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Cohort profile: POPPY II – a population-based cohort examining the patterns and outcomes of prescription opioid use in New South Wales, Australia

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ABSTRACT

Purpose The POPPY II cohort is an Australian state-based cohort linking data for a population of individuals prescribed opioid medicines, constructed to allow a robust examination of the long-term patterns and outcomes of prescription opioid use.

Participants The cohort includes 3 569 433 adult New South Wales residents who initiated a subsidised prescription opioid medicine between 2003 and 2018, identified through pharmacy dispensing data (Australian Pharmaceutical Benefits Scheme) and linked to 10 national and state datasets and registries including rich sociodemographic and medical services data.

Findings to date Of the 3.57 million individuals included in the cohort, 52.7% were female and 1 in 4 people were aged ≥65 years at the time of cohort entry. Approximately 6% had evidence of cancer in the year prior to cohort entry. In the 3 months prior to cohort entry, 26.9% used a non-opioid analgesic and 20.5% used a psychotropic medicine. Overall, 1 in 5 individuals were initiated on a strong opioid (20.9%). The most commonly initiated opioid was paracetamol/codeine (61.3%), followed by oxycodone (16.3%).

Future plans The POPPY II cohort will be updated periodically, both extending the follow-up duration of the existing cohort, and including new individuals initiating opioids. The POPPY II cohort will allow a range of aspects of opioid utilisation to be studied, including long-term trajectories of opioid use, development of a data-informed method to assess time-varying opioid exposure, and a range of outcomes including mortality, transition to opioid dependence, suicide and falls. The duration of the study period will allow examination of population-level impacts of changes to opioid monitoring and access, while the size of the cohort will also allow examination of important subpopulations such as people with cancer, musculoskeletal conditions or opioid use disorder.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The POPPY II cohort study is the most comprehensive postmarketing surveillance study of prescription opioids in Australia and one of the largest studies worldwide.
⇒ The POPPY II cohort consists of approximately 3.57 million adult New South Wales residents who initiated prescription opioids between 2003 and 2018.
⇒ Available data include sociodemographic, clinical and index opioid use characteristics with linkage to healthcare and treatment registries, healthcare services databases, hospitalisation records and mortality data.
⇒ Limitations include the lack of indications for medicine use in dispensing datasets and inclusion of only subsidised dispensed medicines.

INTRODUCTION

There is significant concern about the increased use of prescription opioids over recent years in several countries including the USA, Canada, the UK and Australia.[1] In Australia, opioid dispensings increased almost fourfold between 1990 and 2014.[2] Each year, approximately 3 million Australians are dispensed a prescription opioid and 1.9 million Australians newly initiate a prescription opioid.[3] Consistent increases in the use of strong opioids (eg, oxycodone, fentanyl) have been observed nationally over the last two decades.[2 4 5] Currently, in Australia, strong opioids account for approximately 40% of all prescription opioid dispensings[2] and opioid pack sales in the community,[6] and 70% of total oral morphine equivalent (OME) kilograms sold, with oxycodone use particularly pronounced.[6]

Much of the increase in global prescription opioid use has been attributed to increased prescribing of opioids, particularly strong opioids, for the management of chronic non-cancer pain (CNCP).[2 7] CNCP is a highly prevalent and debilitating condition associated with a large disease and economic burden.[8] Approximately one in five Australian adults are estimated to live with CNCP,[8 9] with as many

as one in two community-dwelling older adults affected.[10] Despite widespread and growing use of opioids for CNCP in high-income countries, evidence supporting their long-term use is limited for this indication.[11] Conversely, there are well-known risks associated with the long-term use of opioids, including adverse effects, overdose, falls and injuries, extramedical use and dependence,[12] leading to recommendations for more judicious prescribing.[13 14]

Numerous population-based studies have examined the relationship between use and opioid-related harms in the Australian population using aggregated data sources.[5] However, a limited number of studies have focused on individual-level patterns and trajectories of use. The few studies examining opioid initiation are limited to specific opioids,[15–17] or focus on relatively short observation periods.[3] Less is known about opioid initiation and use more broadly over extended periods of observation. There are also no Australian general population studies linking multiple information sources on the use of prescription opioids to health outcomes and following individuals from the time of opioid initiation. This paper describes a population-based cohort study that is being undertaken to address these gaps, with a focus on describing the sociodemographic, clinical and index opioid use characteristics at the time of cohort entry. The specific aims of this paper were to:

1. Describe the sociodemographic characteristics of the cohort.
2. Examine the prior health status of the cohort, including medical conditions, health service use and other prescription medicine use.
3. Examine index opioid use characteristics of the cohort, including type and number of opioids initiated, administration route and amount dispensed.

