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Critical Review

A Systematic Review of Prospective Studies Reporting Adverse Events of Commonly Used Opioids for Cancer-Related Pain: A Call for the Use of Standardized Outcome Measures

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Abstract: **Data on the tolerability of opioids in patients with cancer-related pain are limited. Here, we report a systematic review that includes all published prospective studies reporting adverse events (AEs) of morphine, oxycodone, fentanyl, methadone, or hydromorphone for cancer-related pain in patients naive for these opioids. We included 25 studies describing 31 treatment cohorts, made an overview of study characteristics, and reported rates of AEs per type of opioid. The frequency of the most commonly reported AEs varied widely: nausea from 3 to 85%, vomiting from 4 to 50%, constipation from 5 to 97%, drowsiness from 3 to 88%, and dry mouth from 1 to 94%. There was a large heterogeneity among included studies, especially regarding the assessment and reporting of AEs. We describe how differences in assessment and reporting influence outcome rates. Although AEs are an important issue in daily clinical practice, realistic incidence rates of AEs per type of opioid are unknown because of the immense heterogeneity among studies.**

Perspective: ***Although opioid-related adverse events are an important issue when treating cancer-related pain, realistic rates of adverse events per type of opioid are unknown because of immense heterogeneity among studies and lack of systematic assessment and reporting. There is an urgent need for studies with standardized outcome measures and reporting.***

Key words: *Opioids, side effects, adverse events, cancer, pain.*

Pain is prevalent in patients with cancer in all stages of the disease, with the highest prevalence seen in patients with advanced or metastatic disease: 2 of 3 patients experience pain, with more than one-third of these patients grading their pain as moderate or severe.[41] The analgesic ladder as published by the World Health Organization (WHO) is the foundation for the treatment of cancer-related pain. WHO follows a stepwise approach, with weak-acting or step 2 opioids as second-line choice for moderate pain and strong-acting step 3 opioids as third-line choice for moderate to severe pain.[48] This review focuses on the strong-acting opioids (referred to as opioids in this article), which are also used as a first-line opioid in low doses.

Commonly prescribed opioids in the Western world are morphine, oxycodone, fentanyl, and, to a lesser extent, hydromorphone and methadone. Choosing among these opioids is not easy. Only a few randomized controlled trials (RCTs) directly comparing different opioids have been published, and no significant differences in efficacy and tolerability profiles have been shown, with the exception of the finding of less constipation with fentanyl compared with morphine.[5,39,50] The European Association for Palliative Care guidelines state that morphine, oxycodone, or hydromorphone can be used as the first-choice opioid and that fentanyl may be an alternative in some patients, for example in

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cases of problematic oral intake, renal insufficiency, or severe constipation. Methadone should be used only by experienced professionals.[4]

The effect on pain and the occurrence of side effects in an individual patient are assumed to be the result of a complex interplay between pharmacokinetics and pharmacodynamics. Pharmacogenetics may further complicate existing pharmacokinetic-pharmacodynamic relationships.[3,8] Therefore, much research is conducted with the aim of finding clinical, pharmacokinetic, or genetic determinants that will enable true personalized treatment. However, results of such studies have not yielded specific markers or profiles that can guide treatment decisions for individual patients.[1,2,19]

As a result, finding the right opioid in the right dose at the right moment is a matter of trial and error in daily clinical practice. The choice for the opioid to start with in an opioid-naive patient is mainly based on expert opinions, clinical experience, personal preference, and sometimes clinical factors (ie, accessible routes of administration, renal failure). All opioids have shown equal rates of pain control[4,46] but data about side effects are scarce. Obviously, if one of the opioids had a better side effect profile, this opioid would be preferred. Also, differences in the incidence of specific side effects can be relevant in patients who already present with or are at risk for various symptoms. The prevalence and severity of symptoms are high in patients with cancer-related pain and increase with each step up the WHO treatment ladder.[30] In one study, patients not using any opioids experienced a mean of 2.9 (standard deviation [SD] 1.9) symptoms. Among the most prevalent symptoms were insomnia (58%), anorexia (40%), constipation (25%), and nausea (21%).[11] We conducted a systematic review including prospective studies in patients with cancer naive for morphine, oxycodone, fentanyl, methadone, and hydromorphone in which side effects of these commonly used opioids were reported. The objective of this review was to create an overview of the incidence of side effects after starting treatment with opioids for cancer-related pain and to study whether the incidence of (specific) side effects differs among different types of opioids.

Methods

We performed a systematic review in which we included prospective studies reporting on the occurrence of side effects after the start of morphine, oxycodone, fentanyl, methadone, or hydromorphone for cancer-related pain in patients who were naive for these opioids. Pretreatment with codeine phosphate, dihydrocodeine, dextropropoxyphene, or tramadol was allowed.

The following databases were searched up until March, 2015: MEDLINE (PubMed), Embase, Web of Science, and the Cochrane Database of Systematic Reviews. No year limits were applied to the searches and therefore they extend as far back as the year range of each database. Retrievals in Ovid MEDLINE go back to 1976, EMBASE to 1985, Web of Science to 1950, and the Cochrane Library to 1966.

The search terminology included different terms and medical subject headings for cancer, side effects and specific side effects (constipation, nausea, vomiting, delirium, hallucinations, myoclonus, sweating, drowsiness, and dry mouth), all types of trials, and morphine, fentanyl, oxycodone, methadone, and hydromorphone. The search strategies were developed specifically for each database. The search was performed by a staff member of the Medical Library and one of the authors (A.W.O.). In addition, reference lists of relevant studies and reviews found were checked.

