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Title: Increases in controlled-release oxycodone utilisation following the subsidy of oxycodone with naloxone formulations: An Australian population-based study

Running title: Impact of subsidy of oxycodone/naloxone CR in Australia

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Keywords: opioids, oxycodone, pharmacoepidemiology, Australia, drug utilisation

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.4683](https://doi.org/10.1002/pds.4683)

Word count: 3200

Prior presentations:

This work was presented at the 10th Asian Conference on Pharmacoepidemiology in Brisbane, Australia, October 29-31, 2017

Key points

1. We observed rapid uptake of oxycodone/naloxone CR in Australia since its subsidy in 2011; in 2016 it was the most commonly dispensed oxycodone CR formulation for new treatment episodes (91.4%).
2. Growth in dispensing of oxycodone CR was 1.6-fold faster than prior to subsidy of oxycodone/naloxone CR, driven primarily by an increase in dispensing of low strength (≤ 5 mg) formulations.
3. In 2016, people initiating a new oxycodone CR treatment episode were more likely to initiate on lower strengths than those initiating treatment in 2009; the proportion initiating on ≤ 5 mg tablet strengths increased from 26.8% to 49.8% in this period.

ABSTRACT

Purpose: Despite increasing use of oxycodone/naloxone controlled-release (CR) in Australia, little is known about how it has affected the overall oxycodone CR market since its subsidy in 2011.

Methods: We used Pharmaceutical Benefits Scheme dispensing claims (2006-2016) and interrupted time series analysis to examine changes in the quarterly rates of dispensing of oral oxycodone CR formulations (oxycodone/naloxone CR and single-ingredient oxycodone CR) and new oxycodone CR treatment episodes. We also performed a retrospective cohort study in a sample of people initiating a new oxycodone CR treatment episode in 2009, 2012/13 and 2016 to compare opioid utilisation patterns over time.

Results: The subsidy of oxycodone/naloxone CR was associated with a 1.6-fold increase in the growth rate of oxycodone CR dispensing, resulting from rapid uptake of low strength (≤ 5 mg) oxycodone/naloxone CR. In our cohort of initiators, the number of new oxycodone CR treatment episodes increased 2.1-fold between 2009 and 2016; in 2016, 91.4% of new treatment episodes involved oxycodone/naloxone CR. Comparing 2016 to 2009, we observed an increase in people initiating with a tablet strength ≤ 5 mg (Risk difference (RD) = 21.1%, 95% CI 19.9%-22.4%), in people initiating with no other opioid dispensing 90 days prior to initiation (RD = 5.2%, 3.8%-6.6%), and with no further opioid dispensing 90 days after initiation (RD = 8.8%, 7.4%-10.2%).

Conclusions: After its subsidy, the uptake of low-dose oxycodone/naloxone CR was greater than expected if it were substituting the single-ingredient oxycodone CR, resulting in an expansion of the oxycodone CR market.

INTRODUCTION

Oxycodone with naloxone controlled-release (CR) tablets are fixed-dose combination products with equivalent analgesia and similar side effects to single-ingredient oxycodone CR tablets of the same dose.¹⁻³ The addition of naloxone, an opioid antagonist that blocks opioid receptors in the gut, reduces but does not eliminate constipation, a common side effect of opioid therapy.^{4,5} Oxycodone/naloxone CR is only one of a growing number of new opioid products marketed in recent years.⁶

In the United States (US), oxycodone/naloxone CR was FDA approved in 2014 and given abuse-deterrent labelling; however, it was never marketed and marketing plans have now been abandoned.⁶ In Canada, oxycodone/naloxone CR is approved by the regulator, but it is not subsidised on any of the provincial formularies so uptake has been limited.⁷ In 2011, oxycodone/naloxone CR was publicly subsidised in Australia, and is available at a similar cost to patients as the single-ingredient oxycodone CR; as of April 2014, it is the only low dose (≤ 5 mg) oxycodone CR tablet on the market. Australia's unique context allows for an examination of the impact of oxycodone/naloxone CR on overall oxycodone CR utilisation. Furthermore, in contrast to North America where much of the focus has been on the product's

abuse-deterrent properties, oxycodone/naloxone CR is marketed heavily in Australia as a solution to opioid-induced constipation.^{8,9}

Australian data suggests that there has been a change in the utilisation patterns of oxycodone CR, coinciding with the introduction of oxycodone/naloxone CR. First, dispensing of the single-ingredient oxycodone CR has been decreasing, but oxycodone/naloxone CR has increased rapidly.^{10,11} Further, recent data show that while the number of oxycodone dispensings and people being dispensed oxycodone are increasing, the total volume (as measured in milligrams of oxycodone dispensed) is not.¹²

Therefore, the objective of this study was to document the uptake of oxycodone/naloxone CR and how it has affected overall trends in utilisation of oxycodone CR formulations as a whole. We sought to determine whether oxycodone/naloxone CR is being used as a substitute for the single-ingredient oxycodone CR, or whether it is being prescribed to an expanding patient population. We used an interrupted time-series analysis and a retrospective cohort study to examine the impact of the subsidy of oxycodone/naloxone CR on: 1) population-level dispensing of all oxycodone CR formulations; 2) new oxycodone CR treatment episodes; and 3) patterns of opioid utilisation among people initiating on oxycodone CR formulations over time.

