

# Opioid Analgesics: Overview

## Drug utilisation sub-committee (DUSC)

*October 2014*

### Abstract

#### Purpose

To assess the utilisation of PBS listed opioid analgesics.

#### Background

The DUSC previously reviewed opioid use at its February 2010 meeting where it examined PBS opioid use from April 2004 to July 2009.

#### Date of listing on PBS

The following changes PBS opioid listings have occurred since the DUSC analysis in February 2010:

- The PBS maximum quantity of controlled release oxycodone preparations increased in April 2011 from 20 to 28. The maximum quantities of controlled release morphine preparations increased in May 2011. Items with a maximum quantity of 10 were increased to 14 and items with a maximum quantity of 20 were increased to 28.
- Oxycodone with naloxone was PBS listed from 1 December 2011.
- Tapentadol was listed on 1 June 2014.

All other opioid analgesics were PBS listed prior to June 2009.

#### Data Source / methodology

Pharmacy claims data from the DUSC Database was the main source of data. The Department of Human Services (DHS) Supplied Prescriptions Database was used where patient age, utilisation by age groups and patient numbers are presented. Australian Bureau of Statistics population estimates were used for rates of utilisation by population. Utilisation was measured in terms of prescriptions, defined daily doses (DDDs) and DDDs per 1000 population.

## Key Findings

- 2,968,733 people received at least one PBS-listed opioid analgesic in the 12 months from April 2013 to March 2014.
- Total use of opioids, in terms of prescriptions and DDDs/1000 population/day continues to increase.
- Paracetamol with codeine had the highest rate of use in terms of DDDs/1000 population/day. In 2013, oxycodone became the second highest used opioid analgesic, exceeding the use of tramadol.
- Utilisation of oxycodone, fentanyl, buprenorphine and hydromorphone is increasing. The utilisation of morphine and tramadol appear to be decreasing.
- Oxycodone has the highest level of utilisation when adjusted for opioid potency.

## Purpose of analysis

To assess the utilisation of PBS listed opioid analgesics.

## Pharmacology

Opioids work by acting on opioid receptors on neuronal cell membranes in the central nervous system and, to a lesser extent, the peripheral nervous system. There are three main types of opioid receptors:  $\mu$ ,  $\kappa$  and  $\delta$  (mu, kappa and delta). Agonist activity at mu opioid receptors is responsible for analgesia, respiratory depression, euphoria, sedation, decreased gastrointestinal motility leading to constipation and physical dependence. The analgesic activity of most clinically used opioids is due to their agonist activity at the mu receptor.

## Therapeutic Goods Administration (TGA) approved indications

Table 1 presents the TGA approved indications of opioids listed on the PBS.

**Table 1: Dosage and administration of PBS listed opioid analgesics**

Drug	Indication
Codeine	Mild to moderate pain
Buprenorphine	Moderate to severe pain
Fentanyl	Moderate to severe acute or chronic pain.
Hydromorphone	Moderate to severe pain.
Methadone	Pain requiring opioids (morphine).
Morphine	Moderate to severe pain.
Oxycodone	Moderate to severe pain.
Tapentadol	Moderate to severe chronic pain.
Tramadol	Moderate to severe pain.

Source: Product Information

The current Product Information (PI) and Consumer Medicine Information (CMI) are available from [the TGA \(Product Information\)](#) and [the TGA \(Consumer Medicines Information\)](#).

## Dosage and administration

Table 2 presents an overview of morphine dose equivalents and duration of action of PBS-listed opioid analgesics.

