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SYSTEMATIC REVIEW

Potential for Harm Associated with Discharge Opioids After Hospital Stay: A Systematic Review

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Abstract

Introduction Mounting evidence highlights the adverse effects of opioids. In spite of this, clinicians often prescribe excessive number of discharge opioids. The aim of this systematic review is to analyse the potential of harm from discharge opioids after inpatient care including excessive prescribing of discharge opioids, improper handling of unused opioids, and unintentional chronic opioid use.

Methods A systematic search of MEDLINE, EMBASE, and Cochrane databases at the cut-off date of 1 December 2018 was conducted for studies reporting on various harmful effects of discharge opioids after inpatient care.

Results Twenty-eight studies analysed the potential for harm of discharge opioids after various inpatient surgical or medical procedures. On average, patients consumed only 38% of the prescribed discharge opioid pills. Seventy-two percent of patients stored their leftover opioids in an unlocked location, and failure to dispose of unused opioids was reported in 94.5% of patients. These factors may contribute to the increasing rate of opioid misuse and diversion in the community. In addition, discharge opioids contribute to prolonged opioid use; the proportion of opioid-naïve patients still consuming opioids 3 months after hospital discharge is 10.4%. At 6 months, the proportion is 4.4%. Unintentional chronic opioid use is associated with pre-operative opioid use, history of substance use, specific comorbidities, and invasive surgical procedures.

Conclusion This systematic review suggests that the current discharge opioid prescribing practices can be improved. Lack of patient education regarding storage and disposal of opioids also contributes to the increasing rate of opioid misuse, diversion, and unintended long-term use. More high-quality research with comparable outcomes is needed. Evidence-based hospital guidelines and public health policies are needed to improve opioid stewardship.

1 Introduction

Over the recent years, the number of patients discharged from hospital with opioids for ongoing management of acute pain has been rising [1]. One of the reasons is the increasing number of operations performed as day cases or with only a short hospital stay leading to requirements for more aggressive analgesia provision at discharge. Although opioids are very effective analgesics for acute pain, there is a growing public health concern in regard to current prescribing practices after hospital stays [2]. Clinicians often prescribe excessive number of opioids for hospital discharge with little consideration to the possible harmful effects of such inappropriate prescribing practice [3]. The increasing rate of opioid prescription can lead to the development of opioid diversion, misuse, and unintentional long-term use [1, 4]. In the USA, drug poisoning deaths involving any opioid drugs quadrupled from 1999 to 2010 [5], and prescription opioids were involved in 61% of drug poisoning in women [6]. In Australia, there was a doubling in rate of hospital admission due to opioid poisoning between 1999 and 2007 [7] and a 1.7-fold increase in deaths due to opioids between 2002 and 2011 [8]. Opioid overdose in 2016 resulted in death for 1045 Australians aged 15–64 years [9]; the majority of these deaths (76%) were attributable to prescription opioids.

This systematic review will examine the potential for harm of discharge opioids after inpatient care. These include excessive prescribing of discharge opioids, improper storage

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Key Points

Opioids prescribed at discharge from hospital are often exceeding requirements for good pain management.

This oversupply of opioids contributes to misuse and abuse of these medications and continued opioid use long after discharge.

Individualised prescribing practices based on evidence-based guidelines (opioid stewardship) and patient education are required to improve this situation.

of opioids and improper disposal of opioids. The systematic review will also examine the rates of unintentional initiation of chronic opioid use from discharge opioids, as well as factors that may be associated with predisposition to long-term opioid use. Results from this systematic review can be used to guide future hospital guidelines for proper prescribing practice of discharge opioids, as well as shape future public health policies in regard to opioid stewardship [1, 10].

2 Methods

2.1 Search Strategy and Eligibility Criteria

The *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guideline was used in the compilation of this systematic review. A broad systematic search was conducted to gather existing published literature using EMBASE, MEDLINE, and Cochrane databases. The systematic review was registered with PROSPERO (CRD42018105495).

MEDLINE, EMBASE and Cochrane databases were searched from inception to December 1, 2018, for any human clinical study analysing the possible adverse effects of discharge opioids after hospital inpatient care. The databases were searched using the MeSH terms "analgesics, opioid/adverse effects," "analgesics, opioid/toxicity," "analgesics, opioid/administration and dosage," "analgesics, opioid/supply and distribution," with "practice patterns, physicians," "patient discharge," "pain, postoperative," "risk factors," or "surgical procedures, operative". Keyword search via OVID platform of MEDLINE and EMBASE databases was also performed using; "discharge opioid", "patient discharge", "hospital discharge", "analgesics, opioid/ae, po, to [adverse effects, poisoning, toxicity])". All Cochrane databases were searched using the term "opioids", "discharge", "adverse effects". References of relevant articles were also searched to identify further studies.

