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Perceptions, impact and scope of medication errors with opioids in Australian specialist palliative care inpatient services: A mixed methods study (the PERISCOPE project)

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Chapter 2: Prevalence, patient impact and characteristics of opioid errors in adult palliative and cancer care settings: A review of the evidence

2.1 Chapter preface

Chapter 2 details the standardised definitions used to classify opioid errors and patient harm in the PERISCOPE project data. This chapter also reports a systematic review of opioid errors in palliative and cancer care settings.

2.2 Applying standardised definitions of opioid errors and patient harm to the PERISCOPE project data

As noted in Chapter 1, the multiplicity of terms used to define medication errors and categorise patient harm following error, contributes to considerable variations in reporting practices (Lisby, Nielsen, Brock, & Mainz, 2010). Unlike other epidemiological fields in healthcare, no single agreed definition is currently used to classify medication errors globally; although, attempts have been made to standardise medication error classifications (e.g., the National Coordinating Council for Medication Error Reporting and Prevention (1998) Taxonomy of Medication Errors). As such, the PERISCOPE project sought to apply standardised medication error taxonomies and classifications of patient harms from error. Throughout the project, standardised definitions of: i) problem type, ii) error type, and iii) patient harm, were employed to guide data collection and analysis (Allan & Barker, 1990; Lisby et al., 2010). These definitions are described below.

2.2.1 Problem type

As detailed in Chapter 1, clinical incidents in NSW are classified into one of 19 'Principal Incident Types' at the time of reporting (Clinical Excellence Commission, 2019a). For the purposes of the PERISCOPE project, clinical incident data were extracted from incidents notified under the principal incident type '*medication/IV fluid*', under which any medication related incidents are reported. Incidents were then further categorised into *problem type*, according to where in the medication

delivery process the incident occurred (Clinical Excellence Commission, 2019a). Definitions of problem types are described below:

- *Prescribing problem*: the incident involved a problem with the prescribing of a medication, e.g., not prescribed or transcribed when indicated, unclear prescription or transcription, wrong medication, dose, rate, patient etc.;
- *Dispensing problem*: there was a problem during the dispensing process (pharmacy), e.g., problem with labelling, no or delayed dispensing, wrong medication, wrong dose/volume;
- *Administration problem*: the incident occurred during the administration process, e.g., omission or suspected omission, problem with checking procedure, "signing off" or technique, wrong medication, dose, timing, route, patient etc.;
- *Supply/ordering problem*: the incident occurred during the supply or ordering process, e.g., stock not ordered or not supplied, incorrect stock ordered, insufficient stock ordered or supplied;
- *Near miss*: an incident of any problem type listed above, that is intercepted before reaching the patient (Clinical Excellence Commission, 2019a).

2.2.2 Error type

Following categorisation by problem type, a descriptive classification of the opioid incident (‘error type’) (e.g., wrong drug, omitted dose, etc.) was undertaken using the National Coordinating Council for Medication Error Reporting and Prevention taxonomy (‘taxonomy’) (National Coordinating Council for Medication Error Reporting and Prevention, 1998) as outlined in Table 2.1. This taxonomy was developed in the United States (US) in the late 1990s, in response to the need for a standardised language and structure for medication error reporting (National Coordinating Council for Medication Error Reporting and Prevention, 1998). As an equivalent Australian taxonomy could not be identified, this taxonomy was used throughout the PERISCOPE project.

Table 2.1 Classification of error type, adapted from the National Coordinating Council for Medication Error Reporting and Prevention taxonomy (1998)

1. **Omitted dose** *(the failure to administer an ordered dose to a patient before the next scheduled dose, if any; this excludes patients who refuse to take a medication or a decision not to administer*)
2. **Wrong dose**
2.1 Resulting in overdose
2.2 Resulting in under dose
2.3 Extra dose
3. **Wrong strength/concentration**
4. **Wrong drug**
5. **Wrong dosage form**
6. **Wrong technique**
7. **Wrong route of administration**
8. **Wrong rate**
8.1 Too fast
8.2 Too slow
9. **Wrong duration**
10. **Wrong time** (*administration outside a predefined time interval from its scheduled administration time, as defined by each health care facility*)
11. **Wrong patient**
12. **Monitoring error** *(includes contraindicated drugs)*
12.1 Drug-Drug Interaction
12.2 Drug-Food/Nutrient Interaction
12.3 Documented Allergy
12.4 Drug-Disease Interaction
12.5 Clinical
13. **Deteriorated drug error** (*dispensing drug which has expired*)
14. **Other (***any medication error that does not fall into one of the above*)

2.2.3 Patient harm

As described in Chapter 1, all reported clinical incidents are assigned a SAC rating informed by the clinical consequence of the incident (Clinical Excellence Commission, 2019a). However, SAC ratings do not explicitly identify the nature of patient harm as a result of the incident (e.g., patient required monitoring to preclude harm from the incident). As a result, the patient impact of opioid errors identified in the PERISCOPE project was additionally categorised using the National Coordinating Council for Medication Error Reporting and Prevention Index for Categorising Medication Errors ('index') (Hartwig, Denger, & Schneider, 1991). This index categorises the degree of patient harm from medication errors specifically, using nine categories ranging from *circumstances that have the capacity to cause error* (Category A) to *an error occurred that may have contributed to or resulted in the patients' death* (Category I), and is illustrated in Figure 2.1.

