

# BMJ Open The POPPY Research Programme protocol: investigating opioid utilisation, costs and patterns of extramedical use in Australia

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## ABSTRACT

**Introduction:** Opioid prescribing is increasing in many countries. In Australia, there is limited research on patterns of prescribing and access, or the outcomes associated with this use. The aim of this research programme is to use national dispensing data to estimate opioid use and costs, including problematic or extramedical use in the Australian population.

**Methods and analysis:** In a cohort of persons dispensed at least one opioid in 2013, we will estimate monthly utilisation and costs of prescribed opioids, overall and according to individual opioid formulations and strengths. In a cohort of new opioid users, commencing therapy between 1 July 2009 and 31 December 2013, we will examine patterns of opioid use including initiation of therapy, duration of treatment and concomitant use of opioids and other prescribed medicines. We will also examine patterns of extramedical opioid use based on indicators including excess dosing, use of more than one opioid concomitantly, doctor/pharmacy shopping and accelerated time to prescription refill.

**Ethics and dissemination:** This protocol was approved by the NSW Population and Health Services Ethics Committee (March 2014) and data access approved by the Department of Human Services External Review Evaluation Committee (June 2014). This will be one of the first comprehensive Australian studies with the capability to investigate individual patterns of use and track extramedical use. In the first instance our analysis will be based on 5 years of dispensing data but will be expanded with ongoing annual data updates. This research has the capability to contribute significantly to pharmaceutical policy within Australia and globally. In particular, the trajectory of extramedical prescription-opioid use has been the subject of limited research to date. The results of this research will be published widely in general medical, pharmacoepidemiology, addiction and psychiatry journals.

## BACKGROUND

The global increase in prescribed opioid use over the past 30 years has been well

## Strengths and limitations of this study

- Using data on prescriptions reimbursed by the Pharmaceutical Benefits Scheme (PBS), this study will provide novel data on the patterns and costs of opioid use, including extramedical use, in the Australian population. This will provide the most detailed information to date regarding person-level patterns of opioid consumption in Australia.
- The research programme is limited by:
  - The extent to which these data reflect total opioid consumption. The data set used in the PBS data does not include private prescriptions or over-the-counter opioids. In addition, parts of the study will not capture low-cost PBS-listed items dispensed to Australians with the highest patient copayment threshold.
  - Dispensing claims do not detail clinical information, including indication for use, which poses challenges given doses of opioids vary depending on the nature of the pain being managed. However, using complete PBS history for each individual, we will be able to identify patients with a recent cancer treatment history.
  - The absence of gold-standard proxy indicators of extramedical opioid use. As such, we will develop indicators through consultation of the literature and feedback from expert clinicians in the fields of pain, cancer and addiction. Sensitivity analyses will be used to establish whether our conclusions are affected by variations in definitions.

documented.<sup>1–8</sup> In Australia, between 1992 and 2007, there was a 300% increase in the number of opioid prescriptions dispensed in the community.<sup>5</sup> In 2012, 7.4 million opioid prescriptions were dispensed via the Pharmaceutical Benefits Scheme (PBS), costing the Australian government approximately \$A271 million. In the 20-year period 1992–2012, the Commonwealth of Australia subsidised over \$A2 billion in

prescribed opioids, with oxycodone and morphine accounting for \$A1.1 billion.<sup>9</sup> Europe and the USA have seen even larger increases in opioid dispensing than Australia.<sup>10</sup> Despite the Australian government's significant investment in these medicines, we know little about the way they are used in routine clinical care.

The observed global increase in opioid use can be attributed, in part, to the broadening of regulatory and subsidy approval of opioids to manage chronic non-cancer pain; previously use was restricted to the management of cancer pain. As opioid use has increased, so too has the concern from healthcare professionals and the public in relation to the harms of prolonged medical use, including concerns about the appropriateness of prescribing opioids long term and the risk of iatrogenic dependence.<sup>11</sup> The most serious risk associated with opioid use is the harm related to opioid overdose. In the USA, prescribed medicines account for more fatal and non-fatal overdoses than illicit drugs.<sup>12</sup> People dying from opioid overdoses often use other medicines concomitantly such as benzodiazepines, antidepressants, antipsychotics and psychostimulants,<sup>13 14</sup> which may further contribute to the risk of an adverse outcome. In Australia, notable increases in reported opioid prescriptions have occurred.<sup>5</sup> This has been associated with hospital separations for opioid poisoning, treatment episodes<sup>3 9</sup> and deaths attributed to pharmaceutical opioids such as oxycodone.<sup>4 15</sup>

