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Impact of opioid rescue medication for breakthrough pain on the efficacy and tolerability of long-acting opioids in patients with chronic non-malignant pain

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Background. There is little evidence that short-acting opioids as rescue medication for breakthrough pain is an optimal long-term treatment strategy in chronic non-malignant pain. We compared clinical studies of long-acting opioids that allowed short-acting opioid rescue medication with those that did not, to determine the impact of opioid rescue medication use on the analgesic efficacy and tolerability of chronic opioid therapy in patients with chronic non-malignant pain.

Methods. We searched MEDLINE (1950 to July 2006) and EMBASE (1974 to July 2006) using terms for chronic non-malignant pain and long-acting opioids. Independent review of the search results identified 48 studies that met the study selection criteria. The effect of opioid rescue medication on analgesic efficacy and the incidence of common opioid-related side-effects were analysed using meta-regression.

Results. After adjusting for potentially confounding variables (study design and type of opioid), the difference in analgesic efficacy between the 'rescue' and the 'no rescue' studies was not significant, with regression coefficients close to 0 and 95% confidence intervals that excluded an effect of more than 18 points on a 0–100 scale in each case. There was also no significant difference between the 'rescue' and the 'no rescue' studies for the incidence of nausea, constipation, or somnolence in both the unadjusted and the adjusted analyses.

Conclusions. We found no evidence that rescue medication with short-acting opioids for breakthrough pain affects analgesic efficacy of long-acting opioids or the incidence of common opioid-related side-effects among chronic non-malignant pain patients.

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There is evidence to support the use of opioids for carefully selected patients with chronic non-malignant pain.[1 5 28 29 63] An important and controversial issue concerning the management of chronic pain is assessment and treatment of breakthrough pain. Although there is currently no unanimous definition of breakthrough pain in chronic malignant or non-malignant pain,[64] a consensus panel recommendation from 2005 suggested that breakthrough pain should be defined as 'an abrupt, short-lived, and intense pain that "breaks through" the around-the-clock (ATC) analgesia that controls persistent pain'.[6] Subtypes of breakthrough pain include incident (often predictable and precipitated by activity or movement), idiopathic or spontaneous, and end-of-dose pain.[6 64]

Breakthrough pain is best described in patients with malignant pain, leading to a number of adverse effects including a more severe pain syndrome.[13 50 52] However, studies have shown that breakthrough pain is also

prevalent among opioid-treated patients with chronic non-malignant pain conditions and impacts negatively on their quality of life.[8 24 49 59 66 73] In a recent survey of chronic non-malignant pain, 74% of patients (most commonly, low back pain) with opioid-controlled baseline pain reported breakthrough pain, reaching maximum intensity within a median of 10 min and lasting for a median of 60 min.[49] In these prevalence studies, the majority of cases of breakthrough pain were precipitated (incident pain), although end-of-dose pain was also reported.[8 49 59] It was proposed recently that peripheral, central, or both sensitization may be a common component of breakthrough pain in both malignant and non-malignant diseases.[64]

The primary treatment for breakthrough pain in malignant pain is with immediate-release (IR), short-acting opioids on a pre-emptive or as-needed basis, in addition to the usual opioid regimen.[7 36] This strategy has been adopted for chronic non-malignant pain. However, there is little evidence that using short-acting opioids as rescue medication is an optimal long-term treatment strategy in chronic non-malignant pain.

Evidence is needed for the routine long-term use of short-acting opioids for breakthrough pain in patients with chronic non-malignant pain, particularly as there is a school of thought that exposure to short-acting opioids might increase the risk of abuse, opioid tolerance and the need for dose escalation, or inadequate use of opioids. These are important unknown factors in our understanding of opioid usage in pain relief. In addition, many short-acting opioids are ineffective for certain types of breakthrough pain, as their onset of action is outside the window of maximum pain intensity of the breakthrough pain episode.[49 50 52] Rapid onset formulations (e.g. oral transmucosal fentanyl) have been developed to address this.[36 51 60 62 66] We are not aware of any randomized controlled studies comparing the efficacy and tolerability of long-acting opioid treatment in chronic non-malignant pain patients who have access to IR opioids for breakthrough pain and those who do not. We have systematically reviewed the literature to approach this question. We compared the analgesic efficacy and incidence of common opioid side-effects between studies of long-acting opioids in chronic non-malignant pain that did and did not allow the use of IR opioid rescue medication using meta-regression analyses.