Two reviewers (A.W.O., W.H.O.) independently assessed all titles with or without abstracts identified by the search. In case of potentially relevant articles, the full text was obtained to judge if they fulfilled the criteria: 1) it had to be a prospective study; 2) treatment with morphine, oxycodone, fentanyl, methadone, or hydromorphone for cancer-related pain was required; 3) patients had to be naive for these opioids before inclusion in the study; 4) data on specific side effects (constipation, nausea, vomiting, delirium, hallucinations, myoclonus, sweating, drowsiness, and/or dry mouth) were given; and 5) only full-text articles published in English, German, Dutch, or French were considered. When the same cohort of patients was described in multiple articles, the article describing the largest cohort or fulfilling our inclusion criteria best was chosen, provided that no information on adverse events (AEs) was lost.

For studies fulfilling our inclusion criteria, data were extracted independently by 2 authors (A.W.O., W.H.O.), after which extracted data were compared. Disagreements were resolved by discussion between the 2 reviewers. When necessary, a third reviewer (C.C.D.R.) decided.

All studies were assessed in a standardized manner. For each trial included, information was extracted on study design, number of patients who fulfilled the inclusion criteria, opioid treatment (type, route of administration, dosing, and titration), previous analgesic treatment, length of follow-up and loss to follow-up, AE (types of AEs, severity grade of AEs, method and frequency of assessment, number of patients with AEs), and confounding factors (eg, comedication, type of rescue medication, antitumor treatment). For studies including a wider group of patients than defined, only data for the patients fulfilling the inclusion criteria were reported. Opioid doses were recalculated to the median morphine equivalent daily dose (MEDD) (mg/d) according to published equianalgesic dose tables: oral morphine 60 mg/d = parenteral morphine 20 mg/d = transdermal fentanyl 25 μg/h = oral oxycodone 40 mg.[4] For oral methadone, we used a dose conversion ratio of 1:4 (methadone/morphine).[47]

Data on the specific AEs were reported as the percentages of patients with the respective AE. For studies that did not report on the number or percentage of patients with AEs or when there were uncertainties about the data, the corresponding author was contacted with a request for additional information. When available, data on AEs during the first

week of treatment with the opioid were used. When AEs were given on multiple days during the first week, we used the highest percentage. We aimed to study the percentages of mild AEs and the percentages of moderate to severe AEs separately.

Results

The literature search provided a total of 7,077 citations. Fig 1 shows the selection process. Thirty-six studies fulfilled our inclusion criteria. In 10 of these studies, data on the number of patients with AEs could not be extracted because they reported the mean/median AE severity scores or the proportion of days with AEs only. After contacting the authors of these articles, data on the number of patients with AEs were supplied for 5 of these 10 studies. After excluding 6 more studies for various reasons (Fig 1), 25 studies (9 RCTs and 16 cohort studies) describing 31 treatment cohorts with different opioids were included in our analysis.[6,9,14,15,17,18,20,21,23-29,31,32,36,38,40,42-44,49,51] An overview of included studies is given in Table 1. Thirteen studies reported on morphine, 9 on fentanyl, 6 on oxycodone, and 3, all from the same investigator, on methadone. No studies with hydromorphone were included.

Most studies reported data for nausea and constipation. Vomiting, drowsiness, and dry mouth were reported less frequently, and just a few studies reported data on confusion, sweating, or pruritus. None of the studies reported on hallucinations or myoclonus (Table 1). For only a few studies, the occurrence rates per severity grade (mild, moderate to severe) of some AEs were available.[17,18,20,23,24,36,42] We decided to pool all grades because data were insufficient for a comparison of mild versus moderate to severe AEs.

Because the included studies were found to be very heterogeneous, Table 2 gives an overview of study characteristics relevant for interpreting the reported occurrence rates of AEs. The first characteristic is