The title and abstract of identified articles were manually screened by two reviewers using the inclusion and exclusion criteria (Table 1).

In conducting the full-text review, articles that did not analyse cohorts of patients receiving inpatient care were excluded. Articles that did not monitor any harmful effects of discharge opioids longitudinally were also excluded. For this review, harmful effects include anything that causes harm on an individual or population level. This includes over-prescription of discharge opioids, which can predispose patients to chronic opioid use and opioid misuse, as well as unsafe storage of opioids, which can lead to opioid diversion. Data extraction was performed independently by two reviewers using a standardised data extraction form. Disagreements were resolved by discussion between the two review authors.

2.2 Validity Assessment

The risk of bias for cohort studies were assessed using the Newcastle–Ottawa Quality Assessment Scale. The scale evaluates three categories of the studies: (1) *selection*, representing the representativeness of the exposed cohort, selection of non-exposed cohort, ascertainment of exposure, and demonstration that outcome of interest was not present at the start of study; (2) *comparability*, representing the comparability of cohorts on the basis of study design; and (3) *outcome*, representing the assessment of outcome, appropriate length of follow-up, and adequacy of follow up of cohorts. The studies were appraised by awarding stars (*) to each category: 3 or 4 stars for selection, 1 or 2 stars for comparability, and 2 or 3 stars for the outcome signified 'good' quality; 2 stars for selection, 1 or 2 stars for comparability, and 2 or 3 stars for outcomes signified 'fair' quality; and 0 or 1 star for selection, or 0 stars for comparability, or 0 or 1 stars for the outcome domain reflected 'poor' quality. Formal validity assessment was not performed for survey-based studies and retrospective chart reviews, as they are considered low quality with a high potential for bias.

Calculations To calculate adjusted means, values from each study were multiplied by an assigned weighting factor in proportion to the study size and summed together.

Table 1 Inclusion and exclusion criteria for screening

Inclusion criteria	Exclusion criteria
Opioids	Perioperative
Dependence	Outpatient
Inpatient	Emergency department
Prolonged/chronic use	
Hospital discharge	

3 Results

3.1 Literature Search

The literature search identified 1153 articles from inception of the databases to the cut-off date of 1 December 2018. Figure 1 shows the study selection process in a PRISMA Flow Diagram. After removing duplicates and applying the exclusion criteria (Table 1) to the titles and abstracts, 67 articles remained. The full text was then assessed for eligibility, specifically if the article reported on patients who did not all receive inpatient care, or if the article did not measure any adverse effects of discharge opioid longitudinally. Thirty-nine of the initial 67 studies were excluded based upon these criteria.

3.2 Study Characteristics

Table 2 summarises the validity assessment of the included studies. The Newcastle–Ottawa Quality Assessment Scale was applied to 19 eligible articles. The scale identified 5 articles as 'good quality', 0 article as 'fair' quality, and 14 articles as 'poor' quality. Thirteen studies used record linkage to assess outcome, while 6 studies used self-report. Table 3 summarises the characteristics of the included studies. There were 28 studies that analysed the harmful effects of discharge opioids after inpatient care. Eight articles were prospective cohort studies, 11 articles were retrospective cohort studies, 5 articles were survey-based studies, and 4 articles were retrospective chart reviews. The sample size for the studies ranged from 64 to 587 for prospective studies, 338 to 391,139 for retrospective studies, 81 to 2173 for retrospective chart reviews, and 65 to 720 for survey-based studies. The studies were performed in USA ($n=22$), Canada ($n=4$), Australia ($n=1$), and Sweden ($n=1$). There was one study that reported on paediatric inpatients (98% postoperative) [11], while the rest reported on adult patients. Only two of the studies reported on non-surgical inpatient care for musculoskeletal rehabilitation [12] and vaginal delivery [13]; a third reported on patients discharged after surgical or medical inpatient care [14]. Eleven studies included patients having orthopaedic procedures; these included 6 studies after total hip arthroplasty or total knee arthroplasty [15–20], one study each after thoracic surgery [21], femoral shaft fracture [22], any surgical fixation of fractures [23], joint and spine surgery [24], and one study after common

