Karanges Emily (Orcid ID: 0000-0001-7922-2762)
Brett Jonathan (Orcid ID: 0000-0003-3065-7495)

Trends in opioid utilisation in Australia, 2006 – 2015: Insights from multiple metrics

Running head: Opioid use in Australia by multiple metrics

Emily A Karanges[1]

Nicholas A Buckley[2]

Jonathan Brett[1]

Bianca Blanch[3a]

Melisa Litchfield[1]

Louisa Degenhardt[4]

Sallie-Anne Pearson[1,5]

Affiliations

[1]Medicines Policy Research Unit, Centre for Big Data Research in Health, University of New South Wales, Australia, 2052

[2]Discipline of Pharmacology, School of Medical Sciences, University of Sydney, Australia, 2006

[3]Faculty of Pharmacy, University of Sydney, Australia, 2006

[a] Bianca Blanch, current address: Agnes Ginges Centre for Molecular Cardiology, Centenary Institute, Sydney, Australia, 2050

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/pds.4369

[4]National Drug and Alcohol Research Centre, Faculty of Medicine, University of New South Wales

[5]Menzies Centre for Health Policy, University of Sydney, Australia, 2006

Corresponding author

Sallie Pearson

Medicines Policy Research Unit, Centre for Big Data Research in Health

Level 1, AGSM Building (G27), University of New South Wales, Australia, 2052

Phone: +61 2 9385 8895

Email: sallie.pearson@unsw.edu.au

Key words: Australia, defined daily dose (DDD), dispensings, opioids, oral morphine equivalents, pharmacoepidemiology

Key points

- Population-based observational studies have identified increasing trends in opioid use; these studies commonly employ a single population-adjusted, volume-based metric such as number of dispensings, defined daily doses (DDDs) or oral morphine equivalents (OMEs).
- Combining these three volume-based metrics with a person-based measure (number of people dispensed opioids) provides insights into the factors potentially driving these trends.

- We observed increases in subsidised prescribed opioid use in Australia between 2006 and 2015 according to all four metrics, especially our OME-adjusted measure, indicating increasing use of more potent opioids.
- For strong opioids, particularly oxycodone, we observed greater increases in use according to our person- and dispensings-based metrics than our DDD- and OME-based measures, suggesting that increasing numbers of people dispensed opioids at lower average doses may be a greater contributor to these trends than greater exposure per person.
- Employing a combination of metrics provides additional insights into changes in medicine use over time, has utility in studies with access to claims-based data alone or in combination with person-level data, and provides an opportunity for more effective use of existing datasets.

Word count (excluding abstract, tables and figures): 2,701

Prior postings and presentations: None.

Sponsors

This study was funded by the National Health and Medical Research Council (NHMRC) Centre of Research Excellence in Medicines and Ageing (CREMA; 1060407). BB is funded by a University of Sydney Postgraduate Scholarship and CREMA Scholarship Top-Up. JB is

funded by an NHMRC Postgraduate Award and CREMA Scholarship Top-Up. LD is supported by an NHMRC Principal Research Fellowship (1041742). The National Drug and Alcohol Research Centre (NDARC) at the University of NSW is supported by funding from the Australian Government under the Substance Misuse Prevention and Service Improvements Grants Fund. The study sponsors had no role in the collection, analysis or interpretation of data, the writing of the manuscript or the decision to submit the manuscript for publication.

Abstract

Purpose. Population-based observational studies have documented global increases in opioid analgesic use. Many studies have used a single population-adjusted metric (number of dispensings, defined daily doses [DDDs] or oral morphine equivalents [OMEs]). We combine these volume-based metrics with a measure of the number of persons dispensed opioids to gain insights into Australian trends in prescribed opioid use.

Methods. We obtained records of prescribed opioid dispensings (2006 – 2015) subsidised under Australia's Pharmaceutical Benefits Scheme (PBS). We used dispensing claims to quantify annual changes in use according to three volume-based metrics: DDD/1000 pop/day, OME/1000 pop/day and dispensings/1000 pop. We estimated the number of persons dispensed at least one opioid in a given year (persons)/1000 pop using data from a 10% random sample of PBS-eligible Australians.

Results. Total opioid use increased according to all metrics, especially OME/1000 pop/day (51% increase) and dispensings/1000 pop (44%). Weaker opioid use remained stable or declined; strong opioid use increased. The rate of persons accessing weaker opioids only decreased 31% and there was a 238% increase in persons dispensed only strong opioids. Strong opioid use also increased according to dispensings/1000 pop (140%), OME/1000 pop/day (80%) and DDD/1000 pop/day (71% increase).

Conclusions. Our results suggest that the increases in total opioid use between 2006 and 2015 were predominantly driven by a growing number of people treated with strong opioids

at lower medicine strengths/doses. This method can be used with or without person-level data to provide insights into factors driving changes in medicine use over time.