'Extramedical use' is defined as use not as directed by a doctor.<sup>16</sup> Among other things, it may include using more than directed by the doctor; asking for escalating doses; obtaining prescriptions from multiple doctors without their knowledge; tampering with opioids and taking opioids via routes other than intended (eg, snorting or injecting).<sup>16</sup> A 2010 Australian national survey reported a 7.4% lifetime prevalence and 4.2% 12-month prevalence of using medicines such as analgesics, sedatives/hypnotics, methadone, other opioids and steroids when not medically indicated,<sup>17</sup> equating to approximately 1 in 14 Australians engaging in extramedical use of a prescribed medicine in their lifetime (with a higher prevalence in younger age groups).

Observational cohort studies from the USA and Europe have examined the natural history of opioid analgesic use for chronic non-cancer pain.<sup>18</sup> Small retrospective cohort studies have examined treatment duration, pain reduction, adverse drug events<sup>19</sup> and aberrant behaviours.<sup>20</sup> Larger retrospective cohort studies have examined the risk of overdose,<sup>21</sup> the impact on disability,<sup>22</sup> non-medical use,<sup>23</sup> conditions treated in older adults,<sup>24</sup> and rates of adverse events.<sup>25</sup>

However, in Australia, few studies have examined person-level behaviours of people prescribed opioids, prescribing patterns, patterns of use, or the outcomes and costs associated with this use.<sup>26–28</sup> In order to gain a comprehensive understanding of these issues, we have started a programme of research examining the patterns and costs of PBS-subsidised opioid use, including

extramedical use in the Australian population. This protocol summarises the scope of our programme.

## Aims

The overall objective of this research programme is to evaluate the patterns and costs of opioid use in Australia. Specifically, we aim to:

1. Estimate monthly and annual utilisation and costs of prescribed opioids, overall and according to individual opioid formulations and strengths.
2. Examine patterns of opioid use including initiation of therapy, duration of treatment, concomitant use of opioids and other therapy.
3. Examine patterns of extramedical opioid use based on indicators including excess dosing, use of more than one opioid concomitantly, doctor/pharmacy shopping, and accelerated time to prescription refill.

## METHODS AND ANALYSIS

### Setting

Australia has a publically 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 Commonwealth and State/Territory governments), subsidised outpatient services including consultations with medical and selected healthcare professionals (funded by the Commonwealth's Medicare Benefits Scheme) and medicines prescribed in the community and private hospitals (funded by the PBS). Medicines prescribed to public hospital inpatients are covered primarily by hospital budgets.

### Opioids of interest

The prescribed opioids of interest in this study include opioid medicines belonging to the WHO's Anatomical Therapeutic Chemical classification system (<http://www.who.int/classifications/atcddd/en/>) categories N02A, N07B and R05D (table 1). We requested data for all formulations and strengths of these medicines (individual PBS item numbers). Methadone or buprenorphine may be prescribed for the indication of opiate addiction or pain. For the indication of opiate addiction, these medicines are listed under the S100 Highly Specialised Drug Program administered by the individual Australian states rather than under the national funding system. We listed these indications for completeness, however, the Department of Human Services (DHS) do not record dispensings for opioids dispensed under the state-based S100 program. All records we obtain will be for the indication of pain.

### Data of interest

Our research programme will be underpinned by access to dispensing claims processed by the DHS, the PBS administering body. Until recently, DHS only recorded dispensing claims submitted for the payment of a PBS-subsidy. As such, medicines costing less than the patient copayment

**Table 1** Opioids of interest\*

Medicine	ATC code†
Oxycodone	N02AA05, N02AA55
Tramadol	N02AX02
Buprenorphine	N02AE01, N07BC01, N07BC51
Fentanyl	N02AB03
Morphine	N02AA01
Hydromorphone	N02AA03
Methadone	N02AC52, N07BC02
Codeine	N02BE51, N02AA59, N02AA79, R05DA04‡
Tapentadol*	N02AX06

\*Tapentadol PBS-listed from 2014.