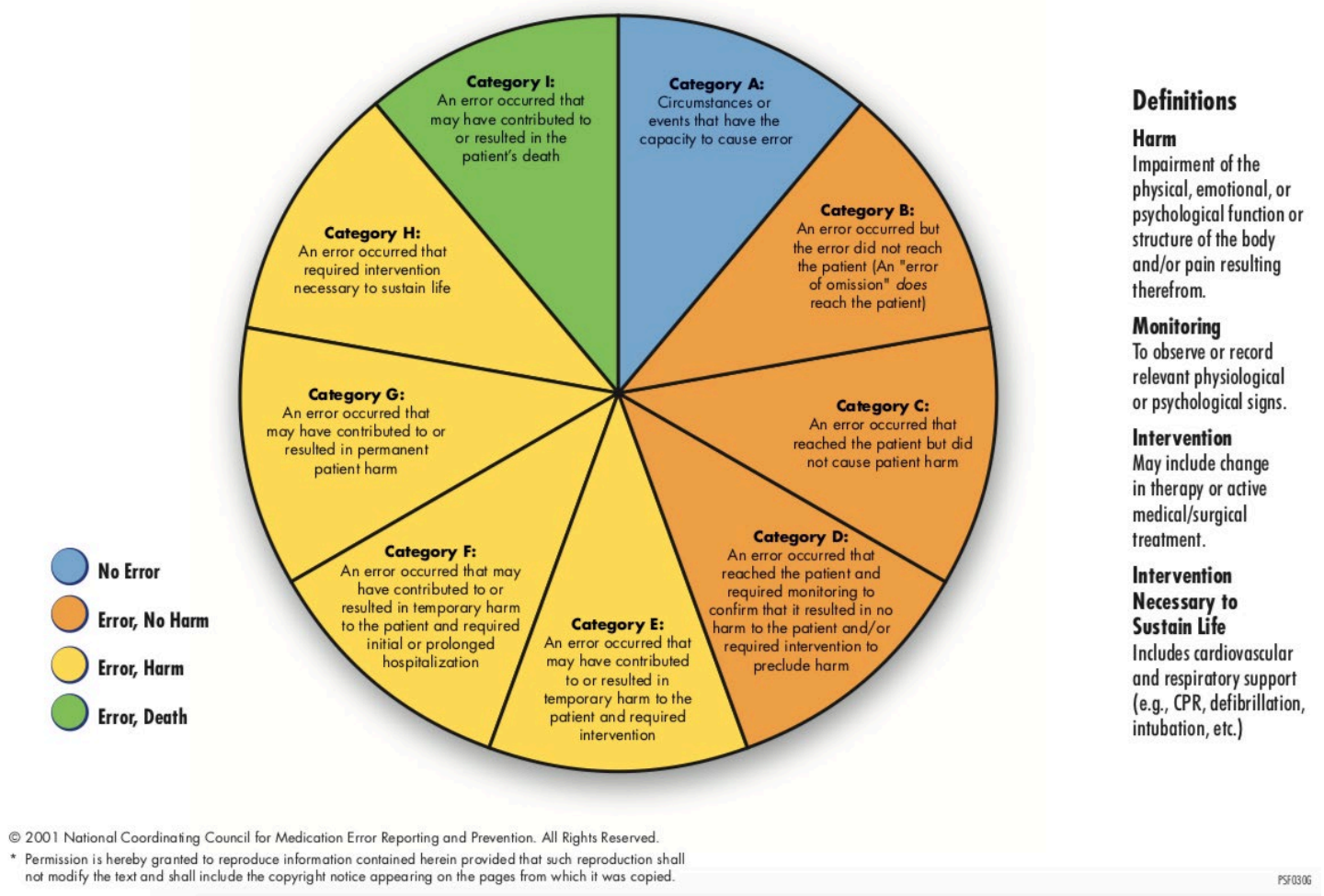

Figure 2.1 The National Coordinating Council for Medication Error Reporting and Prevention Index for Categorising Medication Errors (Hartwig et al., 1991)

Summary

This section has described the standardised definitions used throughout the PERISCOPE project to classify opioid errors and patient harm. The following section reports the systematic literature review undertaken as the first study in the PERISCOPE project.

2.3 Systematic review of the literature

This systematic review was undertaken following the priority setting workshops with senior palliative and cancer care clinicians, reported in Chapter 1 (Heneka, Shaw, Azzi, & Phillips, 2018), to further explore opioid error prevalence, error type and patient harm in palliative and cancer care settings. Both palliative and cancer care settings were included in the systematic review as over three-quarters (78%) of Australian patients utilising palliative care service have a cancer diagnosis (Australian Institute of Health and Welfare, 2014). Additionally, opioids are the cornerstone of pharmaceutical cancer pain management and their use is common in cancer settings (World Health Organisation, 1996).

2.4 Publication reference and citations

This systematic review was published in 2015 in *Palliative Medicine*, a peer reviewed scholarly journal targeting palliative care clinical practice. This chapter contains an edited version of the published systematic review (Appendix 1).

> Heneka, N., Shaw, T., Rowett, D., & Phillips, J. (2015). Quantifying the burden of opioid medication errors in adult oncology and palliative care settings: a systematic review. *Palliative Medicine, 30*(6), 520-532.

Palliative Medicine: Impact factor: 3.78; ISI JCR Ranking 2017: 15/94 (Health Care Sciences & Services), 24/154 (Medicine, General & Internal), 28/180 (Public, Environmental & Occupational Health).

This systematic review has been cited in the following publications/articles:

1. Yardley, I., Yardley, S., Williams, H., Carson-Stevens, A., & Donaldson, L. J. (2018). Patient safety in palliative care: A mixed-methods study of reports to a national database of serious incidents. *Palliative Medicine*, *32*(8), 1353–1362.

2. Bicket, M. C., Kattail, D., Yaster, M., Wu, C. L., & Pronovost, P. (2017). An analysis of errors, discrepancies, and variation in opioid prescriptions for adult outpatients at a teaching hospital. *Journal of Opioid Management*, *13*(1), 51.
3. O'Brien, H., Kiely, F., & Carmichael, A. (2017). Doctor-Related Medication Safety Incidents on a Specialist Palliative Medicine Inpatient Unit: A Retrospective Analysis of Three Years of Voluntary Reporting. *Journal of Pain & Palliative Care Pharmacotherapy, 31*(2), 105-112.
4. Müller-Busch, H. C. (2017). (Patient Safety and Critical Incidents in Palliative Care). *Zeitschrift für Palliativmedizin*, *18*(04), 194-202.

2.5 Overview

Globally, medication errors are one of the leading patient safety risks and the most common type of health care error (Kohn, Corrigan, & Donaldson, 2000). Whilst there is great variation across healthcare services and facilities, reported medication errors account for approximately 20% of hospital errors (Barker, Flynn, Pepper, Bates, & Mikeal, 2002; Thomas & Brennan, 2000). This equates to, on average, at least one medication error per inpatient per day (Institute of Medicine, 2007). Although medication errors are more likely to result in serious patient harm and death than other incident types (Phillips et al., 2001), they are often under-reported (Levinson, 2012) or undetected by hospital staff, even in health care settings with established incident reporting systems (Westbrook et al., 2015). In a recently published study comparing medication errors in acute care, identified by audit versus errors reported to an incident system, only 1.2 incident reports per 1000 identified prescribing errors were identified (Westbrook et al., 2015). Additionally, there were nil incident reports by clinicians for over 2000 clinical administration errors identified during direct observation (Westbrook et al., 2015), suggesting the error rate above could be even higher than currently reported.