Introduction

The increasing use of prescribed opioid analgesics globally has generated widespread concern from clinicians, patients and policymakers.[1-3] Between 2000 and 2010, opioid sales increased five-fold in the US[4] and use more than doubled in Canada.[5] Increases have also been observed in the UK and Australia,[6-8] although their population-adjusted use is only a quarter to a third of that in the US.[9] In part, these trends have been driven by the increasing use of opioids for the treatment of chronic non-cancer pain (CNCP), despite uncertainty about their efficacy in the long-term treatment of this condition.[10, 11] Concerns have also been raised over accompanying increases in extra-medical use, dependence, overdose, and deaths.[1, 11]

While several studies have reported increases in opioid utilisation at the population level, their conclusions are often based on a single volume-based metric.[7, 8, 12, 13] The World Health Organisation (WHO)'s defined daily dose (DDD) methodology[14] is frequently used for quantifying drug utilisation and permits standardisation of use across countries and different medicine formulations and strengths.[8, 12, 13] Utilisation is based on the medicine's DDD, which represents the assumed average maintenance dose per day for the main indication of the medicine, usually established at the time of marketing. However, metrics

based on DDD may underestimate the true utilisation of strong opioids such as oxycodone, buprenorphine and morphine; their DDDs, established based on doses used in cancer pain, are considerably higher than the average doses used in their current primary indication of non-cancer pain.[15-17]

In recognition of these limitations, recent studies have advocated the use of more clinically-relevant measures based on oral morphine equivalents (OMEs).[18-21] Unlike DDDs, OMEs account for the analgesic potency of each opioid. Therefore, studies based on DDDs and OMEs can generate markedly different results when comparing the relative use of specific opioids or conducting cross-country comparisons, particularly where differences in opioid availability or indications for prescribing exist.[21] Indeed, opioid consumption in Australia amounts to approximately one third of that in the US according to DDD-based measures, but over two thirds based on OMEs.[9, 22]

Volume-based metrics such as DDDs, OMEs and number of dispensings are limited in that they permit few conclusions about the number of patients receiving treatment or the quantity dispensed per person. Measures of the number of people receiving prescription opioids, derived from individual-level data, can provide a useful complement to these volume-based analyses.

We previously published an analysis of Australian trends in opioid analgesic use from 1990 to 2014 using one volume-based metric, DDD/1000 pop/day.[23] Here, we provide additional insights into the nature of these trends by examining annual opioid utilisation (overall and

for weaker, strong and individual opioids) between 2006 and 2015 according to multiple metrics: three volume-based metrics (DDD/1000 pop/day, OME/1000 pop/day, and number of opioid dispensings/1000 pop) and a person-based metric (number of persons dispensed opioids/1000 pop).

Methods

Setting and data: Australia has a publically funded universal health care system offering all Australian citizens and permanent residents access to subsidised prescription medicines under the Pharmaceutical Benefits Scheme (PBS), which services the general population, and the Repatriation Pharmaceutical Benefits Scheme (RPBS) for eligible veterans and their dependents. There are two types of PBS beneficiaries and patients pay a co-payment according to their beneficiary status. *Concessional beneficiaries* are patients eligible for government entitlements, such as pensioners, veterans and low-income earners; all other patients are *general beneficiaries*.[24] In 2015, the patient co-payment was AUD$37.70 for general beneficiaries and AUD$6.10 for concessional beneficiaries.[25] Prescribed medicines costing less than the general patient co-payment threshold are not subsidised by the PBS.

We obtained data on prescribed opioid analgesics dispensed to general and concessional beneficiaries under the PBS (excluding RPBS) for the period January 2006 to December 2015 from two data sources. For consistency with our previous study,[23] we employed the database maintained by the Drug Utilisation Sub-Committee (DUSC) of the Pharmaceutical Benefits Advisory Committee (PBAC) of the Department of Health. This database contains

claims-level data on community (non-public hospital) dispensings, with limited capture of prescriptions supplied to public hospital outpatients and inpatients upon discharge. The DUSC database also includes non-subsidised (under co-payment and private) and RPBS dispensings, however we restricted our analyses to PBS-subsidised records to enable direct comparisons with data from our second source, the PBS 10% sample. This is a standard, person-level dataset provided by the Department of Human Services that contains all PBS-subsidised medicine dispensing records for a 10% random sample of PBS-eligible Australians. The sample is selected based on the last digit of each individual's randomly assigned unique identifier.

Medicines of interest. We obtained data for the ten prescription opioid analgesics (including combination products) attracting a PBS subsidy at any time between 2006 and 2015: buprenorphine, codeine, fentanyl, hydromorphone, methadone, morphine, oxycodone, pethidine, tapentadol and tramadol. Codeine and tramadol were classified as weaker opioids; the remainder as strong opioids.[26, 27] We excluded opioid formulations used primarily for indications other than analgesia (e.g. anaesthetics, opioid dependence).

Analysis. We examined annual opioid utilisation in the period 2006 to 2015 using three volume-based metrics (DDD/1000 pop/day, OME/1000 pop/day, number of opioid dispensings/1000 pop) and one person-based metric (number of persons dispensed one or more opioids [persons/1000 pop]). We examined opioid utilisation overall and for strong, weaker and individual opioids. For persons/1000 pop, individuals receiving more than one

discrete opioid in a given year were recorded as receiving each individual drug. Similarly, individuals receiving more than one opioid strength were recorded under both strength categories. As such, we also calculated the number of persons/1000 pop receiving the following: strong opioids only (persons receiving one or more strong opioids but no weaker opioids), weaker opioids only (weaker opioids but no strong opioids) and strong + weak opioids (a combination of strong and weak opioids). All metrics were adjusted using yearly estimates of the total Australian population, obtained from the Australian Bureau of Statistics.[28, 29] We used the DUSC dataset to obtain our volume-based estimates, as these are frequently derived from claims-level data[7, 8, 21] and our person-level dataset, the 10% PBS sample, to estimate persons/1000 pop.