†ATC classification system is an internationally established methodology endorsed by the WHO that is used to classify medicines based on the organ or system on which they act, or their therapeutic and chemical characteristics. Details of the ATC classification system are found online at: <http://www.who.int/classifications/atcddd/en/>.

‡Single ingredient codeine 30 mg tablets (opium alkaloids and derivatives) are ATC coded to the respiratory system R05D and not the nervous system N02A.

ATC, Anatomical Therapeutic Chemical; PBS, Pharmaceutical Benefits Scheme.

threshold were not ascertained in the collection. In effect, low-cost medicines dispensed to beneficiaries with the highest patient copayment threshold (referred to as general beneficiaries) have been underascertained; this issue does not impact on medicines dispensed to beneficiaries with lower copayment thresholds (PBS concessional beneficiaries). In April 2012, DHS began recording below copayment prescriptions.

Our PBS-data requests have been structured in two parts as described below:

*Prevalent user cohort:* comprising Australians dispensed at least one opioid. This is a national cohort of all persons (of any age) prescribed at least one opioid of interest in a given calendar year (with the first year of

data being 2013). The cohort will provide contemporary information about the prevalence of monthly and annual prescribed opioid use across the Australian population, including data from under copayment opioid prescriptions. Data will be updated annually.

*Incident user cohort:* comprising Australians starting new opioid therapy. This is a national cohort focusing on persons dispensed at least one opioid in the period 1 July 2009 to 31 December 2013. Our observation period was chosen as the DHS holds PBS data for a period of only 4 years and 6 months. The data set is updated daily and when each additional day is added, the earliest date in the data set is deleted. Therefore, our exact study period is dependent on the date of extraction. This cohort will be used to examine patterns of prescribed opioid use, including extramedical use. Inclusion criteria are as follows: (1) opioid naïve for at least 3 months prior to the index prescription (see online supplementary appendix A of details on the way in which this was operationalised); (2) aged  $\geq 18$  years at the index prescription. We chose a 3-month wash-out period for cohort inclusion because it was considered sufficient time to ensure that any new, index prescriptions reflected a new 'course' of treatment for a new or recurrent indication. It is possible that some individuals will receive a new prescription under this definition for an indication for which they have been treated previously. However, we will also undertake sensitivity analyses by extending the period of non-use to 6 months. This cohort will also be updated annually.

Tables 2 and 3 detail the variables requested from DHS for the prevalent and incident user cohorts.

### Statistical analysis

We will use best-practice pharmacoepidemiological methods to explore prescribed opioid medicines use in the two cohorts. The general approaches are detailed below:

**Table 2** Variables requested regarding cohort demographics

Variables	Justification
Scrambled patient ID	A unique sequence number enabling person-level analysis and linkage to PBS data set
Month and year of birth	To report demographics of cohort and used to stratify analyses according to age group
Sex	To report demographics of cohort and used to stratify analyses
Month and year of death (mm/yy)	Date of death, in order to censor the follow-up time for each individual in the cohort
Postcode of residence mapped to Statistical Local Area	Used to identify location of residence and map to indices of socioeconomic disadvantage (ie, the <i>Socio-Economic Indexes for Areas</i> (SEIFA)*) and remoteness (ie, the Accessibility/Remoteness Index of Australia (ARIA)†)
Geographic location of residence according to the SA2	Used to identify geographic location of residence to map prescription rates and to evaluate prescription rates according to key demographic characteristics

\*Is a product developed by the ABS that ranks areas in Australia according to relative socioeconomic advantage and disadvantage. The indexes are based on information from the 5-yearly census. Details can be found at: <http://www.abs.gov.au/websitedbs/censushome.nsf/home/seifa>.

†The ABS' Remoteness Areas classification. These are 'Major Cities', 'Inner Regional', 'Outer Regional', 'Remote' and 'Very Remote'. Details have been reported in ref. 54 55.

ABS, Australian Bureau of Statistics; ARIA, Accessibility/Remoteness Index of Australia; PBS, Pharmaceutical Benefits Scheme; SA2, Statistical Area Level 2.

