Article:
Edler-Buggy, S, Birtwistle, J orcid.org/0000-0002-6083-589X, ElMokhallalati, Y et al. (3 more authors) (2020) Regular dosing compared with as needed dosing of opioids for management of chronic cancer pain: systematic review and meta-analysis. Pain, 161 (4). pp. 703-712. ISSN 0304-3959

https://doi.org/10.1097/j.pain.0000000000001755

PAIN Publish Ahead of Print
DOI: 10.1097/j.pain.0000000000001755

Regular dosing compared with as needed dosing of opioids for management of chronic cancer pain: systematic review and meta-analysis

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Pages: Total pages – 32

Page 2-19– Abstract, paper, Acknowledgements, references and legends (figures and appendices).

Additional pages:

5x Tables- 5 pages

3x Figures- 3 pages

5x Appendix-5 pages

Abstract

Opioids are the recommended form of analgesia for patients with persistent cancer pain and regular dosing 'by the clock' is advocated in many international guidelines on cancer pain management. The development of sustained release opioid preparations has made regular dosing easier for patients.

However, patients report that the intensity and impact of their cancer pain varies considerably day to day, and many try to find a trade-off between acceptable pain control and impact of cognitive (and other) adverse effects on daily activities. In acute care settings, (eg post-operative) as needed dosing and other opioid sparing approaches have resulted in better patient outcomes compared with regular dosing.

The aim of this study was to determine whether regular dosing of opioids was superior to as needed dosing for persistent cancer pain. We systematically searched for randomised controlled trials that directly compared pain outcomes from regular dosing of opioids with as needed dosing in adult cancer patients. We identified 4347 records, 25 RCTs meet the inclusion criteria, nine were included in the review and 7 of these included in meta-analysis. We found no clear evidence demonstrating superiority of regular dosing of opioids compared with as needed dosing in persistent cancer pain and regular dosing was associated with significantly higher total opioid doses. There was, however, a paucity of trials directly answering this question and low-quality evidence limits the conclusions that can be drawn. It is clear that further high-quality clinical trials are needed to answer this question and to guide clinical practice.

Keywords: cancer; Pain; opioid; systematic review; meta analysis

Introduction

Opioids, particularly morphine, remain the cornerstone of managing cancer related pain and are advocated in international guidelines [13,21,57,67]. Since the first clinical trial of oral opioids in cancer pain was reported [60], regular dosing of opioids has been the gold standard to achieve consistent pain control for patients. Regular dosing of opioids is more likely to produce a steady plasma drug level correlating with levels of analgesia [22] and could reduce the occurrence of peaks of severe pain and reduce need for additional analgesia [29]. The development of prolonged release oral and transdermal opioid preparations for cancer pain meant that effective plasma concentrations could be reached efficiently and maintained for longer periods. This allows for less frequent regular dosing intervals of 12 hours or longer, improving patient satisfaction and adherence with greater freedom from repetitive dosing, especially at night [29,39,52,62]. In the context of chronic cancer pain immediate release opioid is most commonly used for 'break-through analgesia' with the amount of additional, as needed opioid often used to guide overall titration of regular opioid dose [1].

Pain affects around and 30% to 50% of all people with cancer and opioids do provide good pain control in the majority of cases [69]. In clinical trials, oral morphine can achieve 'good' pain control in 63% of patients, rising to 75% on a switch to a second oral opioid for non-responders [48,49,70]. In head to head clinical trials, there is no difference in efficacy between controlled release (CR) morphine, CR oxycodone, transdermal (TD) fentanyl and TD buprenorphine; good pain control was achieved in around 75% of patients with similar incidence of adverse events [16]. A meta-analysis comparing morphine with oxycodone produced similar findings [53].

Opioid associated adverse effects are feared by patients, particularly cognitive effects such as drowsiness, hallucinations and confusion, as well as constipation [2]. Adverse effects are reported variably with rates from 11-77% and around 10% of patients find these effects intolerable [64,69]. Specific rates of opioid adverse effects in the context of cancer pain are estimated at 25% for constipation, 23% for somnolence, 21% for nausea, 17% for dry mouth, and 13% for vomiting, anorexia, and dizziness [68].
There is no evidence of an increase in adverse effects from the use of low-dose strong opioids instead or higher dose weak opioid [13,38]. The severity and frequency of adverse effects

have, however, been shown to be higher when using regular dosing, higher doses and longer duration [10,41,46,54,64].