**Table 2: Dosage and administration of PBS listed opioids**

Drug	Approximate dose equivalent to 10mg IV/SC morphine <sup>1</sup>	Approximate duration of action
Codeine	200mg oral	4-6 hours (analgesia)
Buprenorphine	0.4mg IM 0.8mg sublingual	7 days (patch)
Fentanyl	100-150mcg SC	72 hours (patch) 1-2 hours (IM)
Hydromorphone	1.5-2mg SC/IM 6-7.5mg oral	2-4 hours (standard release) 24 hours (modified release)
Methadone	complex	8-24 hours (chronic dosing)
Morphine	30mg oral	2-3 hours (standard release) 12-24 hours (modified release)
Oxycodone	14-20mg oral	3-6 hours (standard release) 12 hours (modified release)
Tapentadol	-	12 hours (modified release)
Tramadol	100-200mg IM/IV 150mg oral	4-6 hours (standard release) 12 hours (modified release)

IV = intravenous injection, SC = subcutaneous injection, IM = intra-muscular injection

Source: Product Information (duration of action).

The current Product Information (PI) and Consumer Medicine Information (CMI) are available from [the TGA \(Product Information\)](#) and [the TGA \(Consumer Medicines Information\)](#).

### **PBS listing details (as at 1 July 2014)**

Table 3 presents an overview of opioid analgesics listed on the PBS. Current PBS listing details are available from the [PBS website](#).

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<sup>1</sup> Australian Medicines Handbook Pty Ltd. Australian Medicines Handbook 2013. Adelaide: Australian Medicines Handbook Pty Ltd; 2013.

**Table 3: PBS listings of opioid analgesics.**

<b>Drug and dosage form (brand)</b>	<b>Restrictions (abridged)</b>
<b>Buprenorphine</b>	
Buprenorphine patches	Chronic severe pain
<b>Codeine</b>	
Codeine phosphate tablets	Unrestricted benefit
<b>Fentanyl</b>	
Fentanyl patches	Chronic severe pain
Fentanyl lozenge	Breakthrough pain (palliative care)
<b>Hydromorphone</b>	
Hydromorphone tablets (standard release)	Severe disabling pain
Hydromorphone tablets (modified release)	Chronic severe pain
Hydromorphone injection	Unrestricted benefit
Hydromorphone oral liquid	Severe disabling pain
<b>Methadone</b>	
Methadone tablet	Severe disabling pain
Methadone oral liquid	Chronic severe pain (palliative care)
Methadone injection	Severe disabling pain
<b>Morphine</b>	
<i>Standard release tablets</i>	
Morphine sulfate tablet ( <i>Anamorph</i> )	Severe disabling pain
Morphine sulfate tablet ( <i>Sevredol</i> )	Severe disabling pain due to cancer Severe disabling pain (palliative care)
<i>Modified release tablets or capsules</i>	
Morphine sulfate modified tablets (up to 120mg/tablet)	Chronic severe pain
Morphine sulfate modified tablets 200mg	Chronic severe pain due to cancer Chronic severe pain (palliative care)
<i>Oral liquids</i>	
Morphine hydrochloride oral liquid (standard release)	Severe disabling pain
Morphine controlled release granules for oral suspension (up to 100mg)	Chronic severe pain
Morphine controlled release granules for oral suspension (200mg)	Chronic severe pain due to cancer
<i>Injections</i>	
Morphine sulphate injections	Unrestricted benefit
<b>Oxycodone</b>	

<b>Drug and dosage form (brand)</b>	<b>Restrictions (abridged)</b>
Oxycodone tablet or capsule (standard release)	Severe disabling pain
Oxycodone tablet (modified release)	Chronic severe pain
Oxycodone oral liquid	Severe disabling pain
Oxycodone suppository	Severe disabling pain
<b>Oxycodone + naloxone</b>	
Oxycodone + naloxone tablet	Chronic severe pain
<b>Paracetamol + codeine</b>	
Paracetamol 500mg + codeine phosphate 30mg – 20 tablets	Unrestricted benefit
Paracetamol 500mg + codeine phosphate 30mg – 60 tablets (Authority Required listing)	Severe disabling pain
<b>Tramadol</b>	
Tramadol capsule 50mg (standard release)	Acute pain not responding to aspirin and/or paracetamol
Tramadol tablet (modified release)	Pain not responding to aspirin and/or paracetamol Dose titration in chronic pain not responding to aspirin and/or paracetamol (50mg strength)
Tramadol oral liquid	Pain not responding to aspirin and/or paracetamol
Tramadol injection	Unrestricted benefit (Doctor's bag) Short-term treatment of acute pain
<b>Tapentadol</b>	
Tapentadol tablet (modified release)	Chronic severe pain