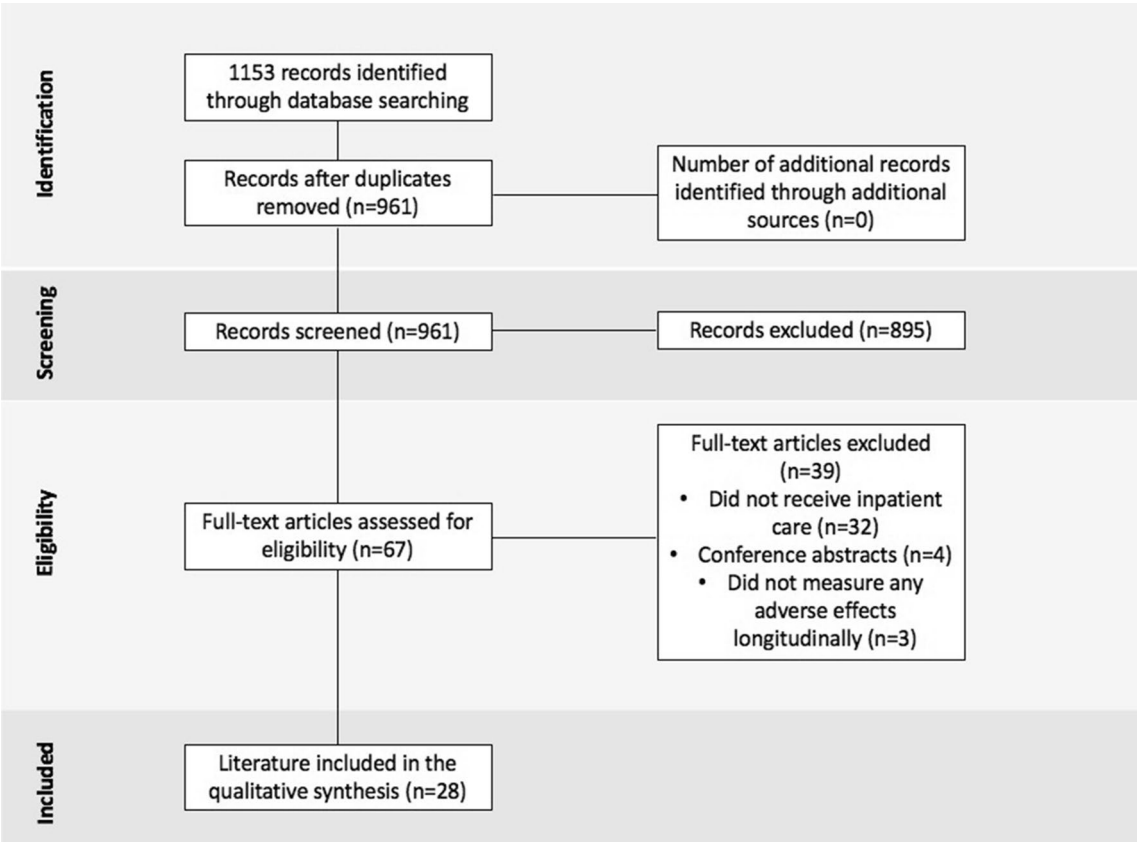

Fig. 1 PRISMA flow diagram of the literature selection

Table 2 Risk of bias assessment (Newcastle–Ottawa Quality Assessment Scale Criteria)

Study	Selection				Comparability	Outcome			
	Representativeness of exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Comparability of cohort	Assessment of outcome	Follow-up long enough to occur (median duration of 3 months)	Adequacy of follow up	Quality Score
Alam (2012) Canada [36]	Representative of the 66 years and older population*	Yes*	Secure records *	Yes*	They adjusted for potential confounding factors, including age, sex, Charlson comorbidity index, socioeconomic status, residence in a long-term care facility, and hospital type*	Record linkage*	Yes*	Retention rate was not clearly stated	Good
Bartels (2016) USA [21]	Selected group of patients with C-section or thoracic surgery	Yes*	Secure records*	Yes*	No clear statements about adjustments of confounders	Self-report	No	Response rate was 26% and 31% for post C-section and thoracic surgery respectively	Poor
Bateman (2016) USA [31]		Yes*	Secure records *	Yes*	No clear statements about adjustments of confounders	Record linkage*	Yes*	All subjects are accounted for*	Poor
Bedard (2017) USA [15]	Selected group of patients with Total Hip Arthroplasty	Yes*	Secure records *	Yes*	No clear statements about adjustments of confounders	Record linkage*	Yes*	All subjects are accounted for*	Poor
Bicket (2018) USA [24]	Selected group of patients undergoing joint or lumbar spine surgery	Yes*	Secure health system's electronic health record (EHR)*	Yes*	No clear statements about adjustments of confounders	Self-report	Yes*	Outcomes at 1 and 6 months were obtained for 82% and 80% of patients respectively*	Poor
Calcaterra (2016) USA [14]	Selected group of patients undergoing medical or surgical inpatient care	Yes*	Secure records *	Yes*	No clear statements about adjustments of confounders	Record linkage*	Yes*	All subjects are accounted for*	Poor
Carroll (2012) USA [37]	Selected group of patients undergoing mastectomy, lumpectomy, thoracotomy, total knee replacement, and total hip replacement	Yes*	Structured interview*	Yes*	No clear statements about adjustments of confounders	Self-report	Yes*	All subjects are accounted for*	Poor

Table 2 (continued)