COHORT DESCRIPTION

POPPY II is a population-based cohort study of adult residents in New South Wales (NSW), Australia, who initiated a prescription opioid between 1 July 2003 and 31 December 2018. Full details of the POPPY II study protocol have been published previously.[18] Opioid use data were derived from administrative pharmaceutical claims data and linked to a range of datasets providing rich information on sociodemographic and clinical characteristics, health service use and health outcomes. Findings are reported in line with RECORD-PE guidelines (online supplemental table S1).[18]

Setting

This study included residents of NSW, the most populous state in Australia. Approximately one-third of the Australian population resides in NSW (7.9 million people in 2018).[19 20] Australia has a publicly funded universal healthcare system entitling all Australian citizens and permanent residents to a range of subsidised health services. This includes free treatment in public hospitals (funded jointly by the Commonwealth (national) and state/territory governments), subsidised outpatient services including consultations with medical and selected healthcare professionals (funded by the Commonwealth's Medicare Benefits Scheme (MBS)), and medicines prescribed in the community and private hospitals (funded by the Commonwealth's Pharmaceutical Benefits Scheme (PBS)).[21]

Each year the Australian government sets two PBS copayment thresholds which represent the maximum amount that an individual is required to pay for prescription medicines, with the government subsidising costs above these thresholds. Individuals are either 'general beneficiaries' and pay a general copayment amount ($A42.50 in 2022) or 'concessional beneficiaries' and pay a concessional (reduced) copayment amount ($A6.80 in 2022). Concessional beneficiaries are generally those who are in receipt of government social welfare benefits, representing approximately 25% of all people accessing PBS medicines.[22]

Source data

The PBS database contains information on prescription medicines that qualify for a benefit under the National Health Act 1953 and for which a claim has been processed. Until July 2012, the PBS dataset captured dispensings (original and repeats) for PBS-listed medicines which attracted a government subsidy (ie, all medicines dispensed to concessional beneficiaries and medicines dispensed to general beneficiaries costing more than the PBS copayment threshold). From July 2012, this was extended to include medicines dispensed under the copayment threshold for general beneficiaries.[21] Dispensings for private prescriptions (ie, those in which individuals pay the full cost, with no government subsidy) were not included; these form an extremely small proportion of overall opioid use (ie, 6%) in Australia.[23 24]

Participants

The cohort comprises adult (≥18 years) NSW residents who initiated a prescription opioid between 1 July 2003 and 31 December 2018. Opioids included were: buprenorphine, codeine, dextropropoxyphene, fentanyl, hydromorphone, methadone, morphine, oxycodone, pethidine, tapentadol and tramadol. Dispensings of methadone or buprenorphine for the treatment of opioid dependence are not recorded in the PBS dataset and were therefore excluded. WHO Anatomical Therapeutic Chemical classification codes[25] and PBS item codes used to define the cohort are detailed in online supplemental table S2.

Observation commenced on the date of index opioid dispensing (cohort entry), defined where there was evidence of no prior opioids dispensed in the previous 365 days. This represents a variation from the original study protocol whereby opioid initiation and cohort inclusion were defined using a 90-day look-back window.[26] Given the 16-year study period, a longer wash-out period was deemed more conservative and

reduces the potential for capturing prevalent users who have a short break in opioid use. This longer look-back period has previously been used in other studies of prescription opioid initiation.[3] Sensitivity analyses were undertaken to examine the impact of adopting a more conservative 365-day look-back window and to assess the profiles of alternative cohort definitions used to overcome issues related to the underascertainment of under copayment prescriptions prior to July 2012 (online supplemental figure S1).

Datasets and linkage procedure

The cohort was extracted from PBS records (2002–2018) by the Australian Institute of Health and Welfare (AIHW) and linked to 10 other national (Commonwealth) and state (NSW, Australian Capital Territory (ACT)) data collections by the AIHW and the NSW Centre for Health Record Linkage using established probabilistic linkage methods to identify likely matches across datasets using a range of demographic information including first name, surname, date of birth, sex and address.[27] ACT is located geographically within the borders of NSW and people may receive healthcare services in both jurisdictions; selected ACT datasets were included in the linkage to capture possible health service use in this jurisdiction. Table 1 provides a detailed summary of the linked datasets in the POPPY II study. A brief overview of included datasets is provided below.