Medication administration may appear to be a relatively simple process; however, there is huge scope for error at each of the more than 30 individual steps involved in the delivery of a single dose of medication (Leape, 2006). Whilst there is no standardised definition of ‘medication error’ (Lisby et al., 2010), the National Coordinating Council for Medication Error Reporting and Prevention, on their website, defines a medication error as:

> *…any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing, order communication, product labeling, packaging, and nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use* (2014, para. 1).

As previously described, medication error categories have also been developed to help standardise reporting and define the relationship between error type and harm (Hartwig et al., 1991; National Coordinating Council for Medication Error Reporting and Prevention, 1998). Error categories include errors of prescribing, dispensing, and administration (Clinical Excellence Commission, 2019a), with the relationship between error and harm ranging from potential for error (no harm to patient) to patient death as a result of an error (Hartwig et al., 1991).

2.5.1 Medication errors in palliative and cancer care settings

Numerous patient-related risk factors, such as advanced age, impaired hepatic or renal function, cognition, chronic comorbidities and polypharmacy are associated with an increased risk of medication error (Lesar, Briceland, & Stein, 1997; Myers & Lynn, 2001). Medication errors disproportionally affect patients receiving cancer treatments and those nearing the end of life due to frailty, the seriousness of their illnesses, the complexity of their treatment regimen(s), and the adverse impact of errors on vulnerable patient populations (Myers & Lynn, 2001; Thomas & Brennan, 2000).

Although several studies report medication errors in adult cancer care, the majority of these errors relate to chemotherapeutic agents, with few studies reporting errors due to other commonly used medications to manage cancer symptoms (Butts & Jatoi, 2011; Ford, Killebrew, Fugitt, Jacobsen, & Prystas, 2006; Muller, 2003; Walsh et al., 2009). Similarly, there is very little empirical research on medication errors in adult palliative care settings (Dietz, Borasio, Schneider, & Jox, 2010).

Data from 13 specialist palliative care units in the United Kingdom (UK) reported approximately two medication errors per occupied bed per annum across all services (Taylor, Fisher, & Butler, 2010). Another UK hospice calculated error rates based on estimated total drug administration, reporting an error rate of 0.03% (Gibbs, 2007). Medication error rates of 2.3 errors/month and 1.3 errors/month were reported in audits of two separate US hospice organisations over an 18 month audit period (Boyer, McPherson, Deshpande, & Smith, 2009). A palliative care inpatient facility in New Zealand, reported an average of 6.6 medication incidents (actual or perceived errors) per month over two years of voluntary reporting (MacLeod, Fletcher, & Ogles, 2011). These medication error rates are thought to reflect under-reporting in the palliative care setting (Currow et al., 2011; Sirriyeh, Armitage, Lawton, & Gardner, 2010), as, in contrast to the error rates reported in the literature, approximately two thirds of surveyed palliative care professionals' perceived medication errors to occur moderately often or frequently (Dietz et al., 2013).

2.5.2 Medication errors with opioids and the potential for patient harm

In addition to patient-related risk factors, several drug classes are associated with an increased risk of medication error. These drugs are classified as high risk and/or high alert medicines because of the heightened risk of causing patient injury or catastrophic harm if used in error (Clinical Excellence Commission, 2019b; Institute for Safe Medication Practices, 2012). Opioids are one example of high-risk medicines and are the most frequently reported drug classes in medication errors causing patient harm (Colquhoun, Koczmara, & Greenall, 2006; Hicks, 2005). Opioid errors have resulted in fatal and serious non-fatal outcomes (Moore, Cohen, & Furberg, 2007; National Patient Safety Agency, 2008; Phillips et al., 2001), and preventable adverse events leading to patient harm (Smith, 2004). A retrospective analysis of opioid errors from an anonymous national medication error reporting database identified 644 harmful errors over a seven year period on patient care units. Six of these opioid errors resulted in death, with more than half reported as administration errors resulting in opioid overdose (Dy, Shore, Hicks, & Morlock, 2007).

Opioids are widely used in palliative and cancer care, and are the primary pharmacological treatment for cancer pain (Australian Adult Cancer Pain

Management Guideline Working Party, 2014; Caraceni et al., 2012; World Health Organisation, 1996). In the palliative care setting, opioids are routinely used to manage a range of cancer and non-cancer pain and other symptoms, including dyspnoea and cough (National Collaborating Centre for Cancer, 2012; Palliative Care Expert Group, 2010). In high income countries the majority of patients utilising palliative care services have a primary diagnosis of cancer (Australian Institute of Health and Welfare, 2014; Kaasa, Torvik, Cherny, Hanks, & de Conno, 2007; National Hospice and Palliative Care Organisation, 2013). Consequently, these patients are likely to receive opioids for pain or symptom management during the course of their illness.

Increasingly, the adult palliative and cancer care populations are composed of older people (Australian Institute of Health and Welfare, 2014) with more than one chronic co-morbid disease, which may alter medication pharmacodynamics and pharmacokinetics (Kemp, Narula, McPherson, & Zuckerman, 2009; Myers & Lynn, 2001). This older population is also likely to be taking other medications for symptom control, particularly at the end of life (Currow, Stevenson, Abernethy, Plummer, & Shelby-James, 2007; Raijmakers et al., 2013). These factors all increase this vulnerable groups' risk of medication error and patient harm (Australian Commission on Safety and Quality in Health Care, 2017; Moore et al., 2007; Myers & Lynn, 2001).

The potential for opioid errors in palliative and cancer care populations may also be higher due to varying routes of administration (Institute of Medicine, 2007), numerous dosage forms with differing potencies, similar drug names (e.g., morphine/hydromorphone, oxycodone/OxyContin®/MS Contin®) and routine dose calculation and conversion in the clinical setting (Cohen, Smetzer, Tuohy, & Kilo, 2007; Dy et al., 2007; Institute for Safe Medication Practices, 2012). There is emerging evidence that the leading cause of medical error in palliative care is associated with drug treatment for symptom control, including opioid prescribing and administration (Currow et al., 2011; Dietz et al., 2013; Dietz et al., 2010). Notwithstanding the scope for opioid errors in cancer care, few studies report medication errors with opioids *per se* in cancer settings (Butts & Jatoi, 2011).

