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SYSTEMATIC REVIEW AND META-ANALYSIS

Effectiveness of interventions on the appropriate use of opioids for noncancer pain among hospital inpatients: A systematic review

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Aims: To summarise the effectiveness of interventions on appropriate opioid use for noncancer pain among hospital inpatients.

Methods: Two reviewers independently searched 6 databases up to March 2018 original research articles reporting on quantitative outcomes of interventions on appropriate opioid use among hospital inpatients. Appropriate opioid use was measured by changes in prescribing, such as the lowest effective opioid dose and duration, or clinical outcomes such as adequate pain control. Quality and intervention complexity assessments were performed by 2 independent reviewers. The full methodological approach was published on PROSPERO (ID: CRD42019145947).

Results: Of 398 full-text articles assessed for eligibility, 37 articles were included in the review. Most articles had a moderate or high risk of bias (27 of 37 studies). Thirty-one articles primarily addressed appropriate opioid use and 6 articles targeted opioid safety as a secondary outcome. A multifaceted approach was the most common primary intervention (16 studies) and adequate pain control was the main outcome measured (14 studies). Health provider education, reinforced by hard-copy material and feedback, was associated with a 13.0 to 29.5% increase in the proportion of opioid prescriptions written in concordance with local guidelines and reduced pain scores ranging from 7.0 to 34.5%. Interventions to improve opioid safety in patient-controlled analgesia reduced medication errors by up to 89.1%.

Conclusion: Interventions involving academic detailing and education, especially when reinforced by feedback, show positive effects on appropriate opioid use among hospital inpatients. Future studies investigating the impact of administrative interventions on opioid use and related outcomes are warranted.

KEYWORDS

hospital, inpatients, intervention, opioid, pain management

1 | INTRODUCTION

Opioid analgesics are commonly used to manage moderate to severe acute pain among hospital inpatients.[1] The National Institute for Health and Care Excellence identified opioids as a high-risk medicine[2] as they account for up to 16.1% of hospital adverse drug events (ADEs).[3-5] Opioid-related ADEs include constipation, nausea, sedation and respiratory depression. The association between opioid-related

ADEs and adverse clinical outcomes, including increased length of hospital stay, costs, rate of readmission and even death, are well documented.[6-9]

Recent attention has been placed upon optimising opioid use and reducing related harms through the development of clinical prescribing guidelines. Guidelines for the management of acute noncancer pain recommend initial nonopioid analgesia, and if insufficient, the addition of the lowest effective dose of immediate-release opioid analgesia for <3–5 days.[10] Although the introduction of these guidelines was associated with some reduction in unnecessary opioid use, further improvements may be observed when linked with additional interventions to reinforce the implementation of these recommendations into clinical practice.[11,12] Therefore, numerous systems-level interventions to promote appropriate opioid prescribing have been implemented internationally in a variety of settings.[13,14]

A 2017 Cochrane review investigated the effectiveness of such interventions to reduce opioid use in the outpatient setting.[15] The interventions reported in the review predominantly involved adjuvant therapies, such as cognitive behavioural therapy. However, these therapies were targeted to address opioid use in the management of chronic pain in the primary care setting, which have limited evidence for treating acute pain among hospital inpatients. Moreover, the overall findings of the review were mixed. Currently, no systematic review has been conducted to investigate the effect of interventions on the appropriate use of opioids in the hospital setting. Therefore, the aim of this systematic review was to investigate the effectiveness of interventions on opioid appropriateness during inpatient admission for noncancer pain.

What is already known about this subject

- Harms related to opioid analgesics among hospital inpatients are well documented.
- A range of interventions have been trialled to improve the appropriate use of opioids, however, they have yielded mixed findings.
- No review has been conducted to summarise the effect of interventions addressing opioid use in the hospital inpatient setting.

What this study adds

- We identified 37 studies using 4 main types of interventions to optimise opioid use, ranging from opioid-targeted strategies such as multifaceted interventions, decision-making tools, and pain-monitoring, to broader medication safety interventions.
- Interventions involving education for health care providers and patients, particularly when reinforced by performance feedback or hard-copy material, contribute towards improved prescribing and clinical outcomes related to opioid use among hospital inpatients.

2 | METHODS

This review was performed in adherence to the *Preferred Reporting Items for Systematic reviews and Meta-Analyses* (PRIMSA) guidelines.[16] The protocol for this systematic review was published on PROSPERO on 27 November 2019 (ID: CRD42019145947).

2.1 | Inclusion and exclusion criteria

Inclusion criteria included original peer-reviewed research articles that reported quantitative outcomes of interventions on appropriate opioid use for noncancer pain during inpatient stay. A significant proportion of hospitalised patients are prescribed opioid analgesics in the emergency department (ED),[1] thus interventions conducted in this setting were included in the review. Given the paucity of clinical trials available in this area, observational studies were also included to capture data relevant to this review. Appropriate use could be measured by changes in prescribing practices, such as using the lowest effective opioid dose and duration or guideline adherence, or clinical outcomes such as reduced pain intensity or length of stay (LOS). We excluded studies which exclusively reported on opioid use related to palliative care, oncology or opioid-substitution therapy as they were outside the scope of this review. Studies focusing on discharge opioid use were excluded as they often included interventions in the primary care setting. We also excluded studies involving participants below the age of 18 years; case reports/series, conference abstracts, expert opinion or literature reviews; or studies written in languages other than English.

2.2 | Search strategy

A systematic search was conducted using 6 electronic databases. This search was applied to Medline (1960–Present) and adapted for Scopus (1960–Present), Embase (1969–Present), Cochrane Central Register of Controlled Trials (1995–Present), International Pharmaceutical Abstracts (1970–Present) and PsycINFO (1963–Present). The last search was run on 21 March 2018.

The search terms applied to all electronic databases were developed with a clinical librarian and integrated 3 key themes: opioid analgesics, by exploding the terms Analgesics, Opioid or Narcotics and listing individual opioid names; interventions that affect prescribing, by using entry term headings describing interventions in adjacency with prescribing; and the hospital inpatient setting, by exploding the entry term Hospital Departments and applying multiple field searches for inpatients, hospital and acute care. Appropriate syntax and subject headings were applied to the same key terms across all databases and the full search strategy is available in . References of relevant articles

were also screened to identify any other potential studies not identified by the search strategy.

2.3 | Data extraction

After the removal of duplicates, 2 authors (S.L. and J.N.) independently screened articles by title and abstract for potentially eligible studies. Full-text articles were then assessed to confirm eligibility. Any discrepancies were brought to a third author (J.P.) for consensus to be made. We extracted author, country and year of the study conducted, study size, design and follow-up period, intervention performed, outcomes and potential sources of bias. Authors were contacted to request additional data where necessary.

2.4 | Quality assessment

Two authors (S.L. and J.N.) independently performed a quality assessment for all included studies using the *Cochrane Risk of Bias Assessment Tool*[17] for randomised controlled trials and the *Risk Of Bias In Non-randomised Studies of Interventions* tool[18] for non-randomised studies. Seven standard allocation criteria categorised studies as possessing low, moderate, high or unclear risk of bias for randomised controlled trials and as possessing low, moderate, serious, critical risk of bias or no information for nonrandomised studies (Appendix 2).

2.5 | Data synthesis

The complexity of each primary intervention was graded according to the *Cochrane Intervention Complexity Assessment Tool for Systematic Reviews (iCAT_SR)*[19] (Appendix 3) by 2 authors (S.L. and J.N.) independently. The overall intervention complexity was calculated by assigning each criteria a score of 0–4, indicating a low or high degree of complexity, and then averaging the total score across all of the criteria. Assessment criteria included the number of active intervention components, behaviour of recipients to which the intervention was targeted, organisational levels targeted, the degree of tailoring required to apply the intervention and the level of skill required to deliver and receive the intervention.

Studies were arranged together by: (i) interventions which addressed appropriate opioid use as a primary or secondary focus (e.g. medication safety interventions in which opioid use was a secondary outcome); (ii) the intervention type (e.g. multifaceted interventions, decision-making tools, pain monitoring). Intervention types were ordered by overall complexity using aggregated iCAT_SR scores.

Heterogeneity between studies was assessed by comparing study design, intervention approach and outcomes. Due to heterogeneity in interventions and reported outcomes between studies, a meta-analysis could not be performed.

3 | RESULTS

The search strategy generated a total of 9424 articles, of which 398 full-text articles were assessed for eligibility. Refinement using the exclusion and inclusion criteria resulted in 36 studies included in the review. One additional article was obtained by manual search of the reference list of identified articles, resulting in a total of 37 articles (Figure 1). Appropriate opioid use was addressed as the primary intervention focus in 31 articles. Six studies involved medication safety interventions and reported on changes in opioid use as a secondary outcome.

3.1 | Study characteristics

Of the 37 articles, there were 4 randomised controlled trials (RCTs), 8 cohort studies, 23 pre–post intervention studies and 2 cross-sectional studies.

Fifteen interventions involved surgical inpatients,[20-34] 3 were implemented in the intensive care unit,[35-37] 7 were conducted in the ED,[38-44] 5 involved geriatric inpatients (≥65 years),[45-49] and the remaining 7 studies were conducted in all inpatients,[50-52] and those receiving patient-controlled analgesia (PCA)[53-55] or transdermal fentanyl.[56]

The interventions were performed in various countries worldwide, with the majority, 14, conducted in the USA (Tables 1–4).[20-23,25,29,31,40,41,50,52,54-56] Due to variability in study type and interventions employed, we summarised the review according to intervention type.

3.2 | Quality assessment

Risk of bias assessment was performed for 4 RCTs and 33 non-randomised studies (). Out of the 31 articles in which opioid use was evaluated as a primary outcome, 24 studies were graded as having either a moderate or serious risk of bias, largely due to confounding or selection of participants into the study.[21-24,26-28,30-32,35-37,39-44,50,52,54-56] A moderate or serious risk of bias was found in 3 of 6 studies in which opioid use was addressed as a secondary outcome.[33,34,48] Selective reporting of outcomes and other risk of bias were unclear in most studies. Due to a significant degree of heterogeneity between intervention approach and outcome measures, a meta-analysis was not deemed suitable.