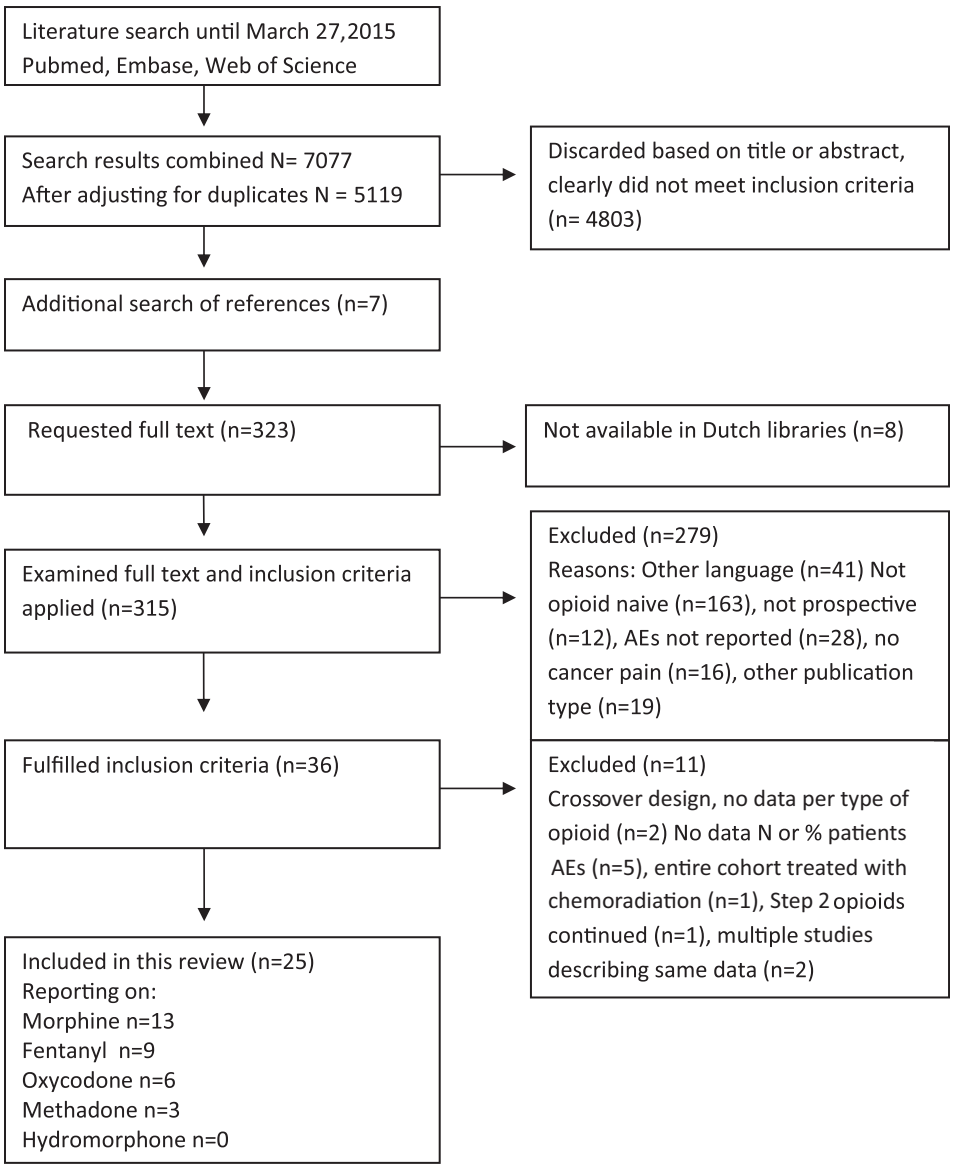

Figure 1. CONSORT diagram of the literature search and selection process.

Table 1. Overview of Included Studies Reporting AEs as an Outcome of Treatment With Opioids for Cancer-Related Pain

Reference	Year	Country	Study Type	Number	Male (%)	Treatment	Rescue Medication	Follow-up (Days)	Number Evaluable (Day 7)	AEs Reported
De Conno et al[6]	2008	Italy	Cohort	159	65	Mo IR	Mo	5	135	N, V, Cs, Dr, Cf
Eyelade et al[9]	2012	Nigeria	Cohort	182	19	Mo IR	Mo	90	166	Cs, Dr, DM
Harris et al[14]	2003	India	RCT	62	76	Mo IV vs IR	Mo IV/IR	7	52	N, V, Cs, Dr, Pr
Hemati et al[15]	2015	Iran	Cohort	86	56	Fe td	?	3	86	N/V, Cs, Dr, Pr
Kang et al[17]	2015	Korea	Cohort	98	64	Fe td	*	25	?	N, V, Cs, Dr, DM
Klepstad et al[18]	2000	Norway	Cohort	40	53	Mo IR → Mo SR	Ke	12	35	N, V, Cs, Sw
Klepstad et al[20]	2003	Norway	RCT	40	56	Mo IR vs SR	Ke	4	34	N, V, Cs
Koizumiet al[21]	2004	Japan	Cohort	22	86	Ox CR	Mo	7	22	N, Cs, Dr
Ljuca and Husic[23]	2010	Bosnia and Herzegovina	Cohort	35	57	Mo IR	Mo	10	35	Cs, Dr, DM
Luczak et al[24]	2002	Poland	Cohort	72	63	Fe td	Mo	28	?	N, V, Cs
Matsui et al[25]	2009	Japan	Cohort	18	50	Fe td	*	9	18	N, V, Cs, Dr, Pr
Mercadante et al[27]	1998	Italy	RCT	20	50	Mo SR	?	†	20	N, Cs, Dr, DM, Cf
				20	45	Me	?	†	20	
Mercadante et al[26]	1999	Italy	Cohort	45	47	Me	?	†	45	N, Cs, Dr, DM, Cf, Sw
Mercadante et al[28]	2008	Italy	RCT	36	45‡	Mo SR	Mo	28	22	N/V, Cs, Dr, DM, Cf
				36	56‡	Fe td	Mo	28	25	
				36	52‡	Me	Mo	28	23	
Mercadante et al[29]	2010	Italy	RCT	30	41‡	Ox CR	Mo	56	24	N, Cs, Dr, DM, Cf
				30	41‡	Mo SR	Mo	56	21	
Mystakidou et al[31]	2004	Greece	Cohort	1507	49	Fe td	Mo	276	1505	N, V, Cs, Sw, Pr
Pan et al[32]	2007	China	Cohort	216	58	Ox CR	?	28	216	N, V, Cs, Dr
Rodriquez et al[36]	1994	Spain	RCT§	42	76	Mo IR	Pcm/cod	7	35	N, Cs, Dr
van Seventer et al[42]	2003	Netherlands	RCT	64	70	Mo SR	Mo	28	47	N, V, Cs, Dr
				67	60	Fe td	Mo	28	63	
Suzuki et al[38]	2008	Japan	Cohort	37	0	Ox CR	Mo	20	37	N, Cs, Dr, Cf
Tawfik et al[40]	2004	Egypt	Cohort	157	38	Fe td	Mo	28	157	N, V, Cs, Dr, DM
Vielvoye et al[43]	2000	Netherlands	Cohort	28	?	Fe td	Mo	28	28	N, V, Cs
Vijayaram et al[44]	2000	India	Cohort	223	34	Mo IR	Mo	68	223	N/V, Cs, Pr
Xiao et al[49]	2014	China	RCT	60	?	Ox CR	?	14	60	N/V, Cs, Dr, Pr
Zhang et al[51]	2014	China	RCT?	114	55	Mo SR	Mo	?	?	N, V, Cs
				57		Ox CR	Mo			

