Title: Estimating the proportion of patients who transition to long-term opioid use following oxycodone initiation in the emergency department

Running Title: Long-term opioid use following ED initiation

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ABSTRACT

Objectives
To report the number of patients discharged from ED with oxycodone immediate release (IR) over 12 months, and estimate the proportion who potentially transition to long-term opioid use, and subsequent injectable heroin use.

Methods
Retrospective observational data was collected from a major tertiary-referral metropolitan ED in Melbourne, Australia describing the number of patients discharged with an oxycodone IR prescription and proportion of discharge scripts filled. This data was projected against published data reporting trends on patients’ trajectory to long-term opioid use, to subsequently estimate the proportion of patients from this cohort that may transition to injectable heroin use.

Results
Of the 87,551 ED presentations in 2018, there were 4,843 prescriptions written for oxycodone IR for 4,102 different patients. An estimated 279 patients may become long-term opioid users following initial ED presentation. Of these 279 patients, 1.4 patients may potentially transition to injectable heroin use.
Conclusions

Modelling opioid use behaviour in an ED population demonstrated the potential development of unintentional long-term opioid use, and associated harms. Prospective study is required to fully understand trajectories of patients dispensed outpatient therapy from Australian EDs.

KEYWORDS

Analgesics, opioid, emergency medicine, prescription drug misuse, opioid-related disorders
INTRODUCTION

The increasing use of prescription opioids and their associated harms are well recognised both locally and internationally.\textsuperscript{1,2}

In the United States, 10.3 million people are estimated to misuse prescription opioids and over 130 people die daily from opioid-related drug overdoses.\textsuperscript{1} In 2017, the US declared the opioid epidemic as a public health emergency.\textsuperscript{1}

Prescribing data and published evidence shows Australia following a similar path. In 2016-17, there were 15.4 million Pharmaceutical Benefits Scheme (PBS) opioid prescriptions dispensed to 3.1 million people.\textsuperscript{2} The most common prescription opioid was oxycodone with 5.7 million prescriptions dispensed to 1.3 million people.\textsuperscript{2} Rising prescription rates have paralleled a dramatic increase in medical and non-medical prescription opioid use. Around 1 in 10 Australians have used at least one type of opioid for illicit or non-medical purposes.\textsuperscript{2} In 2016, the number of opioid deaths (1,119) was the highest since the 1999 (1,245) peak, which was predominantly comprised of heroin-related deaths.\textsuperscript{2}
Opioid-related presentations are common in Australian emergency departments (ED). Daily, 150 hospitalisations and 72 ED presentations involve opioid harm. EDs are on the front line of the opioid epidemic, treating opioid overdoses, pain-related conditions and frequently confronting drug-seeking behaviour. Therefore, EDs are an important intervention site, potentially able to minimize initial prescription opioid exposure, manage acute associated harm and initiate longer-term inpatient or community-based management.

Initial prescription opioid exposure often occurs in the ED during management of acute pain. Patients successfully treated with an opioid/s are often prescribed opioids on discharge. ED clinicians predominately prescribe outpatient opioids for short-term pain management, while assuming long-term use will not be a consequence. However, a growing body of evidence suggests that short-term therapeutic use is a segue to unintended prolonged opioid use in a minority of patients. It is therefore possible that a short course of opioid therapy may trigger iatrogenic dependence.

There is no clear consensus for the definition of ‘long-term opioid use’. The Consortium to Study Opioid Risks and Trends (CONSORT) criteria, defines long-term episodes as lasting longer than 90 days during which opioids are dispensed for 120 or more total days, or 10 or more opioid prescriptions are provided annually. Using this definition, persons surpassing this threshold were highly likely to develop a pattern of long-term regular opioid use.