3.3 | Interventions primarily targeting appropriate opioid use

Thirty-one studies examined the effect of interventions to improve prescribing or clinical outcomes related to opioid use. Interventions used to improve appropriate opioid use for analgesia included 16 articles which employed a multifaceted intervention to educate health

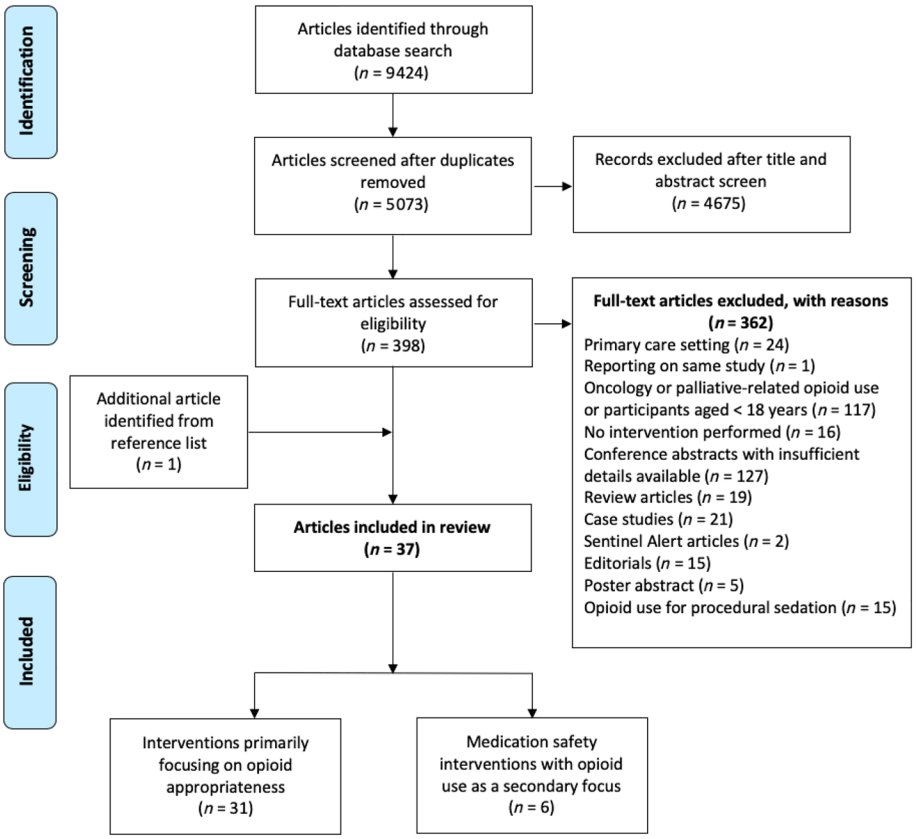

FIGURE 1 Study inclusion and exclusion criteria flow diagram

providers (such as prescribers, nurses, pharmacists) and patients to change opioid use,[20-30,35,38,50-52] 5 studies using decision-making tools to guide opioid prescribing[39-42,56] and 10 that targeted pain monitoring and response to analgesic treatment.[31,32,36,37,43-45,53-55] Predominant prescribing outcomes included the quantity of opioids prescribed and compliance to published guidelines, while clinical outcomes included pain intensity, opioid-related ADEs and patient satisfaction with adequate pain control. To some extent, greater intervention complexity was associated with effectiveness on improving patterns of opioid use ().

3.3.1 | Multifaceted interventions primarily aimed at prescribing

Sixteen studies examined the effect of multifaceted interventions involving education to change patterns of opioid use.[20-30,35,38,50-52] Of these, 8 interventions focused on educating health professionals to improve pain control, primarily through the increased use of opioid analgesia.[20-22,35,38,50-52] An RCT conducted by Taylor *et al*. employed an educational intervention for health care professionals (doctors and nurses) and patients to achieve *adequate analgesia*, defined by a reduction in numerical rating scores (NRS; range 0–10) of at least 2 points and to a target score of <4, clinically representative of *mild* pain. The use of both nonopioid and opioid analgesics was supported to achieve satisfactory pain control. Education was reinforced by physical and electronic dissemination of material and daily audit and feedback provided by site investigators. Patient education was also provided to facilitate communication of the patient's concerns in pain management. While no significant changes in analgesic use were observed in the intervention group, an 11.0% increase in patient education was associated with patient improved satisfaction with pain control (42.9–53.9%; P = .001).[38] Interventions involving health professional education reinforced by hard-copy material to improve pain control were used in 7 studies,[21,22,35,38,50-52] although the definition of prescription appropriateness varied between studies. A study by Bingle *et al*. (1991), conducted in the context of addressing inadequate analgesia, used academic detailing (1-on-1 face-to-face educational outreach) to encourage the prescription of pethidine (meperidine) above a defined dose and frequency.[21] In contrast, in a 2003 study funded by Abbot Pharmaceuticals, Boothby *et al*. implemented academic detailing to discourage the use of pethidine in favour of other analgesics with superior safety-efficacy profiles.[50] Nevertheless, the use of academic detailing was associated with reduced prescription error rates (41.0% *vs* 24.0%; P < .05)[51] and increased compliance of prescribed opioids to predetermined recommendations.[21,50] The provision of patient education to aid shared healthcare decision-making was associated with a significant reduction in LOS from 5.9 to 5.1 days (P < .05), despite no changes in morphine use or pain intensity.[22] Prescriber education through case scenario discussion alone, without further feedback, was not associated with changes in pain intensity or opioid use.[52]

Eight interventions involved health professional education to manage pain by encouraging the use of nonpharmacological measures

TABLE 1 Summary of multifaceted interventions primarily aimed at prescribing in the hospital inpatient setting (n = 16)

Author, year, country	Study size (n; I = intervention, C = standard care)	Study design	Study population Follow-up duration	Intervention[a]		Outcomes	
				Health care professional education	Other	Prescribing	Clinical
Educational interventions to manage pain mainly using opioid analgesics							
Taylor *et al*., 2015, Australia[38]	1317(I: 0 mo = 2323 mo = 2476 mo = 238C: 0 mo = 2013 mo = 1996 mo = 200)	Multicentre, cluster-randomised, controlled intervention trial	ED6 mo	- Multidisciplinary face-to-face education to reduce pain by increasing provision of *adequate analgesia* - Hard copy and email material - Multiple choice self-assessment - Online module - Pain posters	- Audit and feedback (daily) - Patient education	No change in opioid analgesic use	↑ Patient satisfaction with pain management (42.9–53.9%*) ↑ Patient education (80.5% *vs* 86.1% *)
Morisson *et al*., 2009, USA[20]	217(I: 129C: 88)	Controlled prospective propensity score-matched clinical trial	Surgical6 mo	- Multidisciplinary face-to-face health professional education to improve pain management according to local guidelines - Audit and feedback (monthly) - NRS pain evaluation	- Protocols for analgesia, opioid tapering and treatment of opioid-related adverse events	↑ Regular opioid analgesic use (98.0 *vs* 48.0%*) ↑ Concurrent laxatives prescribed (92.0 *vs* 83.0%*)	↓ No or mild pain at rest (66.0 *vs* 51.0%*) and activity (52.0 *vs* 38.0%*) No change in opioid-related adverse effects
Bingle *et al*., 1991, USA[21]	296(I: 147C: 149)	Pre–post intervention study	Surgical 6 mo	- Academic detailing education for physicians encouraging pethidine (meperidine) use - Pen and hard-copy material (*Handbook on the Rational Use of Medication for Pain* by Gerald M. Aronoff and Wayne O. Evans; pethidine dose <75 mg and administration interval longer than		↑ Adherence of pethidine prescriptions to *appropriateness* criteria (30.0 *vs* 43.0% *)	

(Continues)

TABLE 1 (Continued)

Author, year, country	Study size (n; I = intervention, C = standard care)	Study design	Study population Follow-up duration	Intervention[a]		Outcomes	
				Health care professional education	Other	Prescribing	Clinical
				3-hourly defined to be inadequate)			
Boothby *et al.*, 2003, USA[50]	(60I: 30C: 30)	Pre–post intervention study	All inpatient3 mo	- Academic detailing education for physicians discouraging pethidine use - Hard copy pocket cards for physicians and pharmacists - VAS pain evaluation-Bulletin and table-top card material	- Opinion leader - Policy change to replace pethidine with alternative opioids - Removal of pethidine from PCA - Pharmacist medication review	↓ Pethidine use by 29.5% (95% CI 1.97–2.88*) ↑ Pethidine switch to morphine or hydromorphone and nonopioid analgesicsIn 85.0% of orders.	↓ Opioid-related ADEs (53.0 *vs* 23.0%*)
Neitzel *et al.*, 1999, USA[22]	118 (I: 61 C: 57)	Pre–post intervention study	Surgical8 mo	- Physician, pharmacist and nurse 8-h face-to-face education to increase evidence-based pain management (Pain Awareness: Provider Information, Patient Needs syllabus developed by Pain Guidelines Implementation Team 1996) including systematic pain assessment, opioid analgesia, care plan communication - Hard-copy material	- Opinion leader - Patient education	↑ Hydromorphone use by 18.0% No change in morphine use	No change in pain intensity↓ Pethidine use by 48.0%* No change in opioid-related ADEs↓ Hospital LOS from 5.9 to 5.1 ds*
Shaw *et al.*, 2003, Australia[51]	336(I: Pre = 46, Post = 128C: Pre = 116Post = 46)	Pre–post intervention study	All inpatients 6 mo	- Academic detailing education for physicians to increase appropriate opioid prescribing		↓ Prescription error rate for drugs of addiction (41.0 *vs* 24.0%*)	

(Continues)

TABLE 1 (Continued)

Author, year, country	Study size (n; I = intervention, C = standard care)	Study design	Study population Follow-up duration	Intervention[a]		Outcomes	
				Health care professional education	Other	Prescribing	Clinical
				- Hard copy (bookmark) material summarising prescribing guidelines			
VanGulik *et al*., 2010, Netherlands[35]	190 (I: 130 C: 60)	Pre–post intervention study	ICU 3 mo	- Multidisciplinary face-to-face education to increase pain assessment (NRS) and treatment with opioid analgesics - Email and bulletin material	- CPOE	↑ Morphine use (22.6 *vs* 29.3 mg/d*)	↓ Pain intensity (OR 2.54, 95% CI 1.22–5.65*) No change in ICU LOS or MV time
Akce *et al*., 2014, USA[52]	150 (I: 75 C: 75)	Retrospective serial cross-sectional study	All inpatients 12 mo	- Physician face-to-face education through group discussion of opioid case scenarios - Hard copy pocket cards for physicians	- CPOE	No change in opioid use	No change in pain intensity
Educational interventions to manage pain mainly using nonopioid analgesics							
Titsworth *et al*., 2016, USA[23]	96 (I: 48 C: 48)	Prospective, interrupted time-series trial	Surgical 10 mo	- Physician and nurse face-to-face education to increase pain assessment and use of nonopioid analgesia (paracetamol, NSAIDs, ketamine, gabapentin) - NRS pain documentation	- Acute pain service support - Clinical rounds - OME calculation tool- Patient education- Analgesia protocol	No change in morphine use on first postoperative d↓ Morphine use (3rd postoperative d: 72.3 ± 70.7 *vs* 39.2 ± 36.5 mg/d ± SD*)↑ Paracetamol use (56.3 *vs* 75.0%*)↑ NSAID use (8.3% *vs* 31.3%*) ↑ Gabapentin use (12.5 *vs* 33.3%*) No change in hospital LOS	↓ Pain intensity (NRS: 4.31 *vs* 2.94*)
Benditz *et al*., 2016, Germany[24]	367	Prospective cohort study	Surgical24 mo	- Physician and nurse face-to-face education to reduce pain by using nonpharmacological methods, nonopioid	- Adverse drug event evaluation- Internal benchmarking - Monthly audit and feedback- Patient education		↓ Pain intensity by 24.4%*No change in opioid-related ADEs of nausea,

(Continues)

TABLE 1 (Continued)