There is also growing recognition of longer term, more subtle effects of opioid use on immune and endocrine dysfunction, potential increased growth rate of malignancy and increased metastatic rate particularly relating to perioperative opioid use [50,73]. A recent systematic review has examined the possibility that opioids may be associated with reduced survival even in those individuals with short life expectancy, although this proved to be inconclusive [8].

Adherence rates to opioids of only 41% have been reported in cancer patients [61] in part because patients prioritise the ability to be active. This means that on a daily basis patients will 'trade off' poorer pain control in order to reduce opioid adverse effects, depending on whether pain or adverse effects are causing most interference with activity [27,40]. Therefore, opioid dose reduction strategies for cancer pain management that enable good pain control but with fewer adverse effects are important to research.

In recent years, there has been growing concern related to use of opioids for non-cancer pain conditions, the so-called opioid crisis or opioid epidemic. This has impacted upon cancer pain management too, with recognition that cancer patients may misuse opioids [18,19] and risk reduction strategies are now commonly used [2], including an emphasis on opioid-sparing management practices. Higher dosing, continuous and long term duration of opioids are also associated with adverse effects on pain control through development of tolerance and hyperalgesia [52,53]. In this regard, an important lesson has been learned from acute pain contexts (e.g. post-operative pain control) in the use of opioids. Research has demonstrated that as needed analgesia (via patient controlled analgesia (PCA) devices) can provide superior pain control than continuous administration [6,30,43] with lower overall opioid doses and fewer adverse effects. In chronic non-cancer pain contexts, strategies such as dose-reduction or dose-tapering are also associated with improved pain control and fewer adverse effects [4,59,66]. We therefore wanted to examine whether dose reduction strategies in cancer pain should be considered in routine practice.

The aim of this systematic review was to determine whether as needed dosing of opioids resulted in similar pain relief but with fewer adverse effects and lower opioid consumption, than regular dosing for managing cancer pain.

Methods

Study criteria

We conducted a systematic review of randomised controlled trials (RCTs) in accordance with the Centre for Reviews and Dissemination guidelines which include the preferred reporting Items for Systematic reviews (PRISMA) guidance on reporting study selection [44].

Types of studies: RCTs where regular opioid dosing was compared with as needed opioid dosing. For the purpose of this review we considered the as needed groups to be patients who had no access to regularly dosed opioid but had access to immediate release opioid as needed. The regular dosing groups included patients receiving regular dosed opioids with or without additional immediate release preparations to be used as needed.

Type of patients: Studies that included adult patients with pain caused by cancer. Studies that included treatment related pain such as mucositis or chemotherapy induced neuropathies were excluded.

Types of outcome measures: Primary outcome was changes in pain intensity measured using visual analogue scale (VAS), a verbal rating scale (VRS) or a numerical rating scale (NRS), and reported as either mean pain intensity difference or responder rates. Secondary outcomes were overall opioid consumption, specific adverse effects, and any other measurements of quality of life.

Search methods

Electronic databases MEDLINE (Ovid), EMBASE (Ovid) and CINAHL (EBSCO) were searched from 1980 to February 2019 using text words, their synonyms and index terms (e.g. MeSH) for the search concepts (search strategy reported in Appendix 1, available online as supplemental digital content at http://links.lww.com/PAIN/A916). Reference lists of studies found were searched for any additional studies. We also searched ongoing trials databases, the Cochrane library and PubMed for any other potentially includable studies. National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network

(SIGN), Association for Palliative Medicine and the European Association for Palliative Care (EAPC) websites and databases were also searched for potential studies.

Data collection and analysis

Selection of studies: Two review authors (S.E-B and JB) independently assessed potential studies identified as a result of the search strategy. Full texts were obtained for any articles identified that appeared to meet the inclusion criteria or lacked sufficient information to exclude in the title and abstract summary. Final decisions were made by consensus after reading full text of articles. Any disagreements were resolved through discussion and third-party review by author MB.

Data extraction: For eligible studies the following data were extracted: trial design (blinding or open label), details of experimental vs control treatment, dose regimens, duration of treatment, numbers of patients included with cancer overall and numbers of patients in each trial arm, primary and secondary outcomes.