Abbreviations: Mo, morphine; IR, immediate release; N, nausea; V, vomiting; Cs, constipation; Dr, drowsiness; Cf, confusion; DM, dry mouth; IV, intravenous; Pr, pruritus; Fe, fentanyl; td, transdermal; Ke, ketobemidone; Ox, oxycodone; CR, controlled release; SR, slow release; Me, methadone; Sw, sweating; Pcm/cod, paracetamol/codeine; ?, unknown.

NOTE. Five studies were sponsored by a pharmaceutical company.[17,24,40,42,43]

*Rapid-type oral opioid agent.

†Until death.

‡Not at baseline, based on number of patients completing study.

§Versus dypiridone.

pretreatment with weak-acting (WHO step 2) opioids, which was allowed in 7 studies,[6,9,14,23,31,40,42] was an inclusion criterion in 6 studies,[18,20,24,28,43,44] was not allowed in 6 studies,[15,17,21,29,32,38] and was unreported in another 6 studies.[25-27,36,49,51] The second characteristic is the starting dose of treatment and subsequent titration rate (shown as dose after titration and days needed for titration), for which sometimes large differences were seen. The median MEDD at the start was 60 mg, which was also the highest starting dose. In 5 oxycodone studies, substantially lower doses were given at the start (range in MEDD = 15–30 mg) but also after titration (range in MEDD = 25–48.6 mg). In 1 oxycodone study, the starting dose was unknown, but doses after titration were high (MEDD = 198 mg).[49] In 7 of 9 fentanyl cohorts, the MEDD at the start was 60 mg, and in all 3 methadone cohorts, the starting dose was close to 60 mg. The largest variation in treatment doses was seen between the morphine cohorts. The third characteristic is differences in the reporting and the assessment of AEs. Because there was no uniformity in the description of how the AEs were measured, we cited the described methods from each study briefly. In 1 study, AEs were reported only on day 28,[24] and 6 studies reported AEs over the entire follow-up period (range = 14 days to 3 months).[9,17,27,40,43,49] For all other studies, except 1 with unknown time of follow-up and reporting,[51] AEs were available for the first 3 to 10 days of treatment.

We could not include information about comedication and concurrent treatments in Table 2 because of limited data. In some studies antiemetics,[24] laxatives,[9] or both[14] were given as standard, and 1 study[21]

Table 2. Study Characteristics Relevant for the Assessment of Reported Incidences of AEs

Reference	Year	Pretreatment With Step 2 Opioids, Number (%)	Treatment	Dose at Start → Dose After Titration (per 24 h, Mean)	Dose in Oral MEDD (mg/24 h, Mean)	Duration of Titration (Days)	Days or Period (P) After Start on Which AEs Were Reported	Assessment of AEs
De Conno et al[6]	2008	122 (77)	Mo IR	30–60 → 59 mg	30–60 → 59	5	P0–5	The safety was assessed by the physician who recorded AEs related to treatment using an intensity scale from 1 to 3 (mild to severe)
Eyelade et al[9]	2012	33 (18)	Mo IR	30 → 47 mg	30 → 47	7	P0–90	Any reported AEs were documented
Harris et al[14]	2003	Y (?)	Mo IV	60 → 49.8 mg	60 → 49.8	3	1, 2, 7	Groups were reviewed to assess AEs
		Y (?)	Mo IR	30 → 43.2 mg	30 → 43.2			
Hemati et al[15]	2015	0	Fe td	25 → 25 μg	60 → 60	3	P0–3	The severity of side effects was evaluated
Kang et al[17]	2015	0	Fe td	12.5 → 26 μg	30 → 62	8	P0–25	Phone inquiries every 3 d. Investigators used mild, moderate, and severe to describe the intensity of the AEs
Klepstad et al[18]	2000	40 (100)	Mo IR→ Mo SR	60 → 97 mg	60 → 97	2	1, 2, 3, 4, 5, 6, 7	The EORTC-QLQ-C30 questionnaire was administered 3 times during the study
Klepstad et al[20]	2003	20 (100)	Mo IR	60 → 94 mg*	60 → 94*	2	1, 2, 3, 4, 5, 6, 7	AEs were reported on a VRS (not at all to very severe)
		20 (100)	Mo SR	60 → 82 mg*	60 → 82*			
Koizumi et al[21]	2004	0	Ox CR	10 →16.7 mg	15 → 25.2	2	P0–7	By questioning/examining the patients, reviewing patient diaries. Severity (slight to severe) assessed by investigators
Ljuca and Husic[23]	2010	20 (57)	Mo IR	48 → 71.3 mg	48 → 71.3	4–6	P0–10	Side effects were monitored. Dry mouth/drowsiness on a scale of 0–10, constipation grade 0–3
Luczak et al[24]	2002	72 (100)	Fe td	25 → 44.3 μg	60 → 106	7	1, 28	A diary was used. Nausea/vomiting was assessed daily using scale absent to severe
Matsui et al[25]	2010	?	Fe td	12.5 → ? μg	30 → ?	?	2, 7	AEs were classified using CTC 3.0
Mercadante et al[27]	1998	?	Mo SR	32.5 → 109.5 mg	32.5 → 109.5	?	P0–50	The symptoms were assessed by the patient using a scale 0–3 (not at all to awful)
		?	Me	13.6 → 25.2 mg	54.4 → 100.8	?		
Mercadante et al[26]	1999	?	Me	14.4 → 27.2 mg	57.6 → 108.8	?	P0–U	The symptoms were assessed by the patient using a scale 0–3 (not at all to awful)
Mercadante et al[28]	2008	36 (100)	Mo SR	60 → 68.2 mg	60 → 68.2	7	P0–7	The symptoms were assessed by the patient using a scale 0–3 (not at all to awful), unless for constipation, which was monitored on an institutional scale
		36 (100)	Fe td	25 → 39.1 μg	60 → 94	7		
		36 (100)	Me	15 → 15.6 mg	60 → 62.4	7		