Study	Selection				Comparability	Outcome			
	Representativeness of exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Comparability of cohort	Assessment of outcome	Follow-up long enough to occur (median duration of 3 months)	Adequacy of follow up	Quality Score
Clarke (2014) Canada [38]	Representative of patients undergoing major elective surgery*	Yes*	Secure records using several linked population-based administrative databases*	Yes*	No clear statements about adjustments of confounders	Record linkage*	Yes*	All subjects are accounted for*	Poor
Furlan (2016) Canada [12]	Selected group of people undergoing inpatient musculoskeletal rehabilitation	Yes*	Written self-report	Yes*	No clear statements about adjustments of confounders	Self-report	Yes*		Poor
Goesling (2016) USA [16]	Selected group of patients undergoing total knee arthroplasty and total hip arthroplasty	Yes*	Secure records*	Yes*	No clear statements about adjustments of confounders	Record linkage*	Yes*	All subjects are accounted for*	Poor
Hadlandsmyth (2019) USA [17]	Selected group of veterans undergoing total knee arthroplasty.	Yes*	Secure records using the Veterans Health Administration database*	Yes*	No clear statements about adjustments of confounders	Record linkage *	Yes*	All subjects are accounted for*	Poor
Hansen (2017) Australia [18]	Selected group of patients undergoing total knee arthroplasty	Yes*	Secure records using the Department of Veterans' Affairs database*	Yes*	The study control for various factors within the analyses by examining some patient covariates*	Record linkage*	Yes*	All subjects are accounted for*	Good
Hanson (2018) USA [27]	Selected group of patients undergoing laparoscopic cholecystectomy	Yes*	Secure records of a single institution*	Yes*	The study adjusts for age, sex, and diagnosis in a multivariable logistic regression model*	Record linkage*	Yes*	All subjects are accounted for*	Good

Table 2 (continued)

Study	Selection				Comparability	Outcome			
	Representativeness of exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Comparability of cohort	Assessment of outcome	Follow-up long enough to occur (median duration of 3 months)	Adequacy of follow up	Quality Score
Juurlink (2012) Canada [13]	Selected patients who are postpartum	Yes*	Secure records from the Ontario Public Drug Benefit Programme*	Yes*	The study compared baseline characteristics of the two cohorts via standardized differences. *	Record linkage*	Yes*	All subjects are accounted for*	Good
Kim (2018) USA [20]	Selected group of patients undergoing total knee arthroplasty	Yes*	Secure records*	Yes*	No clear statements about adjustments of confounders	Record linkage*	Yes*	All subjects are accounted for*	Poor
Lee 2017 USA [33]	Selected patients undergoing curative-intent surgery	Yes*	Secure records via national data set of insurance claims*	Yes*	Mixed linear models were used to adjust mean daily opioid dose for various baseline measurements*	Record linkage*	Yes*	All subjects are accounted for*	Good
Monitto (2017) USA [11]	Selected pediatric inpatients	Yes*	Secure hospital records*	Yes*	Outcome measures were compared among the groups using Kruskal–Wallis and Dunn's test with Hochberg adjustments for post hoc multiple comparisons*	Self-report	No	All subjects are accounted for*	Poor
Osmundson (2017); USA [32]	Selected patients undergoing caesarean delivery	Yes*	Secure hospital records*	Yes*	No clear statements about adjustments of confounders	Self-report	No	71% of eligible patients completed the survey*	Poor
Tan (2018); USA [29]	Selected patients undergoing abdominal procedures	Yes*	Secure hospital records*	Yes*	No clear statements about adjustments of confounders	Record linkage*	No	Retention rate was not found	Poor

These studies were neither prospective nor retrospective cohort study: Al Dabbagh 2016 Sweden [22]: Retrospective review, Bateman 2017 USA [30]: Survey study, Gangavalli 2017 USA [23]: Survey study, Griffith 2018 USA [26]: Survey study, Hernandez 2017 USA [19]: Retrospective review, Hota 2017 USA [35]: Survey study, Pang 2018 USA [34]: Retrospective review, Sabatino 2018 USA [25]: Prospective review, Stafford 2018 USA [28]: Retrospective review

*Symbolises stars assigned to each category according to the Newcastle–Ottawa Quality Assessment Scale

orthopaedic surgeries [25]. Four studies included patients having abdominal surgery: one study each after abdominal hysterectomy [26], laparoscopic cholecystectomy [27], abdominopelvic surgery with or without intestinal resection [28], and various open or laparoscopic abdominal procedures [29]. Three studies reported on patients having Caesarean sections [30–32]. Two studies included patients having cancer surgery [33, 34]. There was one study after pelvic reconstruction [35]. Three studies included patients undergoing a variety of operations [36–38]. Data collected from all studies spanned between 1997 and 2018.