METHODS

Key events of interest

In December 2011, oxycodone/naloxone CR was subsidised in Australia for treatment of chronic severe disabling pain, the same indication as the single-ingredient oxycodone CR.¹³ On April 1, 2014, the single-ingredient oxycodone CR (≥ 10 mg) was reformulated to be tamper-resistant and the 5 mg strength was withdrawn from the Australian market by the manufacturer. From this date oxycodone/naloxone CR was the only 5 mg oxycodone CR formulation available.

Setting

In Australia, all citizens and permanent residents are entitled to subsidised access to prescribed medicines through the Pharmaceutical Benefits Scheme (PBS), serving the general population, and the Repatriation PBS (RPBS), for eligible veterans and their dependents. The level of subsidy depends on the patient's beneficiary status; concessional beneficiaries (patients eligible for government entitlements, such as people ≥ 65 years and low-income earners) pay a lower co-payment than general beneficiaries. PBS medicines priced below the co-payment threshold are not subsidised by the PBS and the patient pays the entire cost.

Data and study population

1. Trends in population-level oxycodone dispensings

To examine potential impacts on population-level oxycodone CR dispensing, we obtained estimates of all community dispensings (January 2006 to December 2015) from a database maintained by the Drug Utilisation Sub-Committee (DUSC) of the Pharmaceutical Benefits Advisory Committee of the Australian Government

Department of Health. The database contains aggregated, de-identified records of dispensings subsidised under the PBS/RPBS and non-subsidised (under co-payment) dispensings. Records of under co-payment dispensings have only been collected since April 2012, prior to which estimates were ascertained from a Pharmacy Guild Survey of a representative sample of approximately 370 community pharmacies.

We included all oral formulations (tablets) of oxycodone CR, excluding suppositories. During the study period, the single-ingredient oxycodone CR was available in the following strengths: 5 mg (until March 30, 2014 only), 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 80 mg (Table 1). Oxycodone/naloxone CR tablets was available in the following strengths: 5 mg/2.5 mg, 10 mg/5 mg, 20 mg/10 mg, and 40 mg/20 mg. From April 1, 2014, the single-ingredient oxycodone CR (≥ 10 mg) was only available as a tamper-resistant formulation. In December 2014 a generic non-tamper-resistant formulation (≥ 10 mg) was subsidised; however, it was not commonly sold.¹⁴ On May 1, 2016, three new formulations of oxycodone/naloxone CR were introduced: 2.5 mg/1.25 mg, 15 mg/7.5 mg, and 30 mg/15 mg.

2. *Trends in new oxycodone CR treatment episodes*

To investigate changes in new treatment episodes with oxycodone CR formulations, we used person-level PBS dispensing claims (March 2005 to December 2016) for a 10% random sample of PBS-eligible people, approximately 2.5 million people.¹⁵ This is a standard dataset provided by the Department of Human Services for analytical use, selected based on the last digit of each individual's randomly assigned unique

identifier, and captures all dispensed PBS-listed medicines attracting a government subsidy. To protect the privacy of persons in this dataset, all dates of dispensing are offset randomly by +14 or -14 days; the direction of the offset is the same for all records for each individual.

We defined a new treatment episode as a dispensing of any oxycodone CR formulation (single-ingredient oxycodone CR or oxycodone/naloxone CR) with no dispensing of either formulation in the 12 months prior; individuals could have been dispensed a different opioid during this time. Individuals could appear more than once if they initiated multiple treatment episodes that met this criterion. We restricted the population to concessional beneficiaries to ensure complete capture of dispensed medicines during the study period. Approximately 25% of Australians are concession card holders and primarily includes people ≥ 65 years, people with low incomes, and people with disabilities. Approximately 75% of all oxycodone CR dispensings are to concessional beneficiaries.¹⁶ To ascertain beneficiary status, individuals had to have been dispensed only medicines attracting concessional subsidy during the study period (12 months before and after initiation) and have at least one dispensing record for any medicine in the 12 months prior to initiation.