Table 2. Continued

Reference	Year	Pretreatment With Step 2 Opioids, Number (%)	Treatment	Dose at Start → Dose After Titration (per 24 h, Mean)	Dose in Oral MEDD (mg/24 h, Mean)	Duration of Titration (Days)	Days or Period (P) After Start on Which AEs Were Reported	Assessment of AEs
Mercadante et al[29]	2010	0	Ox CR	20 → 23.8 mg	30 → 35.7	7	P0–7	The symptoms were assessed by the patient using a scale 0–3 (absent to severe), constipation using an institutional scale
		0	Mo SR	30 → 35.0 mg	30 → 35.0	7		
Mystakidou et al[31]	2004	1239 (82)	Fe td	25 → 50 μg*	60 → 120	7	0, 2, 7	Side effects were graded according to the CTC
Pan et al[32]	2007	0	Ox CR	10–20 → 21.1 mg	15–30 → 31.7	2	P0–7	All drug-related AEs encountered were reported on the CRF using a scale mild–very serious
Rodriquez et al[36]	1994	?	Mo IR	60 → ? mg	60 → ?	7	P0–7	Possible AEs as a result of drugs administered were recorded using a checklist. Severity was classified by investigators mild to moderate to severe.
van Seventer et al[42]	2003	42 (66)	Mo SR	60 → 105 mg	60 → 105	7	1, 7, 28	Assessed by investigators using scale 1–4 (not at all to very much), questionnaire about bowel function
		48 (72)	Fe td	25 → 67 μg	60 → 160	7		
Suzuki et al[38]	2008	0	Ox CR	10 → 18.9 mg	15 → 28.4	2.3	P0–7	?
Tawfik et al[40]	2004	84 (54)	Fe td	25 → 39.8–43.6 μg	60 → 96–106	28	P0–28	All AEs reported by the patient were recorded and rated by the investigator (mild–severe). Severity of nausea assessed by patient using scale absent–severe. Bowel function was evaluated (normal, constipated, diarrhea, stool frequency, bloating, laxative use)
Vielvoye et al[43]	2000	14 (50)	Fe td	25 → 50 μg	60 → 120	28	P0–28	Any AE that was either mentioned by the patient or reported after a nonleading question was noted by the investigator. Severity mild–severe
Vijayaram et al[44]	2000	223 (100)	Mo IR	50 → 140 mg	50 → 140	4	P0–10	Side effects were evaluated by patient report
Xiao et al[49]	2014	?	Ox CR	? → 54–132 mg	? → 81–198	14?	P0–14?	Side effects should be recorded in detail
Zhang et al[51]	2014	?	Mo SR	60 → 87.5 mg	60 → 87.5	?	?	The adverse reactions were observed
			Ox CR	20 → 32.4 mg	30 → 48.6	?	?	

Abbreviations: Mo, morphine; IR, immediate release; Y (?), yes, numbers unknown; IV, intravenous; Fe, fentanyl; td, transdermal; SR, slow release; EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life C30; VRS, verbal rating scale; CR, controlled release; Me, methadone; Ox, oxycodone; CRF, clinical registration form; ?, unknown; U, follow-up untill death, mean duration of follow-up unknown; CTC, common toxicity criteria. → signifies titration.
*Median dose.

recommended the use of both. In other studies, comedication was given as clinically indicated.[17,27-29,31,42,43,51] One study[38] examined the combination of oxycodone with or without the antiemetic prochlorperazine. For the other studies, no data on comedication/adjuvants were reported. Four studies[18,20,31,44] reported the number of patients treated with chemotherapy, radiotherapy, or both during the study period.

Fig 2 shows the percentage of patients experiencing any grade of nausea, constipation, drowsiness, and dry mouth per study and per type of opioid (red dots, morphine; green, oxycodone; blue, fentanyl; and black, methadone). Each dot represents a treatment cohort of patients treated with a specific type of opioid, and therefore the included studies can be found in the figures more than once if they reported on multiple treatment cohorts. The studies are arranged from left to right in ascending opioid starting doses and, in case of similar starting doses, doses after titration. A solid black ring around a dot signifies that only AEs ascribed to the studied opioid were reported,[6,21,32,36,40,43] whereas a spotted black ring around a dot signifies that this was likely the case but could not be determined for certain based on the information provided.[31,38,44] Studies reporting all AEs regardless of causality with the studied opioid are not circled. In the following section, we describe the information gathered per type of AE, which is summarized in Fig 2.