Author, year, country	Study size (n; I = intervention, C = standard care)	Study design	Study population Follow-up duration	Intervention[a]		Outcomes	
				Health care professional education	Other	Prescribing	Clinical
				and opioid analgesics (German Guidelines of Pain Management in Nursing)- NRS pain evaluation			dizziness or tiredness
Auyong *et al.*, 2015, USA[25]	252 (I: 126 C: 126)	Pre–post intervention study	Surgical 1 mo	- Multidisciplinary face-to-face education regarding updated Enhanced Recovery After Orthopedic Surgery Pathway-Electronic and hard-copy material - NRS pain evaluation	- Multimodal analgesia protocol including regular oral paracetamol, NSAIDs and gabapentin and when-required oxycodone.- Physical therapy- Patient education	↓ Morphine use on postoperative d 1 (IV equivalent 32.0 *vs* 23.5 mg*) and d 2 (IV equivalent 23.3 *vs* 15.9 mg*)	↓ Hospital LOS (76.6 *vs* 56.1 h*)↓ Opioid-related nausea on postoperative d 1 (37.3 *vs* 25.4%*)
Chan *et al.*, 2018, Hong Kong[26]	642 (I: 332 C: 310)	Pre–post intervention study	Surgical 8 mo	-Physician and nurse face-to-face education to encourage safe opioid use, nonopioid analgesia and nurse education to improve PCA safety- NRS pain evaluation	- Audit and feedback (every 6 mo)- Patient education	↑ Morphine use (88.6 *vs* 99.3%*) ↑ Diclofenac use (1.0 *vs* 96.9%)	↓ Pain intensity (VAS > 7; 55.5 *vs* 21.0%*)↑ Pruritus incidence (12.4 *vs* 26.5%*)
Humphries *et al.*, 1997, UK[27]	242 (I: 122 C: 120)	Pre–post intervention study	Surgical12 mo	- Posters and hard-copy material outlining opioid guidelines (Victoria Hospital Blackpool Acute Pain Service) for physician and nursing staff	- Analgesia protocol	↑ Adherence of opioid prescriptions to British National Formulary (41.0 *vs* 61.0%*) and acute pain service (16.0 *vs* 26.0%*)	
Juhl *et al.*, 1996, Denmark[28]	317 (I: 126 C: 191)	Pre–post intervention study	Surgical 12 mo	- Physician and nurse face-to-face 1-d compulsory education to encourage routine use of nonopioid analgesia- Bedside tuition continued until	- Performance feedback - Nurse-administered morphine	↑ Non-opioid analgesic use (15.0 *vs* 94.0%*)	↓ Pain intensity (93.0 *vs* 86.0*)

(Continues)

TABLE 1 (Continued)

Author, year, country	Study size (n; I = intervention, C = standard care)	Study design	Study population Follow-up duration	Intervention[a]		Outcomes	
				Health care professional education	Other	Prescribing	Clinical
				all nurses familiar with new procedures			
Majumder *et al.*, 2016, USA[29]	200 (I: 100 C: 100)	Pre–post intervention study	Surgical 3 mo	- Physician face-to-face education to minimise the use of opioid analgesics and paralytic agents	- Multimodal analgesia (IV hydromorphone, oxycodone, oral gabapentin, paracetamol, NSAIDs)- Patient education	↑ Switch from IV to oral opioid analgesia (2.2 *vs* 3.6 d after opioid initiation*)	↓ Hospital LOS (4.0 *vs* 6.1 d*)↓ Hospital 90-d readmission (16.0 *vs* 4.0%*)
Usichenko *et al.*, 2012, Germany[30]	520 (I: 251 C: 269)	Pre–post intervention questionnaire study	Surgical 14 mo	- Multidisciplinary face-to-face education to increase nonopioid analgesic use - Procedure-specific, multifaceted analgesia protocol (PROSPECT and German Society of Anaesthesiology and Intensive Care Guidelines)- NRS pain evaluation	- 24 h acute pain service- Audit and feedback (every 6 mo)- ADE treatment protocol - Patient education		↓ Pain intensity by 25.0–30.0% on visual rating scale* ↓ Nausea incidence (40.0 *vs* 17.0%*)↓ Vomiting incidence (25.0 *vs* 11.0%*) ↓ Tiredness incidence (76.0 *vs* 30.0%*)↑ Patient satisfaction with pain treatment*↑ QOL*

[a]Sorted in descending order of intervention complexity, as assessed by the iCAT_SR Tool,[19] and subclassified in descending order of study design.[68]

*Denotes statistical significance ($P < .05$).

ED = emergency department; ICU = intensive care unit; VAS = visual analogue scale; NRS = numeric rating scale; CPOE = computerised physician order entry; PCA = patient controlled analgesia; NSAID = nonsteroidal anti-inflammatory drug; LOS = length of stay; ADE = adverse drug event; MV = mechanical ventilation; OR = odds ratio; CI = confidence interval; OME = oral morphine equivalents; IQR = interquartile range; QOL = quality of life; IV = intravenous; PROSPECT = procedure specific postoperative pain management

TABLE 2 Summary of decision-making tools to guide opioid prescribing in the hospital inpatient setting (n = 5)

Author, year, country	Study size (n; I = intervention, C = standard care)	Study design	Study population, Follow-up duration	Intervention[a]		Outcomes	
				Health care professional education	Other	Prescribing	Clinical
Pain assessment tool							
Moustafa *et al.*, 2016, France[39]	434 (I: 214 C: 220)	Pre–post intervention study	ED patients ≥75 years 6 mo	- Physician and nurse face-to-face training for Algoplus tool	- Algoplus pain assessment tool for physicians and nurses	No change in opioid analgesic use	
Prescription drug monitoring program data							
Baehren *et al.*, 2010, USA[40]	179	Prospective quasi-experimental study	ED 1 mo		- PDMP data provision to physicians (Ohio Automated Rx Reporting System; mandatory recording of all controlled substance prescription, ED inclusive)	↓ Opioids prescribed in 25.1% (45 of 179) cases than initially intended	
McAllister *et al.*, 2015, USA[41]	710 (I: 356 C: 354)	Pre–post intervention study	ED 12 mo		- PDMP data provision to physicians (The Electronic-Florida Online Reporting of Controlled Substances Evaluation; nonmandatory recording of controlled drug use and emergency departments exempt)	No changes in number of controlled substance prescriptions	
Computerised physician order entry							
Netherton *et al.*, 2014, Canada[42]	436 (I: 230 C: 206)	Pre–post intervention study	ED 12 mo	- Online CPOE training	- CPOE to increase ketorolac	↑ Fentanyl use (9.7 *vs* 16.7%*)No change in morphine use ↑ Ketorolac use (65.6 *vs* 76.5%*)	
McEvoy *et al.*, 2014, USA[56]	270 (I: 120 C: 150)	Pre–post intervention study	Inpatients receiving transdermal fentanyl 9 mo	- Online and face-to-face CPOE training	- CPOE to restrict transdermal fentanyl transdermal to indications such as persistent, moderate to severe pain in opioid-tolerant patients (US Food and Drug Administration and Joint Commission sentinel event alert)	↑ Adherence of transdermal fentanyl prescriptions to guidelines (48.7–85.0%*)	↓ ADE incidence overall (34.7 *vs* 23.3%*) ↓ Respiratory depression (16.7 *vs* 8.3%*)

[a]Sorted in descending order of intervention complexity, as assessed by the iCAT_SR Tool,[19] and subclassified in descending order of study design.[68]

*Denotes statistical significance ($P < .05$).

ED = Emergency department; PDMP = prescription drug monitoring program; CPOE = computerised physician order entry; ADE = adverse drug event

TABLE 3 Summary of interventions to improve patient monitoring in the hospital inpatient setting (n = 10)

Author, year, country	Study size (n; I = intervention, C = standard care)	Study design	Study population, Follow-up duration	Intervention[a]		Outcomes	
				Health care professional education	Other	Prescribing	2Clinical
Pain monitoring							
Muntlin *et al.*, 2010, Sweden[43]	200 (I: 100 C: 100)	Quasi-experimental study	ED 4 mo	- Optional face-to-face nurse education to increase opioid analgesic use- Analgesic protocol- NRS pain evaluation		↑ Analgesic use (46.0–65.0%*)	↓ Pain intensity (NRS: 3.8 *vs* 2.9*) ↑ Patient satisfaction with pain management (Out of 10: 2.3 *vs* 3.6*)No changes in opioid-related ADEs
Chanques *et al.*, 2006, France[36]	230 (I: 130 C: 100)	Pre–post intervention study	ICU 4 mo	- Face-to-face nurse education to evaluate pain as 'vital sign' - BPS and NRS pain evaluation		No change in morphine use↑ Tramadol use (15.0 *vs* 27.0%*)	↓ Pain incidence (63.0 *vs* 42.0%*) and intensity (NRS > 6, 36.0 *vs* 16.0%*)↓ MV duration (120 [IQR 48–312] *vs* 65 [IQR 24–192] h*)No change in ICU LOS or mortality
Duncan & Pozehl, 2000, USA[31]	240 (I: 121 C: 119)	Pre–post intervention study	Surgical 15 mo	- Face-to-face nurse education of opioid use as 'cornerstone' pain treatment (according to *Acute Pain Management: Operative or Medical Procedures and Trauma: Clinical Practice Guideline* (Agency for Health Care Policy & Research. 1992)- NRS pain evaluation	- Audit and feedback (daily)	↑ Morphine use (OME: 12.70 *vs* 14.54 mg/d*)	↓ Pain intensity (NRS: 3.58 *vs* 3.16*)

(Continues)

TABLE 3 (Continued)

Author, year, country	Study size (n; I = intervention, C = standard care)	Study design	Study population, Follow-up duration	Intervention[a]		Outcomes	
				Health care professional education	Other	Prescribing	2Clinical
Olsen *et al.*, 2016, Norway[37]	650 (I: 398 C: 252)	Pre–post intervention study	ICU 22 weeks	- Face-to-face nurse education to encourage analgesic and nonpharmacologic pain management- Analgesia protocol - NRS and BPS pain evaluation		↑ Fentanyl use as epidural (median 223 *vs* 310 μg*)	↓ Agitation events (3.0 *vs* 6.0%*) ↓ MV duration (median 46 *vs* 79 h*)↓ ICU LOS (median 2.6 *vs* 3.0 d, *P* = 0.04)
Pierik *et al.*, 2016, Netherlands[44]	660 (I: 156 C: 504)	Pre–post intervention study	ED 6 mo	- Education to encourage nonopioid use before opioid analgesia (*Pain management for trauma patients in the chain of emergency care)* - Analgesia protocol- NRS pain evaluation - Leaflet material		↑ Analgesic use (95% CI 11.5–30.9*) ↓ Time to opioid administration (37 *vs* 15 min*)	↑ Pain relief (95% CI 1.8–18.5*)No changes in ED LOS or patient satisfaction
Cui *et al.*, 2017, China[32]	148 (I: 71 C: 77)	Separate sample pre–post intervention study	Surgical 24 mo	- Mandatory nurse education encouraging nonpharmacological pain management- Analgesic protocol- Hard copy guidelines (*Acute Pain Management Handbook for Nurses* developed by Professor Ramani Vijayan, Department of Anaesthiology, University of Malaya, Malaysia)- NRS pain evaluation		↑ Nonopioids and opioid combination use (38.8 *vs* 66.2%*)No change in the opioid use alone↑ Nonpharmacological pain management (60.0 *vs* 96.0%*)	↑ Pain relief (53.0 *vs* 78.0%*)

(Continues)

TABLE 3 (Continued)

Author, year, country	Study size (n; I = intervention, C = standard care)	Study design	Study population, Follow-up duration	Intervention[a]		Outcomes	
				Health care professional education	Other	Prescribing	2Clinical
Manias *et al.*, 2011, Australia[45]	192 (I: 96 C: 96)	Non-equivalent control pre–post intervention study	Geriatric ≥65 years 3 mo	- Face-to-face nurse education to appropriately manage pain using nonpharmacological and pharmacological methods - Pain evaluation using 8 scales (including NRS and VAS)	- Audit and feedback (daily)- Case study discussion	↓ Oxycodone use (Odds reduction by 1.2 times at baseline, 4 times following intervention*)	↓ Pain intensity both at rest and on movement (VAS_{rest} 6.05 *vs* 4.40* and $VAS_{movement}$ 7.42 *vs* 5.27*)
Patient controlled analgesia safety monitoring							
Paul *et al.*, 2010, Canada[53]	25 198(I: 12 193 C: 13 005)	Longitudinal cohort study	Inpatients receiving PCA36 mo	- Nurse face-to-face PCA education for safe use and ADE monitoring	- Mandatory computerised incident reporting- Policy change requiring review of PCA settings during shifts and upon handover- Purchase of new PCA pumps		↓ PCA error rate (OR: 0.28 [95% CI = 0.14, 0.53] *vs* 0.05 [95% CI = 0.001, 0.30] *)
Ferguson *et al.*, 2010, USA[54]	3732 (I: 1979 C: 1753)	Pre–post intervention study	Inpatients receiving PCA 4 mo	- Nurse face-to-face PCA education for safe use and ADE monitoring- Practical competency demonstration- Online module			↓ PCA error rate (0.46 *vs* 0.05%*)
Whipple *et al.*, 1994, USA[55]	4669	Retrospective cross-sectional study	Inpatients receiving PCA		- Computerised PCA ADE monitoring		↓ PCA overdose events (11 *vs* 6 of 294 potential events detected)

[a]Sorted in descending order of intervention complexity, as assessed by the iCAT_SR Tool,[19] and subclassified in descending order of study design.[68]

*Denotes statistical significance ($P < 0.05$).

