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Opioid Use and Harms Associated with a Sustained-Released Tapentadol Formulation: A Post-Marketing Study Protocol

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ABSTRACT

Introduction: It has been argued that pharmacologically tapentadol may have lower abuse potential than other pharmaceutical opioids currently available. However, there has been no comprehensive triangulation of data regarding use and harms associated with this formulation. A sustained-release formulation (SRF) of tapentadol (Palexia®) was released in Australia in 2011 and listed for public subsidy in 2013. We summarise here the methods of a post-marketing study which will measure post-introduction: i) population level availability, ii) extra-medical use and diversion, iii) attractiveness for extra-medical use, and iv) associated harms, of tapentadol compared against other pharmaceutical opioids.

Methods and Analysis: We evaluated key sources on pharmaceutical use and harms in Australia, and were limited to triangulating data from four sources that disaggregate pharmaceutical opioid formulations and captured the tapentadol SRF. These data sources comprised: i) national pharmaceutical opioid community sales data from 2011-2017, ii) national pharmaceutical opioid poisonings reported to Poison Information Centres from 2011-2017, iii) number of vendors on online marketplaces listing pharmaceutical opioids for sale, and iv) data on pharmaceutical opioid extra-medical use, attractiveness, and harms from interviews with people who inject drugs in Australia.

Ethics and Dissemination: Ethics approval is not required for use of pharmaceutical sales data. Ethics approval has been obtained for use of national pharmaceutical opioid poisonings reported to Poison Information Centres (LNR/16/SCHN/44) and for use of online marketplace data and interview data from people who inject drugs (HC12086). Key findings will be published mid-2018 in a peer-reviewed academic journal, and presented at various conferences and professional meetings.

Keywords: opioid; tapentadol; overdose; tamper; substance misuse; harm

STRENGTHS AND LIMITATIONS

- This study will comprise the first published comprehensive assessment of tapentadol SRF use, extra-medical use, attractiveness for extra-medical use, and associated harms.
- The number of data sources is limited relative to other post-marketing studies of pharmaceutical opioids as tapentadol is rarely coded separate to other pharmaceutical opioids in administrative data.
- However, this study will overview a wealth of data from the general population and a group at high risk for extra-medical use, both of which are key to examine when quantifying various impacts of pharmaceutical opioids.
- These findings will have relevance to other countries where tapentadol has recently been introduced or where it may be introduced in the future.

INTRODUCTION

In the past two decades, there has been an increase in the number of pharmaceutical opioids available, and in the prescribing of these drugs, in several high-income countries, including North America and Australia [1]. Indeed, between 1992-2012 the number of pharmaceutical opioid dispensing episodes increased fifteen-fold in Australia [2]. This increase in availability in Australia has been accompanied by greater rates of extra-medical use, defined as use outside the bounds of a doctor's prescription [3]. The risk of opioid dependence and serious adverse events (e.g., overdose) associated with extra-medical use has made addressing this problem a public health imperative [4 5].

Opioids differ in the extent to which they are likely to be associated with hazardous patterns of use due to different potencies (i.e., weak to strong opioids), pharmacokinetic characteristics (e.g., rate of metabolism) and propensities for dependence [6]. The need to reduce extra-medical use must also be balanced against the need for access to opioid therapy for pain. Thus, current public health agency strategies to reduce extra-medical pharmaceutical opioid use and chronic pain prescribing guidelines focus on products which have limited or no abuse potential [7 8].

Tapentadol is a centrally acting opioid analgesic with dual mechanisms of action, specifically μ-opioid receptor agonist and noradrenaline reuptake inhibition. This dual action is thought to result in a lower dose required to produce a given level of analgesia [9]. Clinical trials suggest that tapentadol provides equivalent or superior levels of pain relief for acute and chronic pain similar to oxycodone and morphine, with greater gastro-intestinal tolerability in terms of reduced rates of nausea, vomiting, and constipation [10-13].

A recent review by the World Health Organization's Expert Committee on Drug Dependence [11] concluded that potential for abuse for tapentadol may be similar to or slightly lower than other opioids such as hydromorphone, oxycodone, morphine and tramadol. However, they note that these conclusions are tentative given a lack of data regarding tapentadol "abuse, dependence, diversion, recreational use, or poison control", noting that tapentadol generally does not feature in drug use surveys or surveillance reports. The few studies which have been conducted are based on US samples, and using treatment-seeking populations [14] or evaluation of internet discussions [15 16] and prescribing data [17] to assess extra-medical use, with early indications of rates of abuse and diversion equivalent to hydromorphone and lower than oxycodone and most other strong opioids [14 18].

The immediate release form of tapentadol is registered in Australia for moderate to severe pain, while the sustained release form is registered for severe pain which requires constant opioid treatment and for which no other opioid other treatments are adequate [19]. Although a sustained-release formulation of tapentadol (SRF; Palexia® SR) was released in Australia in 2011, and listed for subsidy on the Pharmaceutical Benefits Scheme in November 2013 [20], no research into rates into dispensing, extra-medical use, and associated harms of the tapentadol SRF has been undertaken in Australia. Given the broader context of rising rates of pharmaceutical opioid use and harms (including overdose), monitoring new formulations in terms of population level pharmaceutical opioid use, and extra-medical use amongst high risk populations (e.g., those reporting extra-medical use of other pharmaceutical use) is critical.

This paper outlines the design for a national post-marketing study of use, extra-medical use, and harms associated with introduction of the tapentadol SRF in Australia. This study will integrate population and sentinel high-risk population data, including national pharmaceutical opioid sales data, interviews with people who inject drugs, and national opioid-related poisoning event data.

METHODS AND ANALYSIS

Study aims

The overarching aim of this study is to identify extra-medical use and diversion of tapentadol SRF, attractiveness for extra-medical use, and associated levels of harms compared to these indicators for other pharmaceutical opioid use. The specific questions we aim to answer are as follows:

1. What is the population level availability of the tapentadol SRF in Australia relative to other pharmaceutical opioids?
2. Are there indications of extra-medical use of the tapentadol SRF (specifically, non-prescribed use, use via routes that require tampering), and how does this compare to other pharmaceutical opioids?
3. What is the relative attractiveness for extra-medical use (i.e., street price) of the tapentadol SRF, and how does this compare to other pharmaceutical opioids?
4. Are there indications of associated harm with the tapentadol SRF (specifically, self-reported non-fatal overdose, as well as intentional poisoning, extra-medical use and abuse as identified through poison information centre data), and how does this compare to other pharmaceutical opioids?

Study design and setting

This study is being conducted in Australia. There are three main components of this study: analyses of existing routine data sources (2011-2017); analyses of data from monitoring online drug marketplaces (2013-2017); and analyses of cross-sectional data collected from a high-risk sentinel group (people who inject drugs) participating in the Illicit Drug Reporting System (IDRS) in 2016.

Most indicator data sets in Australia do not routinely separate tapentadol from other pharmaceutical opioids, precluding any comparison of population-level availability (see Appendix 1). Five data sources were identified which could provide data specific to pharmaceutical opioid brand, thus allowing analysis of use and harms related to tapentadol SRF. Prescription monitoring programme data, although theoretically useful, only exist in one jurisdiction, where registration is voluntary and implementation is not complete or consistent, and utilisation of this programme irregular. Consequently, four data sources were included in this study: pharmaceutical opioid sales data; poison information centre call data; online drug marketplace data; and interviews with people who inject drugs. **Table 1** outlines the relevant outcome for each data source for each research question.

Table 1 approximately here

Pharmaceutical opioid sales data

A third-party access request to obtain pharmaceutical sales data in Australia was approved by IMS Health. These data include all pharmaceutical opioid purchases through pharmaceutical wholesalers and manufacturers who sold direct to pharmacies between 2011 and 2017. Data reflects community sales only, excluding sales to hospitals. However, due to the legal requirements for secure storage of pharmaceuticals in pharmacies, and monitoring and recording of opioids depending on their schedule listing, the number of packs sold over a 12 month period closely approximates the number used.