Nausea

As shown in Fig 2, the reported rates of occurrence of nausea varied from 3 to 85%.[14,27] In all treatment cohorts in which only AEs ascribed to the opioid were

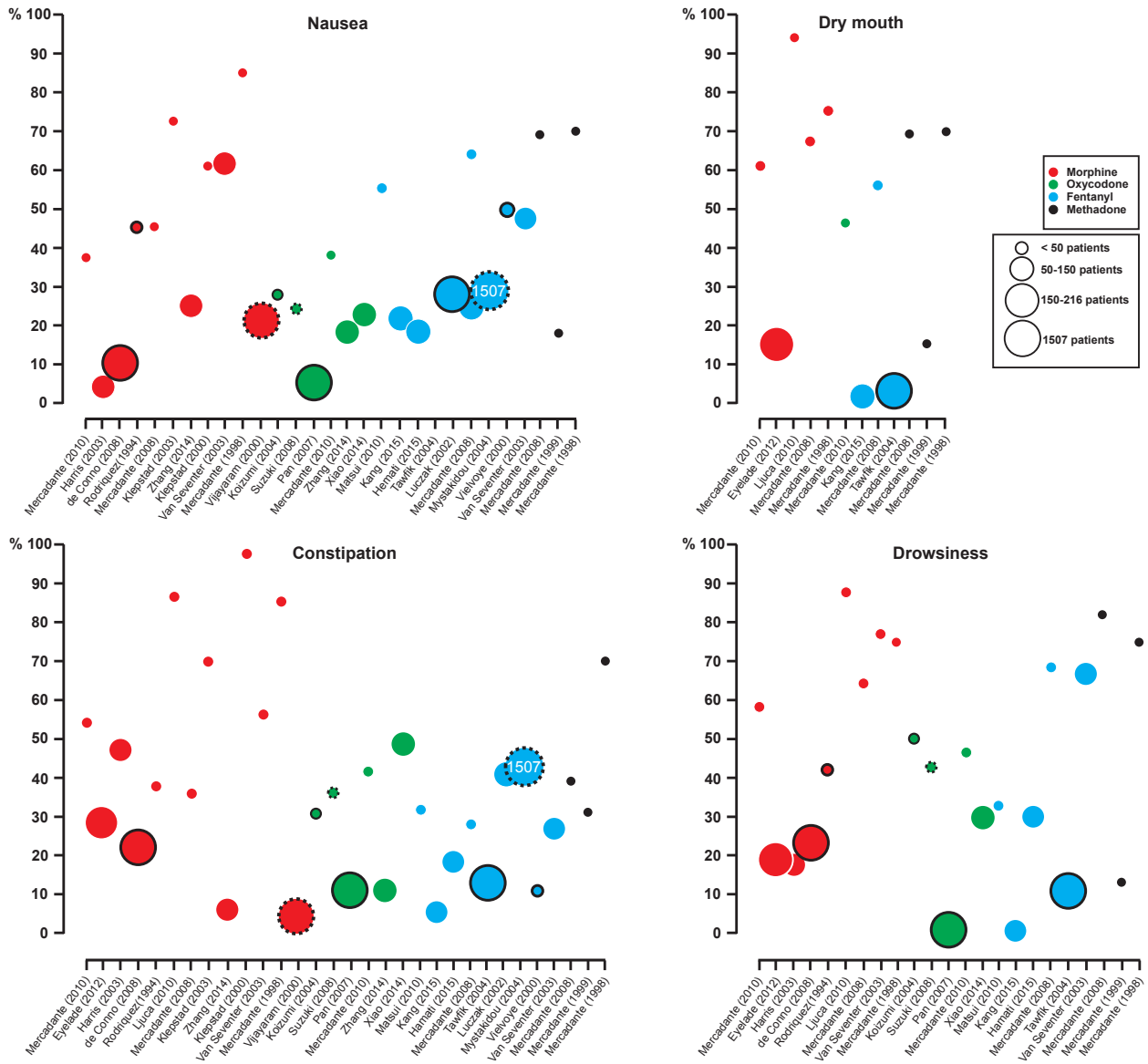

Figure 2. Incidence rates of nausea, dry mouth, constipation, and drowsiness as the percentage of patients with any grade of the AE per study. Studies are arranged per type of opioid and in ascending order of treatment doses (starting and/or doses after titration). For studies reporting only AEs ascribed to treatment, the dots are circled with a solid black ring or a spotted black ring (probably reporting only AEs ascribed to treatment).

reported, the occurrence of nausea was ≤50%, whereas in 8 of 20 cohorts reporting all AEs, rates above 50% were reported. Remarkably low rates were reported in the study by Harris et al,[14] who reported nausea in 3.5% of patients but vomiting in 14.5%. Because studies are arranged in ascending starting/titration doses from left to right, we see a trend in the morphine studies (red dots) showing higher rates of nausea as treatment doses become higher. An exception is the study by Vijayaram et al,[44] who reported a low rate of nausea (21.5%) despite the high morphine doses after titration. In this study, no systematic assessment for AEs was performed, and only AEs spontaneously reported by patients were registered. In the oxycodone, fentanyl, and methadone cohorts, there was less variation in treatment doses; we can see no trend in Fig 2 because the occurrence of nausea varied widely regardless of treatment doses.

At first glance, nausea seems to be less likely to occur in the oxycodone studies. However, low starting and titration doses were used in most of these studies (Table 2), and 3 of the 6 studies reported not all AEs but only AEs ascribed to oxycodone. The heterogeneity among the studies made comparisons between the different opioid types impossible. Although the rates of nausea were high in 2 of 3 methadone studies,[27,28] the rate of nausea was remarkably low in the third methadone study,[26] although these studies seemed similar with respect to dose and assessment method.