Methods

The primary objective of this review was to compare clinical studies, in patients with chronic non-malignant pain, of long-acting opioids that allowed IR opioid rescue medication ('rescue' studies) with those that did not ('no rescue' studies) to determine the impact of opioid rescue medication use on the analgesic efficacy of chronic opioid therapy among. As a secondary objective, the impact of opioid rescue medication use on the tolerability of chronic opioid therapy in terms of common opioid side-effects (nausea, constipation, and somnolence/sedation) was also investigated.

Literature search

The following electronic databases were searched for articles relevant to this systematic review: MEDLINE (1950 to July 2006) and EMBASE (1974 to July 2006). In the MEDLINE search, terms for long-acting opioid analgesics [i.e. ('analgesics-opioid', 'opioid', 'narcotic', 'fentanyl', 'morphine', 'hydromorphone', 'hydrocodone', 'oxycodone', 'oxymorphone', 'codeine', 'dihydrocodeine', 'pethidine', 'meperidine', or 'tramadol') and ('delayed-action preparations', 'long-acting', 'contin', 'OROS', 'SODAS', 'TIMERX', 'sustained-release/action', 'controlled-release/action', 'delayed-release/action', 'extended-release/action', 'slow-release/action', 'timed-release/action', 'modified-release/action', 'continuous-release/action', 'transdermal', 'TTS', 'TDS', 'ER', 'CR', or 'SR') or 'buprenorphine' or 'methadone'] were combined with terms for non-malignant (i.e. 'noncancer', 'nonmalignant', 'nononcologic', 'nontumour', 'multimorbidity', 'low back', 'chronic musculoskeletal', 'osteogenic', 'phantom limb', 'vascular-diseases/disorders', 'chronic pancreatitis', 'coronary arteriosclerosis', 'coronary atherosclerosis', 'neuralgia-postherpetic', 'trigeminal-neuralgia', 'diabetic neuropathies', 'amyloid-neuropathies', 'brachial-plexus-neuropathies', 'mononeuropathies', 'polyneuropathies', 'neuropathy', 'neuralgia', 'arthritis-rheumatoid', 'osteoarthritis', or 'osteoporosis') and pain (i.e. 'pain' or 'analgesia') or terms for specific non-malignant pain disorders (i.e. 'low back pain' or 'complex regional pain syndrome'). A number of study design search terms were also included in the strategy. Equivalent search terms specific to EMBASE were used for the EMBASE search. The full MEDLINE and EMBASE search strategies are given in Supplementary material, Appendix 1.

All English, German, French, Spanish, or Italian language full-text research articles were eligible for inclusion, as long as they met the criteria defined below.

All published, prospective, blinded, or open-label clinical trials with either a randomized or controlled design were eligible. Prospective observational studies were also accepted. Case reports, conference proceedings, or retrospective studies (surveys or audits) were excluded from this review.

Eligible patients were adults aged $\geq$18 yr with chronic non-malignant pain (such as chronic musculoskeletal pain, vascular disorders, chronic pancreatitis, lower back pain, osteogenic pain, coronary artery disease, phantom limb pain, post-herpetic neuralgia, trigeminal neuralgia, diabetic neuropathy, or neuropathic pain). Studies that included patients with malignant pain were eligible only if less than one-third of the study population were patients with malignant pain. Studies in both opioid-naïve patients and patients already on opioids were eligible.

Treatments included in the review were long-acting opioids or opioid formulations [such as methadone, transdermal fentanyl, or sustained-release (SR) morphine] including the weak opioids, tramadol, codeine, and slow-release dihydrocodeine. All routes of administration, other than intrathecal or intraspinal, were eligible. Since intrathecal use of opioids is an invasive method often used as a last resort in a selection of patients unresponsive to other treatments, we felt that that patient group is not comparable with those receiving oral or transdermal opioids. All studies in which one or more opioids was administered for at least 4 weeks, including those that compared one opioid with placebo, other opioids, or other active controls were eligible for inclusion. Studies had to have a flexible dosing regimen (at least during the maintenance phase); studies with specific criteria for dose escalation or dose escalation to a maximum dose were eligible.

Whether an IR opioid was used as rescue medication or not had to be defined. If this information was not given explicitly in the publication, a single attempt was made to contact the authors to obtain this information before the study was excluded.

Studies reporting at least one of the following outcome measures were eligible.

(i) A measure of analgesic efficacy, such as pain relief or pain intensity measured by the Brief Pain Inventory, a visual analogue scale, or equivalent, or patient and investigator global assessment of analgesic efficacy.
(ii) Tolerability: number or percentage of patients reporting either nausea, constipation, or somnolence/sedation (or drowsiness if somnolence/sedation not reported).