There is a positive association between non-medical prescription opioid use and subsequent injectable heroin use. Pooled US data from 2002-2012 shows the incidence of heroin initiation was 19 times higher among those reporting prior non-medical prescription opioid use.
use than those who did not. In a cross-sectional study of 59 patients who self-reported heroin or non-medical opioid use, 35 (59%) reported initial opioid exposure via a legitimate medical prescription, and for 10 patients of this subset, the initial prescription was from an ED. Trajectory analysis suggests that transition to heroin use may be influenced by its cheaper cost, easier accessibility, superior potency, versatility of administration (including non-oral routes), and costs of maintaining use patterns using prescription opioids.

To our knowledge, there is currently no published Australian data examining the potential transition from oxycodone prescribing in ED to long-term use and dependence. This study aims to (i) estimate the trajectory of patients discharged from ED with a prescription for immediate release (IR) oxycodone that transition to long-term use (ii) of those patients prescribed oxycodone IR that transition to long-term use, the proportion that may potentially transition to injectable heroin use.


METHODS

Setting

Retrospective observational study conducted in a major tertiary-referral metropolitan ED in Melbourne, Australia, with an annual attendance rate of over 87,300 patients. The study was approved by the Hospital Human Research Ethics Committee.

Study Design

Retrospective observational data was collected from routinely collected hospital records between 1 January 2018 to 31 December 2018 in the electronic prescribing system (FirstNetTM, Cerner Millenium®; Cerner, Kansas City, USA).

This data was used to undertake two modeling exercises, in order to estimate (1) the proportion of patients who may transition to long-term opiate use and (2) the proportion of patients likely to transition to injectable heroin use.

Model 1: Estimates of long-term opioid use

We estimated the number of patients from this cohort who may become long-term opioid users following ED oxycodone IR initiation (LO) by using published data describing trajectories of opioid use. Modeling was conducted using the following equation:

\[ \text{LO} = A \times B \times C \times D \]

Each variable is derived as follows.

A. Number of patients with a prescription for oxycodone IR on discharge
The number of patients discharged from ED at the study site with a prescription for oxycodone IR was assigned to variable A. Prescriptions were excluded if they were duplicated on the prescribing system during the same ED presentation, or if a patient re-presented to ED during 2018 and received subsequent oxycodone IR prescriptions.

B. Estimation of the number of opioid-naïve patients

The authors reviewed several studies conducted in the United States which utilised data from implemented prescription drug monitoring programs or administration claims data for privately insured or Medicare enrollees to classify a patient’s opioid status. We adopted the definition of opioid-naïve as not filling an opioid prescription within 1 year before the index ED visit due to its face validity from previous studies. By focusing solely on opioid-naïve patients, we aimed to exclude patients with pre-existing chronic pain presenting with an acute exacerbation of pain. There is no published data describing the proportion of Australian ED patients prescribed an opioid for outpatient use who are opioid-naïve.

A study conducted in an urban academic Colorado ED with 80,000 annual presentations, found 52% of the ED study population prescribed an opioid, were opioid-naïve based on examination of the state prescription drug monitoring systems.

As opioid status of the patients defined in variable A were not available in the ED discharge summary, we estimated that 50% of our population would be opioid-naïve. Thus, we equated variable B to 0.5.

C. Estimation of the proportion of discharge scripts filled

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Not all patients who receive an ED prescription subsequently have the medication dispensed. A study conducted within our hospital examining the effect of modifying ED electronic outpatient opioid prescribing systems found 20.7% of patients did not have their prescriptions filled.\(^{16}\) Previous studies in the United States estimate that 12-22% of all ED prescriptions in the adult population are not dispensed.\(^{17,18}\)

Based on these findings, we have assumed that 20% of oxycodone scripts prescribed on ED discharge will not be filled. A value of 0.8 was used for variable \(C\), the proportion of oxycodone scripts filled.