Vomiting

Although vomiting was explicitly reported in fewer studies compared with nausea, in general, the occurrence of vomiting paralleled that of nausea (data not shown), with a broad range of 4 to 50%.[20,32] Four studies reported nausea/vomiting as one AE,[15,28,44,49] and in 3 other studies,[6,14,31] the reported rate of vomiting was higher than for nausea. Based on these data, we were not able to make a comparison between the different opioids.

Constipation

The rate of constipation also ranged widely, from 5 to 97%.[18,44] The pattern of distribution of reported rates was in line with that of nausea. A dose-effect relationship could be seen for the morphine studies and possibly also for the fentanyl studies. The lowest rates were seen in the studies reporting AEs ascribed to opioid treatment (11–38%) and in studies in which no systematic assessment of AEs was performed and only AEs spontaneously reported by patients were given (5–29%).[9,43,44] Regarding differences between the types of opioids, in all fentanyl cohorts, the reported percentage of patients with constipation was <50%, whereas in 6 of 13 morphine cohorts the percentage was >50%.[18,20,23,27,29,42] The reported rates of constipation were also low (10.5–49%) in the oxycodone studies, but as mentioned for nausea, treatment doses were low and 3 out of 6 studies reported only AEs ascribed to treatment.

Drowsiness

Drowsiness was reported for 23 treatment cohorts from 18 studies (Fig 2) and the rates ranged from 3 to 88%.[17,23] The rates again seemed highest in the studies with the highest treatment doses. The lowest rates (3–50%) were seen in studies reporting AEs ascribed to the opioid use[6,21,32,36,38,40] or in studies reporting only AEs spontaneously reported by patients.[9] Compared with the low rates of nausea and constipation in the oxycodone cohorts, the rate of drowsiness was relatively high in 3 of 5 oxycodone studies (43–50%), despite the low treatment doses and the reporting of only treatment-related AEs in 2 of these studies.[21,32]

Dry Mouth

Dry mouth was reported in 12 treatment cohorts from 8 studies (Fig 2), and its occurrence varied from 1 to 94%.[17,23] Despite this huge variation, the rate was ≥48% (median = 68.8%) in 8 of these 12 cohorts. Three studies with low incidence rates (4.5–15.6%) reported either AEs ascribed to the treatment or only AEs spontaneously reported by patients without systematic assessment.[9,26,40] The reason for the low rate (1%) in the study by Kang et al[17] is unknown to us. Overall, the reported rates of dry mouth are high compared with the rates of the other AEs.

Other AEs

Confusion as an AE after starting opioids was reported only in studies by de Conno et al[6] and Mercadante et al,[26-29] and the reported rates ranged from 7 to 80% (data not shown). Sweating was reported in 4 studies and ranged from 5 to 66% of patients.[18,31] Itching was reported in 6 studies and ranged from 0 to 9%[25,44] (data not shown).

We did not find lower rates of AEs in study cohorts pretreated with codeine, tramadol, or dextropropoxyphene compared with cohorts in which the studied opioids were started directly. In general, studies performed in non-Western countries (China, Korea, Iran, India, Nigeria, and Egypt) reported lower rates of AEs compared with studies performed in Western countries and Japan.

Discussion

To our knowledge, this is the first review providing an overview of AEs after starting treatment with morphine, oxycodone, fentanyl, or methadone for cancer-related pain. In general, we found that the occurrence rates of AEs (of any grade) were high, although there was a broad range in reported rates of all AEs. AEs have a negative impact on quality of life, and the number of symptoms has been shown to be associated with heightened psychological distress and poorer quality of life.[33] Symptoms that seem to be of particular impact are drowsiness and dry mouth because both have a high prevalence and are rated as moderate to severe by many patients.[10,30] Both symptoms have been shown to be "quite a bit" or more distressing in about 20% of

patients experiencing them.[33] Drowsiness and other central side effects (hallucinations, confusion) frequently contribute to opioid failure.[8,35] Our data indicated a dose-effect relation, with higher rates of AEs reported in studies with higher opioid starting doses and/or higher doses after titration, but this effect was mainly seen in the morphine cohorts because the variation in treatment doses was less in the studies with fentanyl, oxycodone, and methadone. The striking heterogeneity among included studies made it difficult to compare AEs between the different opioids. Despite this, the rate of constipation seemed to be lower for fentanyl than for morphine, a finding that has previously been reported.[5,13,39,50] Also, the rate of drowsiness was high in the oxycodone cohorts, especially given the fact that low oxycodone treatment doses were used, which probably explains the low rates of nausea and constipation in these cohorts. However, no definite conclusions can be drawn because despite our inclusion criteria, we were confronted with a large heterogeneity among the included studies, leading to broad ranges of reported rates of AEs. Differences in assessment of and subsequent reporting of AEs seem to be of significant influence on the reported rates of AEs. Studies reporting only AEs ascribed to the studied opioid described lower rates than studies reporting all AEs, regardless of the causality with the studied opioid. This is not surprising, because we know that the prevalence of symptoms that can be seen as side effects of opioid treatment is high in patients with cancer, regardless of their treatment with opioids.[11,30] Also, in studies in which no systematic assessment of AEs was performed and only AEs spontaneously mentioned by patients were reported,[9,43,44] low occurrence rates were found, especially for constipation and dry mouth. We can speculate that patients mention these AEs less freely than other AEs when no direct assessment is used.