Despite these findings, and the widespread use of opioids, little is known about the degree of error reporting, or the prevalence and impact of medication errors with opioids ('opioid errors') in the palliative and cancer care settings (Currow et al., 2011; Dietz et al., 2010).

2.6 Objectives

The objectives of Study 1 were to:

i) determine the reported prevalence of opioid errors in adult palliative and cancer care settings;
ii) identify opioid error types reported in these settings; and
iii) determine the patient impact of opioid errors reported in adult palliative and cancer care settings.

2.7 Method

Design: Systematic review.

Reporting of this systematic review was guided by The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA Statement) (Liberati et al., 2009).

2.7.1 Eligibility criteria

Studies were included if they were published in English in a peer-reviewed journal and reported empirical data on opioid medication error prevalence, types or impact on patients within adult palliative care and/or cancer settings ('palliative and cancer care settings'), including inpatient, ambulatory or community care settings. All non-empirical studies, such as review articles and case reports were excluded from the review. The search was limited to studies published since 1980, reflecting the start of significant investment in specialist palliative and cancer care services (Wright, Wood, Lynch, & Clark, 2008).

2.7.2 Information sources and search strategy

A systematic search of the literature was undertaken between August 1 and August 31, 2014 using MEDLINE, Embase, Cumulative Index of Nursing and Allied Health Literature (CINAHL), the Cochrane Library and Scopus databases. The search strategy comprised three sets of terms. Set 1, was designed to capture literature

relating to opioid medications. As there is no single, standardised definition of "medication error" (Lisby et al., 2010), Set 2 aimed to captured terms relevant to 'errors'. A range of search terms relating to medication error, patient safety and adverse medication events were employed to capture relevant citations. Set 3 limited the papers retrieved to palliative and/or cancer care populations, without limiting care settings (i.e., inpatient, ambulatory, community, and home care).

Terms within each set were combined using the Boolean 'OR' operator, and the sets were then combined using the 'AND' operator. Potential search terms were trialed on MEDLINE and mapped to indexed medical subject headings (MeSH). MeSH terms and keywords (.mp) identified in MEDLINE were adapted to each database. Consultation with a specialist research librarian and subject matter experts from palliative care, cancer care, pharmacy and quality and safety, was undertaken to ensure the search strategy was appropriate for the proposed review. A full electronic search strategy utilising the MEDLINE database is included in Table 2.2.

Grey literature was searched using Google Scholar, CareSearch Palliative Care Knowledge Network, PAIS (Public Affairs Information Service) International, The Grey Literature Report (New York Academy of Medicine), System for Information on Grey Literature in Europe, Health Management Information Consortium (HMIC), National Technical Information Service (NTIS), and PsycEXTRA. Additional search strategies included hand searching key journals and reference lists of identified articles for eligible papers, and searching conference abstracts.

2.7.3 Data collection process

A data extraction tool (Higgins & Deeks, 2008) was developed to capture data from potentially relevant studies and accommodate the varying methodologies and reported outcomes. Fields included: study design; setting; data source/participants; medication reported; error definition, measure, prevalence and type; and patient outcomes. Data extraction enabled a summary of both quantitative and qualitative data and informed the data analysis.

Table 2.2 Search strategy example (MEDLINE): conducted August 2014

1. opioid*.mp. or exp Analgesics, Opioid/ 2. opiate*.mp. or exp Morphine/ 3. medication*.mp.	**Set 1**
4. 1 or 2 or 3	
5. error*.mp. or exp Medication Errors/ 6. adverse event*.mp. 7. exp Patient Safety/ or safety.mp. or *Safety/	**Set 2**
8. 5 or 6 or 7	
9. exp Palliative Care/ or exp "Hospice and Palliative Care Nursing"/ or palliative.mp. 10. "palliative care".mp. 11. exp Hospice Care/ or hospice*.mp. 12. exp Terminal Care/ 13. exp Terminally Ill/ 14. dying.mp. 15. death.mp. or *Death/ 16. "end of life".mp. 17. cancer.mp. 18. oncology.mp. or exp Oncology Nursing/ or exp Medical Oncology/ or exp Radiation Oncology/ or exp Oncology Service, Hospital/	**Set 3**
19. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 20. 4 and 8 and 19 21. limit 20 to yr="1980 -Current"	

2.7.4 Study selection

The titles and abstracts of all papers were examined by two authors (NH and JP) to determine if they met the inclusion criteria. Data from potentially relevant papers (n=158) was extracted by one author (NH).

2.7.5 Bias rating and synthesis of results

The methodological quality of included studies was assessed by the first author (NH) using the "QualSyst" systematic review tool (Kmet, Lee, & Cook, 2004). "QualSyst" incorporates two scoring systems to evaluate the quality of both quantitative and qualitative research studies. This tool was considered appropriate for critical appraisal of the included studies due to the varying study designs. The level of evidence for each study was determined using the Australian National Health and Medical Research Council ('NHMRC') evidence hierarchy (Coleman et al., 2009). Due to the range of study designs (quantitative and qualitative), synthesis of results was guided by the narrative synthesis method of Popay and colleagues (2006). This

method provides a framework to systematically and transparently conduct a narrative synthesis while minimising the inherent risk of bias inherent in systematic reviews which employ a narrative approach to synthesis (Higgins & Green, 2011).

2.8 Results

2.8.1 Study selection

The initial search of databases yielded 11,351 papers: MEDLINE (n=2970), Embase (n=7255), CINAHL (n=644), the Cochrane Library (n=6), Scopus (n=476). No papers meeting the inclusion criteria were identified in the grey literature. Removal of duplicates resulted in 9521 papers remaining for screening (Figure 2.2). On the basis of title or abstract, 9396 papers were excluded leaving 125 papers eligible for assessment. Eight additional papers were identified from the eligible papers following a hand search of reference lists. Upon further screening, 133 full text papers were identified for review, 128 papers were excluded as they did not meet the eligibility criteria, leaving five papers (Botterman & Criel, 2011; Dietz, Plog, Jox, & Schulz, 2014; Mayahara, Paice, Wilbur, Fogg, & Foreman, 2014; Shaheen et al., 2010; Turner, Clark, Root, & Hardy, 1994) that reported opioid medication error prevalence, type and/or impact in palliative care and/or cancer settings.