3. *Change in characteristics of initiators over time*

To compare demographic and opioid utilisation characteristics of individuals initiating on oxycodone CR formulations over the course of the study period, we identified three cohorts of initiators in equivalent 12 month periods before/after each of the key events: prior to subsidy of oxycodone/naloxone CR (Period 1; January 2009 to

December 2009); after subsidy of oxycodone/naloxone CR and before the single-ingredient oxycodone CR reformulation/5 mg withdrawal (Period 2; July 2012 to June 2013); and after the oxycodone CR reformulation/5 mg withdrawal (Period 3; January 2016 to December 2016). We chose 1-year time periods so that individuals only appeared once in each time period and counts were directly comparable. However, individuals could be included in more than one time period if they met the definition for initiation more than once. The time periods were also chosen to allow for a buffer before and after each change in the market.

Among initiators, we identified dispensing of strong and weak opioids in the 90 days prior to initiation to identify if people were opioid-naïve or switching from a different opioid; and 90 days after initiation to identify if people were continuing with therapy. Strong opioids included: buprenorphine, fentanyl, hydromorphone, methadone, morphine, pethidine and tapentadol. Weak opioids included: codeine and tramadol. Tapentadol was subsidised in July 2014, while pethidine was de-subsidised in April 2007. We did not include opioid formulations primarily used for indications other than analgesia (i.e. methadone and buprenorphine/naloxone for opioid dependence).

Statistical analysis

1. Trends in population-level oxycodone dispensings

We calculated the number of tablets dispensed of all oxycodone CR combined, the single-ingredient oxycodone CR and oxycodone/naloxone CR tablets per 1000 population per quarter, overall and grouped by tablet strength (≤ 5 mg or >5 mg), as we expected there to be a differential impact by strength due to the withdrawal of the

5 mg single-ingredient oxycodone CR tablet strength. We measured tablets dispensed rather than dispensings because of a change in pack size during the study period. Population estimates were obtained from the Australian Bureau of Statistics.¹⁷ To quantify changes in dispensing, we performed an interrupted time-series analysis using an autoregressive model adjusted for seasonality with variables representing a level shift or step change (i.e. an immediate increase or decrease following the event) and change in slope after both events. The level shift and change in slope variables were dropped from the model if non-significant ($p \geq 0.05$) to achieve a parsimonious model. We included lags where appropriate to account for a delayed impact.

2. *Trends in new oxycodone treatment episodes*

We calculated quarterly counts of new oxycodone CR treatment episodes, overall and by tablet strength (≤ 5 mg or >5 mg). To quantify changes in the number of new treatment episodes, we performed an interrupted time-series analysis as described above.

3. *Characteristics of initiators over time*

We compared the demographic and opioid use characteristics of people initiating in each of the three periods by calculating risk differences adjusted for age and sex using a generalised linear model with a binomial distribution adjusted for correlation within individuals included in more than one time period. All analyses were performed with SAS® V9.4 (SAS Institute Inc., Cary, NC) and R.

Ethics and data access approval

This study has ethics approval from the New South Wales Population and Health Services Research Ethics Committee (2013/11/494). Access to the PBS dispensing claims was approved by the Department of Human Services External Request Evaluation Committee. Ethical approval was not required for use of the DUSC data as they were released in aggregate form.

RESULTS

1. Population-level oxycodone dispensings

1.1 Impact of subsidy of oxycodone/naloxone CR

In the first quarter of the study period (Q1 2006) there were 301.0 oxycodone CR tablets dispensed/1000 population, with the 5 mg oxycodone CR tablet strength accounting for 8% of all oxycodone CR dispensed. Oxycodone CR dispensing grew by 13.6 tablets/1000 population/quarter until Q3 2011 (Figure 1; Table 2). After subsidy of oxycodone/naloxone CR (Q4 2011), the growth rate increased 1.6-fold to 22.0 tablets/1000 population/quarter, driven entirely by increased dispensing of 5 mg oxycodone/naloxone CR. By Q1 2014, there were 839.4 tablets dispensed/1000 population, with the 5 mg tablets comprising 19% of all dispensed oxycodone CR. The majority of 5 mg oxycodone CR dispensed was oxycodone/naloxone CR (58%), while the single-ingredient oxycodone CR predominated in the higher strengths (66%).

1.2 Impact of the oxycodone CR reformulation/5 mg withdrawal

The withdrawal of the 5 mg single-ingredient oxycodone CR in April 2014 (Q2 2014) was entirely offset by an immediate increase (level shift) in dispensing of 5 mg

oxycodone/naloxone CR (Figure 1; Table 2) and the growth rate of 5 mg oxycodone CR increased further. Overall, there was an immediate decrease (level shift) in dispensing of oxycodone CR, due to a decrease in dispensing of >5 mg single-ingredient oxycodone CR, however the growth rate stayed the same.

By the last quarter of the study period (Q4 2015), we observed 1000.9 tablets of oxycodone CR dispensed/1000 population, with 5 mg tablet strengths comprising 21.0% of all oxycodone CR. Oxycodone/naloxone CR was the only formulation dispensed for the ≤ 5 mg strengths and comprised the majority of the >5 mg strengths (58%).