All opioids available in Australia that are indicated for pain can be included and coded according to the World Health Organization's Anatomical Therapeutic Classification system code of A02A 'opioids' and A02B ''other analgesics and antipyretics'. This includes, but is not limited to, tapentadol (N02AX06), buprenorphine (N02AE01), prescription and over-the-counter codeine (N02BA51, N02BE51, N02AA59, R05DA04), dextropropoxyphene (N02AC04, N02AC54), fentanyl (N02AB03), hydromorphone (N02AA03), methadone (N02AC52), morphine (N02AA01), and oxycodone

(N02AA05, N02AA55). Injectable formulations are excluded, being mainly prescribed in hospitals, and formulations of methadone and buprenorphine used solely for the treatment of opioid dependence are excluded. However, over-the-counter codeine is captured in this data source. IMS Health data can be provided from January 2011 to December 2017 aggregated monthly broken down by opioid formulation, brand, strength, and geographic unit.

Poison Information Centre call data

Four Poison Information Centres (PICs) in Australia, based in New South Wales, Queensland, Victoria and Western Australia, together provide nationwide, round-the-clock poisoning advice to healthcare professionals and members of the public. National data will be extracted regarding number of cases of pharmaceutical opioid exposure poisonings (including over-the-counter codeine) reported to PICs. Specifically, opioid-related calls will only be extracted where the exposure type/intent is coded as 'recreational', so as to identify exposures where pharmaceutical opioids were taken for its intoxicating effects [21]. Where the intentional exposure subtype is not available or unclear, calls regarding opioids will undergo a free-text search for markers of extra-medical use and abuse (defined here as use of a drug in a way or for a purpose outside intended medical use, e.g., excess quantity, recreational use, use for non-approved purposes), then manually reviewed by PIC staff and recoded.

Unit-level data collected between January 2011 and December 2017 will be extracted. Data fields to be extracted include call date, age group, gender, state/territory, dose, brand, active ingredients, and route of exposure.

Online drug marketplace data

An existing surveillance system in Australia monitors availability and types of substances sold online via the darknet [22 23]. The darknet is accessible only via The Onion Router (TOR), software that enables anonymous communication. Cryptomarkets (markets operating on the darknet) have been accessed weekly since 2013 using a dedicated user account. Exhaustive snapshots of each accessible marketplace are taken, including details of vendor name, listing description and, where possible, country of origin. For this study, the number of vendors listing illicit pharmaceutical opioids for sale on cryptomarkets between January 2013 and December 2017 will be extracted by brand and by month. This data cannot provide any information about consumers who are buying drugs on the cryptomarkets, or any data on the total number of sales via these sites. However, it does yield timely and sensitive information regarding drug availability online.

Illicit Drug Reporting System data

The Illicit Drug Reporting System (IDRS) is a national illicit drug monitoring system, one part of which comprises annual interviews with ~900 people who inject drugs interviewed in each capital city in Australia. Participants are recruited using multiple methods, including advertisements in street press, newspapers, treatment agencies, needle and syringe programs, and peer referral. To be eligible to participate, participants need to be at least 17 years of age; have injected at least monthly during the six months preceding interview; and have been a resident for at least 12 months in the capital city in which they are interviewed. The interview is administered by trained research staff face-to-face at a time and location convenient to them, and participants receive $AUD40 reimbursement.

The core quantitative interview monitors patterns of drug use and includes questions on price, purity and availability of the main drug types, including pharmaceutical opioids [24]. Data will be used from the 2017 interview (conducted May-June 2017), which included additional items around tapentadol SRF use. These items pertained to:

- Levels of tapentadol extra-medical use: diverted Palexia® SR, swallowed, injected, smoked, snorted (past six month use and number of days)
- Other opioid use (pharmaceuticals and heroin): swallowed, injected, smoked, snorted (past six month use and number of days)
- Street (diverted) price and perceived availability of diverted tapentadol and other opioids
- Attractiveness of tapentadol for use via injection
- Overdose (each opioid).

Data analysis

Population-level data

Opioid utilisation (IMS Health) and intentional pharmaceutical opioid exposure poisonings (PIC) data will be presented graphically over time by opioid type, opioid formulation and, where available tablet strength (nationally and by jurisdiction). Opioid utilisation data will be presented as number of packs and number of oral morphine equivalent (OME) grams; the latter will be computed using published conversion guidelines [25]. Percentage of total OME/packs will be calculated for tapentadol and other opioid formulations to graph the underlying rate of sales. Trends over time in tapentadol sales will be assessed using negative binomial or poison generalised estimating equations (to take into account non-independence), including variables to account for time/seasonality.

PIC data will be presented as rates of intentional pharmaceutical opioid exposure poisonings using IMS sales data as the denominator; specifically, rates per 100,000 OME grams and per 1,000 packs distributed per month. Trends over time in tapentadol exposures will also be modelled using generalised estimating equations.

Various comparators will be used for these analyses, including specific pharmaceutical opioid formulations (e.g., tramadol, oxycodone), and opioids grouped as per WHO guidelines [26] into *strong prescription opioids* (buprenorphine, fentanyl, hydromorphone, methadone, morphine and oxycodone; all listed as 'Schedule 8' opioids in Australian classification of medicines and poisons), *other prescription opioids* (prescribed codeine, dextropropoxyphene, and tramadol; 'Schedule 4' in Australia) and *over-the-counter opioids* (codeine products available at pharmacies without a prescription).

Sentinel data

Cryptomarket and IDRS data will be described using descriptive statistics, with the former graphed as number of vendors for SRF tapentadol and other pharmaceutical opioid formulations by month. Parametric and non-parametric tests of significance, as well as measures of effect size, will be used to describe differences in rates of extra-medical use, diversion, attractiveness, and overdose for tapentadol versus other opioid formulations.

ETHICS AND DISSEMINATION

The authors confirm ethics approval is not required for pharmaceutical sales data. The IDRS has received ethical approval from the University of New South Wales Human Research Ethics Committee (HC12086), as well as from the relevant ethics committees in each jurisdiction. Participants provided informed consent prior to completing the interview. The Sydney Children's Hospitals Network Human Research Ethics Committee has approved the use of data collected by the PIC (*Retrospective review of incidence and toxicity of various exposures from calls to Australian Poisons Information Centres*; LNR/16/SCHN/44).

We plan to publish our findings mid-2018 in a peer-reviewed journal article as per the data sources and outcomes listed in Table 1 and research questions specified in the aims above, and these findings will also be presented at conferences. Publications will comply with STROBE guidelines [27]. Restrictions will apply to the availability of these data as they are used with approval from data

custodians for the purposes of this study, but they may be available following approval from the researchers, custodians of the data, and any other involved third party.

DISCUSSION

This post-marketing study forms part of a growing body of literature detailing comprehensive and transparent monitoring of specific pharmaceutical opioid formulations in regards to key indicators of use, extra-medical use, and harms [28]. Concern is growing regarding rates of pharmaceutical opioid extra-medical use and harms. Consequently, it is important to determine how shifts in the pharmaceutical opioid market, including availability of new formulations, plays out in terms of these outcomes. There has been no such undertaking for tapentadol globally, despite availability in the US for nearly a decade, and indications of a small but growing pharmaceutical opioid market share [17], making the current study critical.

It should be noted that this study is limited in terms of the number of available data sources relative to other post-marketing studies [28]. However, this is a systems-level issue, as tapentadol is not differentiated from other pharmaceutical opioids in most healthcare and law enforcement data coding systems. There are a number of limitations to the chosen data sources as well, primarily: that IMS Health sales data does not index the number of individuals prescribed opioids, nor does PIC data index all individuals with an adverse event, captured in other healthcare sources. However, IMS data is estimated to cover over 94% of all sales nationally [29], making it strong index of pharmaceutical opioid exposure in the community. Similarly, PIC data has complete coverage nationally and captures details related to type of exposure and dose critical to understanding risk of adverse exposure. We would also argue that online drug marketplace data and IDRS are necessary and key sentinel data sources, being established to identify emerging trends in drug use. IDRS participants typically report injecting heroin, methamphetamine and/or pharmaceutical opioids [24], making valid comparison across these substances and across jurisdictions with varying levels of heroin and pharmaceutical opioid availability.

In light of these strengths, we think that triangulation of these sources will provide a clear picture of tapentadol use, extra-medical use, attractiveness and associated harms. We believe these findings will be critical to understanding possible risks in terms of extra-medical use and harms if tapentadol prescribing increases. More broadly though, these findings will help to enhance understanding as to the impact changes in the pharmaceutical opioid market can have on extra-medical use and harms from a policy, industry, clinician and research perspective.