2.8.2 Study characteristics, design and quality

Five empirical studies reporting opioid errors in palliative care and/or cancer settings were included in this review. Methodological quality varied across the studies and the heterogeneity of the reported data precluded a meta-analysis from being undertaken (Table 2.3). All included studies met level IV evidence criteria as per the Australian National Health and Medical Research Council (NHMRC) Evidence Hierarchy (Coleman et al., 2009).

The majority (n=4) of the studies were published after 2010. All studies were undertaken in the Northern Hemisphere, with two studies undertaken in the US and one study each from Belgium, Germany and the UK (Table 2.3). These studies reported data from: two prospective surveys (Dietz et al., 2014; Shaheen et al., 2010); a prospective chart audit (Turner et al., 1994), a longitudinal study (Mayahara et al., 2014), and a retrospective case series (Botterman & Criel, 2011).

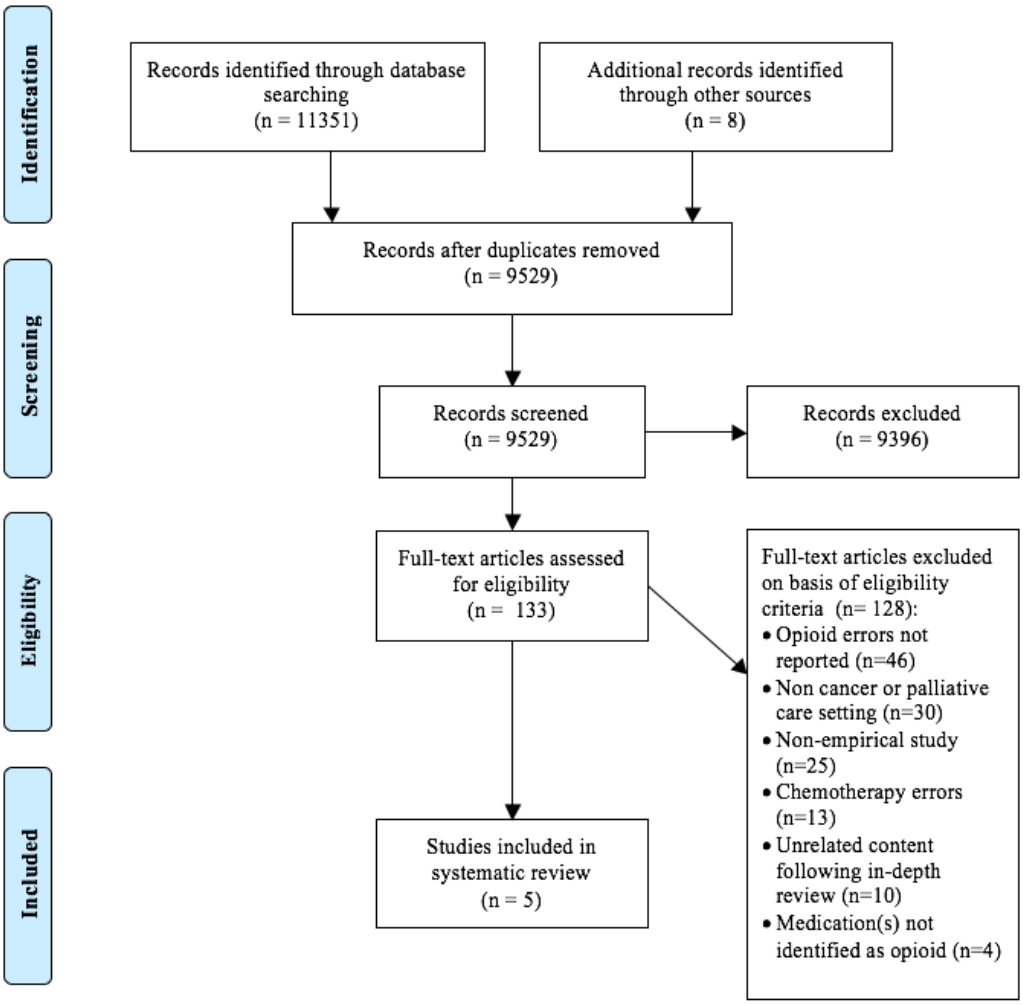

Figure 2.2 PRISMA flowchart of studies through the review process

Most studies reported patient data (Botterman & Criel, 2011; Mayahara et al., 2014; Shaheen et al., 2010; Turner et al., 1994) with one study reporting palliative care clinicians' perceptions and descriptions of medication error (Dietz et al., 2014). Three studies reported chart audit data, respectively assessing general opioid prescribing errors in palliative care inpatients and outpatients with cancer pain (Shaheen et al., 2010), morphine prescribing errors in cancer inpatients (Turner et al., 1994), and dosage errors with transdermal fentanyl in newly admitted palliative care inpatients (Botterman & Criel, 2011).

2.8.3 Settings, participants and opioid medication reported

Inpatient setting data was reported in the majority of studies (n=3) (Botterman & Criel, 2011; Dietz et al., 2014; Turner et al., 1994), with one study reporting both inpatient and outpatient data (Shaheen et al., 2010), and another study reporting data from the home care setting (Mayahara et al., 2014). Data from all but one study (Turner et al., 1994) was generated from the specialist palliative care setting (n=4).

The vast majority of patients admitted to the palliative care setting had a diagnosis of cancer (97%), all of whom had been ordered at least one opioid on or during their admission. The home care study (Mayahara et al., 2014) reported data from patient/caregiver dyads (n=46), with the majority of patients (63%) having a cancer diagnosis.

Medications were variously described as "opioids" (n=1), which encompassed morphine, hydromorphone, methadone, fentanyl and "other" (Shaheen et al., 2010), or "analgesic – mild/strong opioid" (n=1) (Mayahara et al., 2014). One study explicitly assessed morphine use (Turner et al., 1994), while another study identified morphine, diamorphine and fentanyl as opioids of interest, but primarily reported data on transdermal fentanyl (Botterman & Criel, 2011).