Assessment of risk of bias: We assessed risk of bias relating to the primary outcome measure for each included study using the seven criteria outline in the Cochrane Handbook for Systematic Review of Intervention. A full description of the assessment of risk of bias methodology is reported in the appendix 2 (available online as supplemental digital content at http://links.lww.com/PAIN/A916). Two co-authors (SE-B and JB) independently assessed risk of bias, with a third (MB) assisting in reaching a consensus relating to classification where disagreements or uncertainty arose. To assess the overall quality of included evidence a GRADE approach was used. Authors SE-B, JB, YEM and MB discussed all papers included and reached a consensus decision [28].

Data synthesis and analysis: The primary outcome was change in pain intensity, which was reported as either mean pain intensity difference or responder rates. We extracted the mean pain intensity difference at the end of the trial between the two arms to compare treatment efficacy. Regarding responder rates, where responder outcomes were measured (i.e. good or complete pain relief on VRS) this was directly extracted and analysed as event rates. As secondary outcomes, we assessed average daily opioid consumption, and adverse events. The average opioid dose per 24 hours was calculated and converted to morphine equivalent dose for direct comparison (conversion ratios appendix 3, available online as supplemental digital

content at http://links.lww.com/PAIN/A916). Where a range of dosages were examined, the highest dose of the study was used for comparison. For adverse effects, we used frequency counts or mean intensity of adverse effects of opioids.

Data analysis was conducted using Review Manager (RevMan) version 5.3. To summarise the intervention effects, odds ratios (ORs) with 95% confidence intervals were calculated for dichotomous outcomes while weighted mean difference and 95% confidence intervals were calculated for continuous outcomes. When different scales of measurement had been used for an outcome, standardised mean differences (SMDs) with 95% confidence intervals were calculated using the inverse variance method.

To pool continuous and dichotomous outcomes on pain intensity, we re-expressed dichotomous measures of changes in pain intensity as odds ratios and 95% confidence intervals and then changed to SMDs using standard formulae described in sections 7.7.7 and 9.4.6 of the Cochrane Handbook [28] . If a study reported both dichotomous and continuous outcomes, we used continuous outcome data as the most stringent and valid measure of changes in pain intensity. To account for differences in methods and study characteristics, meta-analyses were conducted using random effects models. Heterogeneity was assessed with the I^2 statistic, with a value of 50% or above considered to represent high heterogeneity.

Results

Description of studies

Our search returned 6656 results from which 2309 duplicates were removed. A total of 4347 records were screened. Of 25 full- text reports assessed for eligibility, nine studies met criteria for inclusion in our analysis (Figure 1). The nine included studies are summarised in table 1, they report on 998 cases including 946 individual patients with n=52 included in cross over trials: 605 patients in the regular dosing arm and 393 in the as needed dosing arm. Three of the studies contained a mixed cancer and non-cancer population [7,55,56] . However, each paper reported no significant difference between the two populations and so we have taken the results to be representative of cancer pain. The stage, or severity of malignant disease was not clearly documented within each study, five studies [33,42,47,55,56] recorded the presence of metastasis and this ranged from 41-82% . The mean trial duration and follow up was 12 days and 872 (92%) patients completed the trial period.

In only two studies [12,42] was the primary aim specifically to compare the efficacy of regular dosing with as needed dosing of opioids. The remaining 7 studies aimed to compare the efficacy of a variety of prolonged release or continuously administered opioid preparations in comparison to placebo where as needed immediate release opioid was available for use by both groups. However, we included these studies because it was possible to compare patients dosing as needed (placebo arm) with patients dosing regularly (intervention arm).

There was a range of approaches to assessment of pain severity and treatment outcomes across the included studies. Three studies used a 5 point verbal rating scale (VRS), four studies used an 11 (0-10) point visual analogue scale (VAS) or pain intensity (PI scale) and the remaining two used a 100 mm VAS.

A wide range of opioids were used across the studies. McGuire et al [42] used a range of opioids and it was not possible to establish standardised doses for each arm; this study was therefore not included in the opioid dose meta-analysis. In the remaining studies, the opioids studied were: morphine (n=238), buprenorphine (n=634), hydromorphone (n=44) and codeine (n=60). The approach to co-analgesics was variable across the studies with three studies allowing the use of non-opioids[9,20,42], four studies allowed adjuvant analgesia provided it was already established at steady state[7,33,47,55], one study did not allow any non-trial analgesia[56] and another did not control or comment on other medication [12]. In five studies patients were excluded if they had a history or drug or alcohol abuse [11,20,33,35,56].