### D. Proportion of patients who continued using opioids a year after initial ED visit

To our knowledge, there are no published studies describing the risk of recurrent opioid use in ED patients treated for acute pain in the Australian setting. A study examining the effect of modifying ED electronic prescribing for outpatient opioid analgesics found 24% of pre-intervention patients and 18% of post-intervention patients reported receiving a further opioid analgesia prescription within a month of initial ED visit.\(^{16}\)

Few studies in the United States have attempted to capture the trajectory and proportion of patients who progress to long-term opioid use after their initial ED prescription. In a study of 3.65 million patients, Jeffrey et al. reported that progression to long-term opioid use as defined using the CONSORT criteria, varied depending on patients’ insurance. 6.2% of Disabled Medicare, 3.1% of Aged Medicare and 1.1% of commercial beneficiaries progressed to long-term opioid use.\(^{6}\) Hoppe et al. reported 17% of patients discharged from an urban ED over a 5-month period who filled their first opioid prescription for a minor painful condition were still receiving opioids a year after the index ED visit.\(^{4}\)
Given the differences in the Australian healthcare system regarding health insurance, we have modeled our population against the results of Hoppe et al., as insurance status was not factored into their study design. This assigns variable $D$, the proportion of patients who continued using opioids a year after their initial ED visit, a value of 0.17 (17%).

Model 2: Estimates of transition to injectable heroin use

To estimate the proportion of long-term opioid users (variable $LO$) who may transition to injectable heroin use (variable $H$), we subsequently derived a second equation as follows:

$$H = LO \times ExF.$$

E. Estimation of patients who develop an opioid use disorder

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, defines opioid use disorder as persistent self-administration of opioids for non-medical purposes which can cause clinically significant impairment or distress. A recent literature review of international studies found rates of development of opioid use disorder ranged from 8–12%.
As there is currently no Australian data published, we elected to use the mean of the given range (10% or 0.1) as the value of variable E.

F. Estimation of transition to injectable heroin use.

In the United States, it is estimated that 4–6% of persons who misuse prescription opioids transition to heroin use.\textsuperscript{12,21} These estimates are retrospective and derived by surveying heroin users to determine whether non-medical prescription opioid use was a precursor to heroin initiation.

As there are no Australian estimates available, we took the mean of the given range (5% or 0.05) as the value of variable F.

RESULTS

In 2018 there were 4,102 patients that received an oxycodone IR prescription on discharge (figure 1). LO, the number of patients who may be regularly using opioids one year following ED oxycodone IR initiation was calculated using the formula:

\[ LO = A \times B \times C \times D = 4102 \times 0.5 \times 0.8 \times 0.17 = 278.9 \]

To estimate the transition to injectable heroin use, we used the following formula as discussed above:
Assuming similar trajectories of opioid use in this cohort to previous published data from Australia and the United States, from our cohort of 4,102 patients who received an oxycodone IR prescription in ED, 279 patients will be regularly using opioids after one year, and one patient will transition to injectable heroin use.

DISCUSSION

To our knowledge, this is the first attempt to describe the potential opioid use behaviour of a population of patients prescribed oxycodone within an Australian ED for use in the outpatient setting, and to quantify the potential for transition to long-term opioid and injectable heroin use.

As oxycodone is frequently prescribed on ED discharge to patients presenting with acute pain, it is important to understand the effects of initial exposure and potential for subsequent long-term harm. Our estimates suggest that 278.9 (6.8%) initially opioid-naïve patients became long-term opioid users 1 year after their initial ED visit. Similar rates of long-term opioid use are reported in the post-operative setting. Alam et al. found that 10.3% of patients continued to use opioids one year after a low-pain surgical procedure.14 In one of the few Australian studies, Kardell et al. reported 2.4% opioid-naïve patients continued using opioid analgesia six months after surgery.22 Roughead et al. found 3.9% opioid-naïve Department of Veterans’ Affairs (DVA) gold card holders continued using opioid analgesia, most commonly oxycodone, 90 days after surgical admission.23
ED physicians generally prescribe oxycodone with the intent for short-term use, allowing patients to effectively manage pain after discharge. Long-term potentially harmful consequences of well-intentioned initiation of opioid therapy in the ED may not be recognised as a significant issue by ED physicians, and so highlighting this is important. Providing education regarding opioid initiation and associated harms to all ED healthcare providers is imperative to prevent patient’s unintentional segue to long-term opioid use.