2. *New controlled release oxycodone treatment episodes*

In our cohort of concessional beneficiaries, 92 340 people initiated 102 008 new treatment episodes with any oxycodone CR formulation between April 2006 and December 2016.

2.1 *Impact of oxycodone/naloxone CR subsidy*

In the first quarter of the study period (Q2 2006), we observed 1072 new treatment episodes with oxycodone CR, with 21% of these episodes involving the 5 mg tablet strength (Figure 2; Table 3). Immediately after the listing of oxycodone/naloxone CR, we observed an immediate increase (level shift) in the number of new treatment episodes and the growth rate increased 1.5-fold from 47 to 72 episodes/quarter. This was driven entirely by an increase in initiation with 5 mg oxycodone/naloxone CR and the growth rate for 5 mg formulations increased 2.6-fold, from 20/quarter to

51/quarter. We did not observe a change in the dispensing of >5 mg formulations. By Q1 2014, we observed 2847 new treatment episodes, of which 44% were with a 5 mg strength.

2.2 Impact of the oxycodone CR reformulation/5 mg withdrawal

We observed an immediate increase (level shift) in initiation with 5 mg oxycodone/naloxone CR after the withdrawal of the 5 mg single-ingredient oxycodone CR tablet strength CR (Q2 2014); the overall growth rate in initiation increased to 69/quarter. We did not observe any change in initiation with >5 mg oxycodone CR formulations.

3. Characteristics of initiators over time

We observed 7254 people initiating a new treatment episode with oxycodone CR in Period 1 (2009; prior to the subsidy of oxycodone/naloxone CR), increasing more than 2-fold to 15 068 in Period 3 (2016) (Table 4). In Period 2 (2012/13), when both the single-ingredient oxycodone CR and oxycodone/naloxone CR were available, people ≥85 years were most likely to initiate with oxycodone/naloxone CR versus the single-ingredient oxycodone CR (45.9%), while people <45 years were least likely (28.5%). We also found females and people initiating on lower tablet strengths were more likely to initiate on oxycodone/naloxone CR.

In Period 3 (2016), because of the withdrawal of the 5 mg single-ingredient oxycodone CR in 2014, oxycodone/naloxone CR had almost completely supplanted the single-ingredient oxycodone CR for new treatment episodes, with 91.4% involving the combination product. Similar to Period 2, initiation with

oxycodone/naloxone CR was most common among people ≥ 85 years and people initiating on lower tablet strengths.

In Period 3, we observed a large increase in initiation with ≤ 5 mg tablet strengths; nearly half (49.8%) of new treatment episodes involved ≤ 5 mg strengths compared with 26.8% in Period 1 (Table 5). In absolute numbers, this is a nearly 4-fold increase in the number of people initiating on low strengths (≤ 5 mg) (1946 to 7508). However, the number of people initiating on strengths ≥ 20 mg decreased, both in absolute and relative terms. In Period 3, individuals were also less like to be dispensed a weak opioid prior to initiation (Risk difference (RD) -7.9%, 95% CI -9.2% to -6.7%), and less likely to continue with opioid therapy in the 90 days after initiation (RD -8.8%, 95% CI -10.2 to -7.4). People initiating in Period 3 were also dispensed a smaller amount of oxycodone CR compared to Period 1.

Discussion

We observed a rapid uptake of oxycodone/naloxone CR after its subsidy, and it is currently the main formulation of oxycodone CR dispensed in Australia.

Oxycodone/naloxone CR is now the only low strength (≤ 5 mg) oxycodone CR on the market, yet dispensing of ≤ 5 mg formulations has been increasing at a rate greater than would be expected if it were simply substituting for the single-ingredient oxycodone CR. Similarly, we observed that decreases in use of >5 mg singleingredient oxycodone CR after introduction of the tamper-resistant formulation have been offset by increases in oxycodone/naloxone CR. As a result, overall growth in use of oxycodone CR is increasing.

Several factors are likely driving this increase. First, oxycodone/naloxone CR has potential (although unproven) abuse-deterrent properties.¹⁸ Consequently, recent reports suggest that several Australian pain services are now prescribing oxycodone/naloxone CR in preference to other formulations.¹⁹⁻²¹ However, given the observed decline in use of the tamper-resistant single-ingredient oxycodone CR, it is likely that much of the increased uptake of oxycodone/naloxone CR is related to its effects on opioid-induced constipation. Indeed, the observed uptake of oxycodone/naloxone CR was greatest in older individuals, who often require lower doses and are at greater risk of opioid-induced constipation.