Risk of bias

Table 2 details the assessment of risk of bias. Overall, for the primary outcome measure there was an unclear risk of bias associated with random sequence generation and allocation concealment. The risk of blinding was variable across the studies, in particular the older papers [12,20,42] showed high or unclear risk of bias in blinding of participants and personnel. The remaining papers showed low risk in one or both domains. There was a low risk associated with incomplete data and selective reporting. There was a large degree of variability in sample size across the studies ranging from 17 to 221 with four of the studies

having very small numbers of less than 30 participants, conferring a high risk of bias due to small study sizes and variability. Overall the reporting of methodology across the studies was unclear in part though there were few clear high-risk areas. For the secondary outcome measures of opioid dose, adverse effects, and sleep, there was very low quality of reporting with high variability between each study and incomplete data.

Despite including only RCTs in the review, we downgraded the evidence level based on heterogeneity and design limitations (relating to sample size). Furthermore, several of the included studies had wide confidence intervals, although this was not present in all cases. Therefore, the overall assessment of quality is double downgraded resulting in low to very low-quality evidence.

Pain intensity

Six of the nine studies [7,9,12,33,42,56] did not show a statistically significant difference between regular dosing and as needed dosing of opioid analgesia on pain intensity, while three [20,47,55] studies favoured regular dosing (Table 3). We combined seven studies within the meta-analysis; two were excluded because Broomhead et al [9] did not report pain scores for each arm and Bohme et al. [7] did not provide details on responder rates and pain scores for the groups of patients receiving different opioid doses, only data on mean difference.

Meta-analysis showed no significant difference in pain intensity between regular dosing and as needed dosing strategies, SMD 0.21 [95% C.I. -0.1, 0.52], p=0.18, Figure 2. However, there was significant heterogeneity within the meta-analysis $I^2 = 72\%$. Studies using continuous measures (pain intensity difference) favoured regular dosing but studies using responder rates showed no difference between arms.

Secondary outcome measures

Opioid dose: In eight of the nine studies in which dose data were available, each reported lower opioid doses used in the as needed dosing arm compared to regular dosing arm. We pooled data on five studies [12,20,33,47,56] for meta-analysis; three studies were excluded due to lack of data on specific doses given and their standard deviations. In these five studies, as needed opioid dose was a median 31% of regular opioid dose. The meta-analysis found

significantly lower opioid dose in the as needed dosing arm: SMD -79.92 [95% CI -143.75 to -16.09], p=0.01 (Figure 3). However, there was substantial heterogeneity within this estimate, I^2 = 100%.

Adverse effects: Adverse effects were reported by seven studies [7,12,20,33,47,55,56] (Table 4), using different outcomes and in varying detail. The most commonly reported events included drowsiness, nausea and vomiting. No study reported a significant difference between the two dosing arms and meta-analysis could not be performed.

Other reported outcomes: Sleep disturbance was assessed in five studies [7,12,20,42,55,56] (Table 5) using a variety of different outcomes. For example, percentage of patient achieving >6 hours or mean sleep score. Four studies favoured regular dosing but no statistical testing was undertaken within each study and pooling for meta-analysis was not possible.

There was an insufficient number of studies (<10) to perform sensitivity analysis and investigate the cause of heterogeneity in the meta-analyses. Furthermore, for the same reason, we were unable to assess publication bias by means of funnel plots as suggested by the Cochrane Handbook for Systematic Reviews of Interventions.

Discussion

Main findings

We found no evidence that as needed dosing of opioids for cancer pain resulted in poorer pain control than regular dosing. We could not draw any conclusions about differences in adverse effects because of poor reporting. Although, we found significantly lower opioid doses within as needed dosing arms (inferring lower risk of adverse effects), the substantial heterogeneity limits our confidence in this outcome.

Our finding suggests that the evidence base to underpin current practice is weak and that an as needed dosing strategy may offer benefits in terms of similar pain control but with lower daily doses. Although we were not able to demonstrate a reduction in adverse effects with an as needed dosing strategy, it is reasonable to assume that an opioid dose that is about one third of the regular opioid dose would be associated with fewer or less severe adverse effects [54,64]. Several of the studies excluded patients if there was a history of drug or alcohol

abuse, but there was no further measurement or discussion of nonmedical opioid use or addiction in any of the studies. This could in part be due to the age of each paper and the relatively current recognition of this issue and the fact that each trial was for limited duration.