**Table 3** Pharmaceutical Benefits Scheme (PBS) data on opioid dispensing (and other medication dispensing) history

Variables	Description	Justification
Scrambled patient ID	A unique sequence number	Enable person-level analysis and linkage to sociodemographic data set
Month and year of birth	Month and year when each person was born	Determine age at time of dispensing. Also used as cross-check with data in demographic file
Sex	Sex	Cross-check with data in demographic file
Date of supply	Date medicine is dispensed	Establish temporal relationship in dispensing records
Item code	A unique number which represents the dose form and strength of the pharmaceutical item patients receive	Identify medicines of different forms and strengths
ATC code	Anatomical Therapeutic Chemical classification code	Delineate between medicine types
Generic name	Generic medication name	Delineate between medicine types
Quantity dispensed	Quantity of medicine dispensed	Calculate defined daily dose and durations of treatment
Original or repeat prescription	A variable to distinguish between repeat or new prescription	Understand pattern of treatment
Beneficiary level	General beneficiary±safety net; concession card holder±safety net	Identify level of entitlement and determine comprehensiveness of data capture
PBS benefit	Amount paid by the Australian government	Determine the total cost incurred by the Australian government to supply opioids in a given calendar year
Prescriber scrambled ID	A unique sequence number given to each prescriber	Delineate between scripts written by different doctors
Prescriber location	Postcode mapped to Statistical Local Area	Establish location of practice
Prescriber type	Identifies primary specialty of the prescribing doctor	Identify what type of doctors prescribe medicines of interest
Pharmacy scrambled ID	A unique sequence number given to each dispensing pharmacy	Delineate between scripts dispensed at different pharmacies
Pharmacy location	Postcode mapped to Statistical Local Area	Establish location of pharmacy

1. *Utilisation and costs*: we estimate the monthly and annual prevalence and costs of opioid use overall and according to individual opioid formulations and strengths. Utilisation estimates will be based on number of prescriptions, Defined Daily Dose (DDD) per 1000 population per day or in oral morphine equivalent mg.<sup>29</sup> Analyses will be stratified according to patient age, gender, location of residence and indices of socioeconomic disadvantage. Data from the Australian Bureau of Statistics will determine population estimates for each subgroup of interest. Estimates will also be presented using ESRI ArcGIS (a mapping software programme). This will show overall national patterns of use by geographical area of patient, prescriber or dispensing pharmacy (eg, Statistical Local Area, jurisdictionally), as well as graphical presentation of variations in levels of use. Publicly available data on the demographic characteristics of geographical areas will be obtained from the Australian Bureau of Statistics (age distribution, income, education and unemployment).
2. *Patterns of opioid use*: we will examine patterns of use in the following ways:
  - A. *Median duration of opioid treatment*: defined as the time from the first opioid dispensing record to the last dispensing record plus 30 days. These estimates can also detail different courses of opioid therapy by accounting for breaks in treatment of more than 60 days.
  - B. *Dose escalation*: we will estimate the average daily dose of each opioid prescription dispensed using the internationally recognised DDD unit.<sup>30</sup> At the individual level, we will calculate the changes in average DDDs by prescription and report the number of patients in whom doses are increasing, and by what level, over time.
  - C. *Concomitant opioid and other concomitant medicines use*: we will investigate the concomitant use of multiple opioids, in addition to the use of opioids with other prescribed medicines, such as benzodiazepines, antidepressants and antipsychotics. Concomitant use will generally be defined as the observation of at least two dispensing records from different medicines within a specific time-frame of each other. The rules will vary according to the therapy of interest. Furthermore, we will identify individuals at risk of potentially harmful drug–drug interactions deemed to be clinically relevant in the

literature and common drug information resources.<sup>31–33</sup> These will be examined using a previously published approach<sup>34</sup> overall, and for specific population subgroups such as older adults.