We calculated DDD/1000 pop/day using DDDs assigned by World Health Organisation Collaborating Centre for Drug Statistics Methodology (WHOCC).[14] OME/1000 pop/day was calculated by adjusting DDD/1000 pop/day for opioid potency using the DDD and OME conversion factor of the medicine of interest. We used OME conversion factors compiled by the Australian National Drug and Alcohol Research Centre (NDARC)[18] and DUSC[19] from multiple Australian and international sources (Supplementary Table 1). For combination products, we calculated DDD/1000 pop/day and OME/1000 pop/day for the opioid component only. See Supplementary for more detailed information on the calculation of DDD/1000 pop/day and OME/1000 pop/day. A more comprehensive description of our four metrics is provided in Table 1.

[Insert Table 1]

We completed our analysis using SAS 9.4 and Microsoft Excel 2010 and generated graphs using GraphPad Prism 5.0c.

Ethical and Data Access Approvals. Ethical approval for use of the PBS 10% sample was obtained from the New South Wales Population and Health Services Research Ethics Committee (2013/11/494) and data access was approved by the Australian Department of Human Services External Request Evaluation Committee. DUSC data were provided in de-identified aggregated form; as such, ethical approval was not required.

Results

Trends in subsidised opioid utilisation by individual metrics, 2006 to 2015

[Insert Figure 1, Table 2]

From 2006 to 2015, total opioid utilisation increased according to all metrics (Figure 1, Table 2), with a 51% increase according to OME/1000 pop/day and a 10% increase in the rate of people dispensed at least one opioid (65 persons/1000 pop in 2015). These trends were driven by increases in strong opioid use; the use of weaker opioids remained relatively stable or declined. Strong opioid use increased 140% according to dispensings/1000 pop, approximately twice the percentage increase according to our other volume-based metrics, and there was a 158% increase in the rate of people dispensed strong opioids. Our person-

level analysis also revealed a 238% increase in the rate of people dispensed strong opioids alone and an 80% increase in the rate of those dispensed both strong and weaker opioids in a year, across the study period. In contrast, we observed a 31% decline in the rate of persons dispensed weaker opioids alone and an 11% decline in weaker opioid use according to dispensings/1000 pop.

Comparative trends in the use of individual opioids

Between 2006 and 2015, use of oxycodone, buprenorphine, fentanyl and hydromorphone increased markedly by all metrics (Figure 1, Table 2). With the exception of hydromorphone, the percentage increase differed little between DDD/1000 pop/day and OME/1000 pop/day. Oxycodone use approximately doubled according to these metrics but tripled according to persons/1000 pop. Conversely, the percentage increase in fentanyl and buprenorphine use according to volume-based measures was two or more times the increase in the rate of people dispensed these medicines.

Morphine use declined over the study period, especially according to volume-based metrics (41 – 43% decline compared to an 18% decline according to persons/1000 pop). There was also a 21% decline in the rate of people dispensed codeine and a 16% decline in codeine dispensings, with little change in use according to other metrics.

Use of individual opioids, 2015

[Insert Table 3]

Strong opioids accounted for the majority of total opioid use in 2015 according to OME/1000 pop/day (77%) and dispensings/1000 pop (61%), but just under half by DDD/1000 pop/day (Table 3). Strong opioids were dispensed to 51% of all people dispensed opioids; 18% of those dispensed strong opioids were also dispensed weaker opioids.

Oxycodone and tramadol were among the most utilised opioids according to all metrics. Oxycodone was the leading opioid according to OME/1000 pop/day and dispensings/1000 pop, comprising over a third of opioid use, was received by 40% of people dispensed opioids, but accounted for only 21% of opioid use according to DDD/1000 pop/day. The percentage of total use accounted for by tramadol ranged from 16% according to OME/1000 pop/day to 21% according to persons/1000 pop. Codeine was the most utilised opioid according to persons/1000 pop (dispensed to over 50% of people on opioids) and DDD/1000 pop/day (36%) and was second only to oxycodone according to dispensings/1000 pop. However, codeine comprised only 7% of total opioid use according to OME/1000 pop/day. The proportion of total use comprised by many strong opioids (e.g. fentanyl, morphine, methadone, hydromorphone and tapentadol) was highest according to OME/1000 pop/day.

Discussion

This paper demonstrates the advantages of combining multiple metrics to examine and interpret changes in prescribed medicine use over time. This method not only reduces the potential for misinterpretation of results due to an individual metric's limitations, but can

provide valuable insights into factors contributing to changes in utilisation. In this study, we combined three volume-based metrics and a simple person-level metric to draw conclusions about the probable role of changes in average dose and/or treatment duration and the size of the treated population to changes in opioid use in Australia between 2006 and 2015. Here we discuss the use of this method in the context of our own findings, including its application to studies relying on volume-based metrics alone.

We found increased use of prescribed opioid analgesics over the study period. In agreement with studies from Canada,[30] the UK,[6, 31] and Australia,[23] strong opioid use increased by all metrics while weaker opioid use remained relatively stable or declined. There was a comparatively larger increase in total opioid use according to OME/1000 pop/day than DDD/1000 pop/day, reflecting this shift toward use of strong opioids. For total opioid use, the increase in volume exceeded the increase in persons treated, but this pattern was largely reversed for strong opioids. This apparent contradiction resulted from an increase in the rate of persons treated with strong opioids but a decrease in those treated with weaker opioids alone. Together, these findings suggest that an increase in the number of people dispensed strong opioids was a greater contributor to the growth in opioid use between 2006 and 2015 than an increase in volume resulting from higher average doses or treatment durations. Moreover, the more pronounced increase in dispensings than in other volume-based metrics for strong opioids suggests increasing use of lower medicine strengths or doses.