Selection of studies

Titles and abstracts for studies identified in the literature search were reviewed for inclusion according to the selection criteria described above. Those studies that clearly failed to meet the selection criteria were discarded immediately. The full-text articles were obtained for all studies that appeared to meet the criteria and for those where insufficient information was available in the abstract to determine eligibility. All full-text articles were reviewed independently by two reviewers (H.W. and either J.D. or U.R.) to ensure that all the inclusion criteria were met adequately. Any disagreements between the two reviewers were resolved by discussion and consensus without the need to consult a third party. Where it was not clear whether the use of rescue medication had been allowed during the study or not, a single e-mail (no reminders) was sent out to the corresponding author requesting this information before the article was excluded. For usual care or non-interventional trials that did not explicitly report the use of rescue medication, it was assumed that rescue medication was allowed as per usual clinical practice. Eighty-seven potential studies were identified by MEDLINE and EMBASE and the full text was reviewed; of these, 47 were found on closer inspection to meet all the study selection criteria. The majority of excluded studies failed to meet more than one of the selection criteria and were therefore not excluded on the basis of one criterion. Factors commonly leading to exclusion included: failure to confirm whether opioid rescue medication was allowed or not, study duration <4 weeks, incorrect intervention (e.g. intrathecal administration), or inflexible dosing regimen. An additional study[46] that we were aware was in press at the time of the search and therefore not picked up by the search strategy was also included, as it met all the selection criteria.

Data extraction and outcome measures

The following data were extracted from each of the included studies: study design; type of non-malignant pain or condition studied; patient numbers; intervention (type of opioid and route of administration); duration of treatment; the primary or first reported (in sufficient detail for analysis) analgesic outcome (scale, measure at baseline and endpoint, change in measure or difference *vs* placebo, and measures of variation as appropriate); number, per cent, or both of patients reporting nausea, constipation, or somnolence/sedation (or drowsiness, if somnolence/sedation not reported); and number or percentage of patients using rescue medication (for rescue studies only).

We applied the Jadad criteria for randomized controlled trials to each study to determine the methodological quality and validity of each study.[25] The criteria were applied independently by two reviewers (H.W. and N.M.). There were three disagreements between the two independent reviewers, which were resolved by a third party (A.J.).

In brief, a study received one point for each 'yes' or zero points for each 'no' given in reply to the questions provided in Appendix 2 in the Supplementary material (maximum number of points is 5).

Statistical analysis

The primary outcome was analgesic efficacy and the secondary outcomes were the percentage of patients with nausea, constipation, or somnolence. All outcome variables were analysed in a meta-regression analysis.[68] Meta-analysis would normally be used to investigate the treatment effect within studies, but since there are no studies directly comparing the effect of opioid rescue medication use on long-term analgesic efficacy, we have used meta-regression to make indirect comparisons between the 'rescue' and the 'no rescue' studies.

For the purposes of the analysis, certain study designs were treated in the following way.

- Studies comparing two long-acting opioids were treated as two separate uncontrolled studies.
- In two crossover studies comparing transdermal fentanyl with SR morphine, only the experimental

transdermal fentanyl arm was used in the adverse event (AE) analysis (these studies were both excluded from the primary analysis).
- In studies comparing long- and short-acting opioids, the long-acting opioid arm was treated as an uncontrolled study. The rationale for this is that in equivalence studies of SR opioids, short-acting opioids are often used to show efficacy of the SR formulation. In these studies, patients take the short-acting opioids regularly; therefore, you would expect similar pain control as with the SR opioid.
- Since placebo-controlled studies often allow continuation of non-opioid analgesics during the study period, studies comparing a long-acting opioid with a non-opioid analgesic were treated as placebo-controlled studies.

For each study, the primary pain outcome or the first pain outcome reported in sufficient detail was used in the meta-regression analysis. A measure of the treatment effect, which was the difference between opioid and control in controlled studies and the difference from baseline in uncontrolled studies, was calculated based on the published data. The standard error (SE) of the treatment effect was also calculated, using standard formulas if the necessary information was available. The following assumptions were made for uncontrolled studies, if the necessary information for calculating the SE was not available.

- Mean at baseline or endpoint=median at baseline or endpoint.
- Inter-quartile range (IQR)=1.35×standard deviation (SD) if IQR is specified and SD is missing.
- If measure of variability of the change was unavailable and SD of the endpoint value was available, the SD of the change was assumed to be equal to the SD of the endpoint value.