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COMPETING INTERESTS

Some of the investigators have received investigator-initiated untied educational grants from Reckitt Benckiser/Indivior for studies of buprenorphine-naloxone (BL, LD), buprenorphine depot (BL, LD, MF), naloxone (LD, MF), the development of an opioid-related behavior scale (BL, LD), the pharmacogenetic predictors of treatment success (RA), and a study of opioid substitution therapy uptake among chronic non-cancer pain patients (BL, LD). Some of the investigators have also received investigator-initiated untied educational grants from Mundipharma for post-marketing surveillance of a tamper-resistant opioid formulation (AP, BL, LD, MF).

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AUTHORS' CONTRIBUTIONS

LD, AP, BL, MF, NB, and RC contributed to the development of the study for the purposes of the funding proposal and development of the study design. LD, AP, and BL led writing of the first draft. All authors contributed to the critical review of the manuscript. All authors read and approved the final manuscript.

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3480E-4349X-5163R-5168B-5169C-5170D-5237P-5238Q-5239R-5391R-5393W-5394X-8035X-8146R-8305D-8306E-8349K-8453X-8454Y-8489T-8490W-8491X-8492Y-8493B-8494C-8669G-8670H accessed 29 July 2017.

Table 1: Summary of the primary outcomes from each data source

Research outcome	Pharmaceutical opioid sales data	Interviews with people who inject drugs	Online drug marketplace data	Poisons Information Centre calls
Research Question 1: Exposure				
Population level availability				
Research Question 2: Extra-Medical Use				
Levels of extra-medical use (diverted)				
Injection				
Snorting				
Chewing				
Perceived availability (diverted)				
Research Question 3: Attractiveness				
Attractiveness for extra-medical use (market value)				
Research Question 4: Harms				
Overdose - non-fatal				
Intentional exposure (intentional self-poisoning, misuse, and abuse)				

Appendix 1. Data Sources Reviewed for Inclusion

Source	Sample	Geographic Coverage[1]	Distinguishes opioid type[2]	Distinguishes opioid brand	Comments
Annual/Repeated Data Collections					
National Drug Strategy Household Survey (NDSHS)	Population	National and all states/territories	Yes	No	
National Survey of Mental Health and Wellbeing (NSMHWB)	Population	National and all states/territories	No	No	
Wastewater data	Population	National and all states/territories	Yes	No	
Ecstasy and Related Drug Reporting System (EDRS) interviews	High-risk sentinel	National and all states/territories	Yes	No	
Illicit Drug Reporting System (IDRS) interviews	High-risk sentinel	National and all states/territories	Yes	Yes	Gives opioid type, strength and brand, and includes OTC codeine. Data available from 2017 only
Drug Use Monitoring in Australia (DUMA)	High-risk sentinel	NSW, QLD, SA, WA	Yes	No	
Australian NSP survey	High-risk sentinel	National and all states/territories	Yes	No	
Women and Sexual Health Survey (SWASH)	High-risk sentinel	NSW and WA	No	No	
Gay Community Periodic Survey	High-risk sentinel	SA, ACT, VIC, WA, QLD, NSW, TAS	No	No	
Sales and Dispensing Data Collections					
Prescription sales data	Population	National and all states/territories	Yes	Yes	Gives opioid type, strength and brand, and includes OTC codeine
Pharmaceutical Benefits Scheme	Population	National and all states/territories	Yes	Depends on the opioid type/dose	Item codes for pharmaceutical opioids (the unit by which data can be extracted) do not differentiate by brand where multiple brands offer products of the same strength (e.g., four different brands of morphine products fall under item code '1653B: morphine sulfate 10mg modified release tablet') [30]. Further, only medicines contained in the Schedule of Pharmaceutical Benefits appear in these statistics (excluding over-the-counter codeine), and SRF tapentadol was only listed on the Schedule two years post-introduction (in 2013).
Medicare Benefits Scheme	Population	National and all states/territories	No	No	
Administrative Data Collections					
Poison Information Centre call data	Population	All states/territories	Yes	Yes	Gives opioid type, strength and brand where these characteristics can be identified by the caller, and includes OTC codeine
Ambulance data collections	Population	All states/territories	No	No	
Emergency department data collections	Population	All states/territories	Depends on the coding system	No	
Admitted patient data collections	Population	National and all states/territories	No	No	
Mortality data	Population	National and all states/territories	No	No	
Mental health ambulatory data collections	Population	NSW, VIC, TAS, WA	No	No	
Alcohol and drug treatment helpline calls	Population	All states/territories	Depends on the coding system	No	
Needle-syringe programme data	High-risk sentinel	National and all states/territories	Depends on the coding system	No	
Medically-supervised injecting clinic data	High-risk sentinel	NSW	Depends on the coding system	No	
Prescription monitoring programme data	High-risk sentinel	TAS	Yes	Yes	Incomplete coverage with continued implementation of the programme, with voluntary opt in by pharmacists and general practitioners, and no requirement for use for every

					dispensing episode.
Pharmacotherapy program data	Population	National and all states/territories	Yes	No	
Alcohol and drug treatment services data	Population	National and all states/territories	Yes	No	
Arrest data	Population	National and all states/territories	Yes	No	
Seizure data	Population	National and all states/territories	Yes	No	
Street price data	Population	National and all states/territories	Yes	No	
Criminal court data	Population	National and all states/territories	Yes	No	
Online Monitoring					
Online marketplace monitoring	High-risk sentinel	National	Yes	Yes	Gives opioid brand/dose for sale on online marketplaces. Data is only available from early 2013.

Note. [1] National: collated and reported at national level only; National and all states/territories: collated and reported at national and state/territory-level; All states/territories: collated and reported at the state/territory level only. [2] Distinguishes between types of opioids (e.g., morphine and oxycodone). NSW: New South Wales; QLD: Queensland; SA: South Australia; WA: Western Australia; TAS: Tasmania; Australian Capital Territory; VIC: Victoria.

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Opioid Use and Harms Associated with a Sustained-Released Tapentadol Formulation: A Post-Marketing Study Protocol

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ABSTRACT

Introduction: It has been argued that pharmacologically tapentadol may have lower abuse potential than other pharmaceutical opioids currently available. However, there has been no comprehensive triangulation of data regarding use and harms associated with this formulation. A sustained-release formulation (SRF) of tapentadol (Palexia®) was released in Australia in 2011 and listed for public subsidy in 2013. We summarise here the methods of a post-marketing study which will measure post-introduction: i) population level availability, ii) extra-medical use and diversion, iii) attractiveness for extra-medical use, and iv) associated harms, of tapentadol compared against other pharmaceutical opioids.

Methods and Analysis: We evaluated key sources on pharmaceutical use and harms in Australia, and were limited to triangulating data from four sources that disaggregate pharmaceutical opioid formulations and captured the tapentadol SRF. These data sources comprised: i) national pharmaceutical opioid community sales data from 2011-2017, ii) national pharmaceutical opioid poisonings reported to Poison Information Centres from 2011-2017, iii) number of vendors on online marketplaces listing pharmaceutical opioids for sale, and iv) data on pharmaceutical opioid extra-medical use, attractiveness, and harms from interviews with people who inject drugs in Australia.

Ethics and Dissemination: Ethics approval is not required for use of pharmaceutical sales data. Ethics approval has been obtained for use of national pharmaceutical opioid poisonings reported to Poison Information Centres (LNR/16/SCHN/44) and for use of online marketplace data and interview data from people who inject drugs (HC12086). Key findings will be published mid-2018 in a peer-reviewed academic journal, and presented at various conferences and professional meetings.

Keywords: opioid; tapentadol; overdose; tamper; substance misuse; harm

STRENGTHS AND LIMITATIONS

- This study will comprise the first published comprehensive assessment of tapentadol SRF use, extra-medical use, attractiveness for extra-medical use, and associated harms.
- The number of data sources is limited relative to other post-marketing studies of pharmaceutical opioids as tapentadol is rarely coded separate to other pharmaceutical opioids in administrative data.
- However, this study will overview a wealth of data from the general population and a group at high risk for extra-medical use, both of which are key to examine when quantifying various impacts of pharmaceutical opioids.
- These findings will have relevance to other countries where tapentadol has recently been introduced or where it may be introduced in the future.

INTRODUCTION

In the past two decades, there has been an increase in the number of pharmaceutical opioids available, and in the prescribing of these drugs, in several high-income countries, including North America and Australia [1]. Indeed, between 1992-2012 the number of pharmaceutical opioid dispensing episodes increased fifteen-fold in Australia [2]. This increase in availability in Australia has been accompanied by greater rates of extra-medical use, defined as use outside the bounds of a doctor's prescription [3]. The risk of opioid dependence and serious adverse events (e.g., overdose) associated with extra-medical use has made addressing this problem a public health imperative [4 5].