ED = Emergency department; ICU = intensive care unit; VAS = visual analogue scale; NRS = numeric rating scale; BPS = Behavioural pain scale; PCA = patient-controlled analgesia; LOS = length of stay; ADE = adverse drug event; MV = mechanical ventilation; OR = odds ratio; CI = confidence interval; IQR = interquartile range

TABLE 4 Summary of medication safety interventions involving opioid use as a secondary outcome in the hospital inpatient setting (n = 6)

Author, year, country	Study size (n; I = intervention, C = standard care)	Study design	Study population	Intervention[a]	Outcomes	
					Prescribing	Clinical
Adverse event monitoring						
O'Sullivan *et al*., 2015, Switzerland[46]	737 (I: 361 C: 376)	Cluster randomised controlled trial	Geriatric ≥65 years	- Clinical pharmacist medication review - Computerised decision support		↓ Opioid-related ADEs (50.5 *vs* 31.9%*)
Kjeldsen *et al*., 2013, Denmark[33]	1782(I: 775C: 1007)	Controlled, prospective intervention study	Surgical	- Clinical pharmacist medication review	Opioids involved in 59.0% of clinical pharmacist recommendations (620/1059)	No changes in opioid-related ADEs No changes in 6-mo readmission rate, mortality, number of laboratory tests, or hospital LOS
Bos *et al*., 2016, The Netherlands[34]	11 651 I: 5711C: 5940	Prospective, multicentre, open pre–post intervention study	Surgical	- Clinical pharmacist medication review- Prescriber face-to-face education- Guideline dissemination - CPOE	↓ Opioid use (40.3–37.0%*)	↓ Tramadol and anticholinergic-related ADEs (48–20*)↓ Overall mortality, hospital LOS and 30-d readmission (1. *vs* 1.1% *)
Assessment of prescription appropriateness						
Dalleur *et al*., 2014, Belgium[47]	146 (I: 74C: 72)	Double-blind randomised controlled trial	Geriatric ≥75 years	- STOPP criteria review to reduce PIMs	↓ PIM rate (19.3 *vs* 39.7%*)No significant changes in opioid use	
O'Connor *et al*., 2016, Ireland[48]	732 (I = 360C = 372)	Single-blind cluster randomised controlled trial	Geriatric ≥65 years	- STOPP-START criteria review to reduce PIMs	Opioids accounted for 7.0% of intervention group ADEs	↓ Patients experiencing ≥1 ADE (21.0 *vs* 11.7%; (absolute RR = 9.3%, NNT = 11)
Urfer *et al*., 2016, Swtizerland[49]	900(I: 450C: 450)	Single-centre, quasi-experimental pre–post intervention study	Geriatric ≥65 years	- 5-point checklist for physicians to reduce PIMS and polypharmacy- STOPP-START criteria to review PIMs	No change in opioid use	

[a]Sorted in descending order of study design.[68]

*Denotes statistical significance ($P < .05$).

CPOE = computerised physician order entry; LOS = length of stay; ADE = adverse drug event; STOPP = Screening Tool of Older Person's Prescriptions; START = Screening Tool to Alert doctors to Right Treatment; PIM = potentially inappropriate medication; RR = relative risk; NNT = numbers needed to treat

and nonopioid analgesics, reserving opioid analgesia for stronger pain.[23-30] While these studies shared key education messages and mainly targeted physicians and nurses, distinctions existed between the types of additional strategies used, such as reinforcement with audit and feedback, or patient involvement in decision-making. The use of performance feedback conducted every 1–6 months to reinforce health professional education was associated with significant improvements in the primary outcome of all the studies in which it was applied, including patient satisfaction and reduced pain intensity.[24,26,28,30] Additionally, 2 studies using performance feedback reported 79.0–95.9% increased nonopioid analgesic use[26,28] and 1 study showed a reduction in opioid-related ADEs such as nausea (40.0 *vs* 17.0%; $P < .05$).[30] Of 3 studies using an analgesia protocol to guide pain treatment,[23,25,27] 1 study demonstrated significantly increased use of nonopioid analgesia[23] and 2 studies reported reduced morphine use ranging from 26.6 to 45.8%.[23,25] Patient education was linked to significant improvements in patient satisfaction and quality of life.[30]

3.3.2 | Decision-making tools to guide opioid prescribing

Five studies used tools to guide the appropriate prescribing of opioids.[39-42,56] A pain assessment tool was used in 1 study, which did not report a significant difference in the quantity of opioids used.[39]

Two studies, which assessed whether the provision of prescription drug monitoring programme (PDMP) data influenced prescribers' decisions about the risk of opioid misuse and subsequent analgesic prescription, produced mixed results.[40,41] The study conducted by Baehren *et al*., in which PDMP reporting for outpatient and ED prescriptions was mandatory, reported a 25.0% reduction in opioids prescribed,[40] whereas nonmandatory PDMP use from which the ED was exempt was not associated with significant differences in the prescription of controlled substances.[41]

Two studies used computerised physician order entry to guide prescribing. Both interventions provided online training for prescribers and showed significantly increased compliance of prescribed opioids to regulatory statements such as the Joint Commission Sentinel Event Alert on safe opioid use.[42,56] In addition to online education, 1 study also used face-to-face training to support computerised order entry and reported a reduction in overall ADEs (34.7 *vs* 23.3%, $P = .043$) and respiratory depression (16.7 *vs* 8.3%, $P = .043$).[56]

3.3.3 | Patient monitoring

Ten studies assessed the impact of increased patient monitoring on analgesic use, pain intensity and PCA-related ADEs.[31,32,36,37,43-45,53-55] Seven studies assessed pain intensity by implementing scales such as the numeric rating scale and visual analogue scale.[31,32,36,37,43-45] All interventions were performed primarily by nurses. Of these, 3 interventions focused on pain evaluation as a *vital sign* and treatment using opioid analgesics.[31,36,43] These studies reported significantly increased use of morphine by 12.7% ($P < .05$)[28] and tramadol by 12.0% ($P < .05$),[31] as well as reduced pain intensity; however, no changes in opioid-related ADEs or LOS were shown. In contrast, 4 studies used pain scales to assess pain severity and provide treatment using multimodal strategies including nonpharmacological and nonopioid methods.[32,37,44,45] The use of opioid analgesics varied in these studies, however, significantly increased use of nonpharmacological pain management (60.0 *vs* 96.0%; $P < 0.05$) and nonopioid analgesia (38.8 *vs* 66.2%; $P < 0.05$) were reported.[32] These changes were associated with improved clinical outcomes including reduced pain intensity ranging from 27.2 to 38.5%,[32,45] reduced duration of mechanical ventilation (median 46 *vs* 79 h; $P < .06$), and a nonsignificant reduction in LOS.[37]

Three studies evaluated the impact of increased ADE monitoring to improve PCA safety.[53-55] Interventions to increase nursing assessment of patients' response to PCA and competency demonstration were introduced in 2 studies, both of which demonstrated relative reductions of 82.1–89.1% in the frequency of PCA errors.[53,54] In the remaining study, a computer-based system to monitor PCA errors reported 11 of 294 potential overdose events compared to 6 detected through standard practice.[55]

3.4 | Medication safety intervention studies

Six studies involved medication safety interventions, in which opioid use was addressed as a secondary focus.[33,34,46-49] Of these, 3 studies examined the effects of ADE monitoring[33,34,46] and 3 used specific criteria to assess prescription appropriateness.[47-49]

Clinical pharmacist review of medications was used in all 3 studies which monitored for ADEs.[33,34,46] Medication review alone was not associated with changes in opioid ADEs.[33] However, 2 studies which included additional interventions such as computerised physician order entry and dissemination of drug safety guidelines reported significant reductions in opioid use (40.3–37.0%; $P < .05$) and opioid-related ADEs by 18.6–28.0%.[34,46]

Three studies implemented the Screening Tool of Older Person's Prescriptions and Screening Tool to Alert doctors to Right Treatment (STOPP/START) criteria to evaluate the prevalence of potentially inappropriate prescriptions compared to usual care.[47-49] One RCT using STOPP/START criteria reported reduced rates of inappropriate prescriptions by 20.4% (39.7 *vs* 19.3%; $P < .05$).[47] However, the use these of criteria did not change opioid use.[47-49]

4 | DISCUSSION

4.1 | Principal findings

To our knowledge, this is the first systematic review to evaluate the effectiveness of interventions on appropriate opioid use in the hospital inpatient setting. Multifaceted interventions involving academic

detailing and education, particularly when reinforced by audit and feedback and hard-copy material demonstrated improvements on the appropriate use of opioids, which contributed towards improved clinical outcomes. Patient education was linked to increased patient satisfaction and quality of life. Pain monitoring to determine appropriate treatment was associated with the increased use of nonopioid analgesia and reduced opioid-related ADEs, while still maintaining adequate pain control. Increased concordance of opioid prescribing to published guidelines was reported after the introduction of computerised physician order entry systems. To some extent, increased intervention complexity was associated with increased effectiveness on improving appropriate opioid use. Opioid safety interventions integrating multiple strategies, such as clinical pharmacist review, computerised physician order entry and dissemination of published guidelines, facilitated greater improvements in prescribing and clinical outcomes compared to a single-component approach. However, due to the high risk of bias in many of these studies, these results require further investigation.

4.2 | Comparison with other studies

No other review has been conducted that systematically evaluates the effectiveness of interventions on appropriate opioid use in the hospital inpatient setting. Although there is a Cochrane review (2017) that evaluates the effectiveness of interventions to reduce opioid use in the management of chronic pain, its included studies were all conducted in the primary care setting.[15] The majority of the interventions included in the Cochrane review involved adjuvant therapies such as acupuncture and cognitive behavioural therapy. These interventions may also be useful in the hospital setting; however, the evidence supporting their use for acute pain is limited. Few studies implemented adjuvant therapies in this review. Further research on the impact of nonpharmacological pain management on opioid use in the hospital setting is required.

4.3 | Strengths and limitations

The main strength of this review was the rigorous approach taken in its systematic search. Two independent reviewers determined each study's eligibility and performed quality and complexity assessments. A broad search strategy was developed with a clinical librarian and applied to 6 databases to capture an extensive amount of the available literature. Also, this search was not limited by publication year, which allowed shifts in the clinical focus of opioid use to be captured over time.