The treatment effect for each study was converted where necessary onto a scale of 0–100 (higher scores equal worse pain or less pain relief). This was done by multiplying the treatment effect by 100/maximum scale score. Analgesic effect was analysed in a meta-regression analysis using Stata 9.2.[68] Meta-regression was used to investigate the effect of rescue medication on treatment effect, while controlling for other potentially confounding variables, namely study design, Jadad score, and type of opioid. The regression coefficient from the analysis is the estimated average difference in analgesic efficacy (number of points on a 0–100 scale) between the 'rescue' and the 'no rescue' medication studies; negative values are in favour of rescue medication. For other variables, negative scores are in favour of the specific category in question and positive values are in favour of the reference category.

The percentage of patients treated with long-acting opioid with nausea, constipation, or somnolence/sedation was calculated for each study and the SE of the percentage was calculated as the width of the exact binomial confidence interval divided by 2×1.96 (this is more appropriate for small sample sizes than the normal approximation to the SE). For studies in which the incidence of AEs was reported separately for different parts of the study, the highest incidence values were used. As for the efficacy outcome, meta-regression was used to investigate the effect of rescue medication, while controlling for other potentially confounding variables. The logit of the percentage of patients with each AE was also used as a sensitivity analysis, but the results were similar and are therefore not presented. The logit and SE were calculated by fitting an intercept-only logistic regression model for each outcome. The regression coefficient from the analysis is the estimated average difference in AE incidence (% of patients) between the 'rescue' and the 'no rescue' medication studies; negative values are in favour of rescue medication. For other variables, negative scores are in favour of the specific category in question and positive values are in favour of the reference category.

The entire analysis was done again, this time excluding studies with a Jadad score of 0. The analysis was also run excluding the weak opioids, namely tramadol, codeine, tilidine, and dihydrocodeine.

In addition, the studies that included any patients with malignant pain were excluded and the analysis was re-run. This was done as a sensitivity analysis to ensure that there was an assessment on pure non-malignant pain.

Results

Study characteristics and quality

Forty-eight studies met all of the study selection criteria and were included in the review; of these, 24 studies allowed the use of rescue medication ('rescue' studies) and 24 did not ('no rescue' studies). The characteristics of each included study are summarized in the Supplementary material.[1–4 9–12 14–16 18–23 27 30–35 37–48 54–58 61 65 67 70–72 75] The frequency of the different types of study design (for the purposes of analysis), control group (controlled studies only), and opioid type along with the quality of the included articles in terms of Jadad score is given for the 'rescue' and 'no rescue' studies and overall in Table 1. The maximum time of treatment was 2 yr.

The majority of both the 'no rescue' and the 'rescue' studies were uncontrolled. All but two of the placebo-controlled, parallel-group studies and all the crossover studies (all placebo-controlled) did not allow rescue medication use. The most common control used in the controlled studies was placebo and the most common opioids in the 'no rescue' group were oxycodone and tramadol and in the 'rescue' group, fentanyl. As may be expected, there was an imbalance in study quality between the 'rescue' and the 'no rescue' studies. Most 'rescue' studies were of a low quality (Jadad score of 0 or 1), whereas just

Table 1 Summary of study characteristics and quality. *How the study was treated for the purposes of analysis and does not necessarily reflect the original design of the study. †One study in which the control was non-steroidal anti-inflammatory drug and one study in which the control was morphine-free patients; both were considered as placebo-controlled studies for the purposes of the analysis. ‡Controlled studies only (n=13). §n=26 for the rescue studies, as two of the studies comparing two long-acting opioids were counted twice; each arm was treated as a separate uncontrolled study

Characteristic	No rescue (n=24)	Rescue (n=24)	Total (n=48)
Study design*, *n* (%)			
Placebo-controlled crossover	3 (12.5)	0 (0)	3 (6.3)
Placebo-controlled, parallel-group†	8 (33.3)	2 (8.3)	10 (20.8)
Uncontrolled	13 (54.2)	22 (91.7)	35 (72.9)
Control group, *n* (%)‡			
Active placebo	2 (18.2)	0 (0)	2 (15.4)
Morphine-free	0 (0)	1 (50.0)	1 (7.7)
NSAID	0 (0)	1 (50.0)	1 (7.7)
Placebo	9 (81.8)	0 (0)	9 (69.2)
Type of opioid, *n* (%)§			
Morphine	4 (16.7)	4 (15.4)	8 (16.0)
Oxycodone	6 (25.0)	2 (7.7)	8 (16.0)
Fentanyl	3 (12.5)	13 (50.0)	16 (32.0)
Tramadol	6 (25.0)	1 (3.9)	7 (14.0)
Other	5 (20.8)	6 (23.1)	11 (22.0)
Jadad score, *n* (%)			
0	2 (8.3)	2 (8.3)	4 (8.3)
1	11 (45.8)	21 (87.5)	32 (66.7)
2	0 (0)	1 (4.2)	1 (2.1)
3	0 (0)	0 (0)	0 (0)
4	3 (12.5)	0 (0)	3 (6.3)
5	8 (33.3)	0 (0)	8 (16.7)
Mean (SD) Jadad score	2.6 (2.0)	0.96 (0.36)	1.8 (1.7)