Opioids differ in the extent to which they are likely to be associated with hazardous patterns of use due to different potencies (i.e., weak to strong opioids), pharmacokinetic characteristics (e.g., rate of metabolism) and propensities for dependence [6]. The need to reduce extra-medical use must also be balanced against the need for access to opioid therapy for pain. Thus, current public health agency strategies to reduce extra-medical pharmaceutical opioid use and chronic pain prescribing guidelines focus on products which have limited or no abuse potential [7 8].

Tapentadol is a centrally acting opioid analgesic with dual mechanisms of action, specifically μ-opioid receptor agonist and noradrenaline reuptake inhibition. This dual action is thought to result in a lower dose required to produce a given level of analgesia [9]. Clinical trials suggest that tapentadol provides equivalent or superior levels of pain relief for acute and chronic pain similar to oxycodone and morphine, with greater gastro-intestinal tolerability in terms of reduced rates of nausea, vomiting, and constipation [10-13].

A recent review by the World Health Organization's Expert Committee on Drug Dependence [11] concluded that potential for abuse for tapentadol may be similar to or slightly lower than other opioids such as hydromorphone, oxycodone, morphine and tramadol. However, they note that these conclusions are tentative given a lack of data regarding tapentadol "abuse, dependence, diversion, recreational use, or poison control", noting that tapentadol generally does not feature in drug use surveys or surveillance reports. The few studies which have been conducted are based on US samples, and using treatment-seeking populations [14] or evaluation of internet discussions [15 16] and prescribing data [17] to assess extra-medical use, with early indications of rates of abuse and diversion equivalent to hydromorphone and lower than oxycodone and most other strong opioids [14 18].

The immediate release form of tapentadol is registered in Australia for moderate to severe pain, while the sustained release form is registered for severe pain which requires constant opioid treatment and for which no other opioid other treatments are adequate [19]. Although a sustained-release formulation of tapentadol (SRF; Palexia® SR) was released in Australia in 2011, and listed for subsidy on the Pharmaceutical Benefits Scheme in November 2013 [20], no research into rates into dispensing, extra-medical use, and associated harms of the tapentadol SRF has been undertaken in Australia. Given the broader context of rising rates of pharmaceutical opioid use and harms (including overdose), monitoring new formulations in terms of population level pharmaceutical opioid use, and extra-medical use amongst high risk populations (e.g., those reporting extra-medical use of other pharmaceutical use) is critical.

This paper outlines the design for a national post-marketing study of use, extra-medical use, and harms associated with introduction of the tapentadol SRF in Australia. This study will integrate population and sentinel high-risk population data, including national pharmaceutical opioid sales data, interviews with people who inject drugs, and national opioid-related poisoning event data.

METHODS AND ANALYSIS

Study aims

The overarching aim of this study is to identify extra-medical use and diversion of tapentadol SRF, attractiveness for extra-medical use, and associated levels of harms compared to these indicators for other pharmaceutical opioid use. The specific questions we aim to answer are as follows:

1. What is the population level availability of the tapentadol SRF in Australia relative to other pharmaceutical opioids?
2. Are there indications of extra-medical use of the tapentadol SRF (specifically, non-prescribed use, use via routes that require tampering), and how does this compare to other pharmaceutical opioids?
3. What is the relative attractiveness for extra-medical use (e.g., street price) of the tapentadol SRF, and how does this compare to other pharmaceutical opioids?
4. Are there indications of associated harm with the tapentadol SRF (specifically, self-reported non-fatal overdose, as well as intentional poisoning, extra-medical use and abuse as identified through poison information centre data), and how does this compare to other pharmaceutical opioids?

Study design and setting

This study is being conducted in Australia. There are three main components of this study: analyses of existing routine data sources (2011-2017); analyses of data from monitoring online drug marketplaces (2013-2017); and analyses of cross-sectional data collected from a high-risk sentinel group (people who inject drugs) participating in the Illicit Drug Reporting System (IDRS) in 2016.

Most indicator data sets in Australia do not routinely separate tapentadol from other pharmaceutical opioids, precluding any comparison of population-level availability (see Appendix 1). Five data sources were identified which could provide data specific to pharmaceutical opioid brand, thus allowing analysis of use and harms related to tapentadol SRF. Prescription monitoring programme data, although theoretically useful, only exist in one jurisdiction, where registration is voluntary and implementation is not complete or consistent, and utilisation of this programme irregular. Consequently, four data sources were included in this study: pharmaceutical opioid sales data; poison information centre call data; online drug marketplace data; and interviews with people who inject drugs. **Table 1** outlines the relevant outcome for each data source for each research question.

Table 1 approximately here

Pharmaceutical opioid sales data

A third-party access request to obtain pharmaceutical sales data in Australia was approved by IMS Health. These data include all pharmaceutical opioid purchases through pharmaceutical wholesalers and manufacturers who sold direct to pharmacies between 2011 and 2017. Data reflects community sales only, excluding sales to hospitals. However, due to the legal requirements for secure storage of pharmaceuticals in pharmacies, and monitoring and recording of opioids depending on their schedule listing, the number of packs sold over a 12 month period closely approximates the number used.

All opioids available in Australia that are indicated for pain can be included and coded according to the World Health Organization's Anatomical Therapeutic Classification system code of A02A 'opioids' and A02B ''other analgesics and antipyretics'. This includes, but is not limited to, tapentadol (N02AX06), buprenorphine (N02AE01), prescription and over-the-counter codeine (N02BA51, N02BE51, N02AA59, R05DA04), dextropropoxyphene (N02AC04, N02AC54), fentanyl (N02AB03), hydromorphone (N02AA03), methadone (N02AC52), morphine (N02AA01), and oxycodone

(N02AA05, N02AA55). Injectable formulations are excluded, being mainly prescribed in hospitals, and formulations of methadone and buprenorphine used solely for the treatment of opioid dependence are excluded. However, over-the-counter codeine is captured in this data source. IMS Health data can be provided from January 2011 to December 2017 aggregated monthly broken down by opioid formulation, brand, strength, and geographic unit.

Poison Information Centre call data

Four Poison Information Centres (PICs) in Australia, based in New South Wales, Queensland, Victoria and Western Australia, together provide nationwide, round-the-clock poisoning advice to healthcare professionals and members of the public. National data will be extracted regarding number of cases of pharmaceutical opioid exposure poisonings (including over-the-counter codeine) reported to PICs. Specifically, opioid-related calls will only be extracted where the exposure type/intent is coded as 'recreational', so as to identify exposures where pharmaceutical opioids were taken for its intoxicating effects [21]. Where the intentional exposure subtype is not available or unclear, calls regarding opioids will undergo a free-text search for markers of extra-medical use and abuse (defined here as use of a drug in a way or for a purpose outside intended medical use, e.g., excess quantity, recreational use, use for non-approved purposes), then manually reviewed by PIC staff and recoded.

Unit-level data collected between January 2011 and December 2017 will be extracted. Data fields to be extracted include call date, age group, gender, state/territory, dose, brand, active ingredients, and route of exposure.

Online drug marketplace data

An existing surveillance system in Australia monitors availability and types of substances sold online via the darknet [22 23]. The darknet is accessible only via The Onion Router (TOR), software that enables anonymous communication. Cryptomarkets (markets operating on the darknet) have been accessed weekly since 2013 using a dedicated user account. Exhaustive snapshots of each accessible marketplace are taken, including details of vendor name, listing description and, where possible, country of origin. For this study, the number of vendors listing illicit pharmaceutical opioids for sale on cryptomarkets between January 2013 and December 2017 will be extracted by brand and by month. This data cannot provide any information about consumers who are buying drugs on the cryptomarkets, or any data on the total number of sales via these sites. However, it does yield timely and sensitive information regarding drug availability online.

Illicit Drug Reporting System data

The Illicit Drug Reporting System (IDRS) is a national illicit drug monitoring system, one part of which comprises annual interviews with ~900 people who inject drugs interviewed in each capital city in Australia. Participants are recruited using multiple methods, including advertisements in street press, newspapers, treatment agencies, needle and syringe programs, and peer referral. To be eligible to participate, participants need to be at least 17 years of age; have injected at least monthly during the six months preceding interview; and have been a resident for at least 12 months in the capital city in which they are interviewed. The interview is administered by trained research staff face-to-face at a time and location convenient to them, and participants receive $AUD40 reimbursement.