Combining volume- and person-based metrics: The example of oxycodone

As demonstrated in Table 2, combining multiple metrics can be particularly useful for interpreting changes in the use of individual opioids over time. In the case of oxycodone, the pattern of results closely reflects those observed of strong opioids; the most pronounced increases were in persons/1000 pop followed by dispensings/1000 pop. This suggests that the primary contributors to the increases in oxycodone use were an expanding population of people prescribed oxycodone, who were most likely to be prescribed lower average doses. In support of these conclusions, marked increases in the treatment of opioid naïve individuals with oxycodone have been observed in the community, hospital inpatient settings, emergency departments and upon hospital discharge,[32-34] with the vast majority of these individuals treated with low doses and for short durations.[32, 35] Use of low strength formulations has further increased since the PBS subsidy of oxycodone/naloxone in 2011.[23, 36]

Combining volume-based metrics: The example of buprenorphine

Many pharmacoepidemiological studies investigating trends in medicine use rely on datasets that do not permit person-level analyses. Although many of our insights have been possible due to the inclusion of a person-level metric, studies combining volume-based metrics alone remain valuable. For example, we report a larger increase in buprenorphine use according to DDD/1000 pop/day and OME/1000 pop/day than in dispensings/1000 pop, suggesting that increasing use of higher medicine strengths or doses may have contributed

to these trends. The change is unlikely to be explained by an increase in the average quantity of buprenorphine patches received per prescription in the current example, as the quantity per prescription was fixed over the study period.

This combination of volume-based metrics can also suggest how changes in the treated population may contribute to changes in opioid use over time. Here we can infer that the increasing use of buprenorphine use over the study period was not primarily due to increases in the number of people treated with buprenorphine. We conclude above that the increases in buprenorphine use were likely driven by increasing use of higher doses, yet new users of buprenorphine are most likely to be opioid-naive individuals with less severe pain treated at low doses; buprenorphine is a recommended first-line opioid treatment[37] and, being a partial agonist, is less appropriate for pain relief in opioid-tolerant individuals or for the treatment of severe pain.[38] Our person-level analysis supports our conclusion, with the percentage increase in the rate of persons dispensed buprenorphine 3-4 times lower than the increase in our volume-based metrics.

Cautions in the use of multiple metrics: The example of hydromorphone

Clearly, the insights gained from combining metrics must be evaluated against what is known about the clinical use of the medicine. One must also consider the impact of changes in medicine availability, regulation or subsidy on estimates of medicine use. This is clearly demonstrated through the example of hydromorphone. The pattern of results in Table 2 suggests that, in part, the increases in hydromorphone use were likely driven by a growing

population treated with higher potency formulations. However, we previously reported a profound shift from high potency parenteral formulations to lower potency oral formulations over this period, precipitated by the PBS subsidy of hydromorphone modified-release tablets in 2009.[23] As such, in contrast to our results, we would expect a less pronounced increase in OME/1000 pop/day than DDD/1000 pop/day.

This discrepancy can likely be explained by differences in the accuracy of DDD/1000 pop/day in estimating the use of oral and parenteral formulations. While DDD/1000 pop/day appears relatively accurate for oral hydromorphone, [17] it likely overestimates use of the parenteral formulation, for which the DDD appears lower than the average prescribed daily dose. This likely inflated our estimated DDD/1000 pop/day early in the study period, when the parenteral formulation dominated the market, thereby underestimating the percentage increase between 2006 and 2015.

Limitations

This study only included data on prescriptions subsidised under the PBS (approximately 80% of opioid prescriptions dispensed in 2011),[23] excluding RPBS, under co-payment and private prescriptions, and contains limited data on public hospital dispensings. We did not examine use of over-the-counter (OTC) codeine products as data on these medicines are not available; low-dose OTC codeine products comprise 40-50% of codeine sales in Australia.[39] Our datasets also lack information on prescribed daily dose, duration of treatment and the indication for prescribing.

We derived our volume-based metrics and our person-based metric from two different datasets, therefore it is possible that sampling differences may have influenced our results. However, this is unlikely to have a significant impact; our claims database incorporates whole-of-population dispensings for Australia's 24 million citizens and our person-level data covers a significant representative proportion of the national population. We can therefore be confident as to the widespread generalisability of our results.

Conclusions

Here we demonstrate the power of multiple metrics in interpreting changes in opioid use over time. Using a combination of three volume-based metrics, with or without our person-level metric, we provide insights into the probable contribution of factors such as changes in dose and treatment duration to the observed trends. This method provides an opportunity for better use of existing datasets and as a means of generating hypotheses for further research.

Acknowledgements

This study was funded by the National Health and Medical Research Council (NHMRC) Centre of Research Excellence in Medicines and Ageing (CREMA; 1060407). BB is funded by a University of Sydney Postgraduate Scholarship and CREMA Scholarship Top-Up. JB is funded by an NHMRC Postgraduate Award and CREMA Scholarship Top-Up. LD is supported by an NHMRC Principal Research Fellowship (1041742). The National Drug and Alcohol Research Centre (NDARC) at the University of NSW is supported by funding from the Australian Government under the Substance Misuse Prevention and Service Improvements Grants Fund. The study sponsors had no role in the collection, analysis or interpretation of data, the writing of the manuscript or the decision to submit the manuscript for publication. We thank the Australian Government Department of Health and Department of Human Services for providing the data for this research.

Conflict of interest statement

SP is a member of the Drug Utilisation Sub-Committee (DUSC) of the Pharmaceutical Benefits Advisory Committee (PBAC). The views presented are those of the authors and do not reflect those of the PBAC. LD has received untied educational grants from Reckitt Benckiser and Mundipharma to undertake post-marketing surveillance of new opioid medications in Australia and by Indivior to undertake work examining naloxone for opioid overdose prevention. No funding from these sources relates to the studies reported in this

paper. None of these funders had any knowledge of this study. All other authors have no conflicts of interest.