under half of the 'no rescue' studies were of high quality (Jadad score of 4 or 5). For this reason, Jadad score was included as a term in the meta-regression analysis.

Of the 24 studies included that allowed short-acting opioid rescue medication, seven reported the number or percentage of patients who actually took rescue medication. In these seven studies, the percentage of patients who actually took rescue medication ranged from 11% to 100% (median 57%).[1 19 20 33 35 42 45]

Analgesic efficacy analysis

Of the 48 studies, 40 were included in the meta-regression analysis of analgesic efficacy (Table 2). Eight studies were excluded from the analysis, as it was not possible to calculate either the effect size (n=4) or the SE for the effect size (n=4) based on the published data.

The results of the unadjusted analysis indicated an average difference of six points on a 0–100 scale for efficacy in favour of rescue medication use, although this difference was not significant (P=0.24) (Table 2). As a sensitivity analysis, studies involving any patients with malignant pain were excluded and the analysis was re-run. Four studies were identified and excluded.[19 21 42 75] After excluding studies involving any patients with malignant pain, the average difference was −4.5; 95% CI: −15.38, 6.46; P=0.424.

After adjusting for potentially confounding variables, namely study design and both study design and type of opioid, the difference in analgesic efficacy between the 'rescue' and the 'no rescue' studies was not significant, with regression coefficients close to 0 and 95% confidence intervals that excluded an effect of more than 18 points in each case. The movement of the regression coefficient towards 0 after adjustment for study design is to be expected due to the imbalance in study design between the 'rescue' and the 'no rescue' studies. Excluding studies that involved any patients with malignant pain and adjusting for study design did not affect the results (regression coefficient 1.2; 95% CI: −10.31, 12.82; P=0.831). Very similar results were obtained when the analysis was adjusted for Jadad score and both Jadad score and study design. This is to be expected, as Jadad score is a measure of study quality based on the study design.

Table 2 Analgesic efficacy results. *Reference category is placebo-controlled. †Reference category is morphine. CI, confidence interval

	Regression coefficient	95% CI	*P*-value
Unadjusted analysis			
Rescue medication	−6.3	−16.9, 4.2	0.24
Adjusted for study design			
Rescue medication	−0.3	−11.6, 11.0	0.96
Uncontrolled studies*	−16.8	−30.0, −3.7	0.01
Crossover studies*	−6.9	−28.7, 14.9	0.54
Adjusted for study design and opioid type			
Rescue medication	−5.2	−17.2, 6.9	0.40
Uncontrolled studies*	−16.1	−29.6, −2.6	0.02
Crossover studies*	−10.8	−32.7, 11.0	0.33
Oxycodone†	−5.6	−22.7, 11.5	0.52
Fentanyl†	−2.7	−17.7, 12.3	0.73
Tramadol†	−21.4	−39.2, −3.5	0.02
Other†	−3.5	−20.6, 13.7	0.69

Excluding studies with a Jadad score of 0 did not change the outcome of the analgesic efficacy analysis. Excluding weak opioids from the analysis also did not change the findings.

In the analyses adjusting for study design, a significantly greater analgesic effect was seen for uncontrolled studies *vs* placebo-controlled, parallel-group studies, as would be expected (regression coefficient: −16.8; 95% CI: −30.0, −3.7; P=0.01). This was also true after adjusting for study design and opioid type. Interestingly, significantly better analgesic efficacy was seen in studies of tramadol compared with morphine studies (regression coefficient: −21.4; 95% CI: −39.2, −3.5; P=0.02).

Whether or not opioid rescue medication was allowed did not significantly impact on analgesic efficacy, even after adjusting for potentially confounding variables (study design, Jadad score, or study design and opioid type).