The core quantitative interview monitors patterns of drug use and includes questions on price, purity and availability of the main drug types, including pharmaceutical opioids [24]. Data will be used from the 2017 interview (conducted May-June 2017), which included additional items around tapentadol SRF use. These items pertained to:

- Levels of tapentadol extra-medical use: diverted Palexia® SR, swallowed, injected, smoked, snorted (past six month use and number of days)
- Other opioid use (pharmaceuticals and heroin): swallowed, injected, smoked, snorted (past six month use and number of days)
- Street (diverted) price and perceived availability of diverted tapentadol and other opioids
- Attractiveness of tapentadol for use via injection
- Overdose (each opioid).

Data analysis

Population-level data

Opioid utilisation (IMS Health) and intentional pharmaceutical opioid exposure poisonings (PIC) data will be presented graphically over time by opioid type, opioid formulation and, where available tablet strength (nationally and by jurisdiction). Opioid utilisation data will be presented as number of packs and number of oral morphine equivalent (OME) grams; the latter will be computed using published conversion guidelines [25]. Percentage of total OME/packs will be calculated for tapentadol and other opioid formulations to graph the underlying rate of sales. Trends over time in tapentadol sales will be assessed using negative binomial or poison generalised estimating equations (to take into account non-independence), including variables to account for time/seasonality.

PIC data will be presented as rates of intentional pharmaceutical opioid exposure poisonings using IMS sales data as the denominator; specifically, rates per 100,000 OME grams and per 1,000 packs distributed per month. Trends over time in tapentadol exposures will also be modelled using generalised estimating equations.

Various comparators will be used for these analyses, including specific pharmaceutical opioid formulations (e.g., tramadol, oxycodone), and opioids grouped as per WHO guidelines [26] into *strong prescription opioids* (buprenorphine, fentanyl, hydromorphone, methadone, morphine and oxycodone; all listed as 'Schedule 8' opioids in Australian classification of medicines and poisons), *other prescription opioids* (prescribed codeine, dextropropoxyphene, and tramadol; 'Schedule 4' in Australia) and *over-the-counter opioids* (codeine products available at pharmacies without a prescription).

Sentinel data

Cryptomarket and IDRS data will be described using descriptive statistics, with the former graphed as number of vendors for SRF tapentadol and other pharmaceutical opioid formulations by month. Parametric and non-parametric tests of significance, as well as measures of effect size, will be used to describe differences in rates of extra-medical use, diversion, attractiveness, and overdose for tapentadol versus other opioid formulations.

ETHICS AND DISSEMINATION

The authors confirm ethics approval is not required for pharmaceutical sales data. The IDRS has received ethical approval from the University of New South Wales Human Research Ethics Committee (HC12086), as well as from the relevant ethics committees in each jurisdiction. Participants provided informed consent prior to completing the interview. The Sydney Children's Hospitals Network Human Research Ethics Committee has approved the use of data collected by the PIC (*Retrospective review of incidence and toxicity of various exposures from calls to Australian Poisons Information Centres*; LNR/16/SCHN/44).

We plan to publish our findings mid-2018 in a peer-reviewed journal article as per the data sources and outcomes listed in Table 1 and research questions specified in the aims above, and these findings will also be presented at conferences. Publications will comply with STROBE guidelines [27]. Restrictions will apply to the availability of these data as they are used with approval from data

custodians for the purposes of this study, but they may be available following approval from the researchers, custodians of the data, and any other involved third party.

DISCUSSION

This post-marketing study forms part of a growing body of literature detailing comprehensive and transparent monitoring of specific pharmaceutical opioid formulations in regards to key indicators of use, extra-medical use, and harms [28]. Concern is growing regarding rates of pharmaceutical opioid extra-medical use and harms. Consequently, it is important to determine how shifts in the pharmaceutical opioid market, including availability of new formulations, plays out in terms of these outcomes. There has been no such undertaking for tapentadol globally, despite availability in the US for nearly a decade, and indications of a small but growing pharmaceutical opioid market share [17], making the current study critical.

It should be noted that this study is limited in terms of the number of available data sources relative to other post-marketing studies [28]. However, this is a systems-level issue, as tapentadol is not differentiated from other pharmaceutical opioids in most healthcare and law enforcement data coding systems. There are a number of limitations to the chosen data sources. IDRS reflects a sentinel population at high risk of extra-medical use, and thus will not reflect general population extra-medical use, nor will it cover all aspects of various outcomes (e.g., street price is only one aspect of pharmaceutical opioid attractiveness for extra-medial use). Further, IMS Health sales data does not index the number of individuals prescribed opioids, and PIC data does not index all individuals with an adverse event, captured in other healthcare sources. However, IMS data is estimated to cover over 94% of all sales nationally [29], making it strong index of pharmaceutical opioid exposure in the community. Similarly, PIC data has complete coverage nationally and captures details related to type of exposure and dose critical to understanding risk of adverse exposure. We would also argue that online drug marketplace data and IDRS are necessary and key sentinel data sources, being established to identify emerging trends in drug use. IDRS participants typically report injecting heroin, methamphetamine and/or pharmaceutical opioids [24], making valid comparison across these substances and across jurisdictions with varying levels of heroin and pharmaceutical opioid availability.

In light of these strengths, we think that triangulation of these sources will provide a clear picture of tapentadol use, extra-medical use, attractiveness and associated harms. We believe these findings will be critical to understanding possible risks in terms of extra-medical use and harms if tapentadol

prescribing increases. More broadly though, these findings will help to enhance understanding as to the impact changes in the pharmaceutical opioid market can have on extra-medical use and harms from a policy, industry, clinician and research perspective.

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COMPETING INTERESTS

Some of the investigators have received investigator-initiated untied educational grants from Reckitt Benckiser/Indivior for studies of buprenorphine-naloxone (BL, LD), buprenorphine depot (BL, LD, MF), naloxone (LD, MF), the development of an opioid-related behavior scale (BL, LD), the pharmacogenetic predictors of treatment success (RA), and a study of opioid substitution therapy uptake among chronic non-cancer pain patients (BL, LD). Some of the investigators have also received investigator-initiated untied educational grants from Mundipharma for post-marketing surveillance of a tamper-resistant opioid formulation (AP, BL, LD, MF).

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AUTHORS' CONTRIBUTIONS

LD, AP, BL, MF, NB, and RC contributed to the development of the study for the purposes of the funding proposal and development of the study design. LD, AP, and BL led writing of the first draft. All authors contributed to the critical review of the manuscript. All authors read and approved the final manuscript.

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Table 1: Summary of the primary outcomes from each data source

Research outcome	Pharmaceutical opioid sales data	Interviews with people who inject drugs	Online drug marketplace data	Poisons Information Centre calls
Research Question 1: Exposure				
Population level availability				
Research Question 2: Extra-Medical Use				
Levels of extra-medical use (diverted)				
Injection				
Snorting				
Chewing				
Perceived availability (diverted)				
Research Question 3: Attractiveness				
Attractiveness for extra-medical use (market value)				
Research Question 4: Harms				
Overdose - non-fatal				
Intentional exposure (intentional self-poisoning, misuse, and abuse)				