Contrary to what we assumed and experience in clinical practice, we could not identify a protective effect of pretreatment with codeine phosphate, dihydrocodeine, dextropropoxyphene, or tramadol. However, if we looked at individual studies in which AEs were reported separately for opioid-naive patients and for patients pretreated with codeine or tramadol, pretreated patients had lower rates of AEs than opioid-naive patients, with the exception of constipation.[31,40,43] Therefore, the fact that overall rates of AEs were not lower in pretreated versus naive patients is probably a result of the heterogeneity among the studies.

Our data are in line with findings from previous studies. In a meta-analysis by Reid et al[34] that included 4 studies, 3 comparing oral oxycodone with oral morphine and 1 comparing oral oxycodone with oral hydromorphone, the rate of nausea ranged from 42 to 74%, constipation from 21 to 70%, dry mouth from 33 to 74%, and drowsiness from 31 to 90% in patients treated with oxycodone, morphine, and hydromorphone. No differences were found in AE profiles. A systematic review on RCTs comparing oral morphine with other opioids or placebo concluded that the lack of data in opioid-naive and nonselected populations limited the ability to draw conclusions. However, similar patterns of side effects were seen for morphine, oxycodone, and hydromorphone.[22] A recently published RCT in opioid-naive patients also concluded that side effects between morphine and oxycodone did not differ.[35] A meta-analysis of 3 studies comparing fentanyl with morphine[39] showed lower rates of AEs with fentanyl and morphine (nausea, 19–32% with fentanyl and 22–25% with morphine; constipation, 6–30% with fentanyl and 15–55% with morphine; and drowsiness, 17–25% with fentanyl and 19–52% with morphine) than we have found. One[42] of the 3 studies was also included in our review; the others did not meet our inclusion criteria because of pretreatment with strong-acting opioids, which probably explains the lower rates. In a recent Cochrane review[45] on the impact of morphine, fentanyl, oxycodone, or codeine on patient consciousness, appetite, and thirst, the reported rates of nausea ranged from 14 to 23%, vomiting from 7 to 15%, constipation from 17 to 30%, somnolence from 13 to 24%, and dry mouth from 3 to 47%. This review included only RCTs, and the investigators were also confronted with multiple major problems with AE reporting. The authors call for "the development of definitions for AE's that have a spectrum of severity or importance, and the development of appropriate measurement tools for recording such events to aid clinical practice and clinical research."[45(p2)] In 2 other recent Cochrane reviews,[13,37] the investigators conclude that the quality of the evidence is limited because of important risk of bias, and both studies call for the use of standardized outcome measures. This need was further supported in a study showing that the number of symptoms reported using systematic assessment was eightfold higher than the number of symptoms reported spontaneously.[16] Also, low agreement has been shown between toxicity rates of chemotherapy reported by physicians (using common toxicity criteria) and patients (using a 4-point Likert scale). Lower rates were reported by physicians, supporting the use of patient reported outcomes.[7]

A strength of our review is that we chose to include only patients naive for the opioids studied to minimize bias, because patients with an indication for opioid rotation form a selection of patients not responding well to the previous opioid(s). This selection criterion meant that no studies with hydromorphone could be included, because in none of the studies was hydromorphone used as a first-line opioid. Because hydromorphone is a potent opioid, usually reserved for patients failing treatment with other types of opioids, this was not unexpected.

We must also acknowledge several limitations. First is our decision not to use a scale, checklist, or tool to assess the quality and risk of bias of selected studies. The use of such tools is advocated, and many exist for the assessment of randomized trials. However, we could not find any tools for the assessment of nonrandomized cohort studies, as were most of the selected studies. The GRADE (Grades of Recommendation, Assessment, Development and Evaluation) criteria automatically

allocate observational studies as generating (very) low-quality evidence.[12] We therefore chose to systematically describe all included studies. Also, because AEs were seldom the primary outcome of included studies, we were not able to study the incidence of AEs because some studies reported all symptoms, whereas others reported only symptoms probably related to the opioids. We were therefore able to describe only the occurrence rates of side effects. Despite the large variation in study size, we weighed all studies equally because there were many other differences in possible influencing factors among the studies. Nevertheless, we made the variation in study size visible in Fig 2. Also, we excluded studies in which AEs were reported as changes in mean or median symptom intensity only, although this is probably the most reliable method for assessment, assuming that other causes of symptoms remain stable. Because these studies did not report the number of patients with AEs, we could not compare them with the other studies. Furthermore, the number of studies using symptom intensity scales was too small to make a separate comparison on the occurrence of mild versus moderate to severe AEs. Another limitation is the inevitable heterogeneity in patient populations. Study populations differed in patient characteristics (ie, tumor type, gender, race, body weight) and concurrent treatments (comedication, chemotherapy, and radiotherapy). However, data were too scarce to include these characteristics in this review.

Nausea, vomiting, constipation, drowsiness, and dry mouth are the most reported AEs in patients with cancer-related pain starting with morphine, oxycodone, fentanyl, or methadone; rates of these AEs were found to be high. There seems to be a dose-effect relation, with high starting doses and/or higher doses after titration leading to more side effects. There is a lack of well-performed clinical studies in patients with cancer-related pain in which a systematic assessment with validated scoring systems for AEs is used. Although side effects are important in daily clinical practice, data are insufficient and the true incidence of side effects is still unknown. Future studies should use standardized methods for the assessment and reporting of AEs; consensus on the use of these assessment methods is eagerly awaited.

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