References

1. Manchikanti L, Helm S, II, Fellows B, et al. Opioid epidemic in the United States. Pain Physician. 2012; 15: ES9-38.

2. Haegerich TM, Paulozzi LJ, Manns BJ, et al. What we know, and don't know, about the impact of state policy and systems-level interventions on prescription drug overdose. Drug Alcohol Depend. 2014; 145: 34-47. DOI: 10.1016/j.drugalcdep.2014.10.001.

3. Ling W, Mooney L, Hillhouse M. Prescription opioid abuse, pain and addiction: clinical issues and implications. Drug Alcohol Rev. 2011; 30: 300-5. DOI: 10.1111/j.1465-3362.2010.00271.x.

4. Sullivan MD, Howe CQ. Opioid therapy for chronic pain in the United States: promises and perils. Pain. 2013; 154: S94-S100. DOI: 10.1016/j.pain.2013.09.009.

5. International Narcotics Control Board (INCB). Report 2012 - Narcotic drugs: estimated world requirements for 2013; statistics for 2011. United Nations Publications, New York; 2012. https://www.incb.org/incb/en/narcotic-drugs/Technical_Reports/2011/narcotic-drugs-technical-report_2011.html (accessed 15 March 2017).

6. Zin C, Chen L-C, Knaggs R. Changes in trends and pattern of strong opioid prescribing in primary care. Eur J Pain. 2014; 18: 1343-51. DOI: 10.1002/j.1532-2149.2014.496.x.

7. Blanch B, Pearson S-A, Haber PS. An overview of the patterns of prescription opioid use, costs and related harms in Australia. Br J Clin Pharmacol. 2014; 78: 1159-66. DOI: 10.1111/bcp.12446.

8. Hollingworth SA, Gray PD, Hall WD, et al. Opioid analgesic prescribing in Australia: a focus on gender and age. Pharmacoepidemiol Drug Saf. 2015; 24: 628-36. DOI: 10.1002/pds.3767.

9. International Narcotics Control Board (INCB). Report 2016 - Narcotic drugs: estimated world requirements for 2017; statistics for 2015. United Nations Publications, New York; 2015. https://www.incb.org/incb/en/narcotic-drugs/Technical_Reports/narcotic_drugs_reports.html (accessed 12 April 2017).

10. Chou R, Turner JA, Devine EB, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health pathways to prevention workshop. Ann Intern Med. 2015; 162: 276-86. DOI: 10.7326/M14-2559.

11. Noble M, Treadwell JR, Tregear SJ, et al. Long-term opioid management for chronic noncancer pain. Cochrane Database Syst Rev. 2010: CD006605. DOI: 10.1002/14651858.CD006605.pub2.

12. Garcia Del Pozo J, Carvajal A, Viloria JM, et al. Trends in the consumption of opioid analgesics in Spain. Higher increases as fentanyl replaces morphine. Eur J Clin Pharmacol. 2008; 64: 411-5. DOI: 10.1007/s00228-007-0419-9

13. Hamunen K, Paakkari P, Kalso E. Trends in opioid consumption in the Nordic countries 2002–2006. Eur J Pain. 2009; 13: 954-62. DOI: 10.1016/j.ejpain.2008.11.006.

14. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment, 2017. World Health Organisation, Oslo, Norway; 2016. https://www.whocc.no/atc_ddd_index_and_guidelines/guidelines/ (accessed 1 April 2017).

15. Leong M, Murnion B, Haber P. Examination of opioid prescribing in Australia from 1992 to 2007. Intern Med J. 2009; 39: 676-81. DOI: 10.1111/j.1445-5994.2009.01982.x.

16. Henderson JV, Harrison CM, Britt HC, et al. Prevalence, causes, severity, impact, and management of chronic pain in Australian general practice patients. Pain Med. 2013; 14: 1346-61. DOI: 10.1111/pme.12195

17. Nielsen S, Gisev N, Bruno R, et al. Defined daily doses (DDD) do not accurately reflect opioid doses used in contemporary chronic pain treatment. Pharmacoepidemiol Drug Saf. 2017. DOI: 10.1002/pds.4168

18. Nielsen S, Degenhardt L, Hoban B, et al. Comparing opioids: a guide to estimating oral morphine equivalents (OME) in research. National Drug and Alcohol Research Centre, Sydney, Australia; 2014. https://ndarc.med.unsw.edu.au/resource/comparing-opioids-guide-estimating-oral-morphine-equivalents-ome-research (accessed 18 February 2017).

19. Drug Utilisation Sub-Committee (DUSC). Opioid analgesics: Overview. Australian Government Department of Health, Canberra, Australia; 2014. http://www.pbs.gov.au/info/industry/listing/participants/public-release-docs/opioid-analgesics-overview (accessed 12 April 2017).

20. Hastie BA, Gilson AM, Maurer MA, et al. An examination of global and regional opioid consumption trends 1980-2011. J Pain Palliat Care Pharmacother. 2014; 28: 259-75. DOI: 10.3109/15360288.2014.941132.

21. Svendsen K, Borchgrevink P, Fredheim O, et al. Choosing the unit of measurement counts: the use of oral morphine equivalents in studies of opioid consumption is a useful

addition to defined daily doses. Palliat Med. 2011; 25: 725-32. DOI: 10.1177/0269216311398300.