However, this review had several limitations. Firstly, a meta-analysis could not be performed due to substantial heterogeneity in intervention approach and outcomes (e.g. LOS), limiting the generalisability of our results. Moreover, the majority of studies in the present review involved follow-up periods under 24 months, therefore the long-term sustainability of these interventions is unknown. Finally, some relevant studies may have been omitted. Although we employed a comprehensive search strategy and manually searched reference lists to include all relevant studies, only articles from the designated databases published in English were included. We did not search grey literature, thus introducing a level of publication bias.

4.4 | Policy and research implications

Our findings highlight that the majority of studies were performed in the context of managing patients' pain through the provision of opioid analgesia, whereas fewer addressed patient safety and opioid-related harm. Interventions aimed at increasing the use of opioids reflect recommendations by the American Pain Society in 1995 to evaluate pain as a *vital sign*, contributing to the subsequent rise in the use of opioids to reduce pain.[57] The emphasis on pain treatment may be further attributable to its influence on patient satisfaction, a parameter often linked to physician and institution reimbursement in the USA.[58] However, evidence suggests that the emphasis on reducing pain and under-representation of opioid-related harms have contributed to the present overuse of opioid analgesics, particularly in the management of both acute and chronic noncancer pain.[58,59] Moreover, growing evidence of opioid-related harms, including increased morbidity and mortality, puts into question the safety of extensive opioid use.[60-62] Very few interventions specifically assessed the therapeutic benefit of ongoing analgesic treatment or monitored for cases in which harms related to opioid use outweighed the benefits. Therefore, the implementation of policies to reinforce the equal weighting of opioid-related risks and benefits are warranted to facilitate a balanced approach to pain management.

Additionally, few studies reported the application of best-available evidence to guide the de-escalation of opioids once initiated. Recent literature suggest that a significant proportion of opioids prescribed during hospital admission are continued postdischarge, which may contribute to an increased risk of dependence and unintended harm.[63] Interventions to deprescribe potentially inappropriate medications in older hospitalised adults have been shown to improve prescribing and clinical outcomes.[64] However, limited evidence exists that applies similar principles to assess the ongoing need for opioid analgesia. Hence, there is scope for the development of policies to guide opioid deprescribing in cases where the risks of therapy outweigh the benefits to further contribute towards the safe and efficacious use of opioids.

This review supports the use of certain interventions to improve the safe and efficacious use of opioids, although the definition of opioid appropriateness varied, depending on the context in which the study was conducted. Earlier interventions conducted in the context of inadequate pain treatment encouraged opioid use as effective analgesic agents, before the focus of appropriate use shifted to potential opioid-related harms.[65-67] No consensus could be established from the reviewed articles on the definition of *opioid appropriateness*. Thus, further studies are required to develop an internationally accepted definition of *appropriate opioid use*.

Overall, the quality of evidence was low. No definitive conclusions could be drawn on efficacy on appropriate opioid use by intervention type. Although preliminary data suggest that interventions to improve appropriate opioid use may reduce hospital costs linked to opioid-related harms, further studies are needed to assess their net cost-effectiveness. Intervention complexity appeared to contribute to an extent towards effectiveness on improving patterns of opioid use. However, intervention efficacy may also be influenced by additional factors including retrospective study design, challenges in translating changes in practice to clinical outcome, and intrinsic methods of the interventions. There was a paucity of evidence to inform the feasibility of administrative-level involvement to influence hospital opioid use. Thus, further research is required to address the implementability of executive-level interventions to improve safe and efficacious opioid use in the hospital setting.

5 | CONCLUSION

Interventions involving academic detailing and education, especially when reinforced by performance feedback, show positive effects on appropriate opioid use for hospital inpatients. The development of policies to guide the deprescribing of opioids in cases where opioid-related harms outweigh the benefits are warranted. Future studies on appropriate opioid use for hospital inpatients should focus on the effectiveness of interventions performed at the organisation-level to inform enhanced acute pain management using opioid analgesics.

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CONFLICT OF INTEREST

None declared.

STATEMENT OF ORIGINALITY

This work is submitted for publication in the British Journal of Clinical Pharmacology. The authors declare that this review has not been and, if accepted, will not be published in whole or in part in any other journal. All authors have read and approved the full manuscript in its submitted form.

CONTRIBUTORS

J.P. and D.G. conceived the study and designed the study protocol in collaboration with S.L. S.L. performed data collection and analysis. All authors contributed to its revision. S.L. drafted the manuscript and all authors read and approved the final manuscript.

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COMPETING INTERESTS

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ETHICS APPROVAL

None required.

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APPENDIX A

A.1. | Database search terms

MEDLINE (1960 to Present) (OvidSP).

1. exp Analgesics, Opioid/or exp Narcotics/.β

2. (acetyldihydrocodeine or alfentanil or allylprodine or alphamethylfentanyl or alphaprodine or benzylmorphine or betaprodine or buprenorphine or butorphanol or bremazocine or codeine or contin or dextromoramide or dextropropoxyphene or dezocine or diacetylmorphine or diamorphine or dihydrocodeine or dihydromorphine or dihydromorphone or diphenoxylate or dipipanone or enadoline or ethylketazocine or ethylmorphine or etonitazene or etorphine or fentanyl or heroin or hydrocodone or hydromorphin* or hydromorphone or ketazocine or ketobemidone or lefetamine or levomethadon or levomethadyl or levomethorphan* or levorphanol or loperamide or meperidine or meptazinol or methadone or methadyl or methylmorphine or morphin* or nalbuphine or narcotic* or nicocodeine or nicomorphine or normorphine or noscapin* or ohmefentanyl or opiate* or opioid* or opium or oripavine or oxycodone or oxycontin or oxymorphone or papaveretum or papaverin or pentazocine or percocet or peronine or pethidine or phenazocine or phencyclidine or pholcodine or piritramid* or prodine or promedol or propoxyphene or remifentanil or sufentanil or tapentadol or thebaine or tilidine).tw.

3. 1 or 2.

4. INPATIENTS/or inpatient*.mp. or (inpatient* adj2 hospital*).mp. or (inpatient* adj2 setting*).mp.

5. hospital.mp. or Hospitals/or (hospital* adj2 setting*).mp.

6. exp Hospital Departments/.

7. (acute adj2 care).mp. or acute disease/

8. emergency service, hospital/or trauma centers/or (emergency adj2 department).mp.

9. 4 or 5 or 6 or 7 or 8.

10. ((prescrib* adj2 interven*) or (approp* adj2 prescrib*)).mp.

11. medication errors/or inappropriate prescribing/or pharmacy service, hospital/.

12. Medication Therapy Management/.

13. "Drug Utilization Review"/or drug utili?ation review.mp. or Drug Utilization/or stewardship.mp.

14. drug monitor*.mp. or Drug Monitoring/.

15. Medication Systems, Hospital/

16. intervention*.ti. or (intervention* adj6 (clinician* or collaborat* or design* or doctor* or educa* or impact* or improve* or

individuali* or interdisciplin* or multicomponent or multi-component or multidisciplin* or multi-disciplin* or multifacet* or multi-facet* or multimodal* or multi-modal* or pharma* or physician* or practitioner* or prescrib* or professional* or provider* or tailor* or target* or usual care)).ti,ab.

17. (adherence or alert* or benchmark* or (change adj3 treatment) or computer assist* or support or compute* or clinical decision* or dosing or formulary or guidance or guideline* or impact or justification or overuse or over-prescrib* or overprescrib* or under-prescrib* or underprescrib* or pathway* or program* or programme* or (quality adj3 improv*) or reminder* or restriction* or unnecessary).ti.

18. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17.

19. 3 and 9 and 18.

20. limit 19 to (English language and humans).

A.2. | Appendix (i)

Quality assessment summary of included randomised controlled trials using the *Cochrane Risk of Bias Assessment Tool*[17] (*n* = 4).

Study authors	**Dalleur et al.**[47]	
Bias	**Judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk of bias	Selection through "simple randomisation using drawing of lots"
Allocation concealment (selection bias)	Low risk of bias	"The IGCT nurse provided the evaluator with a list of the patients included in the study, which did not specify allocation group. The evaluator gathered data on the primary outcome."
Blinding of participants and personnel	Low risk of bias	"The attending ward physician (who is responsible for prescriptions during hospitalisation and at discharge), the evaluator (OD), and the patients were blinded to group assignment."
Blinding of outcome assessment (detection bias)	Low risk of bias	Blinding of outcome assessment described in article.
Incomplete outcome data (attrition bias)	Unclear risk of bias	Attrition is described but differences between patients who completed and did not complete the trial was not analysed
Selective reporting (reporting bias)	Low risk of bias	Comprehensive reporting of outcomes. The study protocol is available and all study outcomes are prespecified.
Other bias	N/A	N/A
Overall quality assessment	**Low risk of bias**	
Study authors	**O'Connor et al.**[48]	
Bias	**Judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk of bias	"It was not a double-blinded study in which participants and researchers were blinded to the group randomization of each participant and the end points being assessed by a blinded assessor. Similarly, the intervention participants' attending doctors could not be blinded to their randomization group, because they had to decide whether to accept or reject individual STOPP/START criteria"
Allocation concealment (selection bias)	High risk of bias	Allocation not concealed.
Blinding of participants and personnel	High risk of bias	"The intervention could not be double- blinded (because of its nature)"
Blinding of outcome assessment (detection bias)	High risk of bias	Outcome assessment not blinded.
Incomplete outcome data (attrition bias)	Unclear risk of bias	Attrition is described but differences between patients who completed and did not complete the trial was not analysed
Selective reporting (reporting bias)	Low risk of bias	Comprehensive reporting of outcomes. The study protocol is available and all study outcomes are prespecified.
Other bias	N/A	N/A
Overall quality assessment	**High risk of bias**	

Study authors	O'Sullivan et al.[46]	
Bias	**Judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk of bias	"We cluster-randomised the admitting consultants and their teams into 2 groups prior to study initiation, i.e. intervention or control consultants. At admission, we allocated patients to 1 of 2 groups, i.e. (1) usual pharmaceutical care (control group) or (2) the CDSS-supported SPRM intervention designed to optimise geriatric pharmaceutical care (intervention group), based on the particular consultant with primary responsibility for the patient's care during the index hospital admission. To avoid potentially biased selection of subjects into either arm of the study, we approached prospective trial patients in the order of their admission to the hospital to assess their eligibility for the trial."
Allocation concealment (selection bias)	High risk of bias	Allocation of participants and investigators was not concealed or randomised.
Blinding of participants and personnel	High risk of bias	"Due to the nature of the intervention, it was not possible to blind participating attending doctors …It was not possible for the intervention to be double- blinded due to its nature;"
Blinding of outcome assessment (detection bias)	Low risk of bias	"The primary researcher recorded all documented new symptoms and clinical phenomena from every patient's medical records electronically and these were cross-referenced with the trigger list, thereby minimising (but not abolishing) potential observer bias. In addition, we sought to further attenuate observer bias by including only those ADRs corroborated by the medically trained ADR assessor who was blinded to the group allocation of each patient in the trial."
Incomplete outcome data (attrition bias)	Low risk of bias	"34 patients (17 intervention and 17 control patients) died during their index hospital admission; we included these patients in the final analysis on the basis of adherence to the intention-to-treat principle."
Selective reporting (reporting bias)	Low risk of bias	Comprehensive reporting of outcomes. The study protocol is available and all study outcomes are prespecified.
Other bias	N/A	N/A
Overall quality assessment	**Low risk of bias**	
Study authors	**Taylor et al.[38]**	
Bias	**Judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk of bias	The study authors acknowledge that "patients were not individually randomised. However, the EDs were cluster randomised to early (5 EDs) and late (4 EDs) intervention clusters, using a computer-generated random number function. During periods when study staff were available (usually 0800–1800, 7 days/week), consecutive patients who met the study entrance criteria were recruited."
Allocation concealment (selection bias)	Unclear risk of bias	Not described
Blinding of participants and personnel	Low risk of bias	As reported in the article, "patients were only advised of the study at follow up. This was deliberate in order to minimise the Hawthorne effect. Had patients been aware that they were enrolled in a pain management study, this may have affected their follow-up responses."
Blinding of outcome assessment (detection bias)	Low risk of bias	"Patients were either telephoned or visited in the ward by a site investigator who was blinded to the data that was collected in the ED, including whether the patient had received 'adequate analgesia'"

(Continues)

Study authors	Taylor et al.[38]	
Bias	**Judgement**	**Support for judgement**
Incomplete outcome data (attrition bias)	Low risk of bias	"In total, 1527 patients were recruited although follow-up data were not available for 210 (13.8%). Patients lost to follow up differed only in that fewer were administered any type of analgesia (76.7 *vs* 82.8%, P = 0.04)"
Selective reporting (reporting bias)	High risk of bias	The study authors acknowledge that "satisfaction is highly subjective, affected by a range of confounding variables and difficult to measure accurately. At patient follow up, as our data collectors were aware of the study hypothesis and the intervention status of their ED, measurement bias may have been introduced."
Other bias	N/A	N/A
Overall quality assessment	**Low risk of bias**	

A.3. | Appendix (ii)

Quality assessment summary of included nonrandomised controlled studies using the *Risk Of Bias In Non-randomised Studies of Interventions* tool[18] (*n* = 33).