Strengths and limitations

We adhered to the Centre for Review and Dissemination guidance. We conducted a wide and extensive search for appropriate papers using a sensitive search strategy and believe that we have identified all appropriate studies. We combined pain outcomes using standardised mean differences and we used random effects models within our meta-analysis. We assessed the quality of the evidence using a recognised method.

We found a range of opioids used at a wide range of doses. This might reflect recruitment of patients at different disease stages and with different levels of pain, and is a potential explanation for the heterogeneity within the primary outcome. Within each study patients were deemed as having comparable tumour related pain, comparable co-analgesic use and comparable analgesic requirement through a run-in phase, however, it was not possible to compare this across the studies.

It is also noteworthy that no study addressed the possibility of tolerance or opioid induced hyperalgesia as causes of increasing analgesic requirements and it is not possible to assess this further with the available information. Tolerance, thought to be an adaptive response, acts to progressively neutralise the drug action resulting in increasingly higher doses required to produce a given level of analgesia [15]. Opioid-induced Hyperalgesia (OIH) describes a paradoxical increase in pain sensitivity during ongoing exposure to opioid resulting in pain that is difficult to control and can be made worse with increasing opioid dose. OIH is mediated by the activation of specific pronociceptive processes involving μ-opioid signalling, transcriptional mechanisms, ion-channel dysregulation and effects on microglia [15,23,51,63,71,72]. OIH is seen readily in the case of potent short acting μ-opioid receptor (MOP) agonists [14,25] but also after administration of long acting agents and milder agonists [34,36]. Differentiating between increasing pain severity, tolerance and OIH is challenging [3], and this may be especially problematic in the cancer pain population where a progression of symptoms and pain are often expected as part of the disease process.

With the introduction of novel prolonged release opioids, seven of the nine studies appeared to be conducted for regulatory purposes to demonstrate efficacy of the novel preparation and only two studies [12,42] were designed to specifically compare regular dosing with as needed dosing strategies. Three of the studies examined a mixed population of patients with cancer related and non-cancer related pain [7,55,56] and the data from the malignant versus non- malignant pain cannot be fully separated. However, each of the papers does document no significant differences between the two populations, therefore we have taken the results to be representative of cancer pain.

Our assessment of bias highlighted that most studies were at unclear or low risk methodologically, but small samples sizes were used in many of these: four contained fewer than 100 participants, and another four studies had fewer than 200. Overall, the evidence was double downgraded to low or very low quality, due to heterogeneity and sample size, therefore, this might mean that for our primary outcome, the true effect may be different (in either direction) from our estimate derived from meta-analysis. However, similar outcomes showing at least equivalent pain control with as required opioid dosing and associated lower overall opioid consumption are seen in other areas of non-cancer related pain research. Von Korff et al [32] reported results from 1781 patients with chronic non-cancer pain, showing regular opioid analgesia resulted in substantially higher average daily doses than as required dosing with similar pain intensity levels. For the management of acute sickle cell crises and post-operative pain, patient controlled analgesia, (as needed intravenous opioid) compared to continuous or regularly administered opioid has been demonstrated to provide at least equivalent pain relief in adult and paediatric populations, and has similar total opioid sparing effects [5,17,26,43,58].

Implications for practice and future research

The clinically relevant conclusions than can be drawn from our study are limited due to the low to very low-quality evidence and small numbers of studies. However, our findings do suggest that as needed dosing of opioids for cancer pain may be an alternative and valid dosing strategy in some circumstances and for some patients. For example, an individual who prioritises alertness, independence or function over pain control may be well suited to as needed opioid dosing, particularly as such a patient may find adherence to regular opioid troublesome [61]. Empowerment of patients through more collaborative decision making on opioid dosing also has the potential to improve outcomes [37] and improve engagement with

future care [45]. There is also support for this dosing strategy in other clinical contexts suggesting that our findings are clinically plausible. For example, Von Korff et al found improvement of analgesic associated anxiety as well as comparable pain control with as needed dosing [65]. Even if there was a small effect on pain outcomes in favour of regular dosing, different dosing strategies may also allow more tailored analgesic management for patients, particularly those who prioritise a reduction in adverse effects to maintain function more than reduction in pain [27,40].

Although the clinical implications remain unclear our review highlighted a clear lack of high-quality research supporting current practice recommendations and the potential for alternative dosing strategies to benefit patients. Better designed randomised clinical trials are needed to answer this question definitively, with sufficiently large sample sizes and with standardised outcomes for pain, adverse effects and quality of life.

