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# Comparing opioid types in the persistence of opioid use following surgical admission: a study protocol for a retrospective observational linkage study comparing tapentadol and oxycodone in Australia

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## ABSTRACT

**Introduction** Each year, an estimated two million Australians commence opioids, with 50 000 developing longer-term (persistent) opioid use. An estimated 3%–10% of opioid-naïve patients prescribed opioids following surgery develop persistent opioid use. This study will compare rates of persistent opioid use between two commonly used postoperative opioids, oxycodone and tapentadol, to understand if initial postoperative opioid type is important in determining longer-term outcomes.

**Methods and analysis** A retrospective data linkage study that analyses administrative data from hospital and community pharmacies. Data will be obtained from at least four pharmacies that service large hospitals with comparable supplies of oxycodone and tapentadol. The study will include at least 6000 patients who have been dispensed a supply of oxycodone or tapentadol to take home following their discharge from a surgical ward. The primary outcome measure will be persistent opioid use at 3 months postdischarge for opioid naïve people who receive either immediate release tapentadol or immediate release oxycodone. Hierarchical logistic regression models will be used to predict persistent opioid use, controlling for covariates including comorbidities.

**Ethics and dissemination** Ethics approval has been obtained through the Monash University Human Research Ethics Committee (29977). We will present project findings in a peer-reviewed journal article, in accordance with the REporting of studies Conducted using Observational Routinely-collected health Data statement.

## Strengths and limitations of this study

- Anticipated to be the largest sample of patients prescribed tapentadol, reporting on the outcome of opioid persistence.
- Patients selected from at least four large hospital pharmacies across multiple Australian states.
- Novel linkage with both government subsidised and non-subsidised opioid and non-opioid drugs.
- Data available for up to 12 months prior to surgery and 6 months following surgery to capture known-risk factors for persistence such as opioid experience and psychotropic medication use.
- Retrospective prescription data will be used to identify comorbidities, but may not capture other known risk factors of persistence such as specific surgery type and tobacco use.

## INTRODUCTION

Each year in Australia, an estimated two million people commence opioids, with 50 000 subsequently developing long-term opioid use.[1 2] One group at risk of developing long-term use are those who are commenced on opioids in hospital. Persistent use is the use of postoperative opioids beyond the expected acute pain phase. This is operationalised by many studies as opioid use in postoperative days 90 onwards by patients who were opioid-naïve prior to surgery.[3] One study with over one million surgery patients, found the strongest predictor for later opioid use disorder or overdose was prescription duration, and each additional week of opioid use increased the risk of either of these outcomes by 20%.[4] Persistent opioid use is not consistently associated with clinically significant improvements in pain or function and is associated with harms that increase with higher dose and over time.[3 5]

One US guideline sets the expectation that pain should be improved in a 'matter of weeks' after the acute phase (6 weeks postsurgery) and that opioids are unlikely to be required after this time.[6] A Western Australian guideline on discharge analgesia following surgery recommends prescribing

no more than 5–7 days supply of opioids.[7] However, large comprehensive studies in the USA and Canada found that 3%–10% of opioid-naïve patients supplied with postoperative opioids develop persistent opioid use.[8–12] Fewer studies have documented persistent opioid use in Australia, with most studies limited to single sites or narrow patient populations. A prospective cohort of 1013 elective surgery patients from a Sydney hospital found that more than 10% continued opioid use for more than 90 days after surgery, with those who had orthopaedic surgery, spinal surgery and those with anxiety at greatest risk.[13] Other Australian studies have found that 3%–10% of patients continue opioids in the longer term following surgery.[14–16] Despite a relatively low proportion of postoperative opioid prescriptions resulting in long-term opioid use, due to the high volume of surgeries conducted (eg, 2.7 million annually in Australia), this represents a large overall population that are at risk of developing persistent postoperative opioid use.[17]

Harms related to pharmaceutical opioid use are often reported in aggregate, but there is emerging evidence that effects can vary substantially across pharmaceutical opioid types.[18–21] In experimental settings, different opioids have been demonstrated to have differing pharmacological profiles in terms of side effects that include nausea, constipation[22] and the likelihood of developing long-term use.[23 24] Yet to date, we have limited understanding on whether these opioid-type differences translate to different rates of persistent opioid use in practice.