Table 3 Tolerability analysis: nausea. *Reference category is placebo-controlled. †Reference category is morphine. CI, confidence interval

	Regression coefficient	95% CI	*P*-value
Unadjusted analysis			
Rescue medication	−4.7	−16.2, 6.9	0.43
Adjusted for study design			
Rescue medication	−3.8	−17.1, 9.6	0.58
Uncontrolled studies*	−2.9	−19.1, 13.3	0.73
Crossover studies*	−1.8	−27.0, 23.5	0.89
Adjusted for study design and opioid type			
Rescue medication	−10.9	−25.4, 3.7	0.14
Uncontrolled studies*	0.13	−16.7, 16.9	0.99
Crossover studies*	−4.8	−30.0, 20.4	0.71
Oxycodone†	−2.1	−22.0, 17.8	0.84
Fentanyl†	4.5	−13.1, 22.1	0.62
Tramadol†	−13.0	−33.1, 7.1	0.21
Other†	−18.3	−41.3, 4.7	0.12

Table 4 Tolerability analysis: constipation. *Reference category is placebo-controlled. †Reference category is morphine. CI, confidence interval

	Regression coefficient	95% CI	*P*-value
Unadjusted analysis			
Rescue medication	−5.5	−18.1, 7.2	0.40
Adjusted for study design			
Rescue medication	−0.5	−15.0, 14.0	0.95
Uncontrolled studies*	−15.1	−31.8, 1.6	0.08
Crossover studies*	−14.7	−40.3, 11.0	0.26
Adjusted for study design and opioid type			
Rescue medication	−2.3	−16.8, 12.1	0.75
Uncontrolled studies*	−6.7	−21.3, 8.0	0.37
Crossover studies*	−28.2	−50.9, −5.4	0.02
Oxycodone†	5.1	−13.1, 23.2	0.58
Fentanyl†	−21.9	−38.0, −5.8	0.01
Tramadol†	−27.8	−47.1, −8.5	0.01
Other†	−22.2	−42.4, −1.9	0.03

Table 5 Tolerability analysis: somnolence/sedation. *Reference category is placebo-controlled. †Reference category is morphine. CI, confidence interval

	Regression coefficient	95% CI	*P*-value
Unadjusted analysis			
Rescue medication	−0.1	−11.3, 11.0	0.98
Adjusted for study design			
Rescue medication	2.9	−10.1, 15.9	0.66
Uncontrolled studies*	−8.8	−23.9, 6.3	0.26
Crossover studies*	−6.6	−29.2, 16.1	0.57
Adjusted for study design and opioid type			
Rescue medication	6.4	−6.9, 19.8	0.34
Uncontrolled studies*	−2.9	−16.7, 10.8	0.67
Crossover studies*	−15.2	−36.3, 5.8	0.16
Oxycodone†	20.7	3.4, 38.0	0.02
Fentanyl†	−8.5	−23.9, 7.0	0.28
Tramadol†	−3.8	−21.3, 13.8	0.67
Other†	−2.3	−21.6, 16.9	0.81

AE analysis

Twelve studies were excluded from the analysis of nausea, 13 from the analysis of constipation, and 16 from the analysis of somnolence/sedation, as the data were not reported.

As for analgesic efficacy, there was no significant difference between the 'rescue' and the 'no rescue' studies for the incidence of nausea, constipation, or somnolence (Tables 3–5) in the unadjusted analysis and after adjusting for study design and both study design and type of opioid, with regression coefficients close to 0 and 95% confidence intervals that excluded an effect of more than about 25% for nausea, 18% for constipation, and 20% for somnolence/sedation. Similar results were seen after adjusting for Jadad score and both Jadad score and study design (data not shown).

After adjusting for study design and opioid type, there was a greater difference in the incidence of nausea between the 'rescue' and the 'no rescue' studies in favour of rescue medication (regression coefficient: −10.9; 95% CI: −25.4, 3.7; P=0.14), although the difference was not significant (Table 3).

Studies of fentanyl, tramadol, and 'other' opioids (controlled-release codeine, transdermal buprenorphine, and slow release tilidine) reported significantly less constipation than those of morphine (Table 4). Similarly after adjusting for study design and opioid type, crossover studies also reported significantly less constipation than placebo-controlled, parallel-group studies (regression coefficient: −28.2; 95% CI: −50.9, −5.4; P=0.02; Table 4). Interestingly, the incidence of somnolence/sedation was significantly higher in the oxycodone studies compared with the morphine studies (regression coefficient: 20.7; 95% CI: 3.4, 38.0; P=0.02; Table 5).