Acknowledgements and conflict of interest:

All authors contributed to study design. S. Edler-Buggy and J. Birtwistle performed the searches, data collection, and data analysis with assistance in data synthesis from Y. ElMokhallalati and M.I.Bennett.

S.Edler-Buggy drafted the article. Y.ElMokhallalati contributed to the design of figures. M.I Bennett, P. Good and K. Kindl contributed to writing and editing the article. All authors were responsible for approval of the final draft.

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Figure Legends

Figure 1. Prisma flow diagram

Figure 2. Forest plot of as needed opioid dosing vs regular opioid dosing

Figure 3. Forest plot of total daily opioid consumption in mg morphine equivalent, showing as needed opioid dosing vs regular opioid dosing.

First Author	Year	Region	Study design	Duration
McGuire	1987	Midwestern USA	RCT phase one only	5 days
Bruera	1988	UK	Randomised cross over	6 days
Dhaliwal	1995	Canada and North America	Randomised double blinded cross over	14 days cross over at 7 days
Broomhead	1997	North America + Australia	1st phase of randomised DB CT	14 days
Bohme and Likar	2003	Austria, Germany & Hungary	Randomised double blind placebo controlled.	Run in 5 days followed by 10 days trial.
Sittl gressinger, likar	2004	Germany, Austria, Netherlands	Randomised double blind, placebo controlled.	15 days
Sorge and Sittl	2004	Germany	Randomized, double-blind, placebo-controlled, parallel-group trial	15 days
Poulain	2008	Austria, Germany Poland, Croatia, France Belgium	Randomised placebo controlled.	14 days
Kress	2014	Austria	Randomized-withdrawal, parallel group, active- and placebo-controlled, double-blind phase 3 study	28 days

Table 1. Summary of studies

1st Author & year	*1*	*2*	*3a*	*3b*	*4*	*5*	*6*	*7*	*n=*
(McGuire et al., 1987)	U	U	H	H	L	L	L	H	21
(Bruera et al., 1988)	U	U	H	H	H	L	L	H	44
(Dhaliwal et al., 1995)	U	U	U	H	L	L	L	H	60
(Broomhead et al., 1997)	U	U	L	H	L	L	U	H	17
(Böhme & Likar, 2003)	U	U	L	L	H	L	L	U	152
(Sittl, Griessinger, & Likar, 2004)	U	U	L	H	L	H	L	U	137
(Sorge & Sittl, 2004)	U	L	L	L	L	U	L	U	157
(Poulain et al., 2008)	L	L	L	L	L	L	L	U	188
(Kress et al., 2014)	L	L	L	L	L	L	L	U	221

Table 2. Bias assessment.

High risk- H, Unclear- U, Low risk- L.

- **1** Random sequence generation
- **2** Allocation concealment
- **3a** Blinding of participants
- **3b** Blinding of personnel
- **4** Blinding of outcome assessment
- **5** Incomplete data
- **6** Selective reporting
- **7** Sample size

1st author and year	Treatment arms		Number of patients each arm (% with cancer pain)		Pain intensity Outcome measure (statistical significance/ p value) NS= not Signiant)	Mean 24 hr opioid dose morphine. (NR=not recorded)	Favours for pain intensity outcome
	As needed	*Regular*	*As needed*	*Regular*			
McGuire 1987	Mixed opioid	Mixed opioid	8 (100%)	13 (100%)	*Mean VAS* As needed= 34.7 Regular= 34.72 (NS)	NR	Neutral
Bruera 1988	PCI Hydromorphone	CSCI Hydromorphone	22 (100%)	22 (100%)	*Mean VAS* As needed = 28 Regular = 27 (NS)	As needed= 280mg (328) regular= 302 mg (390)	Neutral
Dhaliwal 1995	Co-codamol 30/300mg	Controlled release (CR) Codeine	30 (100%)	30 (100%)	*Mean VAS* As needed = 36 Regular= 22 (Significant P= 0.0001)	As needed = 8.5mg (5.2) Regular= 27mg (7.9)	Favours regular codeine
Broomhead 1998	Immediate release morphine (10mg doses)	CR morphine (3 preparations)	4 (100%)	13 (100%)		As needed= 147mg Regular = 126mg	Neutral
Bohme and Likkar 2003	Sublingual (SL) buprenorphine (0.2mg doses)	Buprenorphine transdermal system (BPN TDS)	37 (54%)	115 (55%)	*Responder (satisfactory pain on VRS and ≤0.2mg SLBPN)* As needed = 31%	As needed= 40mg Regular= 192mg	Neutral