The Medicare Enrolment File (MEF) records all recipients of medical services subsidised under the Medicare universal health insurance system. The MBS records information on services that qualify for a Medicare benefit under the Health Insurance Act 1973 (most primary healthcare services) including visits to general practitioners and other medical and allied health practitioners. The National Death Index (NDI) records the date and cause/s of death for decedents from each Australian State or Territory. The NSW Admitted Patient Data Collection (NSW APDC) and the ACT Admitted Patient Collection (ACT APC) record inpatient separations from public hospitals (including psychiatric), multipurpose health services, private hospitals and private day procedure centres in NSW and the ACT, respectively. The NSW and ACT Emergency Department Data Collections (NSW EDDC; ACT EDDC) record visits to participating emergency departments in NSW and the ACT, respectively. The Australian Cancer Database (ACD) records all primary cancer diagnoses recorded since 1982. The NSW Controlled Drugs Data Collection (CoDDaC) records all NSW recipients of opioid agonist therapy (methadone or buprenorphine treatment for opioid dependence) from 1985. Finally, the NSW Ambulatory Mental Health Dataset (MH-AMB) records non-admitted mental healthcare services including mental health day programmes, outreach services, community health service contacts and outpatient psychiatric contacts.

Variables

Key variables extracted from each dataset are detailed in table 1. Age was estimated using month and year of birth at the time of cohort entry. Residential postcodes recorded at cohort entry were used to determine the remoteness and socioeconomic characteristics of each individual's area of residence, by linking to the Australian Bureau of Statistics 2016 Remoteness Areas classification system and the 2011 Index of Relative Socio-Economic Disadvantage .[28 29]

Evidence of a range of common medical conditions in the 12 months prior to and including the day of cohort entry were identified using composite indicators that incorporated information from each individual's dispensing history and contact with inpatient hospital services and community mental health services. These were used in conjunction with cancer registry notifications to identify cancer and registrations for opioid agonist therapy treatment to identify opioid use disorder. Use of primary and acute healthcare services in the 12 months prior to and including the day of cohort entry were examined. Use of prescribed non-opioid analgesics and psychotropic medicines in the 3 months prior to and including the date of cohort entry were evaluated. Full details of the codes used to extract medical conditions, medicines and health services of interest are detailed in online supplemental tables S3-S5. Data from the NSW EDDC, ACT APC and ACT EDDC were not used to establish baseline characteristics of the cohort as these datasets do not extend back to the first date of observation for the cohort (see table 1).

Characteristics related to each individual's index opioid dispensing/s at cohort entry were evaluated. Individuals were considered to be dispensed strong opioids if they were dispensed fentanyl, hydromorphone, morphine, oxycodone±naloxone, or methadone or buprenorphine formulations for analgesia, based on their relative potency to morphine (ie, all opioids more potent than morphine when compared in terms of OME) (online supplemental table S2).[30] The total OME milligrams of the index dispensing/s was calculated by multiplying the strength and quantity of dispensed items by published conversion factors,[30] and summing across items.

Patient and public involvement statement

The POPPY II study is guided by a Project Reference Group which includes clinicians with specialist experience treating pain, cancer and substance use disorders. There was no patient or public involvement in the planning, design or conduct of this study.

FINDINGS TO DATE

The POPPY II cohort includes 3 569 433 individuals, representing 22 221 018 person-years of follow-up. Approximately half of the cohort were female (52.7%) and one in four people were aged ≥65 years at cohort entry (26.8%) (table 2). The majority reside in a major city (71.4%) and

