up visit (T2) 17 patients had dropped out (15 had died and 2 had changed the route of drug administration). Of the whole sample, 50 patients were under fixed ATC treatment with PR OXN, 25 patients were under treatment with fixed ATC oral morphine (SR or PR), 20 patients were under treatment with fixed ATC oral PR oxycodone, 2 patients were under treatment with fixed ATC oral PR hydromorphone and none was under treatment with methadone. At the start of the study, subjects were receiving mean OXN doses of 36.0 mg/day (SD 22.38); mean oxycodone doses of 43.25 mg/day (SD 33.17); mean oral morphine doses of 39.40 mg/day (SD 16.43) and mean hydromorphone doses of 24 mg/day (SD 16.0).

At recruitment the mean BFI for the total sample was 35.67 ± 19.38 while it was 35.91 ± 19.61 at T1 (7 days after recruitment) and 34.43 ± 17.03 at T2 (14 days after recruitment) (p-values > 0.05). Given that the BFI reference range for non-constipated patients can be defined as 0–28.8 [16,17], in the oxycodone group 87.5% of patients were constipated at T1 (reported BFI values > 28.8) and 92.3% at T2; in the morphine group 63.6% of patients were constipated at T1 and 75.0% at T2; in the OXN group 45.8% of patients were constipated at T1 and 53.8% at T2. At both T1 and T2 there were more non-constipated patients in the OXN group than in the morphine and oxycodone groups (T1 chi-square = 8.927 p = 0.01 and T2 chi-square = 6.969 p=0.03) Table (2).

Table 1: Patients' *characteristics*.

	N (%) or mean (± SD)
Mean age	76.0 (± 10.1)
Sex	
Male	41 (42.3)
Female	56 (57.7)
Setting	
Inpatients	51 (52.6)
Outpatients	46 (47.4)
Karnofsky Performance Status score	
40	34 (35.0)
30	63 (65.0)
Cancer localization	
Lung	23 (23.7)
Colo-rectal	16 (16.5)
Breast	8 (8.2)
Prostate **Pancreas** **Stomach** **Ovarian/uterin**	9 (9.3) 7 (7.2) 1 (1.0) 9 (9.3)
Urinary system **Liver** **Unknown** **Other**	5 (5.1) 1 (1.0) 3 (3.1) 15 (15.5)
Metastasis	
None **Multiple** **Abdomen**	13 (13.4) 52 (53.6) 7 (7.2)
Bone	15 (15.5)
Lymph Nodes	6 (6.2)
Lung	6 (3.1)
Liver	1 (1.0)

N: Number of Patients
SD: Standard Deviation

The mean baseline pain intensity was NRS 3.49 ± 1.93; after 7 days it was 2.64 ± 1.62 and after 14 days it was 2.23 ±1.45 with a p-value <0.0001 for paired data T0-T1 and a p-value <0.0001 for paired data T1-T2. Data on mean pain intensity at T0-T1-T2 in the three groups and the t-test for paired data are reported in Table (3).

During the study period, 46.4% of patients were under treatment with laxative medications. Lactulose, polyethylene glycol and senna glycoside were the laxatives in use. See Table (4) for the mechanism of action and common AEs of the laxatives reported in this study.

At T2 the oxycodone and the morphine treatment groups had consumed more laxatives (23/28; 82.1%) than the OXN treatment group (17/41; 41.5%) (chi-square 4.27, p-value 0.03). Only 12.6% of patients who took laxatives did not experience adverse effects. See table 5 for descriptive data of adverse effects of laxatives.

DISCUSSION

In the current study, the mean BFI for the total sample of patients ranged between 34.43 and 35.91, showing a mild degree of constipation if compared with the results of the most recent clinical research conducted[20] on chronic cancer pain patients who had a mean BFI score of 63.1 ± 23.5.

This finding might mean that cancer patients with advanced disease can experience improvement in constipation control when they enter a palliative care programme.

BFI modification over the three visits (T0–T1–T2) was not significant, but the mean BFI score in the OXN treatment group was 10 points lower than in the oxycodone and morphine treatment groups. The percentage of non-constipated patients (BFI <28.8) was higher in the OXN group than in the morphine and oxycodone groups, at both T1 and T2 (p<0.05). This result may confirm the efficacy of OXN in OIC management.