					Regular = 40% (NS, (p=0.374))		
Sittl gressinger likar 2004	SL BPN (0.2mg)	BPN TDS	38 (76%)	119 (76%)	*Good or complete pain relief VRS* As needed = 12/37 Regular = 16/36	As needed = 56mg Regular= 192mg	Favours regular BPN TDS, for responders on double criteria. For pain intensity alone- neutral
Sorge and Sittl 2004	SL BPN (0.2mg)	BPN TDS	47 (40%)	90 (30%)	*Mean pain score of good or complete on VRS* As needed = 15/47 Regular = 26/90	As needed= 40mg (24) Regular= 84mg (40)	Neutral
Poulain 2008	SL BPN (0.2mg)	BPN TDS	95 (100%)	94 (100%)	*Mean pain intensity* As needed = 2.7 Regular = 1.5	As needed= 27mg(20) Regular= 184mg (16)	Favours regular BPN TDS
Kress 2014	IR morphine (10mg)	Morphine CR	112 (100%)	109 (100%)	*Responder good or complete pain relief* As needed = 83/111 Regular = 89/109	As needed= 13.7mg (13.7) Regular= 130mg (13.8)	Neutral

Table 3. Study outcomes.

- CSCI= continuous subcutaneous infusion.
- PCI= Patient controlled infusion.
- IR= immediate release.