Table 1 Datasets included in the POPPY II study and key variables of interest

Dataset name and date range	Description of dataset	Purpose of dataset	Key variables of interest*
Pharmaceutical Benefits Scheme (PBS), 1 July 2002–31 December 2018	Records for all PBS-listed medicines for which the Commonwealth pays a subsidy (2002–2012). After 2012, all PBS dispensings are included.	To identify the cohort and the types of opioids and other medicines dispensed.	PBS-item no, date of prescribing and dispensing, patient/pharmacy/prescriber postcodes, provider location, patient copayment amount, government cost.
Medicare Enrolment File (MEF), 1 January 2002–31 December 2018	Contains Medicare enrolment details (eg, name, address history, date of birth). Used by the Australian Institute of Health and Welfare to identify individuals and link records across datasets.	To provide month/ year of birth and sex information for all cohort members.	Month and year of birth, sex.
Medicare Benefits Scheme (MBS), 1 January 2002– 31 December 2018	Claims for all medical and hospital services subsidised by the Commonwealth including doctor visits, pathology tests and imaging.	To identify the use of medical and hospital services.	MBS-item no, date of service, schedule fee, provider charge, benefit paid, patient copayment, provider location.
Australian Cancer Database (ACD), 1 January 1982–31 December 2019	All notifications of primary malignant neoplasms.	To identify individuals potentially treated with opioids for cancer vs non-cancer pain.	Date of diagnosis, topography and morphology codes, degree of spread.
National Death Index (NDI), 1 January 2002–31 December 2019	Death registrations and causes of death.	To calculate mortality rates for the cohort and censor individuals.	Date of death, underlying and contributing causes of death.
NSW Admitted Patient Data Collection (NSW APDC), 1 July 2001–30 June 2019; ACT Admitted Patient Collection (ACT APC), 1 July 2004–30 June 2018	Census of all inpatient episodes in all NSW/ACT public and private hospitals, public multi-purpose services and private day procedure centres.	To identify harms and risks associated with prescribed opioids, ascertain comorbid diseases.	Dates of admission, separation and procedures, diagnostic and procedure codes, admission costs, separation mode, hospital type, hospital location.
NSW Emergency Department Data Collection (NSW EDDC), 1 January 2005–9 July 2019; ACT Emergency Department Data Collection (ACT EDDC), 1 July 2005–2 July 2018	All visits to participating emergency departments in NSW/ACT.	To identify harms and risks associated with prescribed opioids.	Dates of presentation and separation, referral source, arrival mode, visit type, triage, diagnosis, separation mode.
NSW Controlled Drugs Data Collection (CoDDaC), 1 January 1985–31 December 2019.	Opioid substitution therapy (methadone/buprenorphine) treatment episodes in NSW. The data collection system for CoDDaC is the Electronic Recording and Reporting of Controlled Drugs, which was implemented in September 2016 to replace the legacy Pharmaceutical Drugs of Addiction System.	To identify individuals with a history of opioid dependence subsequently prescribed opioids; to examine risk of treatment for iatrogenic opioid dependence.	Treatment entry and exit dates, type of medicine authorised.
Mental Health Ambulatory Collection (MH-AMB), 1 January 2001–30 June 2018	Records on the assessment, treatment, rehabilitation or care of non-admitted mental health patients in NSW.	To identify individuals with mental health disorders and their treatment patterns.	Date of service, mental health diagnoses, services provided.

Although data from the NSW EDDC, ACT APC and ACT EDDC were included in the linkage, information from these datasets were not included in establishing baseline characteristics of the cohort as the date ranges for these datasets do not extend back to the first date of observation for the cohort.
*Most collections hold patient demographics including age, sex.
ACT, Australian Capital Territory; NSW, New South Wales.

Table 2 Sociodemographic characteristics at cohort entry (N=3 569 433)

Sociodemographic characteristic	N (%)
Sex	
Male	1 689 465 (47.3)
Female	1 879 968 (52.7)
Age (years)	
18–24	409 223 (11.5)
25–34	530 172 (14.9)
35–44	559 298 (15.7)
45–54	539 250 (15.1)
55–64	575 164 (16.1)
65–74	512 376 (14.4)
75–84	307 049 (8.6)
85+	136 900 (3.8)
Beneficiary status	
Concessional	1 885 741 (52.8)
General	1 683 692 (47.2)
Remoteness*†	
Major city	2 530 789 (71.4)
Inner regional	767 919 (21.7)
Outer regional	225 738 (6.4)
Remote/very remote	19 162 (0.5)
Relative socioeconomic disadvantage‡§	
Most disadvantaged	651 908 (18.4)
Second quintile	645 752 (18.2)
Third quintile	820 567 (23.2)
Fourth quintile	709 384 (20.0)
Least disadvantaged	714 183 (20.2)
Year of cohort entry	
2003–2006	782 317 (21.9)
2007–2009	407 796 (11.4)
2010–2012	604 655 (16.9)
2013–2015	1 016 199 (28.5)
2016–2018	758 466 (21.2)

*Classified using 2016 Remoteness Area indices.[28]
†Excludes 25 825 individuals with missing values.
‡Classified using Index of Relative Socioeconomic Disadvantage 2011.[29]
§Excludes 27 639 individuals with missing values.