There are consistent findings of a positive association between non-medical prescription opioid use and heroin use. Muhuri et al. reported 79.5% of recent heroin initiates in the US had used prescription opioids for non-medical use prior to commencing heroin. Similarly, Jones found 77.4% reported using prescription opioids prior to initiating heroin use. Our estimates suggest in 2018, we may have contributed to the trajectory of 1.4 (0.034%) initially opioid-naïve ED patients who were discharged with an oxycodone IR prescription to injectable heroin use. Considering there were 8,017,492 Australian public hospital ED presentations in the financial year (2017-2018), our hospital accounts for 1% of these presentations. Extrapolating our data nationally equates to 140 patients who may potentially become injectable heroin users in one year. Despite this small population, these patients are at significant increased risk of death.

The risk of overdose in heroin users is high, especially when used concurrently with other drugs such as benzodiazepines and ethanol. In 2016, 361 (20%) of drug-induced deaths in Australia (1,808) were due to heroin, with death most commonly due to accidental overdose. Among Australians aged 15 to 64 years, the heroin death rate has steadily increased from 0.9 per 100,000 people in 2007 to 2.2. per 100,000 in 2016.
Although our study is modelled on a combination of local data and extrapolates, the potential for opioid harm beyond the ED is evident. Future research is required to validate the association of initial opioid exposures in ED and long-term opioid use. Understanding individual risk factors and trajectory patterns that contribute to long-term opioid use may assist prescribers’ clinical decision making and avoid unnecessary and potentially harmful opioid initiation on discharge. Increasing patient awareness about analgesic plans post ED discharge and the role of non-opioid analgesics and non-pharmacological interventions, versus opioid analgesics may also potentially halt the transition to long-term opioid use.

LIMITATIONS
This study was intended as a preliminary exploration into describing opioid use behaviour in an Australian ED population and potential for subsequent transition to long-term opioid and heroin use. While provocative, our results are limited and may not be representative of the greater Australian ED community and therefore should be interpreted with caution.

The major limitation is the lack of Australian data, particularly in the emergency medicine setting, and reliance on extrapolation against trends reported in the United States. This contributes to uncertainty in our estimates as the results produced may not be reflective of the patterns of drug use occurring in the Australian population. Additionally, external validity is limited by the use of oxycodone prescriptions prescribed on discharge from a single ED. We recognise that our population and prescribing patterns may differ from other EDs at other centres in Australia.
Although numerous opioid analgesics are available for pain management, we focused on oxycodone IR as at the study hospital this comprises over 90% of opioid discharge prescriptions. Limiting our focus to one type of opioid, may result in a potential underestimation of the rates of long-term opioid use.

There is also substantial variability amongst studies referenced in this paper with regards to study design, population and lack of consensus definitions, such as ‘opioid-naïve’ or ‘long-term opioid use’. These differences limit the reproducibility of the results depending on the study used.

CONCLUSION

Opioid initiation in the ED may contribute to long-term opioid use in initially opioid-naïve patients. In this modelling study, we estimate that 7% of opioid-naïve patients discharged from an Australian ED setting with an oxycodone IR prescription will be using opioids regularly 12 months later, and that 1.4 of these patients will transition to injectable heroin use. Further study is required to define the natural history of opioid use in patients discharged with a prescription opioid analgesic from Australian ED settings.
Oxycodone IR prescriptions prescribed on discharge from ED between 1 January 2018 to 31 December 2018

$\text{n} = 4843$

Prescriptions duplicated on the electronic prescribing system during the same ED presentation

$\text{n} = 460$

Unique oxycodone IR prescriptions

$\text{n} = 4383$

Patients who re-presented to ED during 2018 and received a further oxycodone IR prescription

$\text{n} = 281$

Unique patients who received an oxycodone IR prescription

$\text{n} = 4102$
Figure 1. Cohort flow chart
REFERENCES


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