Analgesic efficacy was statistically significant in the whole sample and in the three treatment groups (p<0.05). This finding confirms that oxycodone, OXN or morphine given by the oral route is effective in patients with moderate-to-severe cancer pain. This finding shows that using an opioid antagonist does not result in a decrease of opioid-induced pain relief.

From the study findings, almost half of patients (46.4%) received laxative medication. Laxatives were given based on the doctor's recommendation following common clinical practice. Laxative consumption at T2 was higher in the oxycodone and morphine groups than in the OXN group. These results suggest that, given a similar degree of constipation, patients who are under treatment with oral oxycodone and morphine need more laxatives than patients under treatment with OXN.

The study findings, although the study sample was small, confirm that the targeted approach of administering peripherally

Table 2: Constipated patients at T0-T1-T2 in the three groups (OXN, Oxycodone, Oral morphine).

	OXN		Oxycodone		Morphine		pvalue
	N	Constipatedpatients N (%)	N	Constipatedpatients N (%)	N	Constipatedpatients N (%)	
T0	50	29 (58.0%)	20	13 (65.0%)	25	17 (68.0%)	0.67
T1	48	22 (45.8%)	16	14 (87.5%)	22	14 (63.6%)	0.01
T2	39	21 (53.8%)	13	12 (92.3%)	12	9 (75.0%)	0.03

OXN: Oxycodone/Naloxone
N: Number of patients
T0: Recruitment
T1: 7 days after the recruitment
T2: 14 days after the recruitment
P value corresponding to the chi square test

Table 3: Mean pain intensity NRS values at T0-T1-T2 in the three groups (OXN, Oxycodone, Morphine).

		OXN		pvalue	Oxycodone		pvalue	Morphine		pvalue
		N	Mean (SD)		N	Mean (SD)		N	Mean (SD)	
Paired data	T0 NRS	48	3.60 (1.75)		16	3.62(2.19)		22	3.64 (1.70)	
	T1 NRS	48	2.56 (1.64)	0.001	16	3.00 (1.93)	0.22	22	2.68 (1.29)	0.03
	T0 NRS	41	3.68 (1.81)		14	3.64 (2.34)		14	3.36 (1.28)	
	T2 NRS	41	2.44 (1.53)	0.001	14	2.35 (1.28)	0.07	14	2.14 (1.35)	0.007
	T1 NRS	41	2.61(1.61)		14	2.71 (1.73)		14	2.57 (1.22)	
	T2 NRS	41	2.44 (1.53)	0.41	14	2.36 (2.78)	0.36	14	2.14 (1.35)	0.31

OXN: Oxycodone/Naloxone
N: Number of patients
SD: Standard deviation

Table 4: Laxatives' characteristics.

Category	Molecule	Mechanism of action	Common adverseeffects
Osmotic/ saline	Lactulose	Poorlyabsorbedmolecules create a localosmoticgradientwithin the intestinal lumen (Woolery et al., 2008). Peristalsisisstimulate by increase in pressure from reabsorption of fluid and electrolytes, and decreasedgutpH in the colon (Lee-Robichaud et al., 2010)	Bloating, flatulence, colic and diarrhea
Iso-osmotic	polyethylene glycol	Physiologicallyinert; they are notabsorbed or metabolized in the gut.Increased water content and volume of the stool (Woolery et al., 2008).	Abdominaldistension, abdominalpain, diarrhea
Stimulant	senna glycoside	Peristalsisstimulation due to nerveirritatingeffect in the colonic mucosa. Limited water absorption (Woolery et al., 2008).	Abdominalpain (cramping)

Table 5: Laxatives AEs in the three treatment groups.