Table 3 Evidence of medical conditions* in the 12 months prior to cohort entry

Medical condition	N (%)
Cardiovascular	
Arrhythmia	77 964 (2.2)
Congestive heart failure	153 143 (4.3)
Hyperlipidaemia	733 451 (20.5)
Hypertension	468 467 (13.1)
Ischaemic heart disease	145 137 (4.1)
Endocrine	
Diabetes	297 036 (8.3)
Hyperthyroidism	9834 (0.3)
Hypothyroidism	148 728 (4.2)
Mental and neurological	
Anxiety	264 160 (7.4)
Dementia	39 648 (1.1)
Depression	603 127 (16.9)
Opioid use disorder	13 658 (0.4)
Other substance use disorder	80 928 (2.3)
Parkinson's disease	30 346 (0.9)
Psychoses	99 766 (2.8)
Musculoskeletal	
Osteoporosis	117 684 (3.3)
Rheumatic disease	71 686 (2.0)
Respiratory	
Asthma	349 922 (9.8)
Chronic obstructive pulmonary disease	89 270 (2.5)
Other	
Cancer	207 261 (5.8)
Chronic liver failure	39 012 (1.1)
Hepatitis C	9445 (0.3)
HIV/AIDS	4908 (0.1)
Renal disease	38 566 (1.1)

HIV/AIDS: Human immunodeficiency virus/Acquired immunodeficiency syndrome
*A composite indicator for each medical condition was derived using information from each individual's PBS dispensing history, contact with inpatient hospital services and contact with community mental health services. These datasets were used in conjunction with cancer registry notifications to identify cancer and registrations for opioid agonist therapy treatment to identify opioid use disorder (see online supplemental table S3).
PBS, Pharmaceutical Benefits Scheme.

18.4% are in the most disadvantaged socioeconomic quintile. Comparing the sociodemographic characteristics of individuals in the POPPY II cohort to the general NSW population, our cohort is broadly similar to the general NSW population in 2016–2018 (online supplemental tables S6 and S7). Over the 16-year study period, 533 616 (14.9%) people are known to have died.

Overall, 5.8% of individuals had evidence of cancer in the 12 months prior to cohort entry using a composite indicator (table 3). Almost 1 in 5 (16.9%) individuals had evidence of depression in the previous 12 months. Less than 1% (0.4%) had evidence of a history of opioid use disorder, however, over 2.3% had evidence of a history of other substance use disorders.

Most individuals (97.3%) accessed MBS-subsidised primary healthcare services in the year prior to cohort

Table 4 Health service use in the 12 months prior to cohort entry

Health service use	N (%)	Median visits (IQR)*
Primary health services		
General or allied health services	3 388 652 (94.9)	7 (4–12)
General practitioner visit	3 386 877 (94.9)	7 (4–12)
Allied health practitioner visits		
Any allied health practitioner	316 811 (8.9)	4 (2–5)
Chiropractor	14 330 (0.4)	4 (2–5)
Exercise physiologist	15 509 (0.4)	2 (1–3)
Osteopath	5498 (0.2)	3 (2–5)
Physiotherapist	86 253 (2.4)	3 (2–5)
Podiatrist	96 306 (2.7)	3 (1–4)
Psychologist	126 456 (3.5)	4 (2– 6)
Hospital admissions		
Any inpatient admission	1 358 929 (38.1)	1 (1–2)
Emergency admission	549 992 (15.4)	1 (1–2)
Non-emergency-planned admission	935 394 (26.2)	1 (1–2)
Other type of admission	160 852 (4.5)	1 (1–1)

*Due to skewed distributions, the median (IQR) number of MBS services used is calculated for individuals with evidence of each type of service use.
MBS, Medical Benefits Scheme.