3.3 Pattern of Discharge Opioids Prescription and Consumption

Eight studies reported the amount of prescribed opioids in various units of measurement [11, 19, 22, 26, 27, 29, 30, 34]. Of these, three studies reported in number of pills without detailing the specific medication [26, 30, 34]. In these three studies, the reported number of prescribed opioid pills on discharge ranged from 16.8 to 40 pills per patient with a median of 36.3 pills per patient. The studies did not specify whether the patients were opioid-naïve prior to admission. The reported number of unused opioids ranged from 11.2 to 31.9 pills, with an adjusted mean of 22.5 pills per patient. Therefore, in these studies patients only used 38% of the prescribed opioid pills.

Six studies (including one which also reported pills) reported total prescribed opioids of opioid-naïve patients in oral morphine milligram equivalent (MME) [11, 19, 22, 27, 29, 34]. From those, 5 studies of adult patients reported mean doses ranged from 150 to 225 mg MME, with a median MME of 152.5 mg. One study of paediatric patients reported a median MME of 42 mg.

Three studies surveyed the patients on their perception of the appropriateness of their discharge opioids; On average, 34.7% reported being prescribed too many opioids, and 4.5% reported being prescribed too few opioids.

3.4 Storage and Disposal of Unused Discharge Opioids

Four studies reported on the storage location of discharge opioids in their study cohort; the percentage of patients who left their opioids in an unlocked storage ranged from 63 to 92%, with an adjusted mean of 72%. One study reported that 8% did not know where their opioids were. Five cohort studies reported on the disposal of left-over opioids; the percentage of patients who failed to dispose their unused opioids 2 weeks post-discharge ranged from 94 to 96%, with an adjusted mean of 94.5%. One study reported that 19% of patients were told how to dispose of their leftover opioids.

3.5 Persistent Opioid Use from Discharge Opioids

Sixteen studies reported the overall rate of persistent opioid use after inpatient care [2, 14, 16–20, 22, 24, 25, 28, 31, 33, 36–38]. The proportion of all patients still consuming opioids 3 months post-discharge ranged from 2 to 82%, with an adjusted mean of 22.6%. At 6 months, the proportion ranged from 4 to 69%, with an adjusted mean of 19.2%.

Six articles reported on the rate of persistent opioid use after discharge from surgical inpatient care in adult patients who were opioid naïve prior to hospital admission. At 3 months, the percentage of opioid-naïve patients still consuming opioids ranged from 2 to 16.6%, with an adjusted mean of 10.4%. At 6 months, the percentage ranged from 4 to 8%, with an adjusted mean of 4.2%. After non-surgical inpatient care in adults, one study reported that 28% of opioid-naïve patients were still consuming opioids 6 months after discharge from a musculoskeletal rehabilitation inpatient unit.

Three studies reported specifically on the rate in adult patients with chronic opioid use prior to hospital admission. At 3 months, the percentage ranged from 38 to 82%, with an adjusted mean of 78.1%. At 6 months, the percentage ranged from 35 to 69%, with an adjusted mean of 65.9%. The adjusted average percentage of persistent opioid use for both opioid-naïve patient and chronic opioid users were synthesised at 2 weeks, 1 month, 3 months, 6 months, and 12 months and are presented in Fig. 2.

Sixteen studies of surgical inpatient care in adult patients reported on various associations with prolonged opioid use after inpatient care. Pre-operative opioid use was reported to be a predictor of chronic opioid use in 6 studies. Younger age (as defined by the respective studies) has been associated with chronic opioid use in 6 studies, while two studies reported no effect of age. Increased chronic opioids use was associated with history of other substance use such as tobacco (3 studies), antidepressants (3 studies), benzodiazepine (2 studies), alcohol (1 study), and ACE inhibitor use (1 study). Furthermore, increased chronic opioid use was also associated with preoperative pain disorder such as back pain (3 studies) and myalgia (1 study); psychiatric disorder such as depression (2 studies) and anxiety (1 study) and other specific co-morbidities such as diabetes, heart failure, obesity, pulmonary disease, migraine, history of cerebrovascular disease and history of venous thromboembolism (1 study each). There is conflicting evidence on the association of gender with chronic opioid use.

3.6 Other Potential Harmful Effects of Discharge Opioids

Only one study analysed other harmful events of discharge opioid [13]. This large, retrospective cohort study used medical records of 15,604 mothers to examine whether postpartum