Based on the rapid uptake of oxycodone/naloxone CR, there appears to be a real or perceived need for opioids that reduce the risk of constipation. Opioid-induced constipation is a well-known and common side effect of chronic pain treatment and can negatively affect quality of life.²² To our knowledge, the oxycodone/naloxone CR combination is the only opioid containing naloxone designed to treat constipation primarily marketed as such, rather than for opioid dependence or abuse-deterrence. In Israel, oxycodone/naloxone CR is also marketed for treatment of constipation and use of the combination has likewise been increasing while the single-ingredient product is decreasing.²³ Regardless, the proven benefits of oxycodone/naloxone CR are predominantly for the treatment of pre-existing opioid-induced constipation, whereas it has only shown only a small benefit for prevention.²⁴

In recent years, we also observed an increase in the number of people initiating with low strength oxycodone CR, in preference to weak opioids. While Australian

guidelines recommend initiation with the lowest available strength,²⁵ we observed no reduction in the number of people initiating with higher tablet strengths, and an increase in overall initiation with oxycodone CR. Together this indicates an expansion of the oxycodone CR market after subsidy of oxycodone/naloxone CR and may signify a change from other strong opioids to oxycodone CR. However, we observed no increase in the proportion of initiators who had previous use of other strong opioids, suggesting that switching was minimal. As our study has focussed only on oxycodone CR, we cannot say whether the observed trends are specific to oxycodone, or reflect more general trends in opioid use. Nonetheless, recent Australian data have shown that there has been a decrease in the number of people using weak opioids and an increase in people using strong opioids only.¹² Further research will be needed to determine whether these changes have had any impact on opioid-related adverse events.

It is also noteworthy that there has been an increase in one-off oxycodone CR dispensing, with no other opioid dispensings in the 90 days before or after. In Australia, opioid controlled-release formulations are only subsidised for the treatment of refractory chronic, severe, disabling pain.¹³ Initiation with a long-acting formulation, particularly in the elderly, is not recommended due to the increased risk of unintentional overdose and respiratory depression.^{26, 27} In addition, a single dispensing may indicate either poor tolerability, or off-label use for acute pain. Since our data do not contain any information about the indication for treatment, we cannot draw any conclusions about the appropriateness of prescribing. However, previous

research has found that in Australian general practice, the majority of opioids are prescribed for non-chronic conditions (such as musculoskeletal pain),²⁸ and that compliance with opioid prescribing guidelines is poor.²⁹ Thus it is worrisome that we observed patterns of use that are suggestive of inappropriate use, and warrant further investigation.

Conclusion

We observed a rapid uptake of oxycodone/naloxone CR following its subsidy in 2011, almost completely replacing oxycodone CR for new treatment episodes, particularly among older people. This is likely attributable to its perceived benefits for prevention of opioid-induced constipation and the greater availability of ≤ 5 mg formulations that are no longer available in the single-ingredient formulation. While substitution of the single-ingredient oxycodone CR with oxycodone/naloxone CR was to be expected, overall use and initiation with oxycodone CR has been growing at a faster rate than before the subsidy of oxycodone/naloxone CR, with a shift towards use of lower tablet strengths and a lower volume.

Acknowledgements: We thank the Department of Human Services for providing the data. This research is supported, in part, by the National Health and Medical Research Council (NHMRC) Centre of Research Excellence in Medicines and Ageing (ID: 1060407). BL and LD are supported by the NHMRC (IDs: 1041472, 1135991, 1073858). The National Drug and Alcohol Research Centre at the University of NSW is supported by funding from the Australian Government under

the Substance Misuse Prevention and Service Improvements Grant Fund. The study funders were not involved in the study. All authors performed the research independent of the funders.

Conflict of interest: BL and LD have received investigator-initiated untied educational grants from Reckitt Benckiser/Indivior for studies of buprenorphine-naloxone, buprenorphine depot, naloxone (LD), the development of an opioid-related behaviour scale, and a study of opioid substitution therapy uptake among chronic non-cancer pain patients. BL and LD have received an untied educational grant from Mundipharma Australia to examine the impacts of a tamper-resistant formulation of oxycodone.

Authorship statement: AS, EK, NB, AW and SP contributed to the conception and design of the study. SP acquired the data. AS and EK analysed the data. All authors contributed to interpretation of the data. AS and EK drafted the manuscript and all authors revised it critically. All authors approved the final version to be published and agree to be accountable for all aspects of the work.