Oxycodone is the most common opioid prescribed postoperatively in Australia.[15 25] However, some propose newer atypical opioids such as tapentadol may have advantages as a postoperative opioid analgesic due to the potential for fewer opioid-related side effects.[22] Tapentadol has both opioid agonist and noradrenergic reuptake blocking activity, and in recent years has grown to become one of the most commonly prescribed opioids in Australia.[19 21] As the analgesia provided by tapentadol is provided through a combination of noradrenergic and opioid receptor activity,[26] if the activation of the opioid receptor is a risk factor for persistent opioid use, it is possible tapentadol use may be associated with different rates of persistence or dose escalation compared with other opioid analgesics. Further, central sensitisation has been identified to have an important role in the development of chronic pain, and it has been proposed the noradrenergic mechanism of tapentadol may be important in managing pain associated with these pathophysiological mechanisms.[27] However, there is limited real world evidence to determine whether these mechanisms play a role in the development of persistent opioid use.

One Danish study (n=26 790) found rates of postoperative opioid persistence varied across initial opioid type, however tapentadol was analysed within an 'other opioids' grouping as there were only eight tapentadol patients in the study.[20] Tapentadol has been available for a shorter period of time than oxycodone, so there are fewer studies which capture its use,[21 26 28 29] and no postsurgical persistence studies to our knowledge have investigated tapentadol-prescribed patients as a separate group. Further studies with larger sample sizes are needed to directly compare tapentadol with other opioids to understand if the type of opioid is important in determining longer-term outcomes from opioid use following surgery.

This study will explore if the prevalence of opioid persistence following surgery differs by opioid type using a novel data linkage of hospital and community pharmacy data. The linked data will enable us to determine comparative rates of persistence by opioid type, and explore predictors of persistence, while also considering factors previously reported to increase risk of persistence such as opioid exposure prior to surgery, and comorbidities such as anxiety and depression through medication history.[3 30]

The primary aim of the study is to compare rates of persistent opioid use in opioid naïve patients prescribed one of two pharmaceutical opioids (tapentadol and oxycodone) for postsurgical analgesia. We write this protocol to maximise transparency[31 32] as the proposed study is supported by an untied educational grant from Seqirus, who are the Australian distributors of Palexia (tapentadol).

## METHODS

### Hypotheses

1. Rates of persistent opioid use will be higher for patients prescribed oxycodone compared with tapentadol following discharge, after controlling for relevant covariates.
2. Dose escalation between 3 months and 6 months will be higher for patients initially prescribed oxycodone compared with tapentadol.

### Study design

This is a retrospective data linkage study (see figure 1 for flow chart overview of study design). We will identify patients who were prescribed oxycodone or tapentadol following discharge from a surgical ward through hospital pharmacy databases. Hospital pharmacy medication records will be linked to community pharmacy data to estimate the proportion of patients still being dispensed opioid medications at 3 and 6 months postdischarge, while examining and if required, controlling for relevant covariates.

### Opioids and formulations of interest

The study's two primary pharmaceutical opioids of interest are oxycodone and tapentadol. Oxycodone is the most common opioid used postoperatively in Australia, dispensed to 51% of discharged patients in 2014–2015.[15 25] Tapentadol is being explored as a comparator as a commonly prescribed but newer opioid, where less is known about rates of persistence following surgery.[19 21]

Both products are available in immediate release and modified release forms. Modified release products have an altered timing and/or rate of release of the active drug, and are also known as 'sustained' or 'controlled'