Discussion

In patients with malignant and non-malignant chronic pain treated with ATC opioids, end-of-dose pain is usually managed by increasing the ATC opioid dose or shortening the dosing interval, whereas other types of breakthrough pain are treated with IR short-acting opioids on a pre-emptive or as-needed basis.[7 36] However, there is little

long-term evidence that this is the most appropriate strategy to deal with breakthrough pain in chronic non-malignant patients. We are not aware of any randomized controlled studies that have investigated the impact of IR opioid rescue medication use for breakthrough pain on the efficacy and tolerability of chronic opioid therapy in patients with chronic non-malignant pain. In this review, we have attempted to address this question based on indirect comparisons between studies of long-acting opioids in chronic non-malignant pain that allowed the use of IR short-acting opioids for breakthrough pain and those that did not.

In the meta-regression analysis, whether or not rescue medication was allowed did not significantly impact on analgesic efficacy even after adjusting for potentially confounding variables, such as study design, Jadad score, and opioid type. We assumed that rescue medication was used in studies in which this was not explicitly stated, if they were usual care or non-interventional studies. The analgesic effect was significantly greater in the uncontrolled studies than the controlled studies, which is to be expected as larger effects tend to be seen in uncontrolled studies. These larger effects are often due to the bias inherent in the study design, but there is no reason to assume that those biases are different in rescue *vs* non-rescue studies. Assuming this bias to be constant, we did not attempt to adjust for bias in our analyses, and we do not claim to estimate a valid treatment effect of the opioids under review. These results suggest that allowing treatment of breakthrough pain with short-acting IR opioids is of no additional benefit in terms of long-term analgesic efficacy, but also does not reduce analgesic efficacy in patients with chronic non-malignant pain treated with long-acting opioids.

Alternatively, it may be that the IR opioids used in these studies are not beneficial because their active effect does not coincide with the peak pain intensity of the breakthrough pain episode. This would be particularly important for unpredictable incident pain, which is not precipitated by a known trigger, and idiopathic or spontaneous pain, for which pre-emptive treatment with short-acting opioids is not possible. The onset of breakthrough pain in opioid-treated patients with chronic non-malignant pain is rapid and peaks within a median of 10 min,[8 49 59] whereas the onset of action of most short-acting opioids is between 30 and 60 min.[36] As a consequence, the use of ineffective short-acting opioids may increase their use and lead to needless escalation in the dose of long-acting opioids for baseline pain and associated side-effects, although there is no published literature on this topic to date. Newer rapid-onset formulations of short-acting opioids, including oral trans-mucosal fentanyl citrate and fentanyl buccal tablets, have been shown to be efficacious for the short-term treatment of breakthrough pain and well-tolerated among patients with both chronic non-malignant and malignant pain.[36 51 60 62 74] These studies specifically looked at the short-term effects of these medications on breakthrough pain (up to 2 h after dosing) and did not address the impact of long-term use of short-acting opioids for breakthrough pain in addition to a long-acting opioid regimen on pain control. We were unable to find any studies in malignant pain that directly addressed the impact of short-acting opioid rescue medication use on the long-term analgesic efficacy of long-acting opioid regimens. This is not unexpected as malignant pain treatment is relatively short term and frequent dose adaptations are necessary owing to the increase in pain.

It is unknown whether long-term use of short-acting opioids may increase the risk of tolerance and the need for increasing doses to achieve satisfactory analgesia or increase the risk of opioid addiction, although there is some evidence to suggest a link.[26] Although this study was not designed to specifically look at tolerance, our results show that overall analgesic efficacy of an ATC opioid regimen does not appear to be adversely affected by the availability of short-acting opioids for rescue medication. This topic is highly controversial and requires further research.

There was no evidence for an increase or a decrease in the incidence of the common opioid side-effects such as nausea, constipation, and somnolence/sedation in studies that allowed IR opioid rescue medication compared with those that did not. There was a trend towards a lower incidence of nausea in the rescue medication studies after adjusting for study design and opioid type, although the difference was not statistically significant. It is possible that the effect of opioid type was confounding the effect of rescue medication in the unadjusted analysis. In agreement with our results, a recent study in malignant pain found no significant differences in the incidence of nausea, constipation, and drowsiness between patients prescribed an ATC opioid only and those prescribed an ATC opioid plus an as-needed (PRN) opioid.[69] However, the incidence of these side-effects was higher in the ATC plus PRN group.