	LaxativesAEs N (%)				
	Bloating	Abdominalpain	Abdominaldistension	Diarrohea	
Opioid Treatment	Oxycodone (T1)	13 (81.2)	12 (75.0)	12 (75.0)	1 (6.2)
	Oxycodone (T2)	10 (71.4)	11 (78.5)	9 (64.3)	1 (7.1)
	OXN (T1)	33 (68.7)	30 (62.5)	34 (70.8)	5 (10.4)
	OXN (T2)	30 (96.7)	31 (75.6)	31 (75.6)	5 (12.2)
	Morphine (T1)	21 (95.4)	17 (77.3)	18 (81.8)	2 (9.0)
	Morphine (T2)	12 (85.7)	13 (92.8)	13 (92.8)	0 (0)

OXN: Oxycodone/Naloxone
AEs: Adverse events
N: Number of patients

acting opioid antagonists co-applied with opioid agonists is effective in managing constipation in advanced cancer patients. In our opinion, given that current laxatives do not have a good evidence base [11], a combination of opioid ago- and antagonists should be considered as a possible treatment method for all cancer subjects.

Lactulose, polyethylene glycol and senna glycoside were the laxatives in use. Insufficient evidence exists to determine the efficacy and side effect profiles of lactulose, polyethylene glycol and senna glycoside in the prevention and treatment of constipation. An algorithm for the prophylaxis and ongoing assessment of bowel pattern in palliative care patients [9] recommended prescribing laxative prophylactically in order to anticipate the constipating effects of pharmacological agents such as opioids. In the algorithm [9], the first-line recommended treatment with oral laxative involves a combination of a softener such as polyethylene glycol or lactulose and a stimulant such as senna. The second-line recommended treatment involves the use of a rectal suppository and enema and the possible use of a peripherally specific opioid antagonist. The third-line recommended treatment involves manual evacuation and eventually the use of a peripherally specific opioid antagonist. Based on the current study findings, the OXN combination can be considered as a valid opportunity in palliative care patients taking opioids.

In the study sample, adverse effects that were probably due to laxatives were frequent. The most common adverse effects were bloating and abdominal distension characterized by mild or moderate intensity.

LIMITATIONS

The present study has several limitations. The sample was small due to the short life expectancy and patients' frequent refusal to participate; patients were ineligible if they were unable to self-report pain and constipation (these patients might have experienced pain and OIC as well); there were only 2 patients in treatment with hydromorphone and none with methadone; only four possible laxative AEs were assessed. A randomized clinical trial would have been a more appropriate study design, but there are many barriers to palliative care research [21,22] such as patients' fragility, limited life expectancy and prognostic uncertainty. Although caring for this highly symptomatic population requires the further development of scientific evidence for palliative care, studies are difficult to perform. Despite these limitations, the results of this prospective observational study are encouraging as they demonstrate reasonably good management of constipation in palliative care cancer patients.

CONCLUSION

This observational prospective study describes OIC assessment, analgesic efficacy, laxative consumption and AEs in palliative care cancer patients under treatment with oral WHO step III opioids.

Based on the study findings, palliative care patients with moderate/severe cancer pain, treated with oxycodone or OXN or morphine by the oral route, experienced a similar, statistically significant, analgesic effect. In the study sample, the mean BFI score demonstrated a mild degree of constipation with no significant differences in the three treatment groups. Fourteen days after recruitment, laxative consumption was significantly lower in patients treated with OXN. Adverse effects probably due to laxative medication were common.

Given the demonstrated negative impact of constipation on quality of life in cancer patients, further research should be encouraged to provide evidence-based guidance on the use of the available laxatives or specific-opioid antagonists for the prevention and treatment of OIC.