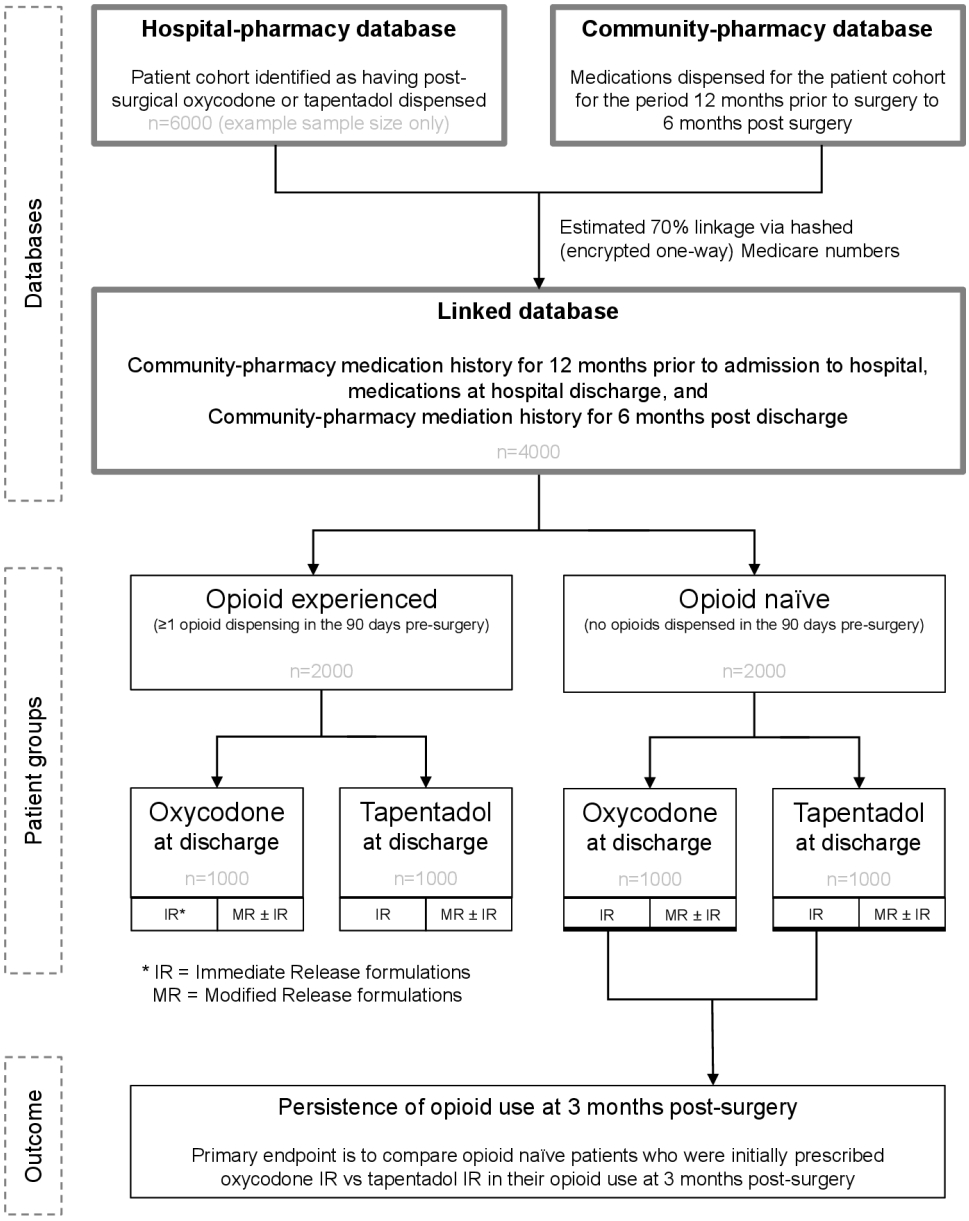


**Figure 1** Flow chart overview of the study design on the persistence of opioid use following surgical admission.

release. Immediate release products are recommended in preference to modified release opioids in the post-operative period for short-term, acute pain management.[7 33] Patients with chronic pain may be discharged from surgery with only their usual modified release opioid, or with additional immediate release opioids following discussion with the patient's usual prescriber and/or a pain specialists' recommendation.[13 33] We will quantify the use of immediate and modified release formulations of each product within the oxycodone and tapentadol groups. The oxycodone-naloxone sustained release product will be considered in the oxycodone modified release group unless there is sufficient volume to enable separate analysis.