Source: July 2014 PBS Schedule

***Date of listing on PBS and changes to listing.***

Since the February 2010 DUSC analysis, the maximum quantity of controlled release oxycodone preparations increased in April 2011 from 20 to 28. The maximum quantities of controlled release morphine preparations increased in May 2011. Items with a maximum quantity of 10 were increased to 14 and items with a maximum quantity of 20 were increased to 28.

Since the February 2010 DUSC analysis, the following opioids have been listed:

- Oxycodone with naloxone was PBS listed from 1 December 2011.
- Tapentadol was listed on 1 June 2014.

Current PBS listing details are available from the [PBS website](#).

## Previous reviews by the DUSC

The DUSC previously reviewed opioid use at its February 2010 meeting where it examined PBS opioid use from April 2004 to July 2009. The analysis found increased use of oxycodone, fentanyl patches and buprenorphine patches. The increase in fentanyl patch use was attributed to the broadening of the restriction to allow use in non-cancer pain in August 2006. Use of methadone, morphine and tramadol appeared stable. Use of hydromorphone was low. Use of opioids was higher in older age groups. The DUSC noted the defined-daily-doses (DDD) for fentanyl and buprenorphine were high and may underestimate use at population level.

The DUSC had previously examined the utilisation of PBS listed analgesics (opioids, paracetamol and aspirin) at its February 2008 meeting. The DUSC noted that the restriction changes that occurred in 2005 and 2006 did not appear to have led to inappropriate use, although use of some products was found to be increasing, particularly in the older population. The use of oxycodone, particularly the 5mg formulation, had been increasing steadily, with the greatest increase occurring in people aged 60 years and over. The analysis found increasing use of paracetamol as an analgesic and decreasing use of aspirin as a PBS subsidised analgesic.

At its October 2013 meeting, the DUSC requested the Secretariat develop research questions for a future analysis of opioid utilisation. This was presented to the Committee at the February 2014 meeting. The DUSC considered that the next utilisation analysis should commence with an update of the 2010 DUSC analysis, including assessing utilisation by age of the patient. However the DUSC considered that any utilisation analysis of all PBS listed opioids should be undertaken after an additional year of below co-payment data is available. The DUSC noted that there is likely to be prescribing of opioids on private prescription and that the Department no longer collects these data. The DUSC considered that the analysis should therefore also include some additional data to quantify private market use. The Secretariat has been unable to include private market data for the current utilisation analysis. The report focuses of opioids supplied through the PBS and RPBS.

## Methods

Data were extracted from the DUSC database and the Department of Human Services (DHS) Supplied Prescriptions database using Anatomic Therapeutic Classification codes. Data were extracted for N02A (analgesics – opioids) and R05DA (codeine – cough suppressant). The R05DA code was extracted as well as the N02A codeine because the PBS listings are identical.

The DUSC database contains PBS dispensing data including information on prescriptions, quantity and date of supply. The DUSC database combines data on PBS/RPBS prescriptions submitted to the Department of Human Services (DHS) for payment of a subsidy by the Government, with an estimate of under general under co-payment prescriptions based on dispensing data from a sample of pharmacies to the end of March 2012, replaced by actual under copayment data from DHS from 1 April 2012. The DUSC database also includes an

estimate of private prescriptions based on dispensing data from a sample of pharmacies to August 2012. As the private prescription data were only available for part of the study period, these data have not been included.