22. Pain and Policy Studies Group. Opioid consumption motion chart. University of Wisconsin Carbone Cancer Center, Madison; 2017. https://ppsg.medicine.wisc.edu/chart (accessed 10 April 2017).

23. Karanges EA, Blanch B, Buckley NA, et al. Twenty-five years of prescription opioid use in Australia: a whole-of-population analysis using pharmaceutical claims. Br J Clin Pharmacol. 2016; 82: 255-67. DOI: 10.1111/bcp.12937

24. Mellish L, Karanges EA, Litchfield MJ, et al. The Australian Pharmaceutical Benefits Scheme data collection: a practical guide for researchers. BMC research notes. 2015; 8: 634. DOI: 10.1186/s13104-015-1616-8

25. Australian Government Department of Health. 2015 PBS co-payment and safety net amounts. Department of Health, Canberra, Australia; 2015. http://www.pbs.gov.au/info/news/2015/01/2015-pbs-co-payment-safety-net-amounts (accessed 13 March 2017).

26. Caraceni A, Hanks G, Kaasa S, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. Lancet Oncol. 2012; 13: e58-68. DOI: 10.1016/S1470-2045(12)70040-2.

27. Royal Australasian College of Physicians (RACP). Prescription opioid policy: Improving the management of chronic non-malignant pain and prevention of problems associated with prescription opioid use. RACP, Sydney, Australia; 2009.

https://www.ranzcp.org/Files/Resources/Submissions/cnmp-pdf.aspx (accessed 1 April 2017).

28. Australian Bureau of Statistics (ABS). Australian Historical Population Statistics, 2014; table, Cat. no. 3105.0.65.001. ABS, Canberra, Australia; 2014. http://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/3105.0.65.001Main+Features12014?OpenDocument (accessed 1 February 2017).

29. Australian Bureau of Statistics (ABS). 3101.0 - Australian Demographic Statistics, Jun 2015. ABS, Canberra, Australia; 2016. http://www.abs.gov.au/AUSSTATS/abs@.nsf/allprimarymainfeatures/6CBA90A25BAC951DCA257F7F001CC559?opendocument (accessed 10 April 2017).

30. Fischer B, Jones W, Rehm J. Trends and changes in prescription opioid analgesic dispensing in Canada 2005–2012: an update with a focus on recent interventions. BMC Health Serv Res. 2014; 14: 90. DOI: 10.1186/1472-6963-14-90.

31. Ruscitto A, Smith B, Guthrie B. Changes in opioid and other analgesic use 1995–2010: Repeated cross-sectional analysis of dispensed prescribing for a large geographical population in Scotland. Eur J Pain. 2015; 19: 59-66. DOI: 10.1002/ejp.520.

32. Gisev N, Pearson S-A, Blanch B, et al. Initiation of strong prescription opioids in Australia: cohort characteristics and factors associated with the type of opioid initiated. Br J Clin Pharmacol. 2016; 82: 1123-33. DOI: 10.1111/bcp.13026

33. Gadzhanova S, Bell JS, Roughead EE. What analgesics do older people use prior to initiating oxycodone for non-cancer pain? A retrospective database study. Drugs Aging. 2013; 30: 921-6. DOI: 10.1007/s40266-013-0115-7.

34. Steele B, Stevens J. Where oh where has your Endone script gone? The oxycodone epidemic. In: Australiasian Anaesthesia 2013. Riley R (ed). Australian and New Zealand College of Anaesthetists: Melbourne, 2013; 193-8.

35. Rogers KD, Kemp A, McLachlan AJ, et al. Adverse selection? A multi-dimensional profile of people dispensed opioid analgesics for persistent non-cancer pain. PLOS ONE. 2013; 8: e80095. DOI: 10.1371/journal.pone.0080095.

36. Degenhardt L, Bruno R, Ali R, et al. The introduction of a potentially abuse deterrent oxycodone formulation: Early findings from the Australian National Opioid Medications Abuse Deterrence (NOMAD) study. Drug Alcohol Depend. 2015; 151: 56-67. DOI: 10.1016/j.drugalcdep.2015.02.038.

37. Analgesic Expert Group. Therapeutic Guidelines: Analgesic. Version 6. Melbourne, Australia: Therapeutic Guidelines Limited; 2012.

38. Australian Medicines Handbook 2015 (online). Adelaide, Australia: Australian Medicines Handbook Pty Ltd; 2015. Available from: http://amhonline.amh.net.au/.

39. Gisev N, Nielsen S, Cama E, et al. An ecological study of the extent and factors associated with the use of prescription and over-the-counter codeine in Australia. Eur J Clin Pharmacol. 2016; 72: 469-94. DOI: 10.1007/s00228-015-1995-8

Table 1. Description of metrics used to quantify opioid utilisation in this study and their potential to interpret trends in opioid use when used in isolation.