In Australia, oxycodone immediate release, oxycodone modified release, and tapentadol modified release products are listed under the government's Pharmaceutical Benefits Scheme, but tapentadol immediate release is not.[34] For general patients, all products cost less than the government subsidy threshold (ie, are available for less than US$30). For concession patients, the cost of tapentadol immediate release would be approximately US$14 and the subsidised price for the other products approximately US$4, with price variation across pharmacies.[35 36]

## Definitions and outcomes

### Opioid naïve patient

Consistent with the expert consensus statement on persistent postoperative opioid use,[3] this study will define opioid naïve as no opioid supplied within the 90-day period prior to surgery, as a pragmatic and previously used definition of opioid naïve that will not unnecessarily exclude cases, but will ensure that those included would not be currently opioid tolerant.

### Opioid experienced patient

Preoperative opioid use is a well-established major risk factor for persistent opioid use so opioid experienced patients are often treated as a separate patient category in persistent opioid use incidence rate studies.[3] We will classify those who have received one or more opioid dispensings within the 90-day period prior to surgery as opioid experienced. These opioid dispensings will include all types of opioid (eg, oxycodone, oxycodone-naloxone, tapentadol, codeine, tramadol, fentanyl) and formulations (eg, immediate release and modified release). Patients receiving methadone or buprenorphine in formulations indicated for opioid use disorder treatment will be excluded from the study, as their pain management requirements following surgery are likely to be different.[37]

### Persistent postoperative opioid use

The broad concept of persistence relates to the accumulation of time between initiation and discontinuation of a treatment, such as a prescribed drug.[38] There are a range of ways to potentially define this study's primary outcome of persistent postoperative opioid use.[3 39] We will define persistent use as ongoing dispensing with no more than a 60-day gap between opioid prescriptions, and examine two binary-coded persistence outcomes:[40] (1) Still receiving opioids at 3 months postsurgery, for opioid naïve patients who receive either immediate release tapentadol or immediate release oxycodone at discharge and[25 41] and (2) Still receiving opioids at 6 months postsurgery, for opioid naïve patients who receive either immediate release tapentadol or immediate release oxycodone at discharge.

### Dose escalation

Opioid dose escalation is considered an indicator of opioid tolerance and is this study's exploratory secondary outcome. Dose escalation will be defined as at least a 20% increase in average daily opioid dose between 3 months and 6 months following surgery.[42] Opioid dose will be represented in oral morphine equivalents (OME), a metric which allows for the comparison of different opioids on the same analgesic effect scale.[43] Dose escalation will be examined using three binary-coded measures: (1) Dose escalation of ≥20% between 3 and 6 months as a proportion of discharge OME; (2) Dose escalation of ≥20% at 6 months as a proportion of OME at 3 months; and for patients who were prescribed opioids prior to surgery, a third measure will be considered, consistent with the consensus statement for definition of persistence in opioid experienced patients; (3) Dose escalation of ≥20% between 3 and 6 months as a proportion of the average daily OME from 90 days prior to surgery.

## Observation period

Patients who had surgeries from approximately January 2016 to January 2021 will be identified from the hospital pharmacy database. These same patients will have data extracted from the community pharmacy database for up to 12 months prior to their surgery, and 6 months postsurgery. This perioperative community pharmacy data will allow for the identification of co-morbidities around the time of surgery and the identification of the primary outcome of persistence. Therefore, the observation period for the patients will be approximately January 2015 to July 2021. At the time of submitting this protocol in 2021, we have not yet commenced data extraction of the hospital pharmacy and community pharmacy data. We plan to extract the data, and commence data cleaning and data linkage in the first quarter of 2022, with analysis to commence in approximately March 2022.