3. *Extramedical use*: indicators of extramedical opioid use—we will adopt measures of extramedical use described previously in the literature<sup>16</sup> and report on the rates of these patterns of extramedical use:
  - A. *Excess dosing*: defined as average daily dosing outside guideline recommendations.<sup>35–37</sup>
  - B. *Concomitant opioid use*: as described above.<sup>36 38</sup>
  - C. *Doctor shopping*: opioid prescriptions written by more than one doctor and dispensed within a specific time-frame.<sup>14 39–45</sup>
  - D. *Pharmacy shopping*: dispensing opioid prescriptions at more than one pharmacy within a specified time-frame.<sup>40–44</sup>
  - E. *Accelerated prescription refill*: repeated dispensing of opioid prescriptions earlier than the estimate of when the prescription is complete.<sup>36 37 46–49</sup>

The medication possession ratio and refill compliance rate are measures which use administrative data to assess adherence to medicines. We have included accelerated prescription refill as one of our measures of extramedical use.

We may restrict some of our analyses to concession card-holding populations only, as not all opioid medicines of interest are above the general beneficiary copayment amount. Other medicines of interest including benzodiazepines and psychotropic medicines such as antidepressants, antipsychotics and central nervous system stimulants, also fall below the general beneficiary copayment. We will also undertake analyses with and without persons dispensed cancer medicines to establish how the inclusion of patients with cancer (who generally receive significantly higher opioid doses than patients without cancer) impacts on our estimates.

### Data access approval

Data access has been approved by the DHS External Review Evaluation Committee (MI0166). However, DHS have recently advised that it may be necessary to restrict our cohorts due to the considerable amount of data they will be required to provide to us. For example, to access the entire dispensing history of all people dispensed an opioid in our incident user cohort, it has been estimated that we would be provided with 40% of the entire DHS data holdings. As such, our cohorts may be restricted to a 10% random sample of the national opioid user cohort.

### Consent and privacy considerations

*Use and Disclosure of Information*: Commonwealth data are governed under the Privacy Act 1988. Information Privacy Principle (IPP) 2 under the Privacy Act 1988 provides that personal information should not be used or disclosed for any purpose other than the primary

purpose of the collection. We have obtained approval for the use of data for a secondary purpose: that of research involving access to person-level information. Under IPP2.1(d), use or disclosure for another purpose is allowed if (A) it is necessary for research and it is impracticable to gain consent AND (B) the use is in accordance with the Section 95A guidelines (which provides a process to resolve the conflict that may arise between the public interest in privacy and the public interest in medical research).

*Consent*: The waiver for individual consent was approved by the Population and Health Services Research Ethics Committee in accordance with Section 95A of the Commonwealth Privacy Act 1988. This was because:

- ▶ There were hundreds of thousands of people in the cohort, so it was not possible or practical to obtain consent because of the large study population.
- ▶ Obtaining consent would prejudice the scientific value of the research due to the high participation rates required for unbiased samples (at least 90%),<sup>50</sup> and the Australian evidence about the sociodemographic differences between participants who consent to data linkage research and those who do not.<sup>51</sup>
- ▶ We believe the public interest in this research outweighs the public interest in privacy protection. We consider the benefits to be great and the risk to be small. Currently we know little about the way in which opioids are used in the real world marketplace. Our research has the potential to address key issues such as the risks and benefits of prescribing opioids in Australia. These findings are likely to have national and global significance.

We have minimised the risk to personal privacy by ensuring:

- ▶ Only researchers involved in data analysis will have access to the data.
- ▶ Data will be securely stored at both sites (see below).
- ▶ The research team will not be in possession of any personally identifying information. The files released to the research team will not contain patients' name, rather a unique patient number will be generated by the DHS staff.

Finally, all data will be presented in aggregated form only and potentially identifiable information will not be published. We will suppress data with small cell sizes.

### Confidentiality of data and record retention

This is a collaborative project involving two research teams, one based at the National Drug and Alcohol Research Centre, The University of New South Wales, Australia, and one based at the Faculty of Pharmacy, The University of Sydney. To ensure consistency between the analyses and research teams, decision rules will be developed in group meetings and all analyses will be conducted in SAS so all relevant code can easily be shared where necessary. The confidentiality of records will be ensured by strict adherence to the study protocol in relation to access to, transfer and storage of study data.

## DISCUSSION

The rate of pharmaceutical opioid use is increasing across the globe. However, the actual extent of such use and extramedical use, is currently unknown. The research programme outlined in this protocol will be the first large-scale and nationally representative Australian study to examine patterns of opioid use, including extramedical use, and the costs associated with this use. Previously, PBS opioid dispensing data has typically been analysed using aggregated data.<sup>5-9</sup> This research will also form the foundation of additional studies that can examine the medical consequences of excessive prescription opioid use. This type of research will be possible by access to emergency department and hospitalisation plus cause of death data.