Study authors	Akce et al.[52]	
Bias	**Judgement**	**Support for judgement**
Bias due to confounding	Moderate risk of bias	The study authors acknowledge the potential for confounding factors; however, these have not been controlled for by study design or statistical analyses.
Bias in selection of participants into the study	Low risk of bias	Randomised selection of participants into the study.
Bias in classification of interventions	No information	Classification of interventions not explicitly described.
Bias due to deviations from intended interventions	No information	Deviation from intended interventions of the study is not adequately described.
Bias due to missing data	Serious risk of bias	Attrition of data is described but not analysed.
Bias in measurement of outcomes	Low risk of bias	Double data abstraction and data entry to minimise bias in measurement of outcomes.
Bias in selection of the reported result	Serious risk of bias	Retrospective data recorded.
Overall quality assessment	**Moderate risk of bias**	
Study authors	**Auyong et al.[25]**	
Bias	**Judgement**	**Support for judgement**
Bias due to confounding	Low risk of bias	Potential risk of bias due to confounding accounted for by statistical analysis including logistic regression models
Bias in selection of participants into the study	Low risk of bias	Consecutive selection of participants into the study
Bias in classification of interventions	Low risk of bias	Intervention groups clearly defined
Bias due to deviations from intended interventions	No information	Potential deviations from intended interventions not described.
Bias due to missing data	Low risk of bias	No missing data reported.
Bias in measurement of outcomes	Moderate risk of bias	Outcome assessors not blinded to intervention status.
Bias in selection of the reported result	Moderate risk of bias	Multiple logistic regression models used to compare binary secondary outcomes which may increase the risk of bias arising from selective reporting of results.
Overall quality assessment	**Low risk of bias**	

Study authors	Baehren et al.[40]	
Bias	**Judgement**	**Support for judgement**
Bias due to confounding	Serious risk of bias	Potential confounding factors not controlled for by study design or statistical analyses.
Bias in selection of participants into the study	Serious risk of bias	The study authors acknowledge that "Enrolment was based on a convenience sample "
Bias in classification of interventions	Low risk of bias	Clear classification of intervention groups.
Bias due to deviations from intended interventions	Serious risk of bias	As reported in the article, "the number of patients treated by each physician is not the same."
Bias due to missing data	No information	Attrition of data not reported.
Bias in measurement of outcomes	Low risk of bias	"Subjects were identified only by the research assistants who reviewed the triage information patients were assigned a sequential number"
Bias in selection of the reported result	Moderate risk of bias	Primary outcomes clearly reported. Multiple outcome measurements within secondary outcome domains.
Overall quality assessment	**Moderate risk of bias**	
Study authors	**Benditz et al.[24]**	
Bias	**Judgement**	**Support for judgement**
Bias due to confounding	Serious risk of bias	Potential confounding factors not addressed by experimental design or statistical analyses. Patients informed of study but all received same intervention; health care professionals had increased experience with protocol over time.
Bias in selection of participants into the study	Low risk of bias	The study authors state "no patients were available on Mondays, which may also represent some kind of selection bias. …Wards to be visited were randomized daily by drawing a number to prevent selection bias."
Bias in classification of interventions	Moderate risk of bias	Classification of interventions not clearly defined.
Bias due to deviations from intended interventions	No information	No information to describe potential deviations from intended interventions.
Bias due to missing data	Serious risk of bias	As acknowledged in the article, "We have no information about the excluded patients."
Bias in measurement of outcomes	Low risk of bias	The study authors state "To avoid any interviewer–patient interaction bias, the nurse informed the patients that she was working independently from the health care team, that all information or judgment given in the interview would be treated confidentially, and that participation was voluntary. Data were anonymized after the interview."
Bias in selection of the reported result	Low risk of bias	Primary and secondary outcome measurements reported in article tables.
Overall quality assessment	**Moderate risk of bias**	
Study authors	**Bingle et al.[21]**	
Bias	**Judgement**	**Support for judgement**
Bias due to confounding	Serious risk of bias	Potential confounding factors not addressed by experimental design or statistical analyses
Bias in selection of participants into the study	Serious risk of bias	Potential bias introduced by selection of participants into the study not controlled in the study.
Bias in classification of interventions	No information	Limited description of the differences between the 3 detailing interventions
Bias due to deviations from intended interventions	Moderate risk of bias	Intervention groups moderately defined, which may introduce a certain degree of bias due to deviations of intended interventions.

(Continues)

Study authors	Bingle et al.[21]	
Bias	**Judgement**	**Support for judgement**
Bias due to missing data	No information	Attrition data not described.
Bias in measurement of outcomes	Serious risk of bias	Retrospective chart audit, limited description of process. Pre and post screening performed by different people.
Bias in selection of the reported result	Low risk of bias	Primary and secondary outcome measurements reported in article tables.
Overall quality assessment	**Serious risk of bias**	
Study authors	**Boothby et al.[50]**	
Bias	**Judgement**	**Support for judgement**
Bias due to confounding	Serious risk of bias	Potential confounding factors not addressed by experimental design or statistical analyses
Bias in selection of participants into the study	Serious risk of bias	Selection of participants into the study done by convenience sampling.
Bias in classification of interventions	Low risk of bias	Intervention groups clearly defined.
Bias due to deviations from intended interventions	No information	No information to describe potential deviations from intended interventions.
Bias due to missing data	No information	Attrition data not described.
Bias in measurement of outcomes	Low risk of bias	The study authors report that "data were normalized with regard to the varying hospital census".
Bias in selection of the reported result	Low risk of bias	Primary and secondary outcome measurements reported in article tables.
Overall quality assessment	**Moderate risk of bias**	
Study authors	**Bos et al.[34]**	
Bias	**Judgement**	**Support for judgement**
Bias due to confounding	Serious risk of bias	Co-morbidities e.g. Charlson's and polypharmacy not accounted for as can increase risk of ADRs—although age, sex etc. were
Bias in selection of participants into the study	Serious risk of bias	Not just index admission, re-admissions were included—can skew data as some can be predisposed to drug related problems; could not be adjusted for in analysis
Bias in classification of interventions	Low risk of bias	Clear classification of intervention groups, pre and post groups separated by 3 mo.
Bias due to deviations from intended interventions	No information	No information to describe potential deviations from intended interventions.
Bias due to missing data	No information	No attrition of data described.
Bias in measurement of outcomes	Low risk of bias	The authors of the study report that "By blinding all case record forms with respect to the study period before assessment by the experts and by correcting for confounders, the probability of bias was minimized."
Bias in selection of the reported result	Low risk	Primary and secondary outcome measurements reported in article tables.
Overall quality assessment	**Serious risk of bias**	
Study authors	**Chan et al.[26]**	
Bias	**Judgement**	**Support for judgement**
Bias due to confounding	Serious risk of bias	Postop D2–3 may be insufficient to titrate PRN agents to optimal analgesia so pain ratings may not reflect full potential of the intervention regimen Also unclear if patients aware of involvement in active intervention aimed at improving pain—may have placebo if patients were aware

(Continues)

Study authors	Chan et al.[26]	
Bias	**Judgement**	**Support for judgement**
Bias in selection of participants into the study	Serious risk of bias	Patients not randomised; recruitment periods were different lengths
Bias in classification of interventions	Low risk of bias	Fully prospective study
Bias due to deviations from intended interventions	No information	Not described.
Bias due to missing data	Serious risk of bias	The authors acknowledge that "there are some missing data in both surveys, especially the second questionnaire." 29.5% missing data in the intervention group (Group B).
qBias in measurement of outcomes	Serious risk of bias	Surveys completed by patients; risk of deviation or subjective interpretation. Outcome assessors were not blinded.
Bias in selection of the reported result	No information	Not described.
Overall quality assessment	**Serious risk of bias**	
Study authors	**Chanques et al.[36]**	
Bias	**Judgement**	**Support for judgement**
Bias due to confounding	Low risk of bias	Accounted for delirium and intensive care unit handicaps in communicating pain. Healthcare professionals blinded to results of assessments in control phase.
Bias in selection of participants into the study	Low risk of bias	Prospective, consecutive recruitment of participants into the study.
Bias in classification of interventions	Low risk of bias	Clear classification of interventions.
Bias due to deviations from intended interventions	No information	Strategies to address potential deviations from intended interventions not adequately described.
Bias due to missing data	Moderate risk of bias	Attrition data described, but no analysis was performed.
Bias in measurement of outcomes	Serious risk of bias	Potential for subjective measurement of pain scores. Duration of intervention period was 8 weeks longer; bigger sample size (but interrater reliability established). Cannot blind healthcare professionals who administer RASS and BPS
Bias in selection of the reported result	No information	Not described.
Overall quality assessment	**Moderate risk of bias**	
Study authors	**Cui et al.[32]**	
Bias	**Judgement**	**Support for judgement**
Bias due to confounding	Serious risk of bias	Postop main medication assessed by may be swayed as surgeons informed of intervention; cannot guarantee that they did not change practices per protocol—which nurses may have picked up during their rounds together
Bias in selection of participants into the study	Serious risk of bias	Selection of participants into the study by convenience sampling.
Bias in classification of interventions	Low risk of bias	Clear classification of interventions.
Bias due to deviations from intended interventions	No information	Strategies to address potential deviations from intended interventions not adequately described.
Bias due to missing data	Low risk of bias	16 and 15 nurses completed, though unclear how many patients were recruited then excluded due to missing data or other reasons
Bias in measurement of outcomes	Serious risk of bias	Questionnaire measurement of outcomes; potential for subjective interpretation and response.
Bias in selection of the reported result	No information	Not described.
Overall quality assessment	**Moderate risk of bias**	