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Table 1. Dates of availability of oxycodone CR formulations

Strength of oxycodone component	Single-ingredient oxycodone CR		Oxycodone/naloxone CR
	Date of first subsidy	Date of last subsidy	Date of first subsidy
2.5 mg			May 1, 2016
5 mg	November 1, 2003	March 30, 2014 [†]	December 1, 2011
10 mg	May 1, 2000 [‡]		December 1, 2011
15 mg	April 1, 2009 [‡]		May 1, 2016
20 mg	May 1, 2000 [‡]		December 1, 2011
30 mg	April 1, 2009 [‡]		May 1, 2016
40 mg	May 1, 2000 [‡]		December 1, 2011
80 mg	May 1, 2000 [‡]		

[†]Withdrawn from the Australian market by the manufacturer

[‡]From April 1, 2014 these strengths were available as tamper-resistant formulations only

Table 2. Trends in tablets dispensed per 1000 population, by strength and formulation (January 1, 2006 to December 31, 2015)

	Tablets dispensed /1000 population		Period 1 (Q2 2006 to Q3 2011)	Period 2 (Q4 2011 to Q1 2014)		Period 3 (Q2 2014 to Q4 2015)	
	Start of study (Q1 2006)	End of study (Q4 2015)		Level shift (95% CI)	Quarterly slope (95% CI) [†]	Level shift (95% CI)	Quarterly slope (95% CI)
	n (%)	n (%)	Quarterly slope (95% CI)	Level shift (95% CI)	Quarterly slope (95% CI) [†]	Level shift (95% CI)	Quarterly slope (95% CI)
All oxycodone CR	301.0 (100.0)	1000.9 (100.0)	13.6 (12.7 to 14.5)	25.2 (12.6 to 37.8)	22.0 (20.3 to 23.80)	-32.8 (-45.8 to -19.7)	22.0 (20.3 to 23.8) [‡]
5 mg tablet strengths							
All oxycodone CR	24.3 (8.1)	210.2 (20.1)	2.4 (2.3 to 2.5)	4.2 (1.0 to 7.4)	8.6 (8.0 to 9.1)	-36.3 (-39.7 to -32.9)	11.1 (10.1 to 12.1)
Single-ingredient oxycodone CR	24.3 (8.1)	0 (0.0)	2.4 (2.3 to 2.5)	3.0 (0.2 to 5.8)	-1.7 (-2.3 to -1.2)	N/A	N/A
Oxycodone/naloxone CR	0 (0.0)	210.2 (20.1)	N/A	N/A	10.4 (10.1 to 10.7)	36.4 (33.3 to 39.6)	10.9 (10.4 to 11.5)
>5 mg tablet strengths							
All oxycodone CR	276.7 (91.9)	790.7 (79.0)	11.7 (11.1 to 12.4)	24.2 (12.4 to 36.0)	11.7 (11.1 to 12.4)	No level shift	11.7 (11.1 to 12.4) [‡]
Single-ingredient oxycodone CR	276.7 (91.9)	335.2 (33.5)	11.4 (10.4 to 12.4)	No level shift	-11.2 (-13.6 to -8.8)	-27.8 (-44.8 to -10.9)	-18.0 (-22.8 to -13.3)
Oxycodone/naloxone CR	0 (0.0)	455.5 (45.5)	N/A	N/A	27.2 (26.2 to 28.2)	16.2 (6.3 to 26.0)	27.2 (26.2 to 28.2) [‡]

CR = Controlled-release; N/A = not applicable

Period 1: Before subsidy of oxycodone/naloxone CR in December 1, 2011 (Q4 2011)

Period 2: After subsidy of oxycodone/naloxone CR but before single-ingredient oxycodone CR reformulation/5 mg withdrawal in April 1, 2014 (Q2 2014)

Period 3: After reformulation and withdrawal of 5 mg single-ingredient oxycodone CR

[†] Change in slope lagged by one quarter

[‡] Slope unchanged from previous period

Table 3. Trends in new oxycodone CR treatment episodes among concessional beneficiaries, by formulation and tablet strength (April 1, 2006 to December 31, 2016)

	Period 1 (Q2 2006 to Q3 2011)	Period 2 (Q4 2011 to Q1 2014)		Period 3 (Q2 2014 to Q4 2015)	
	Quarterly slope (95% CI)	Level shift [†] (95% CI)	Quarterly slope [†] (95% CI)	Level shift [†] (95% CI)	Quarterly slope [†] (95% CI)
All oxycodone CR	47 (42 to 53)	111 (5 to 218)	72 (60 to 84)	147 (10 to 283)	72 (60 to 84) [‡]
≤5 mg tablet strengths[§]					
All oxycodone CR	20 (19 to 22)	143 (93 to 193)	51 (45 to 57)	No level shift	69 (64 to 74)
Single-ingredient oxycodone CR	20 (19 to 22)	No level shift	-38 (-43 to -33)	N/A	N/A
Oxycodone/naloxone CR	N/A	N/A	105 (93 to 118)	185 (60 to 309)	64 (50 to 79)
>5 mg tablet strengths					
All oxycodone CR	25 (23 to 27)	No level shift	25 (23 to 27) [‡]	No level shift	25 (23 to 27) [‡]
Single-ingredient oxycodone CR	27 (24 to 30)	-164 (-235 to -94)	-66 (-74 to -58)	No level shift	-36 (-45 to -28)
Oxycodone/naloxone CR	N/A	N/A	101 (92 to 109)	No level shift	48 (39 to 58)