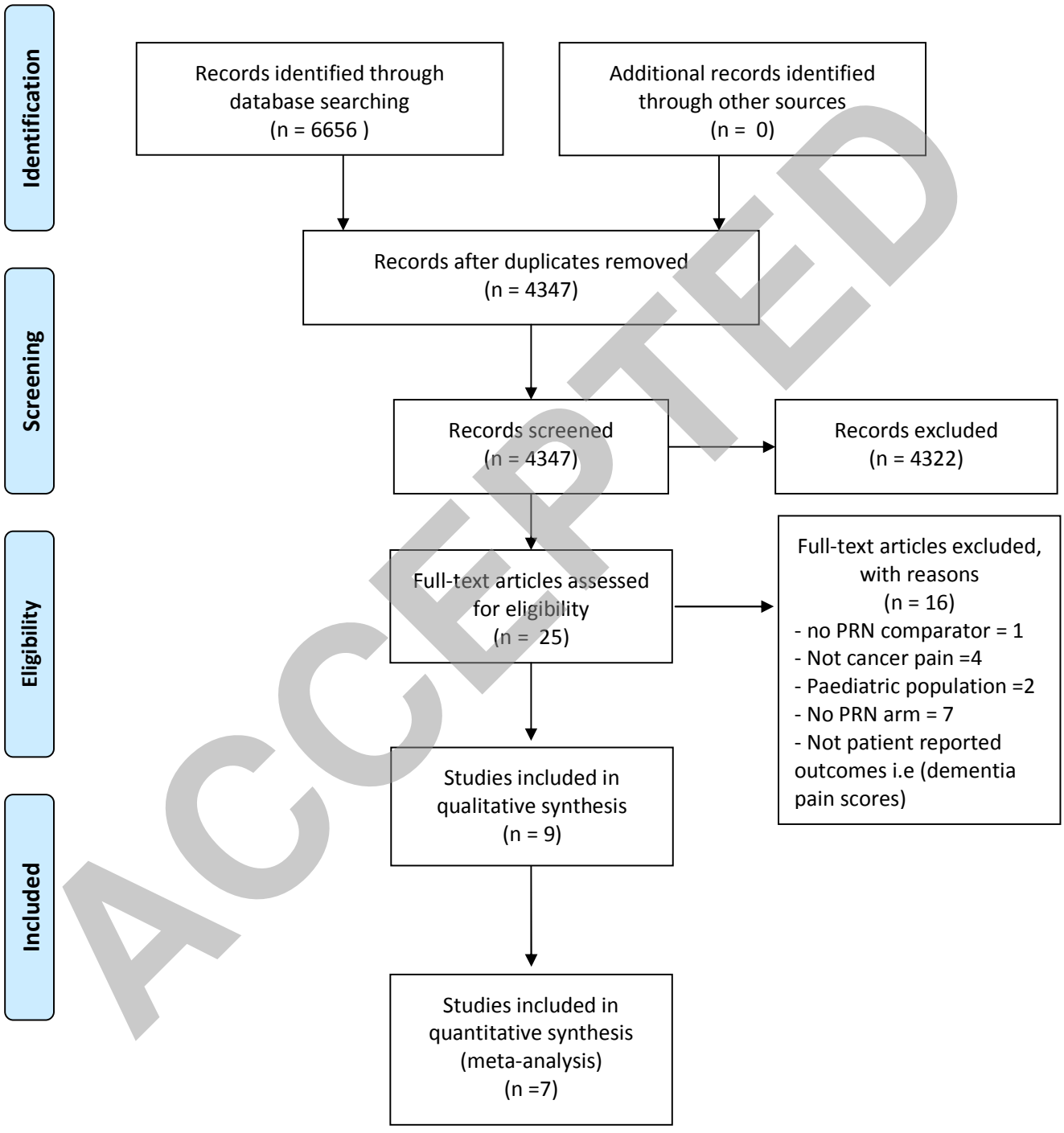
1st Author & year	**Gastrointestinal (Nausea & Vomiting) % of patients**	**Other GI**	**Neurological (Drowsiness/ somnolence)**	**Other neuro**	**Other AEs**	**Overall adverse events**	**Favours (i.e fewer SEs)**
McGuire 1987	NM	NM	NM	NM	NM	NM	***NM***
Bruera 1988	As needed= 22 Regular= 26	As needed= 24% Regular= 24%	As needed= 39% Regular=39%	As needed= 33% Regular =36% (Depression)	NM	NM	As needed - ***not significant***
Dhaliwal 1995	As needed = 14.7 Regular= 40 (P=0.013)	As needed= 27.5 regular= 26.5	As needed= 0% Regular=14.3 (P=0.025)	As needed = 14% Regular =19% (Headache, Dizziness)	NM	As needed = 11% regular= 17%	***PRN***
Broomhead 1998	NM	NM	NM	NM	NM	NM	***NM***
Bohme and Likkar 2003	As needed= 0 Regular= 5	NM	NM	NM	Skin reactions in 10-20% of all patients, as needed and regular.	NM	As needed - ***not significant***
(1) Sittl gressinger likar 2004	Not specified	Not specified	Not specified	Not specified	Not specified	As needed = 73.7% regular= 80.5%	As needed - ***not significant***
Sorge & Sittl, 2004)	As needed= 8% Regular=15%	NM	As needed =1% Regular =2%	As needed = 9% Regular =14% (headache,	As needed = 25% regular= 35.6% (Skin reactions)	As needed = 42.6% Regular = 54.4%	As needed - ***not significant***

				dizziness)			
(3) Poulain	As needed=14% Regular=17%	NM	As needed = 2% Regular= 4%	NM	NM	NM	As needed - ***not significant***
Kress 2014	As needed=8.95 Regular=10%	As needed= 11.6 Regular= 11.2	As needed=1.8% Regular= 4.2%	As needed =11.6% Regular =11.2% (dizziness)	NM	As needed = 56% regular= 62.4%	As needed - ***not significant***

Table 4- Adverse events % of patient reporting each adverse event
NM= not measured

1st Author & year	**Overall comment on sleep**	➢ **>6 hours sleep**	**Favours**
McGuire 1987	*% patients with sleep disturbed by pain* As needed = 67% Regular = 65%		Neutral
Bruera 1988	*Average hours of undisturbed sleep* As needed = 6 FI=6.7		Regular , not significant
Dhaliwal 1995	Comment on over night use of analgesia, sleep not measured,		Not measured
Broomhead 1998	Not measured		Not measured
Bohme and Likkar 2003		As needed = 35% Regular = 50%	Favours Regular
Sitt, Gressinger likar 2004	Mean sleep score 4-1 (>6, 3-6, 2-3, <2) As needed = 3.17 Regular = 3.24	As needed =36.7% Regular =43.9%	Favours Regular for > 6 hr Duration but neutral overall
Sorge & Sittl 2004		As needed = 40.4% Regular= 35.6%	Favours Regular
Poulain 2008	Not measured		Not measured
Kress 2014			Not measured

Table 5: Sleep outcomes



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