Table 3 Characteristics of the included studies

Reference	Population	Procedure	Study design	Duration of trial	Method	*N*	Response rate
Al Dabbagh (2016) Sweden [22]	≥ 16 years	Surgery for femoral shaft fracture	Retrospective chart review	2005–2008	Swedish National Hospital Discharge Register	891	
Alam (2012) Canada [36]	≥ 66 years	Short stay surgery	Retrospective cohort study	April 1,1997–December 31, 2008	Linked, population based administrative data	391,139	
Bartels (2016) USA [21]	≥ 18 years	Caesarean section and thoracic surgery	Prospective cohort study	November 2014–November 2015	Survey via email or postal mail	116 (Caesarean section), 107 (thoracic)	26% (Caesarean section) 31% (thoracic)
Bateman (2017) USA [30]	≥ 18 years	Caesarean delivery	Survey-based study	September 2014–March 2016	Phone	720	
Bateman (2016) USA [31]	12–55 years, opioid naïve in the year prior to delivery	Caesarean delivery	Retrospective cohort study	2013–2011	Clinformatics Data Mart	80,127	
Bedard (2017) USA [15]		Total Hip Arthroplasty	Retrospective cohort study	January 2007–June 2015	Humana database	37,393	
Bicket (2018) USA [24]	≥ 18 years	Elective same-day or inpatient joint and spine surgery	Prospective cohort study	August–November 2016	Survey via telephone calls	140	1 month (115, 82%) 6 months (110, 80%)
Calcaterra (2016) USA [14]	≥ 15 years	Any surgical or medical inpatient care	Retrospective cohort study	1 January–31 December 2011	Electronic query of health records	6689	
Carroll (2012) USA [37]		Mastectomy, lumpectomy, thoracotomy, total knee replacement, total hip replacement	Prospective cohort study	January 2007–April 2009	Questionnaires	109	
Clarke 2014 Canada [38]	≥ 66 y	One of nine prespecified elective major surgical procedures	Retrospective cohort study	1 April 2003–31 March 2010	Several linked population-based administrative databases	39,140	
Furlan (2016) Canada [12]	≥ 18 years	Inpatient musculo-skeletal rehabilitation	Prospective cohort study	October 2011–September 2013	Interviewed during admission. Follow-up via telephone interview	64	
Gangavalli (2017) USA [23]	18–89 years	Surgical fixation of fractures	Survey-based study	Over a 10-month period	Paper survey in a private outpatient clinic	182	
Goesling (2016) USA [16]	≥ 18 years	Total knee arthroplasty (TKA) and total hip arthroplasty (THA)	Prospective cohort study	March 2010–May 2013	1 and 3 months via telephone, 6 months via mail	574	

Table 3 (continued)

Reference	Population	Procedure	Study design	Duration of trial	Method	*N*	Response rate
Griffith (2018) USA [26]		Abdominal hysterectomy Minimally invasive hysterectomy e.g. Laparoscopic hysterectomy, Vaginal hysterectomy	Survey-based study	January 2015–April 2016	Physician via e-mail Patient via telephone	96 physicians 147 patients	51 (53.1%) physician 56 (38.1%) patients
Hadlandsmyth (2018) USA [17]	Veterans	Total knee arthroplasty (TKA)	Retrospective cohort study	2013–2015	VHA datasets	6653	
Hansen (2017) Australia [18]	≥ 18 years	Total knee arthroplasty (TKA)	Retrospective cohort study	1/1/2001–31/12/2012	DVA administrative claims database	15,020	
Hanson (2018) USA [27]	≥ 18 years	Laparoscopic cholecystectomy	Retrospective cohort study	January 1 2014–December 31 2016		1606	
Hernandez 2017 USA [19]		Total knee arthroplasty (TKA)	Retrospective chart review	January 1 2012–May 1 2012	[Their own] institutional total joint registry	105	
Hota (2017) USA [35]	≥ 18 years	Gynaecologic and/or pelvic reconstructive surgery	Survey-based study	April–August 2016	Questionnaires	65	
Juurlink, (2012) Canada [13]	≥ 16 years	Delivery	Retrospective cohort study	April 1,1998–March 1, 2008	Ontario Public Drug Benefit Programme	7804	
Kim (2017) USA [20]		Total knee arthroplasty (TKA)	Retrospective cohort study	February–June 2016	Institution database	338	
Lee (2017) USA [33]	≥ 18 years	Curative-intent cancer surgery	Retrospective cohort study	January 1, 2010–June 30, 2014	Insurance claims	68,463	
Monitto (2017) USA [11]	1–21 years	Inpatient for moderate-to-severe pain as a result of surgery and/or painful medical condition	Prospective cohort study	October 2014–December 2015	Telephone interview	587	343 (66%) completed at least 1 interview 102 completed both
Osmundson 2017 USA [32]		Caesarean delivery	Prospective cohort study	May 25–August 30 2016	Phone or email	179	
Pang (2018) USA [34]	≥ 18 y	Surgery for oral cavity cancer	Retrospective chart review	January 1 2011–September 31 2016	Electronic medical records	81	
Sabatino (2018) USA [25]	≥ 18 years	Orthopaedic procedures	Survey-based study	Their institution fiscal year 2015	Telephone survey	557	
Stafford (2018) USA [28]		Abdominopelvic procedure with intestinal resection	Retrospective chart review	January 1 2008–December 31 2014	Lahey Hospital and Medical Center prospective colorectal surgery database	2173	
Tan (2018) USA [29]	≥ 18 years	Open and laparoscopic abdominal procedures	Prospective cohort study	February 2014–January 2017	Clinical visit	176	

maternal prescription of codeine is associated with risk of harm to new-borns. The study found no association between maternal codeine use with infant hospital readmission rate or any adverse neonatal outcome.