2.8.4 Definitions, identification and measure of error

There were various definitions of "error" employed across the studies, including deviations from: opioid dosing strategies from local practice (Botterman & Criel, 2011), local palliative care prescribing guidelines (Turner et al., 1994); US Agency for Health Care Policy and Research recommendations (Botterman & Criel, 2011; Shaheen et al., 2010), European Association of Palliative Care recommendations (Botterman & Criel, 2011; Shaheen et al., 2010), World Health Organisation guidelines (Botterman & Criel, 2011; Shaheen et al., 2010), and American Pain Society recommendations (Shaheen et al., 2010). In the home care setting, an "error" was defined as any deviation by the caregivers from the prescribed analgesic medication made by the patient's health care provider when the analgesic was administered (Mayahara et al., 2014). One study examined perceptions of error types by palliative clinicians and, as such, did not explicitly define "error" (Dietz et al., 2014).

Table 2.3 Summary of included studies

Study, Year, Country	**Design** **NHMRC level of evidence** (Coleman et al., 2009)	**Setting**	**Data source/ participants**	**Focus**	**Error definition**	**Error measure**	**Error prevalence (% of patients with at least one opioid error)**	**Quality of methods (QualSyst)** (Kmet et al., 2004)
Dietz et al., (2014) **Germany**	Exploratory, cross-sectional survey IV	Specialist palliative care institutions	Palliative care professionals (n=46)	Incidents palliative care professionals perceive as typical errors in their practice, and descriptions of events	Described by participants	n/a – qualitative data only reported	n/a – qualitative data only reported	20/20[a]
Mayahara et al., (2014) **US**	3-day, mixed methods longitudinal study: prospective survey and audit IV	Palliative care – home setting	Patient pain and medication diary Patient/ caregiver dyads (n=46)	Analgesic errors by non-professional home-hospice caregivers	Deviations from prescribed analgesic medication when the analgesic was administered	% of patients where error identified	49	18/18[b]
Botterman & Criel, (2011) **Belgium**	Retrospective chart audit IV	Specialist palliative care - inpatient	Patient charts (n=1154)	Patterns of transdermal fentanyl orders in patients admitted to a palliative care inpatient unit	Deviations from international guidelines; frank signs and symptoms of opioid toxicity	% of patients where error identified	63 (patients prescribed transdermal fentanyl only)	15/18[b]

Table 2.3 Summary of included studies (cont.)

Study, Year, Country	**Design** **NHMRC level of evidence** (Coleman et al., 2009)	**Setting**	**Data source/ participants**	**Focus**	**Error definition**	**Error measure**	**Error prevalence (% of patients with at least one opioid error)**	**Quality of methods (QualSyst)** (Kmet et al., 2004)
Shaheen et al., (2010) **US**	Prospective survey IV	Palliative care – inpatient and outpatient	Patient charts - patients with cancer pain (n=117)	Identification of common errors in opioid use through assessment of clinicians' opioid prescribing practices	Deviations from local and international opioid dosing strategies	% of patients where error identified	70	18/18[b]
Turner et al., (1994) **UK**	Prospective snapshot audit IV	Specialist cancer hospital	Patient charts containing morphine order (N=144) Pre audit (n=73); post audit (n=71)	Assessment of the quality and quantity of clinicians' morphine prescribing in accordance with local palliative care unit guidelines, pre and post guideline review	Deviations from local palliative care prescribing guidelines	% of patients where error identified	Not defined	7/18[b]

[a] Quantitative data scoring system /18; [b] Qualitative data scoring system /20

Three studies identified errors through patient chart audit, either retrospectively (Botterman & Criel, 2011) or prospectively (Shaheen et al., 2010; Turner et al., 1994). Comparisons of patients' medication diaries with the analgesic medication regimen prescribed by the patients' health care provider were used to identify errors in the home care setting (Mayahara et al., 2014). An anonymous survey asking palliative care clinicians' to describe a typical case in which an error occurred was used to identify error types and causes across palliative care institutions (n=168) in one state in Germany (Dietz et al., 2014). None of the studies included in this review utilised clinical incident reports as a method for opioid error identification or employed observations to detect opioid errors in the clinical setting.

The four studies reporting patient data, reported errors as a percentage of patients in which an error was deemed to have occurred, based on comparison to pre-established prescribing and dosing criteria. Each study examined differing aspects of opioid use, including: general opioid prescribing practices (Shaheen et al., 2010), morphine prescribing and administration practices (Turner et al., 1994), fentanyl dose on, and during, admission to the palliative care service (Botterman & Criel, 2011), and 'as-needed' ('PRN') opioid administration by non-professional caregivers (Mayahara et al., 2014).

2.8.5 Error prevalence

There was great variation in the reporting of opioid errors across the included studies (Table 2.4). One study examined prescribing patterns for patients with cancer pain (n=117), incorporating a range of opioids, (i.e., morphine, hydromorphone, methadone, fentanyl, oxycodone and "other opioids") to identify errors in opioid prescribing and dosing strategies (Shaheen et al., 2010). This study identified at least one incorrect opioid order in 70% of patients with cancer pain over an 80-day audit period (Shaheen et al., 2010). Dosage errors were identified in 63% of patients (n=199) prescribed transdermal fentanyl in a study examining patterns of strong opioid use in patients newly admitted to a specialist palliative care inpatient unit over a seven year period (n=1154) (Botterman & Criel, 2011). Two audits of morphine prescribing practices in a specialist cancer hospital were conducted over one day each, 13 months apart. The audits were undertaken at baseline (n=73) and following changes to the hospital based palliative care departments' prescribing guidelines

(n=71). Whilst the overall prevalence of opioid errors was not directly reported in this study, error prevalence by error type ranged from 5% to 81% across both audit days (Turner et al., 1994). For non-professional family caregivers in the home care setting, administering both strong and mild opioids, an administration error prevalence of 49% was reported in a longitudinal study conducted over three consecutive days (Mayahara et al., 2014).

2.8.6 Error type

The predominant error types in the clinical setting related to deviations from opioid prescribing guidelines (Table 2.4). Despite different local and national guidelines being utilised across the two studies that audited opioid prescribing strategies for patients with cancer (Shaheen et al., 2010; Turner et al., 1994), several common deviations from opioid prescribing guidelines were identified. These included no PRN analgesia ordered for patients with regular opioid orders (17-29% of patients), no pre-emptive prescribing of anti-emetics and/or laxatives to treat opioid side-effects (15-24% of patients), and incorrect opioid dosing intervals (11-81% of patients). One of these studies (Turner et al., 1994) also reported changes in the frequency of deviations from opioid prescribing guidelines following a review of local guidelines, including errors relating to regular analgesia orders (PRN oral morphine only ordered/nil regular analgesia ordered), ordering multiple PRN analgesics, and ordering multiple opioids form the same class (Turner et al., 1994).