Data were also extracted from the DHS Supplied Prescriptions database for the period between October 2009 and April 2014 inclusive. These data include patient date of birth and is used for analyses based on patient age, total patients receiving opioid analgesics and distribution of use.

The amount of drug supplied was standardised using defined daily doses (DDDs) and DDDs/1000 population. The defined daily dose (defined by the World Health Organization Collaborating Centre for Drug Statistics Methodology) corresponds to an estimated mean daily dose used for a drug's principal indication in adults ([http://www.whocc.no/atc\\_ddd\\_index/](http://www.whocc.no/atc_ddd_index/)). These figures were calculated using the methodology described in the Australian Statistics on Medicines 2010 [2]. The DDDs for opioid analgesics are presented in Appendix 1. The DUSC noted the DDD for codeine is based on the lower dose for use as a cough suppressant. The DUSC also noted the DDDs for strong opioids were developed when the main use of strong opioids was for end-of-life cancer pain.

Population data for utilisation by age groups were from the Australian Demographic Statistics published by the Australian Bureau of Statistics [3]. The analyses use the population estimate for 1 June of the relevant calendar year. The figures for 2014 used the population from 1 June 2013.

Rolling annual averages are presented in some of the figures where there are substantial monthly variations. Where rolling annual averages are presented in graphs, they represent the average of the point it is plotted at and the three quarters preceding.

As this analysis is based on date of supply, there may be small differences when compared with publicly available Medicare Australia date of processing data. Medicines supplied to general patients costing less than general patient contribution do not receive a PBS benefit and are therefore not included in publicly available data.

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<sup>2</sup> Department of Health and Ageing. Australian Statistics on Medicines 2010. Canberra: Commonwealth of Australia; 2012.

<sup>3</sup> Australian Bureau of Statistics. Australian Demographic Statistics. Canberra: Australian Bureau of Statistics. Cat. No. 3010.0.

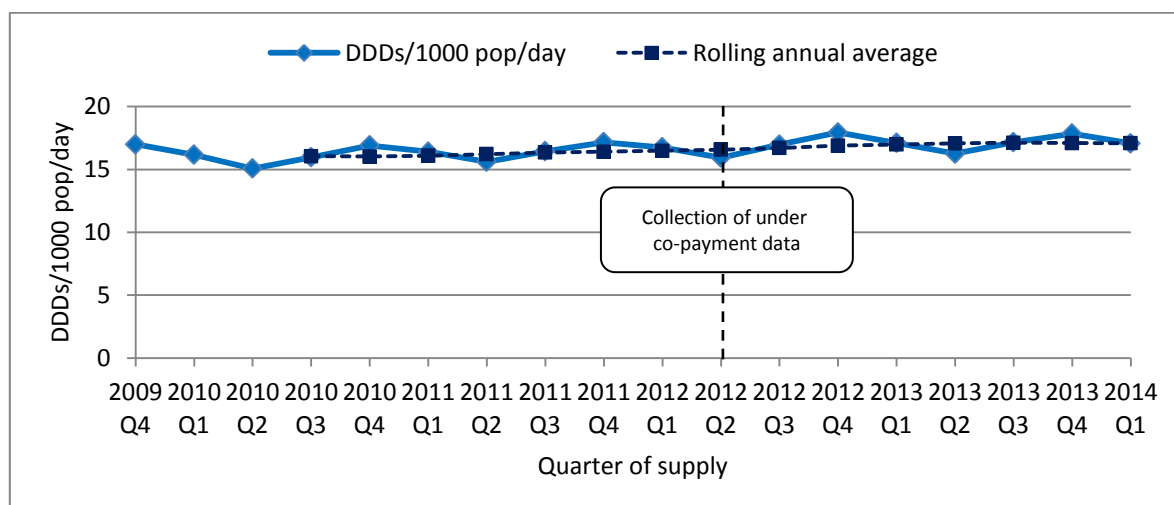
## Results

### Analysis of drug utilisation

#### Overall utilisation

In the 12 months from April 2013 to March 2014, 2,968,733 people received at least one PBS-listed opioid analgesic. Of these individuals, approximately 5% (152,847 people) accounted for 61% of opioid utilisation in terms of opioid DDDs supplied over the year.