## Data sources

### Hospital pharmacy data (site selection)

To enable inclusion of a sufficient number of patients on tapentadol and minimise risk of selection bias, we will focus on hospital pharmacies with high patient volume and common use of both oxycodone and tapentadol. We will access information on opioid volumes supplied to individual Australian hospitals through the health information and clinical research company IQVIA (iqvia.com). We will focus on private hospitals as 58% of Australian admissions involving surgeries occur in private hospitals; more specifically, two-thirds of all elective surgeries, and two-thirds of joint replacement surgeries are performed within private hospitals.[17 44] Also, public hospitals usually have hospital formularies limiting which opioids are prescribed, which may introduce bias where some opioids are second line and limited to patients with specific risk factors or contraindications.[45] We will include at least four hospital pharmacy study sites from multiple jurisdictions of Australia, associated with hospitals with at least 500 beds, to ensure we reach the proposed sample size.

### Surgical patients (study population)

The cohort will include all patients in the hospital pharmacy dataset who meet the following criteria:

1. Discharged from a surgical ward.
2. Received oxycodone or tapentadol from the hospital pharmacy following discharge from a surgical ward.

### Community pharmacy data

Data on prescriptions dispensed within Australian community pharmacies will be obtained from NostraData, a healthcare analytics and technology firm (www.nostradata.com.au). There are approximately 5800 pharmacies in Australia and the NostraData's database captures about 4500 pharmacies, more than 70% of total prescription volume from Australian community pharmacies.

For the cohort of patients who are matched with community pharmacy data, we will extract medication histories prior to surgical admission to identify covariates that may influence persistence outcomes such as opioid use histories, and medical comorbidities such as anxiety. We will use the Rx-risk algorithm, a validated measure to

determine comorbidities based on prescription medicine dispensing.[30] The RxRisk-V classification tool will be used to identify treatment for medical conditions in the 12 months prior to surgery based on ATC codes for medicines dispensed in the NostraData database, a method which as has been validated in the Australian setting.[46] In addition to determining comorbidities, we will also determine duration of pain via analysis of analgesic medications dispensed prior to surgery, examining common non-opioid prescription analgesics classes including non-steroidal anti-inflammatory drugs, gabapentinoids, and antidepressants commonly used for treatment of chronic pain (eg, duloxetine). We will examine whether these characteristics vary between the two groups prior to surgery, and control for relevant covariates in the analysis if they differ between the two patient groups.

## Data linkage

All pharmacy patient data will be de-identified. The cohort of patients treated at eligible hospital pharmacies will be matched with the community pharmacy panel based on 'hashed' Medicare card numbers. The hash algorithm converts the 11 numbers in the Medicare card number into a non-reversible 20 alphanumeric code, meaning that patients cannot be reidentified.

## Variables

Table 1 lists the main study variables. Where data are available from both community and hospital pharmacy sources, we will include both in the linked database and use it as a validity check.

## Analysis plan

### Descriptives

Data cleaning will follow standard pharmacoepidemiology algorithms for processing prescription data into patient binary exposure status.[40] Descriptive statistics of postoperative opioid use will be presented in means, medians and percentages for quantities/dosages/OME by patient type (opioid naïve or opioid experienced) and type of discharge opioid (oxycodone or tapentadol). Days of postsurgical opioid use and types of opioid used will be presented in the form of means, median values and density plots.

**Table 1** List of variables to be considered

| Variable | Type of pharmacy data | | Description/considerations |
|---|---|---|---|
| | Hospital | Community | |
| Age | ✓ | ✓ | Patient age at time of surgery, calculated from date of birth. |
| Sex | ✓ | ✓ | |
| Ward specialty (discharge ward as proxy for surgery type) | ✓ | | The ward type will include the type of surgical ward the patient was discharged from—broad categories such as orthopaedic, general medicine, plastics and neurosurgery. |
| Comorbidities | | ✓ | Using Rx risk algorithm. Medication mapped categories include conditions associated with persistence risk such as anxiety, depression, pain and alcohol dependency.[3 30] Of note is that pain catastrophising is correlated with other negative effects such as anxiety and depression[30 52 53] and medications for anxiety may be interpreted as a proxy for pain catastrophising. |
| Prior opioid use | | ✓ | Any prescribed opioid use in the 12 months prior to surgery |
| Quantity of opioids supplied | ✓ | ✓ | 1. Quantity of tablets<br>2. Dosage of opioid (eg, 5 mg)<br>3. Total opioid quantity supplied in dispensing (tablet number multiplied by the dosage)<br>4. Total opioid quantity dispensed in oral morphine equivalent |
| Pain duration | | ✓ | Analgesic medications in the 12 months prior to surgery. Duration of continuous analgesia as a proxy for chronic pain. |
| Socioeconomic status (SES) (SEIFA proxy) | ✓ | ✓ | The Socio-Economic Indexes for Areas (SEIFA) is calculated by the Australian Bureau of Statistics using over a dozen census data points such as household income, and proportion of people with postschool qualifications.[54] It is commonly used in epidemiology as a robust proxy for SES.[50 51] The primary SEIFA allocated to a participant will be based on their postcode at time of surgery. |
| Socioeconomic status (concession card proxy) | ✓ | ✓ | Certain Pharmaceutical Benefit Scheme patients hold concession cards such as the 'Healthcare card', available to individuals who receive welfare payments or other types of government benefit.[55] The concession status allocated to the participant will be based on their status at time of surgery. |