No studies were found that analysed direct harm such as respiratory depression, overdose, or death of discharge opioids to individuals.

4 Discussion

This systematic literature review identified 28 studies analysing the harmful effects of discharge opioids after inpatient care. The studies were either prospective cohort studies, retrospective cohort studies, survey-based studies, or retrospective chart reviews, and each focused on various surgical or medical procedures. Data regarding mean opioid prescription, leftover opioids, storage of opioids, disposal of leftover opioids, rate of chronic opioid use, and other harmful effects of discharge opioids were synthesised from the full text.

Findings from this systematic review suggest that discharge opioids are not consumed in total. Unused discharge opioids (in 62% of patients in this systematic review) can lead to prolonged opioid use, but also abuse, misuse and diversion [1]. There are a number of reasons why health care providers might discharge patients with too many opioids. Physicians are inclined to give excess opioids under the assumption that more discharge opioids are equal to better pain control. Furthermore, there is often little formal education about postoperative pain management, appropriate prescribing practices and concepts of multimodal analgesia [39]. Although there is currently little consensus of what constitutes appropriate discharge opioid prescribing, it is important for hospitals to have evidence-based guidelines that are continually revised as further evidence accumulates. Available evidence is summarised in a document [40]; discharge prescribing guidelines are not yet utilised by many Australian hospitals [41] despite increasing data supporting the beneficial effect of opioid stewardship programmes on discharge prescribing [42–44].

This systematic review found a high number of improper storage and disposal methods of discharge opioids, suggesting a gap in patient education regarding proper handling of discharge opioids [45]. Minimising this gap is crucial in reducing opioid diversion. There is little published data on the current rate of opioid diversion and misuse from patients discharged with opioids after inpatient care, although studies have reported that the most common source of prescription opioids for non-medical use in USA and Australia is a friend or relatives [46–48].

This systematic review also identified numerous studies reporting that discharge opioid prescribing intended for short-term management of pain can lead to chronic use. There are various risk factors associated with increased rate of prolonged opioid use, which include pre-operative opioid use, substance uses, co-morbidities, and specific surgical procedures. The evidence for association between age and gender with chronic opioid use is conflicting, and more high-quality research is needed to establish a consensus. The risk factors identified serve as a reminder that clinicians should consider the medical history, medication history, and social history of each individual patient before prescribing discharge opioids, instead of relying on a one-size-fits-all approach [1].

Adverse effects of discharge opioids are increasingly reported. Opioid-induced ventilatory impairment (OIVI) is the most feared adverse effect of opioids due to potential fatal consequences [1], although there is little published data on risk factors for OIVI specific to patients discharged after inpatient care. Risk factors for inpatient OIVI, which include sleep disordered breathing, fatigue, obesity, and COPD, have presumed significance when discharging patients on opioids [40, 49]. Furthermore, patients using opioids are also at an increased risk of falling, in particular in the early period of opioid use [50, 51]. Moreover, opioid use has been associated with increased sedation and psychomotor impairment, which may interfere with their driving ability [52] and increase risk of fatal accidents [53]. This may have implications for the discharge management of patients on opioids, in particular as recently introduced opioids [54] or dose increases are more relevant than long-term stable dosing [52].

To our knowledge, this is the first systematic review to explore the possible harmful effects of discharge opioids after hospital inpatient stay. Data from this review can be used to construct specific guidelines for better opioid stewardship. This systematic review is written in accordance with the PRISMA guideline, ensuring a high standard of reporting quality. Another strength of this systematic review is in the large number of included studies.

This systematic review has several limitations. First, there were no randomised controlled trials identified by the search method, and hence there is a high risk of bias in all the included studies. Second, most of the included studies used surveys to collect their data, which is prone to responder bias. Patients might have underestimated the number of opioids they consumed due to the negative perception associated with chronic opioid use. Third, some of the studies are incomparable due to differences in their study design. The different units for dose of discharge opioids such as MME or number of pills makes it harder to compare the opioid prescribing patterns. To address this limitation, we separated the studies reporting in MME from those reporting number