CR = Controlled-release; N/A = not applicable

Period 1: Before subsidy of oxycodone/naloxone CR in December 1, 2011 (Q4 2011)

Period 2: After subsidy of oxycodone/naloxone CR but before single-ingredient oxycodone CR reformulation/5 mg withdrawal in April 1, 2014 (Q2 2014)

Period 3: After reformulation and withdrawal of 5 mg single-ingredient oxycodone CR

[†]Level shift and change in slope lagged by one quarter

[‡]Slope unchanged from previous period

[§] 2.5 mg/1.25 mg, 15 mg/7.5 mg and 30 mg/15 mg oxycodone/naloxone CR tablets were introduced in May 2016

Table 4. Uptake of oxycodone/naloxone CR and characteristics of concessional beneficiaries initiating a new oxycodone CR treatment episode, by time period

	Period 1 cohort (Jan 1, 2009 to Dec 31, 2009)	Period 2 cohort (Jul 1, 2012 to Jun 30, 2013)		Period 3 cohort (Jan 1, 2016 to Dec 31, 2016)	
	New treatment episodes, n (%)	New treatment episodes, n (%)	% initiated on oxycodone/naloxone CR, (95% CI)	New treatment episodes, n (%)	% initiated on oxycodone/naloxone CR, (95% CI)
No. people initiating oxycodone CR	7254 (100.0)	10 301 (100.0)	40.0 (39.0 to 40.9)	15 068 (100.0)	91.4 (91.0 to 91.9)
Age (years)					
<45	985 (13.6)	1044 (10.1)	28.6 (26.0 to 31.5)	1487 (9.9)	86.1 (84.2 to 87.8)
45-64	1598 (22.0)	2000 (19.4)	34.3 (32.3 to 36.4)	2771 (18.4)	87.3 (86.0 to 88.5)
65-84	3876 (53.4)	5849 (56.8)	42.5 (41.2 to 43.8)	8613 (57.2)	92.6 (92.0 to 93.1)
85+	795 (11.0)	1408 (13.7)	45.9 (43.4 to 48.5)	2197 (14.6)	95.7 (94.7 to 96.5)
Sex					
Female	4171 (57.5)	6017 (58.4)	42.4 (41.2 to 43.7)	8777 (58.3)	92.5 (92.9 to 93.0)
Male	3083 (42.5)	4284 (41.6)	36.5 (35.1 to 37.9)	6291 (41.8)	90.0 (89.2 to 90.7)
Initial tablet strength					
≤5 mg	1946 (26.8)	4152 (40.3)	48.9 (47.4 to 50.4)	7508 (49.8)	100.0 (-)
10-15 mg	3682 (50.8)	4581 (44.5)	33.9 (32.5 to 35.3)	6193 (41.1)	83.7 (82.8 to 84.6)

20-30 mg	1068 (14.7)	1038 (10.1)	33.2 (30.4 to 36.2)	879 (5.8)	76.5 (73.5 to 79.1)
40-80 mg	234 (3.2)	206 (2.0)	24.3 (18.9 to 30.6)	93 (0.6)	40.9 (31.4 to 51.9)
Multiple	324 (4.5)	324 (3.2)	43.2 (37.9 to 48.7)	395 (2.6)	94.4 (91.7 to 96.3)

CR = controlled-release

Period 1: Before subsidy of oxycodone/naloxone CR in December 1, 2011 (Q4 2011)

Period 2: After subsidy of oxycodone/naloxone CR but before single-ingredient oxycodone CR reformulation/5 mg withdrawal in April 1, 2014 (Q2 2014)

Period 3: After reformulation and withdrawal of 5 mg single-ingredient oxycodone CR

Table 5. Opioid dispensing 90 days prior to and 90 days after initiation with oxycodone CR among concessional beneficiaries, by time period