A study examining transdermal fentanyl orders prior to admission to a specialist inpatient palliative care unit, found patients transferred from hospital or the home care setting had been ordered a three-fold higher median oral morphine equivalent dose than patients treated with oral, intravenous and subcutaneous morphine (Botterman & Criel, 2011). Nearly two thirds (63%) of these patients had signs and symptoms of opioid overdose or toxicity noted on or during their admission to the palliative care unit (Botterman & Criel, 2011). The majority (70%) of these patients had been transferred from hospital to the palliative care unit, and, prior to admission, were capable of taking oral analgesia as per opioid administration guidelines, yet had been inappropriately prescribed transdermal rather than oral opioids (Botterman & Criel, 2011).

Table 2.4 Reported opioid error type and prevalence as percentage of patients

Opioid error type	Dietz et al., (2014)	Mayahara et al., (2014)	Botterman & Criel, (2011)	Shaheen et al., (2010)	Turner et al., (1994)
Deviations from opioid prescribing guidelines	**%**	**%**	**%**	**%**	**% Pre guideline change/ % post guideline change**
1. No PRN analgesia ordered	*	*	*	17	26/29
2. PRN oral morphine only ordered/nil regular analgesia	*	*	*	*	43/5
3. Multiple PRN analgesics ordered	*	*	*	*	32/*
4. Opioid side effects not prescribed for	*	*	*	15	24/22
5. Incorrect dosing intervals	*	*	*	11	81/81
6. Multiple opioids from same class ordered	*	*	*	10	*
7. Incident pain not treated	*	*	*	8	*
8. Incorrect route/ formulation for pain type	a	*	b	8	*
9. Inadequate trial of initial opioid	*	*	*	5	*
10. More than one opioid changed at a time	*	*	*	2	*
11. Inappropriate dose ordered	a	*	63[c]	*	*
Titration errors	**%**	**%**	**%**	**%**	**%**
1. Failure to titrate	*	*	*	9	*
2. Incorrect titration	a	*	*	*	*
Opioid conversion errors	**%**	**%**	**%**	**%**	**%**
1. Incorrect dose conversion for new route	a	*	*	3	*
2. Incorrect dose calculation for opioid rotation	*	*	*	2	*

Table 2.4 Reported opioid error type and prevalence as percentage of patients (cont.)

Opioid error type	Dietz et al., (2014)	Mayahara et al., (2014)	Botterman & Criel, (2011)	Shaheen et al., (2010)	Turner et al., (1994)
Administration errors	**%**	**%**	**%**	**%**	**%**
1. No analgesic administered	*	21	*	*	*
2. Too low a dose of prescribed analgesic administered	*	9	*	*	*
3. Over the counter medication instead of prescribed analgesic administered	*	6	*	*	*
4. Discontinued prescribed mild opioid administered	*	6	*	*	*
5. Sedative administered, not prescribed analgesic	*	6	*	*	*
6. Too high a dose of prescribed analgesic administered	*	3	*	*	*
7. Discontinued prescribed strong opioid administered	*	1	*	*	*
Perceptions of opioid errors	**%**	**%**	**%**	**%**	**%**
1. Incorrect titration and conversion of opioids	a	*	*	*	*
2. Over dosage of opioids caused by fear of the patient's pain	a	*	*	*	*
3. Inappropriate switch from oral to subcutaneous morphine	a	*	*	*	*
Adverse effects	**%**	**%**	**%**	**%**	**%**
1. *"Appearance of adverse drug effects (from opioid over dosage)"*	a	*	*	*	*
2. "Patient suffers from severe withdrawal symptoms (opioid switching)"	a	*	*	*	*
3. Higher pain intensity when analgesic regimen not adhered to	*	d	*	*	*
4. Signs and symptoms of opioid overdose or toxicity due to transdermal fentanyl	*	*	b	*	*

** Not reported*
[a] *Qualitative example reported*
[b] *"large majority" - actual numbers not reported*
[c] *Transdermal fentanyl only*
[d] *Non-professional caregivers' adherence to analgesic regimen correlated significantly with mean worst pain score: 0.37 (p≤.001)*

Clinicians involved in a study exploring palliative care professionals' perceptions and experience of error types, acknowledged that wrong route and wrong dose errors were common in the palliative care setting; however, these perceived error types were not quantified in this study (Dietz et al., 2014). Opioid titration and conversion errors were reported in two studies (Dietz et al., 2014; Shaheen et al., 2010), accounting for nine percent and five percent of errors, respectively. In the home care setting, administration errors by non-professional caregivers were primarily due to caregivers withholding opioid analgesia even though it was indicated (21% of caregivers), or giving too low a dose of opioid analgesia (9%) (Mayahara et al., 2014). None of the included studies reported administration errors made by clinicians.

2.8.7 Patient impact

While patient impact was described in terms of opioid overdose/toxicity and pain intensity, none of the studies explicitly rated the degree of patient harm resulting from opioid errors. In one study, patients receiving inappropriately high doses of fentanyl on admission to a palliative care unit were observed to have frank signs and symptoms of opioid overdose or toxicity (details not specified); however, no deaths were reported as a result of opioid overdose (Botterman & Criel, 2011). In the home care setting, errors with opioid analgesia, administered by nonprofessional caregivers occurred in almost half (49%) of all administrations (n=422) over the three day study period, with 21% of patients receiving no analgesia when they reported pain (Mayahara et al., 2014). This study identified a significant correlation between nonprofessional caregiver administration error and mean worst pain score (0.37, $p \geq .001$) (Mayahara et al., 2014). Two other studies also noted the importance of timely and adequate pain management in patients with cancer pain and how effective pain management may be compromised if prescribing guidelines are not adhered to (Shaheen et al., 2010; Turner et al., 1994). A qualitative study described palliative care professionals' observations of adverse effects from opioid over dosage and the severe withdrawal symptoms caused by inappropriate opioid switching (Dietz et al., 2014).