Metric[†]	Description	Interpreting trends		
		What it can tell us	Caveats	What it can't tell us
Volume-based				
DDD/1000 pop/day	Population-level rate of defined daily doses (DDD) dispensed per day; DDD is the assumed average maintenance dose per day for the medicine's primary indication (at the time of DDD assignment). Possible to estimate the proportion of the population treated daily with a medicine, provided there is high concordance between the DDD and the prescribed daily dose (this is generally not true for	Changes in utilisation, standardised according to different doses used for different formulations and medicine strengths.	Potential for under- or over-estimates of utilisation if poor alignment between DDD and the prescribed daily dose. May misrepresent changes in utilisation where the average prescribed daily dose changes over the study period (e.g. reduction in average dose with shift in use from cancer to chronic non-cancer pain)	Whether changes are driven by treatment-related factors (such as duration or dose) or the number of people treated.

	opioids).			
OME/1000 pop/day	Population-level rate of oral morphine equivalent (OME) milligrams dispensed per day.	Changes in utilisation, adjusted for opioid strength/analgesic potency, standardised across different formulations and medicine strengths. Higher clinical relevance than DDD/1000 pop/day.	Potential for under- or over-estimates of utilisation if poor alignment between the OME conversion factor and the true analgesic potency. Developed based on doses used in chronic pain; conversion factors may differ for acute dosing.	Whether changes are driven by treatment-related factors (such as duration or dose) or the number of people treated.
Dispensings/1000 pop	Population-level rate of number of prescriptions dispensed; does not distinguish between prescriptions of different strengths or quantities.	Changes in the number of dispensings. Useful for measuring resource consumption and expenditure.	May misrepresent changes in utilisation of a given medicine where the average amount or strength dispensed per prescription changes over time. Comparisons of use between medicines may be problematic due to differences in available formulations and the strength/quantity dispensed per prescription.	Whether changes are driven by prescription-related factors (strength, quantity), treatment-related factors (duration, dose) or the number of people treated.

Person-based				
Persons/1000 pop	Rate of people dispensed an opioid at least once in a given year.	Changes in the proportion of the population with at least one opioid dispensing in a year.	May misrepresent changes in utilisation where the number of dispensings, medicine strength or quantity per person changes over time. Does not provide information on whether a person uses more than one specific opioid in a year.	Whether changes are driven by prescription-related factors (number of dispensings, strength, quantity) or treatment-related factors (duration, dose, use of multiple opioids concurrently).

[†]All metrics are standardised to the yearly Australian population.

DDD: Defined daily dose; OME: oral morphine equivalent

Table 2. Percentage change (2006 to 2015) in PBS-subsidised prescribed opioid utilisation according to each metric, with an interpretation of the results based on their combination. Arrows approximate the relative change in each metric *within* a medicine (row), but are not intended to represent the magnitude of the percentage change in metrics across different opioids.

	DDD/1000 pop/day (% change)	OME/1000 pop/day (% change)	Dispensings/ 1000 pop (% change)	Persons/1000 pop (% change)	Interpretation of trends across metrics[‡]
Oxycodone	102 ↑	105 ↑	166 ↑↑	207 ↑↑↑	A larger increase in persons and dispensings than by DDD and OME suggests growing population treated at lower strengths or doses
Buprenorphine	803 ↑↑↑	803 ↑↑↑	619 ↑↑	262 ↑	A smaller increase in persons than volume suggests increasing cumulative annual treatment duration and/or use of higher strengths or doses. The latter is more likely for buprenorphine, where the increase in DDD and OME exceeds the increase in dispensings
Fentanyl	321 ↑↑	316 ↑↑	360 ↑↑	148 ↑	
Morphine	-43 ↓↓	-43 ↓↓	-41 ↓↓	-18 ↓	A smaller decrease in persons than volume suggests decreasing cumulative annual treatment duration and/or use of lower strengths or doses, likely in a declining population of existing patients
Hydromorphone	271 ↑	421 ↑↑	1,230 ↑↑↑	500 ↑↑	A larger increase in persons and OME compared to DDD suggests a growing population treated with a higher potency formulation. The particularly large increase in dispensings suggests increasing annual cumulative treatment durations or lower quantities per dispensing[§]
Codeine	-5 ↔	-5 ↔	-16 ↓	-21 ↓	A decrease in persons and dispensings (e.g. codeine) with no change in DDD and OME suggests use of higher strengths or doses, likely in a

Methadone	-3	-3	-16	-7	declining population of existing patients. Where there is no decrease in dispensings (e.g. tramadol), increasing cumulative annual treatment duration may play a larger role in the change
	↔	↔	↓	↔	
Tramadol	-2	-2	-4	-13	
	↔	↔	↔	↓	
Strong	71	80	140	158	A larger increase in persons and dispensings than DDD and OME suggests a growing population treated with strong opioids at lower doses, especially with strong opioids only
	↑	↑	↑↑	↑↑	
Strong only[†]	—	—	—	238	
				↑↑↑	
Weaker + Strong[†]	—	—	—	80	
				↑	
Weaker	-4	-3	-11	-17	A decrease in persons and dispensings with no real change in DDD and OME suggests increasing yearly treatment exposure and/or use of higher strengths or doses, likely in a declining population of existing patients. This is especially true in people dispensed weaker opioids alone
	↔	↔	↓	↓↓	
Weaker only[†]	—	—	—	-31	
				↓↓↓	
Total	21	51	44	10	A smaller increase in persons than OME and dispensings suggests increasing use of high potency opioids. The increase in DDD is lower due to the under-representation of strong opioid use by this metric[¶]
	↑↑	↑↑↑	↑↑↑	↑	

[†]Can only be calculated using person-level data

[‡]Interpretations refer to the dominant drivers of change as indicated by the combination of metrics and are not intended to represent all possible contributing factors

[§]This interpretation does not accurately reflect the factors contributing to the increased use of hydromorphone. An explanation of this discrepancy is provided in the discussion.

[¶]The DDDs of some strong opioids (e.g. oxycodone, morphine) were established based on doses used in cancer pain. These doses are higher than those commonly used in chronic non-cancer pain; therefore DDD/1000 pop/day underestimates the utilisation of these opioids.

DDD: defined daily dose; OME: oral morphine equivalent; ↔ approximately no change in utilisation

Table 3. Estimates of PBS-subsidised prescription opioid utilisation estimates and percentage of total use comprised by individual, strong and weaker opioids in 2015 according to each metric.