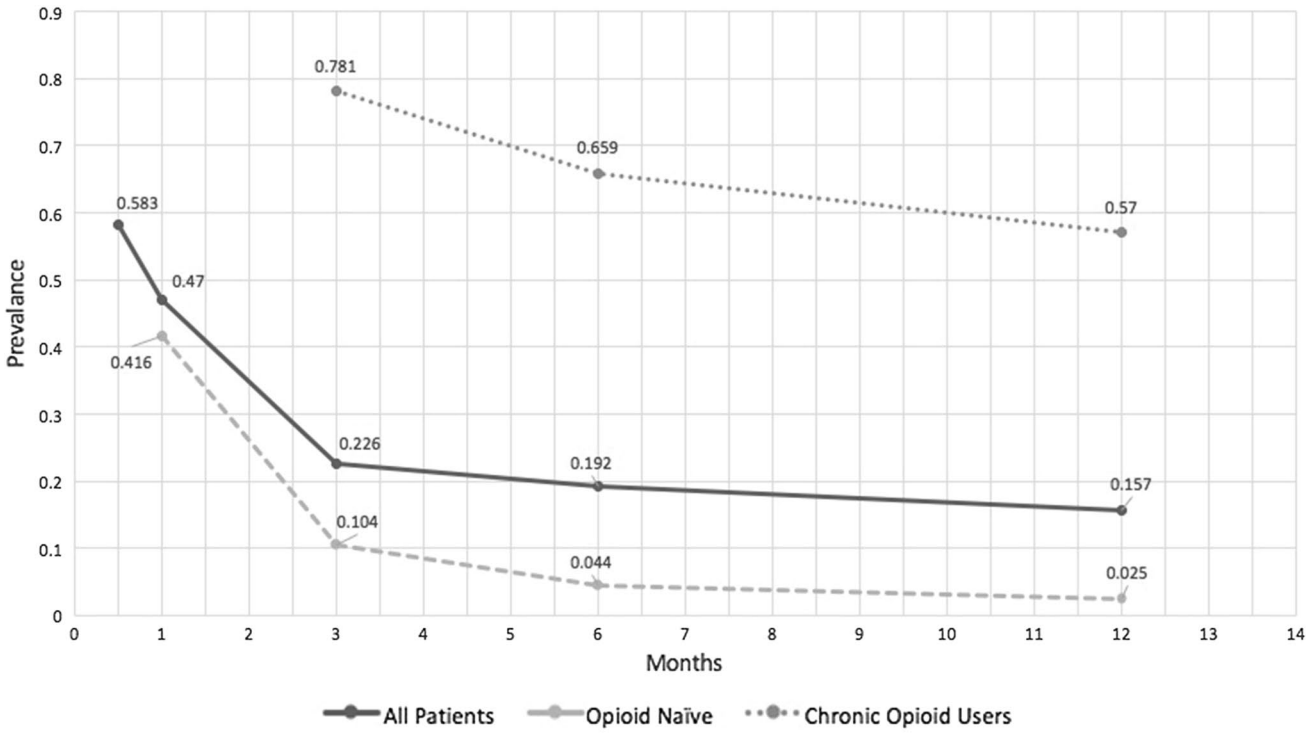

Fig. 2 Time course of the prevalence of ongoing opioid use after discharge for all, previously opioid-naïve and chronically opioid using patients

of pills and did separate calculations for each group. Non-standardised definitions of chronic opioid use and varying lengths of study period also increase the difficulty in comparing data between different studies. To address this limitation, we decided on the comparable set points of proportion of patients still taking opioids at certain time intervals post-discharge from the hospital. Data were reported at 2 weeks, 1 month, 3 months, 6 months, and 12 months.

5 Conclusion

This systematic review provides evidence of the potential for harm of discharge opioids after hospital stay, and that the current discharge opioid prescribing practices can be improved. High rates of unused opioids were identified. There is a lack of patient education regarding proper storage of discharge opioids and disposal of unused opioids. These contribute to the reservoir of unused opioids in the community, and subsequently the increasing rate of opioid misuse, diversion, and unintended long-term use. Future research involving randomised controlled trials, with large sample size and comparable study design are needed to build upon the current data. There is also a need for future research to quantitatively measure other possible harmful effects of discharge opioids such as OIVI, falls, and driving impairment. This systematic review should be used as reference for the creation of specific hospital guidelines for opioid stewardship. Clinicians also need to tailor their discharge opioid management plan according to the individual patient's history, rather than a one-size-fits-all approach.

Compliance with Ethical Standards

Conflicts of interest Gerardo Arwi has no conflicts of interest to declare. Unrelated to this study, the Anaesthesiology Unit of the University of Western Australia, but not Professor Schug personally, has received research and travel funding and speaking and consulting honoraria from Aspen, Biogen, Foundry, Grünenthal, Indivior, iXBiopharma, Komipharm, Luye Pharma, Mundipharma, Pfizer, Phosphagenics, Pierre Fabre, Seqirus and Xgene within the past three years. Since October 2019, again unrelated to this study, Professor Schug personally has received travel funding, speaking and consulting honoraria from Aspen, ESA, Grünenthal, HealthEd, Seqirus, Therapeutic Guidelines and WAPHA.

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