	Period 1 cohort (Jan 1, 2009 to Dec 31, 2009)	Period 2 cohort (Jul 1, 2012 to Jun 30, 2013)	Period 3 cohort (Jan 1, 2016 to Dec 31, 2016)	Age- and sex-adjusted risk difference (Period 3 – Period 1)
	n (%)	n (%)	n (%)	% (95% CI)
No. people initiating oxycodone CR	7254 (100.0)	10 301 (100.0)	15 068 (100.0)	
Initial tablet strength				
≤5 mg	1946 (26.8)	4152 (40.3)	7508 (49.8)	21.1 (19.9 to 22.4)
10-15 mg	3682 (50.8)	4581 (44.5)	6193 (41.1)	-8.8 (-10.2 to -7.4)
20-30 mg	1068 (14.7)	1038 (10.1)	879 (5.8)	-7.5 (-8.4 to -6.6)
40-80 mg	234 (3.2)	206 (2.0)	93 (0.6)	-1.7 (-2.2 to -1.3)
Multiple	324 (4.5)	324 (3.2)	395 (2.6)	-1.8 (-2.4 to -1.3)
Opioids dispensed 90 days before initiation				
None	3454 (47.6)	4622 (44.9)	8033 (53.3)	5.2 (3.8 to 6.6)
Oxycodone IR	1668 (23.0)	2803 (27.2)	3443 (22.9)	-0.2 (-1.0 to 1.4)
Any strong opioid (excluding oxycodone IR)	932 (12.9)	1646 (16.0)	1718 (11.4)	-1.8 (-2.7 to -0.9)
Any weak opioid	2497 (34.4)	3231 (31.4)	3890 (25.8)	-7.9 (-9.2 to -6.7)
<i>Codeine, paracetamol/codeine</i>	1799 (24.8)	2226 (21.6)	2679 (17.8)	-6.4 (-7.6 to -5.3)
<i>Tramadol</i>	987 (13.6)	1339 (13.0)	1616 (10.7)	-2.7 (-3.6 to -1.8)
Opioids dispensed in 90 days after initiation				
None	2205 (44.2)	4738 (46.0)	8011 (53.2)	8.8 (7.4 to 10.2)
Oxycodone IR	3232 (44.6)	4828 (46.9)	6771 (44.9)	0.6 (-0.8 to 2.0)
Any strong opioid (excluding oxycodone IR)	1238 (17.1)	1663 (16.1)	2035 (13.5)	-4.2 (-5.1 to -3.2)
Any weak opioid	1994 (27.5)	2554 (24.8)	3144 (20.9)	-5.4 (-6.6 to -4.2)
<i>Codeine, paracetamol/codeine</i>	1401 (19.3)	1688 (16.4)	1988 (13.2)	-5.1 (-6.1 to 4.0)
<i>Tramadol</i>	786 (10.8)	1078 (10.5)	1395 (9.3)	-1.1 (-1.9 to -0.3)

Total oxycodone CR quantity dispensed in 90 days after initiation				
≤150 mg	1124 (15.5)	2192 (21.3)	4410 (29.3)	13.6 (12.5 to 14.6)
151-300 mg	2034 (28.0)	2449 (23.8)	3443 (22.9)	-4.9 (-6.1 to -3.7)
301-1000 mg	2164 (29.8)	2913 (28.3)	4230 (28.1)	-2.1 (-3.4 to -0.8)
>1000 mg	1932 (26.6)	2747 (26.7)	2985 (19.8)	-6.7 (-7.9 to -5.4)
No other opioid dispensings in 90 days before OR 90 days after initiation		1336 (18.4)	1848 (17.9)	3484 (23.1)
				4.8 (3.4 to 5.9)

CR = controlled release; IR = immediate release

Period 1: Before subsidy of oxycodone/naloxone CR in December 1, 2011 (Q4 2011)

Period 2: After subsidy of oxycodone/naloxone CR but before single-ingredient oxycodone CR reformulation/5 mg withdrawal in April 1, 2014 (Q2 2014)

Period 3: After reformulation and withdrawal of 5 mg single-ingredient oxycodone CR

Figure 1. Oxycodone CR tablets dispensed per 1,000 population per quarter, by strength and formulation

Legend: Oxycodone/naloxone CR subsidy: December 1, 2011 (Q4 2011); introduction of tamper-resistant formulation and withdrawal of 5 mg single-ingredient oxycodone CR: April 1, 2014 (Q2 2014)

Figure 2. New treatment episodes with oxycodone CR, by strength and formulation among concessional beneficiaries

Legend: Subsidy of oxycodone/naloxone CR: December 1 (Quarter 4), 2011; introduction of tamper-resistant formulation and withdrawal of 5 mg single-ingredient oxycodone CR: April 1, 2014 (Q2 2014). 2.5 mg/1.25 mg, 15 mg/7.5 mg and 30 mg/15 mg oxycodone/naloxone CR tablets were introduced in May 2016.

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Title:

Increases in controlled-release oxycodone utilisation following the subsidy of oxycodone with naloxone formulations: An Australian population-based study

Date:

2019-01-01

Citation:

Schaffer, A. L., Karanges, E. A., Buckley, N. A., Wilson, A., Degenhardt, L., Larance, B. & Pearson, S. -A. (2019). Increases in controlled-release oxycodone utilisation following the subsidy of oxycodone with naloxone formulations: An Australian population-based study. PHARMACOEPIDEMIOLOGY AND DRUG SAFETY, 28, (1), pp.97-105. WILEY. <https://doi.org/10.1002/pds.4683>.

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