Study authors	Duncan and Pozehl[31]	
Bias	**Judgement**	**Support for judgement**
Bias due to confounding	Serious risk of bias	Potential confounding factors not addressed by experimental design or statistical analyses
Bias in selection of participants into the study	Moderate risk of bias	Retrospective audit of patient medical records.
Bias in classification of interventions	Low risk of bias	Clear classification of interventions.
Bias due to deviations from intended interventions	No information	Strategies to address potential deviations from intended interventions not adequately described.
Bias due to missing data	Moderate risk of bias	Attrition data described, but no analysis was performed
Bias in measurement of outcomes	Serious risk of bias	Self-reported pain intensity ratings; potential for subjective measurement.
Bias in selection of the reported result	No information	Not described.
Overall quality assessment	**Moderate risk of bias**	
Study authors	**Ferguson et al.[54]**	
Bias	**Judgement**	**Support for judgement**
Bias due to confounding	Serious risk of bias	Confounding factors acknowledged but could not be controlled for due to the nature of the hospital setting.
Bias in selection of participants into the study	Low risk of bias	All patient-controlled analgesia (PCA) errors in hospital over set period.
Bias in classification of interventions	Low risk of bias	Intervention groups clearly defined.
Bias due to deviations from intended interventions	Serious risk of bias	Acknowledged potential for deviations from intended interventions.
Bias due to missing data	No information	Missing data not reported.
Bias in measurement of outcomes	Low risk of bias	Data PCA errors were objective and carried a lower potential for subjective interpretation.
Bias in selection of the reported result	No information	Not described.
Overall quality assessment	**Moderate risk of bias**	
Study authors	**Humphries et al.[27]**	
Bias	**Judgement**	**Support for judgement**
Bias due to confounding	Serious risk of bias	No adjustments made to account for potential confounding factors.
Bias in selection of participants into the study	Low risk of bias	All eligible patients included in analysis.
Bias in classification of interventions	Low risk of bias	Intervention group clearly defined.
Bias due to deviations from intended interventions	No information	Potential deviations from intended interventions not described.
Bias due to missing data	Low risk of bias	Study authors report no attrition of data.
Bias in measurement of outcomes	Moderate risk of bias	Outcome assessors not blinded to intervention status.
Bias in selection of the reported result	No information	
Overall quality assessment	**Moderate risk of bias**	
Study authors	**Juhl et al.[28]**	
Bias	**Judgement**	**Support for judgement**
Bias due to confounding	Serious risk of bias	Measurement of pain scores depends on the day which postoperative patients were interviewed; was not consistent between patients nor between pre–post intervention periods.
Bias in selection of participants into the study	Moderate risk of bias	Prospective and consecutive patient inclusion. However, nurses' participation was voluntary, which is susceptible to volunteer bias.
Bias in classification of interventions	Low risk of bias	Prospective study and clear pre–post periods.

(Continues)

Study authors	Juhl et al.[28]	
Bias	**Judgement**	**Support for judgement**
Bias due to deviations from intended interventions	Low risk	Intervention groups clearly defined to minimise deviation from intended interventions.
Bias due to missing data	Moderate risk of bias	Attrition described but no analysis performed.
Bias in measurement of outcomes	Moderate risk of bias	Nurses who assessed subjective pain could not be blinded; good that McGill Pain Questionnaire translated by 3 qualified people
Bias in selection of the reported result	Moderate risk of bias	Reporting of anaesthetists' *vs* surgeons' prescribing patterns were nonconsistent (converse figures reported)
Overall quality assessment	**Moderate risk of bias**	
Study authors	**Kjeldsen et al.[33]**	
Bias	**Judgement**	**Support for judgement**
Bias due to confounding	Serious risk of bias	Diff number of patients treated with NSAIDs (one of the risk drugs) which can affect (opioid) analgesia requirements and possibly subsequent recs (Table 1)
Bias in selection of participants into the study	Low risk of bias	Controlled prospective study design, analysis performed on 2 groups to ensure similar cohorts.
Bias in classification of interventions	Low risk of bias	"To ensure standardized interventions, an information sheet was developed for each of the risk medications"
Bias due to deviations from intended interventions	No information	Strategies to address potential deviations from intended interventions not adequately described.
Bias due to missing data	Moderate risk of bias	Reasons for exclusion; differs slightly between the 2 groups
Bias in measurement of outcomes	Low risk of bias	Comprehensive reporting of outcomes
Bias in selection of the reported result	Low risk of bias	Selection of reported results addressed
Overall quality assessment	**Serious risk of bias**	
Study authors	**Majumder et al.[29]**	
Bias	**Judgement**	**Support for judgement**
Bias due to confounding	Moderate risk of bias	Confounding variables are addressed to an extent by study design (e.g. restriction of included patients).
Bias in selection of participants into the study	Low risk of bias	Consecutive selection of participants into the study.
Bias in classification of interventions	Low risk of bias	Intervention groups clearly defined.
Bias due to deviations from intended interventions	No information	Potential deviations from intended interventions not described.
Bias due to missing data	Low risk of bias	Study authors report no attrition of data.
Bias in measurement of outcomes	Moderate risk of bias	Outcome assessors not blinded to intervention status of the participant.
Bias in selection of the reported result	Low risk of bias	Reported results reflect predefined primary and secondary outcome measures.
Overall quality assessment	**Low risk of bias**	
Study authors	**Manias et al.[45]**	
Bias	**Judgement**	**Support for judgement**
Bias due to confounding	Moderate risk of bias	Potential confounding factors addressed to an extent by study design.
Bias in selection of participants into the study	Low risk of bias	Consecutive patient recruitment into the study.
Bias in classification of interventions	Low risk of bias	Clear classification of interventions.
Bias due to deviations from intended interventions	No information	Strategies to address potential deviations from intended interventions not adequately described.
Bias due to missing data	Low risk of bias	No missing data reported.

(Continues)

Study authors	Manias et al.[45]	
Bias	**Judgement**	**Support for judgement**
Bias in measurement of outcomes	Low risk of bias	The study authors report "The research assistant who collected data from both groups was blinded to group assignment. In addition, nurses in each hospital were not informed about their allocated group."
Bias in selection of the reported result	No information	Not described.
Overall quality assessment	**Low risk of bias**	
Study authors	**McAllister et al.[41]**	
Bias	**Judgement**	**Support for judgement**
Bias due to confounding	Serious risk of bias	Potential confounding factors not addressed by experimental design or statistical analyses
Bias in selection of participants into the study	Low risk of bias	All eligible participants included into the study.
Bias in classification of interventions	Low risk of bias	Clear classification of interventions.
Bias due to deviations from intended interventions	No information	Strategies to address potential deviations from intended interventions not adequately described.
Bias due to missing data	No information	Missing data not described.
Bias in measurement of outcomes	Low risk of bias	Clear documentation of outcome measurement.
Bias in selection of the reported result	No information	Not described
Overall quality assessment	**Moderate risk of bias**	
Study authors	**McEvoy et al.[56]**	
Bias	**Judgement**	**Support for judgement**
Bias due to confounding	Serious risk of bias	Potential confounding factors not addressed by experimental design or statistical analyses
Bias in selection of participants into the study	Low risk of bias	Retrospective analysis of electronic medication orders.
Bias in classification of interventions	Low risk of bias	Clear classification of intervention groups.
Bias due to deviations from intended interventions	No information	Strategies to address potential deviations from intended interventions not adequately described.
Bias due to missing data	Low risk of bias	Study authors reported no missing data.
Bias in measurement of outcomes	Low risk of bias	Clear documentation of outcome measurement.
Bias in selection of the reported result	Serious risk of bias	The authors acknowledge that "the duration of postintervention assessment and sample size were not the same as the preintervention assessment. This may have affected the overall results due to variance in prescribing patterns."
Overall quality assessment	**Moderate risk of bias**	
Study authors	**Morisson et al.[20]**	
Bias	**Judgement**	**Support for judgement**
Bias due to confounding	Low risk of bias	Study design involved propensity score matching with control participants. Statistical analyses to control for confounding factors included logistic regression models.
Bias in selection of participants into the study	Low risk of bias	All eligible participants were enrolled in the study.
Bias in classification of interventions	Low risk of bias	Intervention groups clearly defined.
Bias due to deviations from intended interventions	No information	Potential deviations from intended interventions not described.
Bias due to missing data	Low risk of bias	Details of subject enrolment clearly outlined and no other missing data reported.
Bias in measurement of outcomes	Low risk of bias	The study was double-blinded. Participants were not informed as to whether they were enrolled in the

(Continues)

Study authors	Morisson et al.[20]	
Bias	**Judgement**	**Support for judgement**
		intervention or control unit and outcome assessors were blinded to participant group.
Bias in selection of the reported result	Low risk of bias	Primary and secondary outcome measurements reported in article tables.
Overall quality assessment	**Low risk of bias**	
Study authors	**Moustafa et al.[39]**	
Bias	**Judgement**	**Support for judgement**
Bias due to confounding	Serious risk of bias	Potential confounding factors not addressed by experimental design or statistical analyses
Bias in selection of participants into the study	Low risk of bias	Prospective, consecutive selection of participants into the study.
Bias in classification of interventions	Moderate risk of bias	Classification of interventions not explicitly described.
Bias due to deviations from intended interventions	No information	Strategies to address potential deviations from intended interventions not adequately described.
Bias due to missing data	Low risk of bias	No attrition of data (100% pain assessment performed)
Bias in measurement of outcomes	Serious risk of bias	The study authors acknowledge "ED personnel were aware (in the second phase only) of the main outcome of the study and it is likely that the Hawthorne effect had an impact on pain assessment, but it did not so much on analgesics treatment."
Bias in selection of the reported result	No information	Not described.
Overall quality assessment	**Serious risk of bias**	
Study authors	**Muntlin et al.[43]**	
Bias	**Judgement**	**Support for judgement**
Bias due to confounding	Serious risk of bias	Potential confounding factors not addressed by experimental design or statistical analyses
Bias in selection of participants into the study	Serious risk of bias	The authors report "Patients were approached to take part in the study 24 h a day, weekdays and weekends until the desired number of patients had been included." Convenience sampling may introduce bias into the study.
Bias in classification of interventions	Serious risk of bias	Clear classification of interventions, however, phases B and A2 were not as explicitly described as A1.
Bias due to deviations from intended interventions	No information	No information to describe potential deviations from intended interventions.
Bias due to missing data	Moderate risk of bias	Excluded data is described, however, differences between included and excluded patients were not analysed
Bias in measurement of outcomes	Serious risk of bias	Questionnaire reporting of outcomes; potential for discrepancies between researchers
Bias in selection of the reported result	No information	Not described.
Overall quality assessment	**Serious risk of bias**	
Study authors	**Neitzel et al.[22]**	
Bias	**Judgement**	**Support for judgement**
Bias due to confounding	Serious risk of bias	Potential confounding factors not addressed by experimental design or statistical analyses. Patient pain experience may affect length of stay.
Bias in selection of participants into the study	Serious risk of bias	Selection of participants into the study by convenience sampling.
Bias in classification of interventions	Low risk of bias	Intervention groups clearly described.