From a clinical perspective, we will investigate common opioid utilisation patterns and identify behaviour indicative of extramedical use of opioids. Furthermore, we will investigate the prevalence of potentially inappropriate combinations of medicines prescribed with opioids, estimating the number of individuals at risk of adverse drug events due to potentially harmful drug–drug interactions. Together, this information could provide a strong evidence base for targeted future intervention programmes to identify and treat high-risk individuals across Australia, as well as form the basis of developing appropriate harm-reduction strategies.

From a public health perspective, this research programme will serve as an important first step to understanding and monitoring prescription opioid use, costs and extramedical use of opioids, now and into the future. Regulators across jurisdictions currently use different criteria for authorising long-term opioid therapy, identifying at-risk patients and measuring potentially problematic opioid use. Valid indicators are required to identify the emergence of problems and provide information that will allow the extent of the problem to be monitored. Therefore, through the development of robust proxies or indicators of extramedical opioid use, this study will yield a useful surveillance tool for public health authorities. Currently no universally accepted indicators exist,<sup>52</sup> and given the growing problem of opioid use in Australia and globally, the indicators have many potentially useful future applications.

## Limitations

It is important to acknowledge several limitations of these data. The first relates to the extent to which these data reflect total opioid consumption in Australia. As noted earlier, until 2012 only medicines reimbursed under the PBS appear in the PBS collection. Items costing less than the general beneficiary contribution did not receive a PBS benefit and was not captured in the collection. This is particularly problematic for selected opioids. Private prescriptions are also not included in the PBS collection, which account for an unknown but potentially substantial number of opioid prescriptions in Australia. Finally, these data do not include opioids that are available in

pharmacies without a prescription (over-the-counter opioids), which in Australia includes codeine, the unit sales of which were more than 15 million in 2013 (personal communication, Gisev N, Nielsen S, Bruno R, *et al*, 2014). Notwithstanding these limitations, the data we will use certainly comprise the most detailed information to hand about person-level patterns of opioid consumption in Australia, permitting detailed estimates of clinical issues that are of increasing community concern and great public health importance.

Second, dispensing claims do not detail clinical information, particularly that relating to indication for use. This poses particular challenges given opioids are prescribed at different doses depending on the nature of the pain being managed; dosing for cancer and non-cancer pain are likely to differ significantly. Given we will be provided with the PBS dispensing history of all opioid-treated patients, we have the capacity to undertake sensitivity analyses excluding patients with a cancer treatment history. However, this approach will not be definitive as cancer medicines dispensing history is likely to be a specific but not sensitive proxy for a cancer diagnosis.

The final limitation relates to the extent to which indicators of extramedical use accurately reflect the problem. However, we will develop our proxies through a process of consultation of the extant literature,<sup>53</sup> and ongoing discussion with and feedback from expert clinicians in the fields of pain, cancer and addiction. We will make ongoing efforts to generate valid indicators to the fullest extent possible. Our use of sensitivity analyses to check whether our conclusions are affected by variations in definitions will also be a feature of our analyses.

## Conclusions

This is a novel Australian research programme of opioid use, costs and extramedical use at an individual level, and with ongoing updates over time. This research has the capability to contribute significantly to pharmaceutical policy within Australia and globally.

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**Contributors** All authors had involvement in development of the original protocol document on which this manuscript was based. LD, SP, BB, NG and BL contributed to the design of the study and revision to the manuscript. LD and SP drafted the first iteration of the manuscript. NG led the preparation of applications to relevant ethics committees, with input from SP, LD, BB and BL. All authors edited the manuscript and approved the final draft.

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**Competing interests** LD and BL have received untied educational grants from Reckitt Benckiser and Mundipharma to conduct postmarketing surveillance of new opioid medications in Australia.

**Ethics approval** This research programme has been approved by the NSW Population and Health Services Ethics Committee (HREC/13/CIPHS/50) and data access approved by the Department of Human Services External Review Evaluation Committee (MIO166).

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**Data sharing statement** No data are publicly available.

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