Table 5 Analgesic and psychotropic medicines dispensed in the 3 months prior to cohort entry

Type of medicine use	N (%)
Any non-opioid analgesic medicine	961 535 (26.9)
Paracetamol	339 226 (9.5)
Pregabalin	29 512 (0.8)
Gabapentin	4055 (0.1)
Triptans	19 294 (0.5)
Pizotifen	6497 (0.2)
Non-steroidal anti-inflammatory drugs (NSAIDs)	690 876 (19.4)
Non-selective NSAIDs	349 312 (9.8)
Selective Cox-2 inhibitors	368 051 (10.3)
Any psychotropic medicine*	732 319 (20.5)
Antidepressants	338 367 (9.5)
Antiepileptics†	65 749 (1.8)
Antipsychotics	190 246 (5.3)
Anxiolytics	169 061 (4.7)
Hypnotics/sedatives	142 641 (4.0)

*Classified according to WHO Anatomical Therapeutic Chemical categories.[25]
†Excludes pregabalin and gabapentin.

entry (table 4). A smaller proportion of the cohort (8.9%) accessed an allied health professional during this time, with a median (IQR) number of visits of 4 (2–5). Over one-third of the cohort (38.1%) was admitted to an NSW hospital in the 12 months prior to cohort entry, mostly for non-emergency planned admissions (26.2%).

In the 3 months prior to cohort entry, 26.1% of individuals were dispensed a non-opioid analgesic, most commonly a non-steroidal anti-inflammatory drug (19.4%) (table 5). Less than 10% (9.5%) were dispensed paracetamol and 0.8% were dispensed pregabalin. Overall, 1 in 5 individuals (20.5%) were dispensed a psychotropic medicine, including 9.5% dispensed an antidepressant.

Less than one-quarter (22.2%) were dispensed a strong opioid at their index opioid dispensing; the most commonly dispensed opioids were paracetamol/codeine (61.3%) and oxycodone (16.3%) (table 6). More than 95% of individuals were dispensed one opioid only (97.3%) or an oral formulation (97.6%) at their index dispensing, and most opioids were prescribed by medical practitioners (91.3%), followed by dental practitioners (7.1%).

In sensitivity analyses modifying the look-back window to identify new opioid use and assessing alternative ways of accounting for the undercapture of under copayment dispensings prior to July 2012, very few differences in cohort characteristics were identified (online supplemental tables S8–S17). The one exception was the cohort restricted to concessional beneficiaries (2002–2018), which was an older, more socioeconomically disadvantaged population with evidence of more medical conditions, and more health service and medicine use. These characteristics are consistent with the requirements for eligibility for concessional benefits.

FUTURE PLANS

The POPPY II cohort will be updated periodically, both extending the follow-up duration of the existing cohort, and including new individuals who have subsequently initiated opioids. The size of the cohort, length of study period and robustness of the data that has been linked will allow for a number of aspects related to opioid use to be examined, falling into three broad categories: opioid utilisation, health outcomes and analyses among important subpopulations. Work related to opioid utilisation includes examinations of individual opioid use trajectories over time, characteristics and predictors of different opioid use patterns, and development of a data-informed method to assess time-varying opioid exposure. Important health outcomes will be examined, including fatal and non-fatal overdose, all-cause and cause-specific mortality, transition to opioid dependence, suicide, falls and other injuries, and health service utilisation following opioid initiation. The size of the dataset and inclusion of

Table 6 Index opioid use characteristics at cohort entry

Opioid use characteristic	N (%)
Opioid*	
Buprenorphine	51 269 (1.4)
Codeine	229 574 (6.4)
Dextropropoxyphene	1576 (<0.1)
Fentanyl	21 067 (0.6)
Hydromorphone	3838 (0.1)
Methadone	1126 (<0.1)
Morphine	50 553 (1.4)
Oxycodone	582 236 (16.3)
Oxycodone/naloxone	88 921 (2.5)
Paracetamol/codeine	2 189 582 (61.3)
Pethidine	932 (<0.1)
Tapentadol	10 674 (0.3)
Tramadol	405 922 (11.4)
Opioid type††	
Strong opioid	744 369 (20.9)
Other opioid	2 776 497 (77.8)
Both strong and other opioid	48 567 (1.4)
No of opioids‡‡	
1	3 474 225 (97.3)
2 or more	95 208 (2.7)
Administration route*	
Oral	3 482 921 (97.6)
Transdermal	72 263 (2.0)
Parenteral	21 189 (0.6)
Other	525 (<0.1)
Prescriber type	
Medical practitioner	3 259 491 (91.3)
Dental practitioner	254 037 (7.1)
Both medical and dental	2500 (0.1)
Other/missing	54 106 (1.5)
Total oral morphine equivalent milligrams	
<100	2 395 081 (67.1)
100–249	820 314 (23.0)
250–499	208 695 (5.8)
500–749	65 984 (1.8)
750+	79 359 (2.2)

*Categories are not mutually exclusive.
†Strong opioids: buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone±naloxone Other opioids: codeine, dextropropoxyphene, pethidine, tapentadol, tramadol.
‡Accounts for different types of opioids only and not different formulations and strengths of the same opioid.
PBS, Pharmaceutical Benefits Scheme.

all adults in NSW will allow for the in-depth examination of clinically important subpopulations, such as people diagnosed with cancer, musculoskeletal conditions, mental health conditions or opioid use disorder, as well as opioid exposure following hospital admission. Finally, the duration of the study period (currently 16 years) will also allow for an examination of the population-level impact of changes including regulatory responses to opioid-related harms.