Appendix 1. Data Sources Reviewed for Inclusion

Source	Sample	Geographic Coverage[1]	Distinguishes opioid type[2]	Distinguishes opioid brand	Comments
Annual/Repeated Data Collections					
National Drug Strategy Household Survey (NDSHS)	Population	National and all states/territories	Yes	No	
National Survey of Mental Health and Wellbeing (NSMHWB)	Population	National and all states/territories	No	No	
Wastewater data	Population	National and all states/territories	Yes	No	
Ecstasy and Related Drug Reporting System (EDRS) interviews	High-risk sentinel	National and all states/territories	Yes	No	
Illicit Drug Reporting System (IDRS) interviews	High-risk sentinel	National and all states/territories	Yes	Yes	Gives opioid type, strength and brand, and includes OTC codeine. Data available from 2017 only
Drug Use Monitoring in Australia (DUMA)	High-risk sentinel	NSW, QLD, SA, WA	Yes	No	
Australian NSP survey	High-risk sentinel	National and all states/territories	Yes	No	
Women and Sexual Health Survey (SWASH)	High-risk sentinel	NSW and WA	No	No	
Gay Community Periodic Survey	High-risk sentinel	SA, ACT, VIC, WA, QLD, NSW, TAS	No	No	
Sales and Dispensing Data Collections					
Prescription sales data	Population	National and all states/territories	Yes	Yes	Gives opioid type, strength and brand, and includes OTC codeine
Pharmaceutical Benefits Scheme	Population	National and all states/territories	Yes	Depends on the opioid type/dose	Item codes for pharmaceutical opioids (the unit by which data can be extracted) do not differentiate by brand where multiple brands offer products of the same strength (e.g., four different brands of morphine products fall under item code '1653B: morphine sulfate 10mg modified release tablet') [30]. Further, only medicines contained in the Schedule of Pharmaceutical Benefits appear in these statistics (excluding over-the-counter codeine), and SRF tapentadol was only listed on the Schedule two years post-introduction (in 2013).
Medicare Benefits Scheme	Population	National and all states/territories	No	No	
Administrative Data Collections					
Poison Information Centre call data	Population	All states/territories	Yes	Yes	Gives opioid type, strength and brand where these characteristics can be identified by the caller, and includes OTC codeine
Ambulance data collections	Population	All states/territories	No	No	
Emergency department data collections	Population	All states/territories	Depends on the coding system	No	
Admitted patient data collections	Population	National and all states/territories	No	No	
Mortality data	Population	National and all states/territories	No	No	
Mental health ambulatory data collections	Population	NSW, VIC, TAS, WA	No	No	
Alcohol and drug treatment helpline calls	Population	All states/territories	Depends on the coding system	No	
Needle-syringe programme data	High-risk sentinel	National and all states/territories	Depends on the coding system	No	
Medically-supervised injecting clinic data	High-risk sentinel	NSW	Depends on the coding system	No	
Prescription monitoring programme data	High-risk sentinel	TAS	Yes	Yes	Incomplete coverage with continued implementation of the programme, with voluntary opt in by pharmacists and

					general practitioners, and no requirement for use for every dispensing episode.
Pharmacotherapy program data	Population	National and all states/territories	Yes	No	
Alcohol and drug treatment services data	Population	National and all states/territories	Yes	No	
Arrest data	Population	National and all states/territories	Yes	No	
Seizure data	Population	National and all states/territories	Yes	No	
Street price data	Population	National and all states/territories	Yes	No	
Criminal court data	Population	National and all states/territories	Yes	No	
Online Monitoring					
Online marketplace monitoring	High-risk sentinel	National	Yes	Yes	Gives opioid brand/dose for sale on online marketplaces. Data is only available from early 2013.

Note. [1] National: collated and reported at national level only; National and all states/territories: collated and reported at national and state/territory-level; All states/territories: collated and reported at the state/territory level only. [2] Distinguishes between types of opioids (e.g., morphine and oxycodone). NSW: New South Wales; QLD: Queensland; SA: South Australia; WA: Western Australia; TAS: Tasmania; Australian Capital Territory; VIC: Victoria.

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Opioid Use and Harms Associated with a Sustained-Released Tapentadol Formulation: A Post-Marketing Study Protocol

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ABSTRACT

Introduction: It has been argued that pharmacologically tapentadol may have lower abuse potential than other pharmaceutical opioids currently available. However, there has been no comprehensive triangulation of data regarding use and harms associated with this formulation. A sustained-release formulation (SRF) of tapentadol (Palexia®) was released in Australia in 2011 and listed for public subsidy in 2013. We summarise here the methods of a post-marketing study which will measure post-introduction: i) population level availability, ii) extra-medical use and diversion, iii) attractiveness for extra-medical use, and iv) associated harms, of tapentadol compared against other pharmaceutical opioids.

Methods and Analysis: We evaluated key sources on pharmaceutical use and harms in Australia, and were limited to triangulating data from four sources that disaggregate pharmaceutical opioid formulations and captured the tapentadol SRF. These data sources comprised: i) national pharmaceutical opioid community sales data from 2011-2017, ii) national pharmaceutical opioid poisonings reported to Poison Information Centres from 2011-2017, iii) number of vendors on online marketplaces listing pharmaceutical opioids for sale, and iv) data on pharmaceutical opioid extra-medical use, attractiveness, and harms from interviews with people who inject drugs in Australia.

Ethics and Dissemination: Ethics approval is not required for use of pharmaceutical sales data. Ethics approval has been obtained for use of national pharmaceutical opioid poisonings reported to Poison Information Centres (LNR/16/SCHN/44) and for use of online marketplace data and interview data from people who inject drugs (HC12086). Key findings will be published mid-2018 in a peer-reviewed academic journal, and presented at various conferences and professional meetings.

Keywords: opioid; tapentadol; overdose; tamper; substance misuse; harm

STRENGTHS AND LIMITATIONS

- This study will comprise the first published comprehensive assessment of tapentadol SRF use, extra-medical use, attractiveness for extra-medical use, and associated harms.
- The number of data sources is limited relative to other post-marketing studies of pharmaceutical opioids as tapentadol is rarely coded separate to other pharmaceutical opioids in administrative data.
- However, this study will overview a wealth of data from the general population and a group at high risk for extra-medical use, both of which are key to examine when quantifying various impacts of pharmaceutical opioids.
- These findings will have relevance to other countries where tapentadol has recently been introduced or where it may be introduced in the future.

INTRODUCTION

In the past two decades, there has been an increase in the number of pharmaceutical opioids available, and in the prescribing of these drugs, in several high-income countries, including North America and Australia [1]. Indeed, between 1992-2012 the number of pharmaceutical opioid dispensing episodes increased fifteen-fold in Australia [2]. This increase in availability in Australia has been accompanied by greater rates of extra-medical use, defined as use outside the bounds of a doctor's prescription [3]. The risk of opioid dependence and serious adverse events (e.g., overdose) associated with extra-medical use has made addressing this problem a public health imperative [4 5].

Opioids differ in the extent to which they are likely to be associated with hazardous patterns of use due to different potencies (i.e., weak to strong opioids), pharmacokinetic characteristics (e.g., rate of metabolism) and propensities for dependence [6]. The need to reduce extra-medical use must also be balanced against the need for access to opioid therapy for pain. Thus, current public health agency strategies to reduce extra-medical pharmaceutical opioid use and chronic pain prescribing guidelines focus on products which have limited or no abuse potential [7 8].

Tapentadol is a centrally acting opioid analgesic with dual mechanisms of action, specifically μ-opioid receptor agonist and noradrenaline reuptake inhibition. This dual action is thought to result in a lower dose required to produce a given level of analgesia [9]. Clinical trials suggest that tapentadol provides equivalent or superior levels of pain relief for acute and chronic pain similar to oxycodone and morphine, with greater gastro-intestinal tolerability in terms of reduced rates of nausea, vomiting, and constipation [10-13].

A recent review by the World Health Organization's Expert Committee on Drug Dependence [11] concluded that potential for abuse for tapentadol may be similar to or slightly lower than other opioids such as hydromorphone, oxycodone, morphine and tramadol. However, they note that these conclusions are tentative given a lack of data regarding tapentadol "abuse, dependence, diversion, recreational use, or poison control", noting that tapentadol generally does not feature in drug use surveys or surveillance reports. The few studies which have been conducted are based on US samples, and using treatment-seeking populations [14] or evaluation of internet discussions [15 16] and prescribing data [17] to assess extra-medical use, with early indications of rates of abuse and diversion equivalent to hydromorphone and lower than oxycodone and most other strong opioids [14 18].

The immediate release form of tapentadol is registered in Australia for moderate to severe pain, while the sustained release form is registered for severe pain which requires constant opioid treatment and for which no other opioid other treatments are adequate [19]. Although a sustained-release formulation of tapentadol (SRF; Palexia® SR) was released in Australia in 2011, and listed for subsidy on the Pharmaceutical Benefits Scheme in November 2013 [20], no research into rates into dispensing, extra-medical use, and associated harms of the tapentadol SRF has been undertaken in Australia. Given the broader context of rising rates of pharmaceutical opioid use and harms (including overdose), monitoring new formulations in terms of population level pharmaceutical opioid use, and extra-medical use amongst high risk populations (e.g., those reporting extra-medical use of other pharmaceutical use) is critical.

This paper outlines the design for a national post-marketing study of use, extra-medical use, and harms associated with introduction of the tapentadol SRF in Australia. This study will integrate population and sentinel high-risk population data, including national pharmaceutical opioid sales data, interviews with people who inject drugs, and national opioid-related poisoning event data.