### Hypothesis 1: comparing the rates of persistent opioid use between groups

This analysis will estimate differences in persistent opioid use between postoperative patients prescribed oxycodone and those prescribed tapentadol.

Differences in incidence of persistent opioid use at 3 months and 6 months postsurgery between patients supplied oxycodone compared with those prescribed tapentadol at discharge will be expressed as Incidence Risk Ratio derived from Poisson/negative binomial multivariable regressions. A range of co-variates have been established to be related to postsurgical persistence including patient characteristics (age, comorbidity, pain duration, concurrent medications, socioeconomic status) and clinical characteristics such as broad surgery type.[8 9 11–13 25 47] Reliably captured covariates will be included in our regression analyses.

To further explore the predictors of persistent opioid use, two hierarchical logistic regression models will be developed: one to explore predictors of persistent opioid use at 3 months postsurgery, and the second to explore persistent use at 6 months postsurgery. Each model will have two nested models—the first model will contain only covariates such as patient demographics, and the second main-effects model will contain the covariates and opioid-specific variables (eg, prior opioid use and type of opioid supplied at discharge). Sensitivity analyses will test the interaction between patient type and type of prescribed opioids.

### Hypothesis 2: comparing dose escalation between groups

This analysis will be performed to examine the dose escalation among patients prescribed postsurgical oxycodone compared with tapentadol. The risks of dose escalation for patients discharged with oxycodone relative to those discharged with tapentadol will be expressed as HR derived from Cox regression models. Study groups will be dummy-coded. The regression analysis will control for relevant covariates (eg, age, opioid experience and other patient characteristics, gender, surgery type). Sensitivity analysis will test the interaction between patient type and type of prescribed opioids.

## Sample size

We will aim to identify at least 6000 patients who have been discharged following surgery with prescription opioids, with approximately half (ie, n=3000) expected to be opioid naïve[48] and half opioid experienced patients.

Given the 70% coverage of the community pharmacy database of Australian prescriptions (www.nostradata.com.au), a sample size of 3000 will lead to an estimated 2100 linked participants in each sample group (ie, opioid naïve and opioid experienced patients). Based on known patient numbers discharged with tapentadol at proposed study sides, these numbers are feasible, and will allow a sample size of at least 2000 opioid naïve patients and 2000 opioid experienced patients to be discharged on oxycodone and tapentadol respectively, who are able to be linked with hospital pharmacy data.

We will specifically test the hypothesis that persistent opioid use will be lower with tapentadol compared with conventional opioids. Current estimates of persistent opioid use in opioid naïve people range from 6% to 10% postdischarge. We propose that this would be lower (estimated at 3% if tapentadol is associated with a meaningful reduction in persistent opioid use, from 6% to 3%). As persistence in opioid use is predominantly driven by individual factors outlined above we have calculated our sample size estimate assuming independence between individuals from common sites. To enable 90% power to detect a minimum of a 3% change in persistent opioid use following specific surgeries between those receiving tapentadol and conventional opioids we would need a sample size of at least 2004 people for subgroup analysis.

## Ethics

Ethics approval has been obtained through the Monash University Human Research Ethics Committee (29977).

## Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

## Data statement

Researchers interested in using these data may approach data custodians at NostraData and Icon. Access fees for data and/or analyses may apply.

## Dissemination

We will present project findings in a peer-reviewed journal article as well as at relevant scientific conferences. Findings will be reported in accordance with the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement, an extension of the The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement for reporting items specific to observational studies using routinely collected health data.[49] Data will be stored on NostraData's servers. Request to access the data can be made through the Monash University research team.

# DISCUSSION

This study aims to compare the rates of postsurgical opioid persistence between oxycodone and tapentadol using linked Australian hospital and community pharmacy data.

## Strengths

This study will be using a novel linkage to produce a unique dataset that will allow for a patient observation period that considers co-comorbidities from up to 12 months prior to surgery, and outcomes 6 months postsurgery. The linked dataset is distinct from the more commonly used Pharmaceutical Benefits Scheme (government subsidy)

database, as it will cover all opioids, such as the newer atypical opioid, tapentadol IR, which is not subsidised under the Scheme.

We use common definitions of persistence, and where there are multiple definitions we will use sensitivity analyses to examine whether different definitions change our conclusions.

This study will contribute to the limited current literature on opioid-specific persistence, especially as it considers the newer atypical opioid tapentadol. This is likely one of the largest international cohorts of real-world outcomes for tapentadol patients. Further, this study will comprise one of the largest Australian samples on persistence, collected from multiple sites and across multiple jurisdictions.

## Limitations

This study, similar to the majority of studies on persistence, will be retrospective with data from prescription databases,[3] so may not reflect actual opioid consumption by patients. For example, patients may have filled a prescription without using the medication. However, where patients have not used their initial medication, it is unlikely they would seek further supplies.

Surgery patients with unlinked community pharmacy data may reflect instances where they had their prescriptions filled in pharmacies not captured by the study's community pharmacy database, or where patients did not fill a prescription (other than their hospital pharmacy prescription) during the observation period. However, we do not believe this would bias the findings as there is no reason why these patients would be more likely to be prescribed one opioid of interest over the other.

This study will capture prescription analgesia use. Some forms of lower-strength analgesia such as lower-dose non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol are available without a prescription in pharmacies, and in some cases, supermarkets. Most of these lower strength purchases will not be captured in the community pharmacy database.

Risk factors previously reported to modify risk of persistent postoperative opioid use such as tobacco use, opioid use disorder, and specific surgery type may not be available through the study's prescription-based datasets unless patients have been prescribed medications for them (such as acamprosate for substance use disorder). Though the majority of surgeries occur within private hospitals, the demographics of this population skew toward advantage and the results may not be representative of the general population.[17] Similarly, as tapentadol IR is not government subsidised, the population receiving tapentadol IR may skew toward advantage. We will recruit both opioid groups from the same sites, and will use a robust proxy[50 51] to describe our cohort and control for socioeconomic status in our analyses.

In conclusion, this study will examine the research question of whether postsurgical persistence varies according to opioid type, with one of the largest samples of tapentadol patients, while controlling for a variety of known risk factors such as opioid experience.

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**Contributors** SN, NB, TL, JE, TX and JS conceptualised the study with input into the study design from JE, MdG and DIL. TL and SN wrote the initial draft, which was revised with input from in collaboration with all authors. SN and TX developed the analysis plan with input from all authors. All authors read and approved the revised protocol manuscript.

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**Disclaimer** The funders will have no role in the study design, study conduct, analysis or data interpretation. Prior to publication, Seqirus will have the opportunity to review the manuscript and provide comment on factual inaccuracies, if identified.

**Competing interests** TL, SN and DL have been investigators on untied education grants from Seqirus (CSL). In the past 5 years, SN has been an investigator on untied education grants from Indivior, unrelated to the current work. SN has provided training to healthcare professionals on identifying and treating codeine dependence for which her institution has received payment from Indivior. DL has received speaking honoraria from the following: Astra Zeneca, Indivior, Janssen-Cilag, Lundbeck, Servier and Shire, and has participated on Advisory Boards for Indivior and Lundbeck.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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