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REFERENCES

1. WHO Expert Committee Cancer pain relief and palliative care. Geneva: World Health Organization. 1990.
2. Caraceni A, Hanks G, Kaasa S, Bennett MI, Brunelli C, Cherny N, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. Lancet Oncol. 2012; 13: 58-68.
3. Caraceni A, Pigni A, Brunelli C. Is oral morphine still the first choice opioid for moderate to severe cancer pain? A systematic review within the European Palliative Care Research Collaborative guidelines project. Palliat Med. 2011; 25: 402-409.
4. King SJ, Reid C, Forbes K, Hanks G. A systematic review of oxycodone in the management of cancer pain. Palliat Med. 2011; 25: 454-470.
5. Pappagallo M. Incidence, prevalence, and management of opioid bowel dysfunction. Am J Surg. 2001; 182: 11-18.
6. Freye E, Latasch L. Development of opioid tolerance - molecular mechanisms and clinical consequences. Anasthesiol Intensivmed Notfallmed Schmerzther. 2003; 38: 14-26
7. Abramowitz L, Béziaud N, Labreze L, Giardina V, Caussé C, Chuberre B, et al. Prevalence and impact of constipation and bowel dysfunction induced by strong opioids: a cross-sectional survey of 520 patients with cancer pain: DYONISOS study. J Med Econ. 2013; 16: 1423-1433.
8. Clark K, Byfieldt N, Dawe M, Currow DC. Treating constipation in palliative care: the impact of other factors aside from opioids. Am J Hosp Palliat Care. 2012; 29: 122-125.
9. Larkin PJ, Sykes NP, Centeno C, Ellershaw JE, Elsner F, Eugene B, et al. The management of constipation in palliative care: clinical practice recommendations. Palliat Med. 2008; 22: 796-807.
10. Coluzzi F, Pappagallo M. National Initiative on Pain Control. Opioid therapy for chronic noncancer pain: practice guidelines for initiation and maintenance of therapy. Minerva Anestesiol. 2005; 71: 425-433.
11. Ahemdzai SH, Boland J. Constipation in people prescribed opioids. BMJ ClinEvid. 2010; 2407.
12. Reimer K, Hopp M, Zenz M, Maier C, Holzer P, Mikus G, et al. Meeting the challenges of opioid-induced constipation in chronic pain

management a novel approach. Pharmacology. 2009; 83: 10-17.

13. Candy B, Jones L, Larkin PJ, Vickerstaff V, Tookman A, Stone P. Laxatives for the management of constipation in people receiving palliative care. Cochrane Database Syst Rev. 2015; 13.

14. Holzer P, Ahmedzai SH, Niederle N, Leyendecker P, Hopp M, Bosse B, et al. Opioid-induced bowel dysfunction in cancer-related pain: causes, consequences, and a novel approach for its management. J Opioid Manag. 2009; 5: 145-151.

15. Rentz AM, van Hanswijck de Jonge P, Leyendecker P, Hopp M. Observational, nonintervention, multicenter study for validation of the Bowel Function Index for constipation in European countries. Curr Med Res Opin. 2011; 27: 35-44.

16. Rentz AM, Yu R, Müller-Lissner S, Leyendecker P. Validation of the Bowel FunctionIndex to detect clinically meaningful changes in opioid induced constipation. J Med Econ. 2009; 12: 371-383.

17. Ueberall MA, Müller-Lissner S, Buschmann-Kramm C, Bosse B. The Bowel Function Index for evaluating constipation in pain patients: definition of a reference range for a non-constipated population of pain patients. J Int Med Res. 2011; 39: 41-50.

18. Lee JJ, Lee MK, Kim JE, Kim HZ, Park SH, Tae JH, et al. Pain relief scale is more highly correlated with numerical rating scale than with visual analogue scale in chronic pain patients. Pain Physician. 2015; 18: 195-200.

19. U.S. Department of Health and Human Services NIH, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. 2010; 4.

20. Ahmedzai SH, Nauck F, Bar-Sela G, Bosse B, Leyendecker P, Hopp M. A randomized, double-blind, active-controlled, double-dummy, parallel-group study to determine the safety and efficacy of oxycodone/naloxone prolonged-release tablets in patients with moderate/severe, chronic cancer pain. Palliat Med. 2012; 26: 50-60.

21. Sigurdardottir KR, Haugen DF, van der Rijt CC, Sjøgren P, Harding R, Higginson IJ, et al. Clinical priorities, barriers and solutions in end-of-life cancer care research across Europe. Report from a workshop. Eur J Cancer. 2010; 46: 1815-1822.

22. LeBlanc TW, Lodato JE, Currow DC, Abernethy AP. Overcoming recruitment challenges in palliative care clinical trials. J Oncol Pract. 2013; 9: 277-282.

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