METHODS AND ANALYSIS

Study aims

The overarching aim of this study is to identify extra-medical use and diversion of tapentadol SRF, attractiveness for extra-medical use, and associated levels of harms compared to these indicators for other pharmaceutical opioid use. The specific questions we aim to answer are as follows:

1. What is the population level availability of the tapentadol SRF in Australia relative to other pharmaceutical opioids?
2. Are there indications of extra-medical use of the tapentadol SRF (specifically, non-prescribed use, use via routes that require tampering), and how does this compare to other pharmaceutical opioids?
3. What is the relative attractiveness for extra-medical use (e.g., street price) of the tapentadol SRF, and how does this compare to other pharmaceutical opioids?
4. Are there indications of associated harm with the tapentadol SRF (specifically, self-reported non-fatal overdose, as well as intentional poisoning, extra-medical use and abuse as identified through poison information centre data), and how does this compare to other pharmaceutical opioids?

Study design and setting

This study is being conducted in Australia. There are three main components of this study: analyses of existing routine data sources (2011-2017); analyses of data from monitoring online drug marketplaces (2013-2017); and analyses of cross-sectional data collected from a high-risk sentinel group (people who inject drugs) participating in the Illicit Drug Reporting System (IDRS) in 2016.

Most indicator data sets in Australia do not routinely separate tapentadol from other pharmaceutical opioids, precluding any comparison of population-level availability (see Appendix 1). Five data sources were identified which could provide data specific to pharmaceutical opioid brand, thus allowing analysis of use and harms related to tapentadol SRF. Prescription monitoring programme data, although theoretically useful, only exist in one jurisdiction, where registration is voluntary and implementation is not complete or consistent, and utilisation of this programme irregular. Consequently, four data sources were included in this study: pharmaceutical opioid sales data; poison information centre call data; online drug marketplace data; and interviews with people who inject drugs. **Table 1** outlines the relevant outcome for each data source for each research question.

Table 1 approximately here

Pharmaceutical opioid sales data

A third-party access request to obtain pharmaceutical sales data in Australia was approved by IMS Health. These data include all pharmaceutical opioid purchases through pharmaceutical wholesalers and manufacturers who sold direct to pharmacies between 2011 and 2017. Data reflects community sales only, excluding sales to hospitals. However, due to the legal requirements for secure storage of pharmaceuticals in pharmacies, and monitoring and recording of opioids depending on their schedule listing, the number of packs sold over a 12 month period closely approximates the number used.

All opioids available in Australia that are indicated for pain can be included and coded according to the World Health Organization's Anatomical Therapeutic Classification system code of A02A 'opioids' and A02B ''other analgesics and antipyretics'. This includes, but is not limited to, tapentadol (N02AX06), buprenorphine (N02AE01), prescription and over-the-counter codeine (N02BA51, N02BE51, N02AA59, R05DA04), dextropropoxyphene (N02AC04, N02AC54), fentanyl (N02AB03), hydromorphone (N02AA03), methadone (N02AC52), morphine (N02AA01), and oxycodone

(N02AA05, N02AA55). Injectable formulations are excluded, being mainly prescribed in hospitals, and formulations of methadone and buprenorphine used solely for the treatment of opioid dependence are excluded. However, over-the-counter codeine is captured in this data source. IMS Health data can be provided from January 2011 to December 2017 aggregated monthly broken down by opioid formulation, brand, strength, and geographic unit.

Poison Information Centre call data

Four Poison Information Centres (PICs) in Australia, based in New South Wales, Queensland, Victoria and Western Australia, together provide nationwide, round-the-clock poisoning advice to healthcare professionals and members of the public. National data will be extracted regarding number of cases of pharmaceutical opioid exposure poisonings (including over-the-counter codeine) reported to PICs. Specifically, opioid-related calls will only be extracted where the exposure type/intent is coded as 'recreational', so as to identify exposures where pharmaceutical opioids were taken for its intoxicating effects [21]. Where the intentional exposure subtype is not available or unclear, calls regarding opioids will undergo a free-text search for markers of extra-medical use and abuse (defined here as use of a drug in a way or for a purpose outside intended medical use, e.g., excess quantity, recreational use, use for non-approved purposes), then manually reviewed by PIC staff and recoded.

Unit-level data collected between January 2011 and December 2017 will be extracted. Data fields to be extracted include call date, age group, gender, state/territory, dose, brand, active ingredients, and route of exposure.

Online drug marketplace data

An existing surveillance system in Australia monitors availability and types of substances sold online via the darknet [22 23]. The darknet is accessible only via The Onion Router (TOR), software that enables anonymous communication. Cryptomarkets (markets operating on the darknet) have been accessed weekly since 2013 using a dedicated user account. Exhaustive snapshots of each accessible marketplace are taken, including details of vendor name, listing description and, where possible, country of origin. For this study, the number of vendors listing illicit pharmaceutical opioids for sale on cryptomarkets between January 2013 and December 2017 will be extracted by brand and by month. This data cannot provide any information about consumers who are buying drugs on the cryptomarkets, or any data on the total number of sales via these sites. However, it does yield timely and sensitive information regarding drug availability online.

Illicit Drug Reporting System data

The Illicit Drug Reporting System (IDRS) is a national illicit drug monitoring system, one part of which comprises annual interviews with ~900 people who inject drugs interviewed in each capital city in Australia. Participants are recruited using multiple methods, including advertisements in street press, newspapers, treatment agencies, needle and syringe programs, and peer referral. To be eligible to participate, participants need to be at least 17 years of age; have injected at least monthly during the six months preceding interview; and have been a resident for at least 12 months in the capital city in which they are interviewed. The interview is administered by trained research staff face-to-face at a time and location convenient to them, and participants receive $AUD40 reimbursement.

The core quantitative interview monitors patterns of drug use and includes questions on price, purity and availability of the main drug types, including pharmaceutical opioids [24]. Data will be used from the 2017 interview (conducted May-June 2017), which included additional items around tapentadol SRF use. These items pertained to:

- Levels of tapentadol extra-medical use: diverted Palexia® SR, swallowed, injected, smoked, snorted (past six month use and number of days)
- Other opioid use (pharmaceuticals and heroin): swallowed, injected, smoked, snorted (past six month use and number of days)
- Street (diverted) price and perceived availability of diverted tapentadol and other opioids
- Attractiveness of tapentadol for use via injection
- Overdose (each opioid).

Data analysis

Population-level data

Opioid utilisation (IMS Health) and intentional pharmaceutical opioid exposure poisonings (PIC) data will be presented graphically over time by opioid type, opioid formulation and, where available tablet strength (nationally and by jurisdiction). Opioid utilisation data will be presented as number of packs and number of oral morphine equivalent (OME) grams; the latter will be computed using published conversion guidelines [25]. Percentage of total OME/packs will be calculated for tapentadol and other opioid formulations to graph the underlying rate of sales. Trends over time in tapentadol sales will be assessed using negative binomial or poison generalised estimating equations (to take into account non-independence), including variables to account for time/seasonality.

PIC data will be presented as rates of intentional pharmaceutical opioid exposure poisonings using IMS sales data as the denominator; specifically, rates per 100,000 OME grams and per 1,000 packs distributed per month. These analyses will be restricted to those cases explicitly identified as a pharmaceutical opioid exposure poisoning attributable to a type of opioid (e.g., tapentadol, oxycodone) as per the criteria identified above. Trends over time in tapentadol exposures will also be modelled using generalised estimating equations.

Various comparators will be used for these analyses, including specific pharmaceutical opioid formulations (e.g., tramadol, oxycodone), and opioids grouped as per WHO guidelines [26] into *strong prescription opioids* (buprenorphine, fentanyl, hydromorphone, methadone, morphine and oxycodone; all listed as 'Schedule 8' opioids in Australian classification of medicines and poisons), *other prescription opioids* (prescribed codeine, dextropropoxyphene, and tramadol; 'Schedule 4' in Australia) and *over-the-counter opioids* (codeine products available at pharmacies without a prescription).

Sentinel data

Cryptomarket and IDRS data will be described using descriptive statistics, with the former graphed as number of vendors for SRF tapentadol and other pharmaceutical opioid formulations by month. Parametric and non-parametric tests of significance, as well as measures of effect size, will be used to describe differences in rates of extra-medical use, diversion, attractiveness, and overdose for tapentadol versus other opioid formulations.