Figure 1 presents the overall utilisation of opioids in DDDs/1000 population/day.

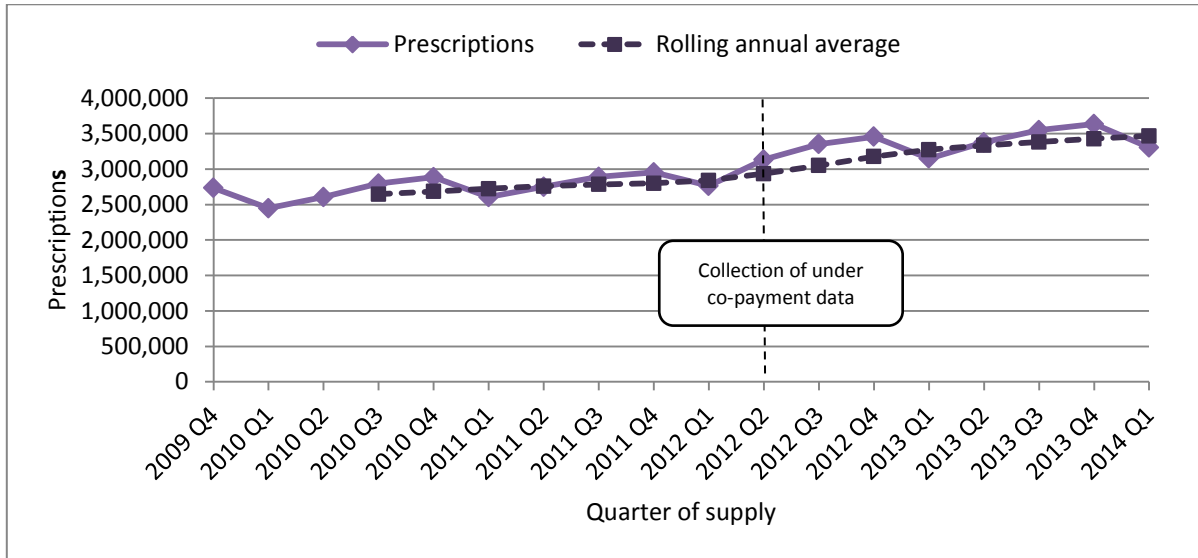


**Figure 1: R/PBS opioid utilisation in DDDs/1000 population/day**

Source: DUSC Database, extracted August 2014

The rolling annual average of DDDs/1000 population/day supplied has increased from 15.73 to 17.06 in the data period. The DUSC noted a sponsor response stating that opioid utilisation in DDDs/1000 population/day has been stable. The DUSC disagreed with this statement and considered this to be a large increase, given that the DDDs for strong opioids are based on the much higher doses used to treat patients with cancer pain. The DUSC considered that opioids are predominantly used for chronic non-cancer pain and the increase in DDDs/1000/day from 15.7 to 17.1 to be a substantial increase and could reflect a large increase in the number of patients accessing opioids for non-cancer pain.

Figure 2 presents the number of opioid prescriptions supplied on the R/PBS.