2.9 Discussion

Despite the routine use of opioids in palliative and cancer care settings (Australian Adult Cancer Pain Management Working Group, 2013; Australian Institute of Health and Welfare, 2014), and the potential for patient harm due to opioid error (Dy et al., 2007), this review has identified that the scope and patient impact of opioid errors in palliative and cancer care settings is an under-explored area of patient safety.

Opioid error prevalence

Overall opioid error prevalence in palliative and cancer care settings was difficult to ascertain as audit periods in these studies varied, and each study focused on a single narrow area of error, such as deviations from local and national opioid prescribing guidelines (Shaheen et al., 2010; Turner et al., 1994), transdermal fentanyl dosage (Botterman & Criel, 2011), or non-professional caregiver opioid administration errors (Mayahara et al., 2014). Hence the prevalence of opioid errors in palliative and cancer care settings in this review ranged from 17% to 81% .

While there is also wide variation in reported opioid error prevalence in the acute care setting (Carson, Jacob, & McQuillan, 2009; Denison Davies et al., 2011; Humphries, Counsell, Pediani, & Close, 1997) these opioid error rates provide the best baseline for comparison with the error prevalence rates reported in palliative and cancer care settings. A retrospective audit in an acute general hospital in Ireland found opioid errors accounted for 12% of all reported medication errors (n=448) over a five-year period (Carson et al., 2009). In a 24-hour snapshot audit of medical and surgical patients in teaching hospital in the UK, 27% of patient charts with an opioid order (n=330) were found to have an opioid error (Denison Davies et al., 2011). In a large district general hospital, also in the UK, a prescribing audit of intramuscular opioid analgesics over a two week period identified errors in 60% of opioid prescriptions (n=120) (Humphries et al., 1997). Outside of acute care, 79% of reported analgesic medication errors (n=3949) over a two-year period in US nursing homes were related to opioid errors (Desai et al., 2013). Notably, the prevalence of opioid errors is often considerably higher in studies where audits of patient charts are undertaken (Denison Davies et al., 2011; Humphries et al., 1997) compared to when incident reports alone are utilised (Carson et al., 2009), reflecting the widespread

under-reporting of medication errors that is known to occur in the clinical setting (Levinson, 2012; Westbrook et al., 2015).

Opioid error types

The most common opioid errors identified in this review related to under prescribing of opioids for cancer pain (Shaheen et al., 2010; Turner et al., 1994), failure to order PRN analgesia for patients with regular opioid orders (Shaheen et al., 2010; Turner et al., 1994), incorrect dosing intervals (Shaheen et al., 2010; Turner et al., 1994), incorrect route or formulation for pain type (Botterman & Criel, 2011; Shaheen et al., 2010), and failure to pre-emptively prescribe for opioid side effects (Shaheen et al., 2010; Turner et al., 1994). Opioid prescribing strategy errors are also commonly reported in the acute care setting (Carson et al., 2009; Denison Davies et al., 2011; Dy et al., 2007; Humphries et al., 1997; Jenkins, Tuffin, Choo, & Schug, 2005), suggesting this is a widespread problem, and not unique to palliative and cancer care settings.

A notable absence in the empirical palliative and cancer care literature were reports of opioid administration errors in the clinical setting. A small number of case reports have described opioid administration errors in cancer and palliative care populations related to wrong route errors (Barrett & Sundaraj, 2003) and wrong dose errors (Blinderman, 2010; Butts & Jatoi, 2011). Given the routine use of opioids in palliative and cancer care settings, it is highly likely that opioid administration errors are prevalent in this setting, and this warrants further investigation.

Patient impact

The harm experienced by patients as a result of opioid errors was not specifically reported in any of the included studies in this review, rather patient impact was observed relative to pain intensity (Mayahara et al., 2014) and the immediate adverse effects from an opioid over dosage (Botterman & Criel, 2011; Dietz et al., 2014). The lack of detailed patient harm data resulting from opioid errors prevented an assessment of the relationship between error type and patient harm being undertaken.

2.9.1 Implications for future research

This review has highlighted the paucity of literature examining and reporting opioid error prevalence, type and patient harm in palliative and cancer care settings. As

identified in this review, the prevalence of opioid errors in these care settings is not readily identifiable, and, in the case of opioid administration errors, not reported at all.

There is scope for future research in the palliative and cancer care setting which quantifies and identifies opioid error types, in addition to those related to deviations from prescribing guidelines (e.g., opioid administration errors), and identifies the degree of patient harm from opioid errors. A comparison of opioid error prevalence, patient impact and characteristics in palliative and cancer care settings, relative to other acute care settings will be beneficial to better understand opioid errors in the palliative and cancer care service delivery context. Reviews of local, state-wide and national data on reported opioid errors, categorised by setting, may also be indicated. Additionally, exploring palliative care clinicians' perceptions of opioid error in their services, will provide valuable insights into the phenomena of opioid errors from the clinician's perspective.

2.9.2 Limitations

This review excluded papers not published in English, which may contribute to the risk of selection bias. Data extraction was undertaken by a single reviewer to assess eligibility of included studies; however, multiple independent reviewers rated study quality (NH, JP, TS). It is possible that some studies may not have been identified through database searching due to the multiplicity of terms used to describe medication errors (Lisby et al., 2010). Drug interactions with opioids and prescribing errors relating to adjuvant medications recommended for use with opioids (e.g., non-opioid analgesia, aperients, anti-emetics), were not explicitly identified as part of this review. The heterogeneity of the data reported in the included studies limits generalisability of this review in oncology and palliative care settings.

2.10 Summary

This systematic review examined the reported prevalence, types and impact of opioid medication errors in palliative and cancer care settings. Despite routine use of opioids for the management of cancer pain and end of life symptoms in a population already vulnerable to harm from medication errors, little remains known about the prevalence, patient impact and characteristics of opioid errors in palliative and cancer

care settings. There is a need to further explore opioid error types, other than those resulting from deviations from opioid prescribing guidelines, and the degree of patient harm resulting from these errors, from both patient data and the perspectives of palliative care clinicians, to better understand and address the patient safety issues in these vulnerable patient populations.

The following chapter (Chapter 3) reports the methodology used in the mixed methods PERISCOPE project to better understand the prevalence and patient impact of opioid errors in specialist palliative care inpatient services, and identify opioid error contributory and mitigating factors in this specialist setting.

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