ETHICS AND DISSEMINATION

The authors confirm ethics approval is not required for pharmaceutical sales data. The IDRS has received ethical approval from the University of New South Wales Human Research Ethics Committee (HC12086), as well as from the relevant ethics committees in each jurisdiction. Participants provided informed consent prior to completing the interview. The Sydney Children's Hospitals Network Human Research Ethics Committee has approved the use of data collected by the PIC (*Retrospective review of incidence and toxicity of various exposures from calls to Australian Poisons Information Centres*; LNR/16/SCHN/44).

We plan to publish our findings mid-2018 in a peer-reviewed journal article as per the data sources and outcomes listed in Table 1 and research questions specified in the aims above, and these

findings will also be presented at conferences. Publications will comply with STROBE guidelines [27]. Restrictions will apply to the availability of these data as they are used with approval from data custodians for the purposes of this study, but they may be available following approval from the researchers, custodians of the data, and any other involved third party.

DISCUSSION

This post-marketing study forms part of a growing body of literature detailing comprehensive and transparent monitoring of specific pharmaceutical opioid formulations in regards to key indicators of use, extra-medical use, and harms [28]. Concern is growing regarding rates of pharmaceutical opioid extra-medical use and harms. Consequently, it is important to determine how shifts in the pharmaceutical opioid market, including availability of new formulations, plays out in terms of these outcomes. There has been no such undertaking for tapentadol globally, despite availability in the US for nearly a decade, and indications of a small but growing pharmaceutical opioid market share [17], making the current study critical.

It should be noted that this study is limited in terms of the number of available data sources relative to other post-marketing studies [28]. However, this is a systems-level issue, as tapentadol is not differentiated from other pharmaceutical opioids in most healthcare and law enforcement data coding systems. There are a number of limitations to the chosen data sources. IDRS reflects a sentinel population at high risk of extra-medical use, and thus will not reflect general population extra-medical use, nor will it cover all aspects of various outcomes (e.g., street price is only one aspect of pharmaceutical opioid attractiveness for extra-medial use). Further, IMS Health sales data does not index the number of individuals prescribed opioids, and PIC data does not index all individuals with an adverse event, captured in other healthcare sources. However, IMS data is estimated to cover over 94% of all sales nationally [29], making it strong index of pharmaceutical opioid exposure in the community. Similarly, PIC data has complete coverage nationally and captures details related to type of exposure and dose critical to understanding risk of adverse exposure. We would also argue that online drug marketplace data and IDRS are necessary and key sentinel data sources, being established to identify emerging trends in drug use. IDRS participants typically report injecting heroin, methamphetamine and/or pharmaceutical opioids [24], making valid comparison across these substances and across jurisdictions with varying levels of heroin and pharmaceutical opioid availability.

In light of these strengths, we think that triangulation of these sources will provide a clear picture of tapentadol use, extra-medical use, attractiveness and associated harms. We believe these findings will be critical to understanding possible risks in terms of extra-medical use and harms if tapentadol prescribing increases. More broadly though, these findings will help to enhance understanding as to the impact changes in the pharmaceutical opioid market can have on extra-medical use and harms from a policy, industry, clinician and research perspective.

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COMPETING INTERESTS

Some of the investigators have received investigator-initiated untied educational grants from Reckitt Benckiser/Indivior for studies of buprenorphine-naloxone (BL, LD), buprenorphine depot (BL, LD, MF), naloxone (LD, MF), the development of an opioid-related behavior scale (BL, LD), the pharmacogenetic predictors of treatment success (RA), and a study of opioid substitution therapy uptake among chronic non-cancer pain patients (BL, LD). Some of the investigators have also received investigator-initiated untied educational grants from Mundipharma for post-marketing surveillance of a tamper-resistant opioid formulation (AP, BL, LD, MF).

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AUTHORS' CONTRIBUTIONS

LD, AP, BL, MF, NB, and RC contributed to the development of the study for the purposes of the funding proposal and development of the study design. LD, AP, and BL led writing of the first draft. All authors contributed to the critical review of the manuscript. All authors read and approved the final manuscript.

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Table 1: Summary of the primary outcomes from each data source

Research outcome	Pharmaceutical opioid sales data	Interviews with people who inject drugs	Online drug marketplace data	Poisons Information Centre calls
Research Question 1: Exposure				
Population level availability				
Research Question 2: Extra-Medical Use				
Levels of extra-medical use (diverted)				
Injection				
Snorting				
Chewing				
Perceived availability (diverted)				
Research Question 3: Attractiveness				
Attractiveness for extra-medical use (market value)				
Research Question 4: Harms				
Overdose - non-fatal				
Intentional exposure (intentional self-poisoning, misuse, and abuse)				

Appendix 1. Data Sources Reviewed for Inclusion

Source	Sample	Geographic Coverage[1]	Distinguishes opioid type[2]	Distinguishes opioid brand	Comments
Annual/Repeated Data Collections					
National Drug Strategy Household Survey (NDSHS)	Population	National and all states/territories	Yes	No	
National Survey of Mental Health and Wellbeing (NSMHWB)	Population	National and all states/territories	No	No	
Wastewater data	Population	National and all states/territories	Yes	No	
Ecstasy and Related Drug Reporting System (EDRS) interviews	High-risk sentinel	National and all states/territories	Yes	No	
Illicit Drug Reporting System (IDRS) interviews	High-risk sentinel	National and all states/territories	Yes	Yes	Gives opioid type, strength and brand, and includes OTC codeine. Data available from 2017 only
Drug Use Monitoring in Australia (DUMA)	High-risk sentinel	NSW, QLD, SA, WA	Yes	No	
Australian NSP survey	High-risk sentinel	National and all states/territories	Yes	No	
Women and Sexual Health Survey (SWASH)	High-risk sentinel	NSW and WA	No	No	
Gay Community Periodic Survey	High-risk sentinel	SA, ACT, VIC, WA, QLD, NSW, TAS	No	No	
Sales and Dispensing Data Collections					
Prescription sales data	Population	National and all states/territories	Yes	Yes	Gives opioid type, strength and brand, and includes OTC codeine
Pharmaceutical Benefits Scheme	Population	National and all states/territories	Yes	Depends on the opioid type/dose	Item codes for pharmaceutical opioids (the unit by which data can be extracted) do not differentiate by brand where multiple brands offer products of the same strength (e.g., four different brands of morphine products fall under item code '1653B: morphine sulfate 10mg modified release tablet') [30]. Further, only medicines contained in the Schedule of Pharmaceutical Benefits appear in these statistics (excluding over-the-counter codeine), and SRF tapentadol was only listed on the Schedule two years post-introduction (in 2013).
Medicare Benefits Scheme	Population	National and all states/territories	No	No	
Administrative Data Collections					
Poison Information Centre call data	Population	All states/territories	Yes	Yes	Gives opioid type, strength and brand where these characteristics can be identified by the caller, and includes OTC codeine
Ambulance data collections	Population	All states/territories	No	No	
Emergency department data collections	Population	All states/territories	Depends on the coding system	No	
Admitted patient data collections	Population	National and all states/territories	No	No	
Mortality data	Population	National and all states/territories	No	No	
Mental health ambulatory data collections	Population	NSW, VIC, TAS, WA	No	No	
Alcohol and drug treatment helpline calls	Population	All states/territories	Depends on the coding system	No	
Needle-syringe programme data	High-risk sentinel	National and all states/territories	Depends on the coding system	No	
Medically-supervised injecting clinic data	High-risk sentinel	NSW	Depends on the coding system	No	
Prescription monitoring programme data	High-risk sentinel	TAS	Yes	Yes	Incomplete coverage with continued implementation of the programme, with voluntary opt in by pharmacists and

					general practitioners, and no requirement for use for every dispensing episode.
Pharmacotherapy program data	Population	National and all states/territories	Yes	No	
Alcohol and drug treatment services data	Population	National and all states/territories	Yes	No	
Arrest data	Population	National and all states/territories	Yes	No	
Seizure data	Population	National and all states/territories	Yes	No	
Street price data	Population	National and all states/territories	Yes	No	
Criminal court data	Population	National and all states/territories	Yes	No	
Online Monitoring					
Online marketplace monitoring	High-risk sentinel	National	Yes	Yes	Gives opioid brand/dose for sale on online marketplaces. Data is only available from early 2013.

Note. [1] National: collated and reported at national level only; National and all states/territories: collated and reported at national and state/territory-level; All states/territories: collated and reported at the state/territory level only. [2] Distinguishes between types of opioids (e.g., morphine and oxycodone). NSW: New South Wales; QLD: Queensland; SA: South Australia; WA: Western Australia; TAS: Tasmania; Australian Capital Territory; VIC: Victoria.