	DDD/1000 pop/day		OME/1000 pop/day		Dispensings/1000 pop		Persons/1000 pop[‡]	
	Utilisation	%	Utilisation	%	Utilisation	%	Utilisation	%
Buprenorphine	0.6	4.6	65.1	6.9	54.4	11.8	6.3	9.6
Codeine	5.0	35.8	65.1	6.9	101	22.0	33.8	51.7
Fentanyl	1.1	7.9	131	13.9	24.4	5.3	2.6	4.0
Hydromorphone	0.4	2.7	34.8	3.7	6.4	1.4	0.7	1.1
Methadone	0.3	2.4	39.0	4.1	3.4	0.7	0.3	0.5
Morphine	0.9	6.5	90.6	9.6	21.9	4.8	3.2	4.9
Oxycodone	2.9	21.0	330	35.0	160	34.8	25.9	39.6
Tapentadol	0.2	1.7	39.1	4.1	8.6	1.9	1.8	2.8
Tramadol	2.5	17.5	147	15.6	79.6	17.3	13.9	21.2
Strong	6.5	46.7	729	77.5	279	60.7	33.2	50.8
Weaker	7.5	53.3	212	22.5	180	39.3	43.8	67.0
Strong only[†]	—	—	—	—	—	—	21.6	33.0
Weaker only[†]	—	—	—	—	—	—	32.2	49.2
Weaker + Strong[†]	—	—	—	—	—	—	11.6	17.7
Total	14.0	100	942	100	459	100	65.4	100

[†]Can only be calculated using person-level data

[‡]Percentages do not add to 100 as persons can be dispensed more than one opioid in a given year
DDD: defined daily dose; OME: oral morphine equivalent

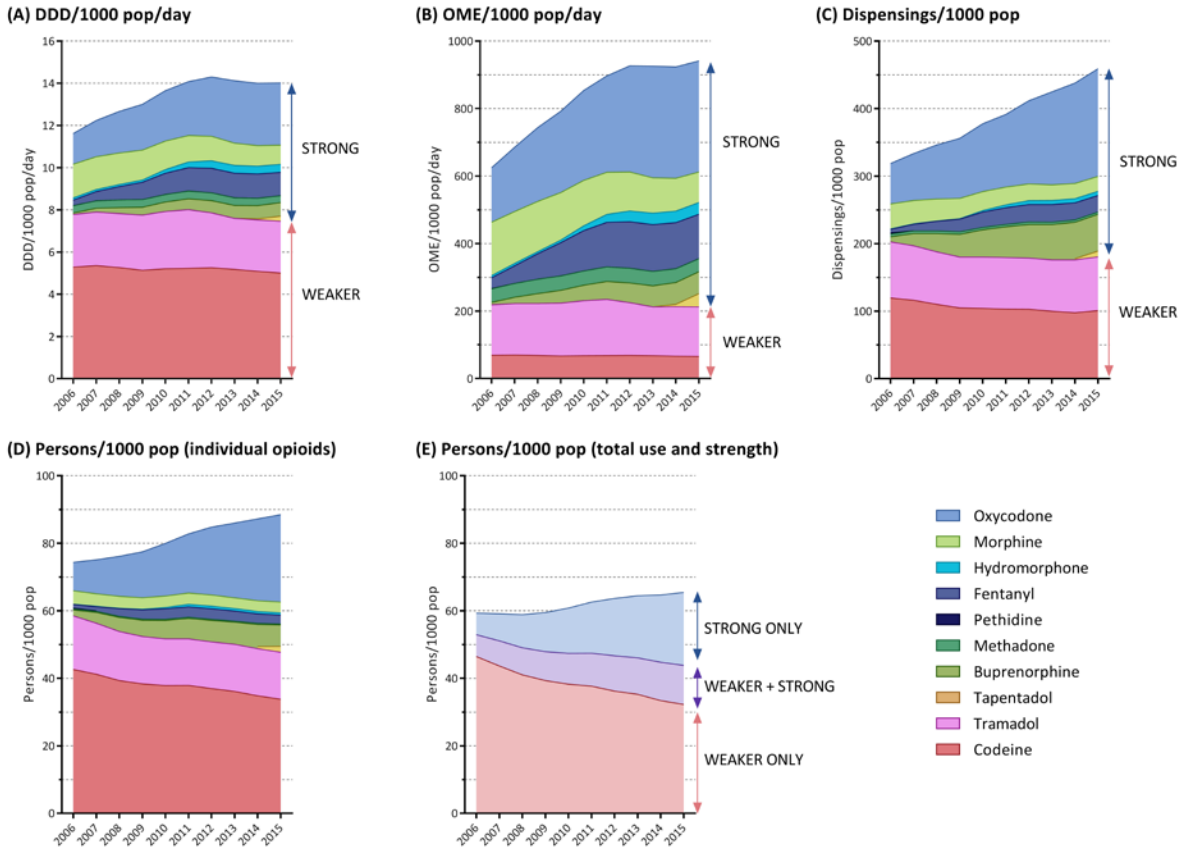

Figure 1. Trends in PBS-subsidised prescribed opioid utilisation, by individual opioids and opioid strength, according to (A) defined daily doses (DDD)/1000 pop/day, (B) oral morphine equivalents (OME)/1000 pop/day, (C) dispensings/1000 pop, and (D) and (E) persons/1000 pop. As a person can be dispensed more than one opioid in a given year, (D) does not accurately represent use according to persons/1000 pop for opioids overall or by strength; these estimates are shown in (E).