(Continues)

Study authors	Neitzel et al.[22]	
Bias	**Judgement**	**Support for judgement**
Bias due to deviations from intended interventions	No information	Strategies to address potential deviations from intended interventions not adequately described.
Bias due to missing data	Low risk of bias	Reasonably complete data collection
Bias in measurement of outcomes	Moderate risk of bias	Outcome assessors not blinded to the intervention status of the participants. Provider survey is potentially subjective.
Bias in selection of the reported result	No information	Not described
Overall quality assessment	**Moderate risk of bias**	
Study authors	**Netherton et al.[42]**	
Bias	**Judgement**	**Support for judgement**
Bias due to confounding	Serious risk of bias	The authors acknowledge "We have not been able to adjust for confounders; so the increase in ketorolac use seen in Calgary EDs may be due to secular changes, that is, physician knowledge about ketorolac use for acute pain, or due to an influx of newly trained ED physicians who may have been familiar with its use in their residency training programs"
Bias in selection of participants into the study	Low risk of bias	Random selection of participants into the study.
Bias in classification of interventions	Low risk of bias	Clear classification of interventions.
Bias due to deviations from intended interventions	No information	Not described.
Bias due to missing data	Moderate risk of bias	Attrition data described, but no analysis performed; "Excluding patients arriving by Emergency Medical Service may have led to the exclusion of the most severe presentations of renal colic."
Bias in measurement of outcomes	Moderate risk of bias	Outcome assessors were not blinded to the intervention status of the study participants.
Bias in selection of the reported result	No information	Not described.
Overall quality assessment	**Moderate risk of bias**	
Study authors	**Olsen et al.[37]**	
Bias	**Judgement**	**Support for judgement**
Bias due to confounding	Serious risk of bias	The authors acknowledge "A pre–post intervention design has weaknesses, as confounding variables could influence the outcome, but differences in baseline variables between groups were controlled, using regression analysis"
Bias in selection of participants into the study	Serious risk of bias	Non-consecutive recruitment of eligible patients into the study.
Bias in classification of interventions	Low risk of bias	Clear classification of interventions.
Bias due to deviations from intended interventions	No information	Potential deviation from intended interventions not adequately described.
Bias due to missing data	Moderate risk of bias	Attrition data described, but no analysis was performed.
Bias in measurement of outcomes	Serious risk of bias	Potential for subjective pain assessment; "we did not have independent observers assessing pain in the control group"
Bias in selection of the reported result	Serious risk of bias	No results re pain events or even any of the 3 pain tools; high risk of selective reporting
Overall quality assessment	**Serious risk of bias**	

Study authors	**Paul et al.**[53]	
Bias	**Judgement**	**Support for judgement**
Bias due to confounding	Low risk of bias	The authors report that potential confounding factors were addressed. "Cases where the cause of the critical incident was attributed to patient factors were excluded from this study"
Bias in selection of participants into the study	Low risk of bias	"Two reviewers (B.B., A.M.) obtained and examined all Hamilton Health Sciences Acute Pain Service (HHS APS) critical incident reports (*n* = 642) dating from 1 February 2002 to 28 February 2009. Each report was reviewed to determine whether the event involved a PCA setup, programming, or administration error. Any discrepancies were resolved through consensus or discussion with a third reviewer"
Bias in classification of interventions	Low risk of bias	Classification of interventions between intervention and control groups explicitly described.
Bias due to deviations from intended interventions	No information	Potential deviation from intended interventions not adequately described.
Bias due to missing data	No information	Missing data not described.
Bias in measurement of outcomes	Moderate risk of bias	Outcome assessors not blinded to the intervention status of participants.
Bias in selection of the reported result	No information	Not described
Overall quality assessment	**Low risk of bias**	
Study authors	**Pierik et al.**[44]	
Bias	**Judgement**	**Support for judgement**
Bias due to confounding	Serious risk of bias	The study authors acknowledge that "There are a number of important potential confounding factors, e.g. severity of injury, knowledge and experience of pain management, which were not measured and may have differed in both periods No adjustments could be made."
Bias in selection of participants into the study	Low risk of bias	Consecutive patient recruitment of participants into the study.
Bias in classification of interventions	Low risk of bias	Clear classification of interventions.
Bias due to deviations from intended interventions	No information	Potential deviations from intended interventions not adequately described.
Bias due to missing data	Low risk of bias	No attrition of data.
Bias in measurement of outcomes	Serious risk of bias	The authors report "The percentage of patients who were actually administered analgesics might be underestimated. Even though the ED staff was instructed to list all medications, some may have neglected to do so, especially for over-the-counter analgesics."
Bias in selection of the reported result	Low risk of bias	Objective selection of reported results described.
Overall quality assessment	**Moderate risk of bias**	
Study authors	**Shaw et al.**[51]	
Bias	**Judgement**	**Support for judgement**
Bias due to confounding	Serious risk of bias	Potential confounding factors not addressed by experimental design or statistical analyses
Bias in selection of participants into the study	Low risk of bias	Analysis of all eligible prescription error rates according to predefined criteria.
Bias in classification of interventions	Low risk of bias	Clear intervention methodology and classification described.
Bias due to deviations from intended interventions	Low risk of bias	Hard copy material provided to study participants, unlikely to produce deviation across participants.

(Continues)

Study authors	Shaw et al.[51]	
Bias	**Judgement**	**Support for judgement**
Bias due to missing data	No information	Missing data not described.
Bias in measurement of outcomes	Low risk of bias	Quantitative analysis of prescription error rates.
Bias in selection of the reported result	Unclear	Not described
Overall quality assessment	**Low risk of bias**	
Study authors	**Titsworth et al.[23]**	
Bias	**Judgement**	**Support for judgement**
Bias due to confounding	Serious risk of bias	Potential confounding factors not addressed by experimental design or statistical analyses. Patient questionnaire performed, no blinding of patients described, potential for patients to answer more positively due to nonanonymity
Bias in selection of participants into the study	Low risk of bias	"Systematic random sampling was used to identify every 10th postoperative neurosurgical patient admitted preintervention and every 17th patient postintervention"
Bias in classification of interventions	Low risk of bias	Explicit classification of interventions.
Bias due to deviations from intended interventions	Low risk of bias	Intended interventions were clearly documented to minimise risk of bias introduced by deviation from intervention.
Bias due to missing data	Moderate risk of bias	Excluded data is described, however, differences between included and excluded patients were not analysed
Bias in measurement of outcomes	Serious risk of bias	"Nurses collected pain scores and were aware of the initiative; this could have potentially influenced patient-reporting practices, resulting in response bias."
Bias in selection of the reported result	No information	Not described.
Overall quality assessment	**Moderate risk of bias**	
Study authors	**Urfer et al.[49]**	
Bias	**Judgement**	**Support for judgement**
Bias due to confounding	Low risk of bias	Potential confounding factors addressed by restriction of participant sample to patients aged 65 years and above.
Bias in selection of participants into the study	Low risk of bias	Consecutive selection of participants into the study.
Bias in classification of interventions	Low risk of bias	Clear distinction between use and no use of 5-point checklist.
Bias due to deviations from intended interventions	No information	Potential deviation from intended interventions not adequately described.
Bias due to missing data	Moderate risk of bias	Excluded data is described, however, differences between included and excluded patients were not analysed
Bias in measurement of outcomes	Low risk of bias	"Data were recorded on a standardized case report form and anonymized before statistical analysis."
Bias in selection of the reported result	Moderate risk of bias	"it was not possible to blind the 2 investigators assessing medication appropriateness, because charts used for chart review contained hospitalization dates, dates of laboratory examinations etc."
Overall quality assessment	**Low risk of bias**	
Study authors	**Usichenko et al.[30]**	
Bias	**Judgement**	**Support for judgement**
Bias due to confounding	Serious risk of bias	History of opioid use and opioid tolerance may affect pain experience and pain scores. Potential confounding factor(s) not adjusted for.

(Continues)

Study authors	Usichenko et al.[30]	
Bias	**Judgement**	**Support for judgement**
Bias in selection of participants into the study	Low risk of bias	Prospective, consecutive recruitment of participants into the study
Bias in classification of interventions	Low risk of bias	Clear classification of intervention groups.
Bias due to deviations from intended interventions	Low risk of bias	Interventions clearly defined and no deviation from intended interventions reported.
Bias due to missing data	Low risk of bias	91% and 85% survey completion rate; proportions similar across groups
Bias in measurement of outcomes	Moderate risk of bias	Potential for subjective reporting of pain in surveys using visual rating scale
Bias in selection of the reported result	Moderate risk of bias	Power calculations done
Overall quality assessment	**Moderate risk of bias**	
Study authors	**VanGulik et al.[35]**	
Bias	**Judgement**	**Support for judgement**
Bias due to confounding	Serious risk of bias	Nurses not blinded to intervention; bedside manner or attention to detail/pain may become more astute as they gain more experience with pain medication especially over 15 mo.
Bias in selection of participants into the study	Unclear risk of bias	Unclear if patient selection was random or consecutive for total knee arthroplasty patients.
Bias in classification of interventions	Low risk of bias	Clear classification of intervention groups, prospective study design.
Bias due to deviations from intended interventions	Low risk of bias	The study authors report "the patients were neither aware of nor trained in the pain management programme and they were asked exactly the same question in both phases, though by different persons"
Bias due to missing data	No information	Only 1.3% of records missing from retrospective audit.
Bias in measurement of outcomes	Serious risk of bias	The study authors report "The pain scores in the control group were asked when patients were at rest, not undergoing interventions, which may have led to relatively low pain levels at that particular moment … . during the intervention phase, nurses were trained to be more alert of high NRS levels compared to the control phase"
Bias in selection of the reported result	No information	Not described
Overall quality assessment	**Moderate risk of bias**	
Study authors	**Whipple et al.[55]**	
Bias	**Judgement**	**Support for judgement**
Bias due to confounding	Serious risk of bias	Potential confounding factors not addressed by experimental design or statistical analyses
Bias in selection of participants into the study	Serious risk of bias	Retrospective review of PCA errors. No strategies to minimise selection bias reported.
Bias in classification of interventions	Low risk of bias	Clear classification of intervention groups.
Bias due to deviations from intended interventions	Low risk of bias	Objective review of PCA errors using defined criteria.
Bias due to missing data	Low risk of bias	No attrition of data due to the nature of the study.
Bias in measurement of outcomes	No information	Measures to reduce bias in outcome measurement not described
Bias in selection of the reported result	No information	Not described.
Overall quality assessment	**Moderate risk of bias**	

A.4. | Appendix

Intervention complexity assessment.

Summary of complexity assessment of interventions primarily addressing appropriate opioid use opioids in the hospital inpatient setting (*n* = 31).

Intervention type (n)	Primary author	Shania's iCAT Score*	Average iCAT Score
Multifaceted interventions primarily aimed at prescribing (16)	Taylor[38]	9.0	10.4
	Morisson[20]	9.0	
	Bingle[21]	9.0	
	Boothby[50]	13.0	
	Neitzel[22]	13.0	
	Shaw[51]	9.0	
	VanGulik[35]	10.0	
	Akce[52]	9.0	
	Titsworth[23]	14.0	
	Benditz[24]	14.0	
	Auyong[25]	10.0	
	Chan[26]	8.0	
	Humphries[27]	8.0	
	Juhl[28]	10.0	
	Majumder[29]	12.0	
	Usichenko[30]	10.0	
Decision-making tools to guide opioid prescribing (5)	Moustafa[39]	8.0	7.4
	Baehren[40]	7.0	
	McAllister[41]	7.0	
	Netherton[42]	8.0	
	McEvoy[56]	7.0	
Interventions to improve patient monitoring (10)	Muntlin[43]	8.0	7.3
	Chanques[36]	8.0	
	Duncan[31]	7.0	
	Olsen[37]	7.0	
	Pierik[44]	8.0	
	Cui[32]	7.0	
	Manias[45]	8.0	
	Paul[53]	7.0	
	Ferguson[54]	7.0	
	Whipple[55]	6.0	

*Overall intervention complexity was calculated by assigning each criteria a score of 0 to 4, indicating a low or high degree of complexity using the Cochrane Intervention Complexity Assessment Tool for Systematic Reviews (iCAT_SR).[19]