In our analysis, the rate of constipation was significantly lower in the transdermal fentanyl, long-acting tramadol, and 'other opioid' studies than in the studies of long-acting morphine formulations. In addition, the rate of somnolence was significantly higher in the long-acting oxycodone studies than in the morphine studies. Previous randomized studies comparing transdermal fentanyl and SR oral morphine in chronic non-malignant and malignant pain have shown significantly lower rates of constipation with transdermal fentanyl.[1 2 17] Since fentanyl crosses the blood–brain barrier more rapidly than morphine, it exerts its analgesic effects at lower doses which have less intestinal action when compared with morphine.[53] Furthermore, the transdermal route bypasses opioid receptors in the intestine.[53] The lower rates of constipation in the tramadol and 'other opioid' (three of the four studies were with weak opioids) studies are probably a result of the relatively weak μ-receptor binding in the gut of these weak opioids compared with morphine. We are unaware of any randomized controlled studies comparing long-acting formulations

of oxycodone and morphine that show significantly higher rates of somnolence or sedation with oxycodone. The difference in somnolence rates between the oxycodone and morphine studies in our analysis is unlikely to be a result of the over-representation of studies that did not allow rescue medication among the oxycodone studies, as this was corrected for in the adjusted analyses, but it may have been due to the formulation used. OxyContin® contains an IR portion and the higher fluctuations in plasma levels of oxycodone may induce sedation.

As expected, there was an imbalance in study quality between studies allowing rescue medication use and those that did not, with more poorer quality studies in the rescue group. Observational and usual care studies, which are of lower quality than randomized controlled studies, are less likely to prohibit rescue medication use. We therefore corrected for study design and Jadad score in the meta-regression analysis, but results before and after this adjustment were similar.

It is important to note that our findings do not imply that rescue medication is needless. The studies published to date have not been designed specifically to address the topic of rescue medication, and therefore this paper should only be seen as a review of the findings to date. More research is needed in this area to provide a clearer answer. Ideally, data would be provided from a randomized trial in which patients have, or do not have, rescue medication which collects data on pain, tolerability, and dose escalation. In the absence of such a study, we have attempted to summarize the available literature and make the limitations of these data clear in our findings.

Our results do not rule out an effect of opioid rescue medication on analgesic efficacy or the incidence of common opioid side-effects, owing to a number of limitations concerning the study design. For the same reason, we cannot rule out that the higher AE rates associated with some opioids were due to random variation. The first limitation is the heterogeneity of included studies, with a wide range of study designs, patient populations, and treatment durations. We have attempted to correct for some, but not all, of these potentially confounding variables in the meta-regression analysis. Secondly, the fact that rescue medication was allowed does not necessarily mean that it was used and the number or percentage of patients who took rescue medication was not specifically or clearly reported in most of the 'rescue' studies. For example, several studies were usual care studies and rescue medication use was not a specific outcome of the study. However, this would be expected to reflect the usual clinical situation, where short-acting opioids are available for use on an as-needed basis. Thirdly, although we excluded short-term studies of <4 weeks, it may be that the studies included in the review were not sufficiently long enough to determine the long-term effects of using short-acting opioids as rescue medication in chronic non-malignant pain. Fourthly, the outcome measure of analgesic efficacy may be too crude to assess more subtle swings in pain that are nonetheless of clinical relevance. This is due, at least in part, to the time scale. The short time window of breakthrough pain may not necessarily overlap with the time that the pain questionnaire was filled out. It is also possible that studies may avoid patients with a clinical need for short-acting opioids to deal with flares of pain. Finally, the literature search was not completely systematic, as our database search was limited to MEDLINE and EMBASE and we did not include any hand searching. It is therefore possible that some studies may have been missed and excluded from the analysis.

Our results do not suggest that treatment of breakthrough pain with short-acting IR opioids is of additional benefit in terms of long-term analgesic efficacy or that it reduces analgesic efficacy in patients with chronic non-malignant pain treated with long-acting opioids. There is also no evidence that allowing opioid rescue medication use increases or decreases the incidence of the common opioid side-effects nausea, constipation, and somnolence/sedation. Compared with morphine studies, the constipation rate was significantly lower in the fentanyl, tramadol, and 'other opioid' studies, and the somnolence rate was significantly higher in the oxycodone studies.

This analysis has tried to collate data from a number of studies that did not set out to measure rescue medication as a primary outcome. Taking this into account, conclusions must be drawn with caution. A randomized controlled trial of long-term treatment with a long-acting opioid in chronic non-malignant pain plus or minus opioid rescue medication is needed to inform decisions on breakthrough pain management in this patient population.

Supplementary material

Table S1 and Appendices can be found as Supplementary material in *British Journal of Anaesthesia* online.

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