STRENGTHS AND LIMITATIONS

A key strength of the POPPY II cohort is extensive population-based capture of adults initiating prescription opioids over a 16-year period in NSW, the most populous jurisdiction in Australia. Through linkage to multiple health datasets, we have established a critical data resource on the health status of individuals in the cohort prior to, during and after opioid use to assess the health outcomes of prescription opioid use. Importantly, we have been able to draw on each of the linked datasets in the study to obtain the most detailed profile to date of the health status of individuals prior to opioid initiation, including the use of a composite measure to define common medical conditions.

As in any study using linked administrative data, a major limitation is understanding the extent of record capture across each of the data sources. The PBS dataset is the central data source in our study and is the most comprehensive dataset available for studies of medicines use at the individual level in Australia.[21] Although we have examined various cohort definitions to overcome issues related to the undercapture of under copayment dispensings prior to 2012, with minimal variation in the results, several limitations remain. Indications for medicine use are not routinely recorded and as the dataset only contains records of subsidised medicines dispensed, we were unable to identify individuals who initiated an unsubsidised opioid or those individuals who may have been initiated on an opioid in a public hospital prior to being prescribed and dispensed medicines in primary care. However, as previous research has shown that PBS records account for almost 90% of all prescription opioid use in Australia,[23] this is not expected to have a major impact on the generalisability of study findings. Finally, given the extensive follow-up period, it is important to acknowledge that practice changes may occur over time that may impact on overall patterns of use, however, these are less likely to impact the results from exposure–outcome studies. To assess any time-related impacts on our findings, we will examine the time of cohort entry in statistical models.

COLLABORATION

To protect privacy and confidentiality, approval for the linkage of health data in NSW is provided under strict conditions for the storage, retention and use of the data.

The current approval permits storage of the data at one site (UNSW Sydney) for up to 7 years following the date of publication of results. We encourage interested parties to contact us to discuss potential secondary data analyses. Requests for data access can be submitted to NG (n.gisev@unsw.edu.au) for review by the POPPY II investigator team. Potential collaborators will be required to gain approval for data access and specific secondary analyses from relevant ethics committees.

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Contributors All authors had involvement in developing the original protocol document upon which this manuscript was based. The study idea was conceived by NG, S-AP, TD and LD. NG, S-AP, TD, DCC, FB, SL, AD, RPM, AW, LD, TM and LB provided input to the study design, and developing the research questions and statistical analysis plan. NG and LD drafted the first iteration of the manuscript. NG, S-AP, TD, DCC, FB, SL, AD, RPM, AW, LD, TM and LB reviewed the manuscript and approved the final draft. NG accepts accountability for all aspects of the work and is the guarantor for this study

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Ethics approval This study involves human participants and the study protocol received full ethical approval from the Australian Institute of Health and Welfare (AIHW) Ethics Committee (EO2016/4/314), NSW Population and Health Services Research Committee (2017/HRE0208), the ACT Health Human Research Ethics Committee (ETHLR.18.094), and the ACT Calvary Public Hospital Bruce Ethics Committee (5-2019). A waiver of the requirement to obtain consent was granted by the reviewing ethics committees due to the nature of the data (ie, population-based data linkage).

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Data availability statement Data are available on reasonable request. To protect privacy and confidentiality, approval for the linkage of health data in NSW is provided under strict conditions for the storage, retention and use of the data. The current approval permits storage of the data at one site (UNSW Sydney) for up to seven years following the date of publication of results. We encourage interested parties to contact us to discuss potential secondary data analyses. Requests for data access can be submitted to A/Prof Natasa Gisev (n.gisev@unsw.edu.au) for review by the POPPY II investigator team. Potential collaborators will be required to gain approval for data access and specific secondary analyses from relevant ethics committees.

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