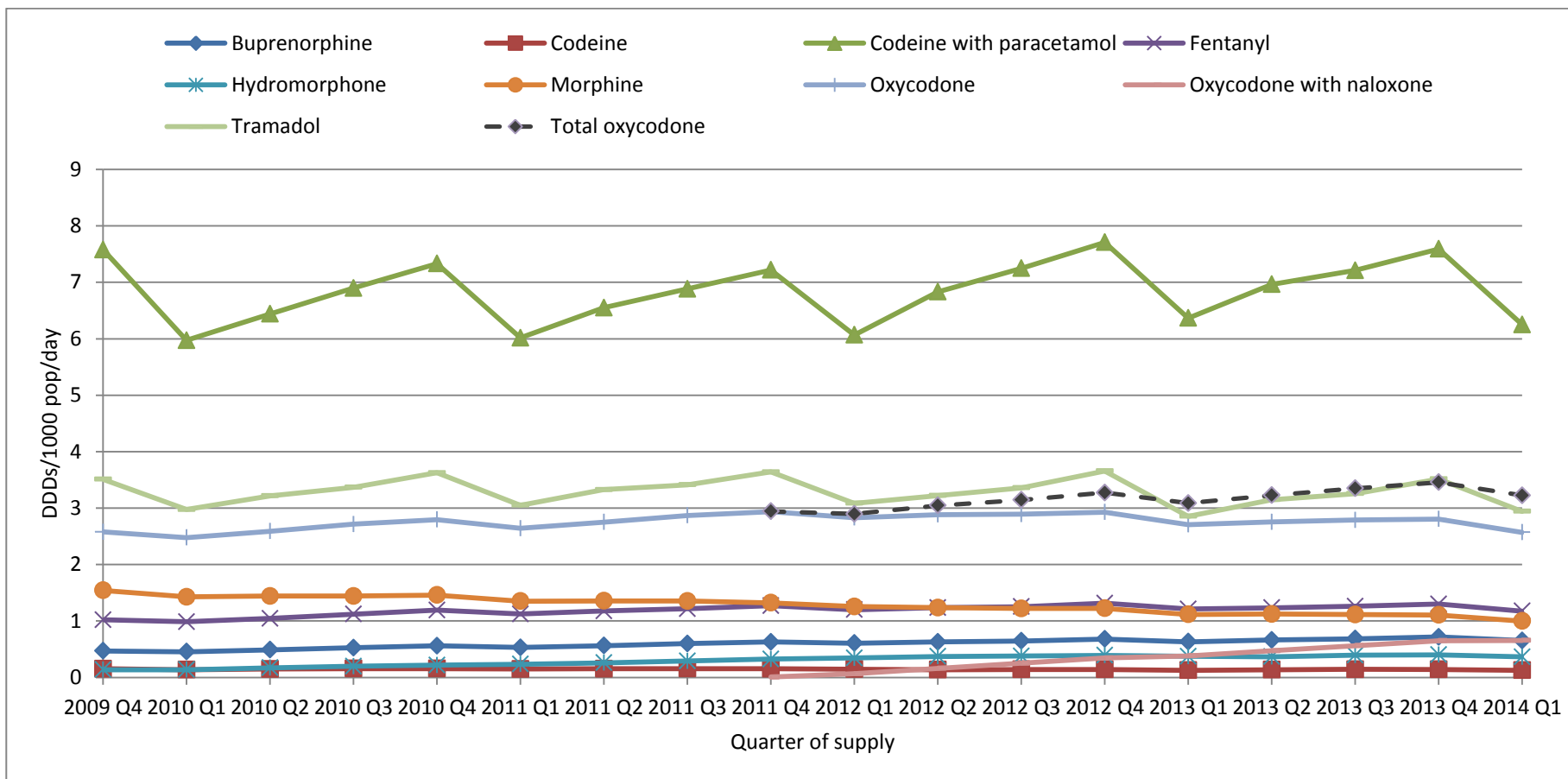


**Figure 2: R/PBS opioid utilisation in prescriptions**

Source: DUSC Database, extracted August 2014

The number of opioid prescriptions supplied has increased since the second half of 2009. Some of the increase is likely to be due to increases in data capture due to the collection of under co-payment prescription data.

Figure 3 presents utilisation of opioid analgesics by DDDs/1000 population/day by drug. The utilisation of oxycodone is presented for plain oxycodone and the oxycodone with naloxone combination separately as well as total oxycodone.



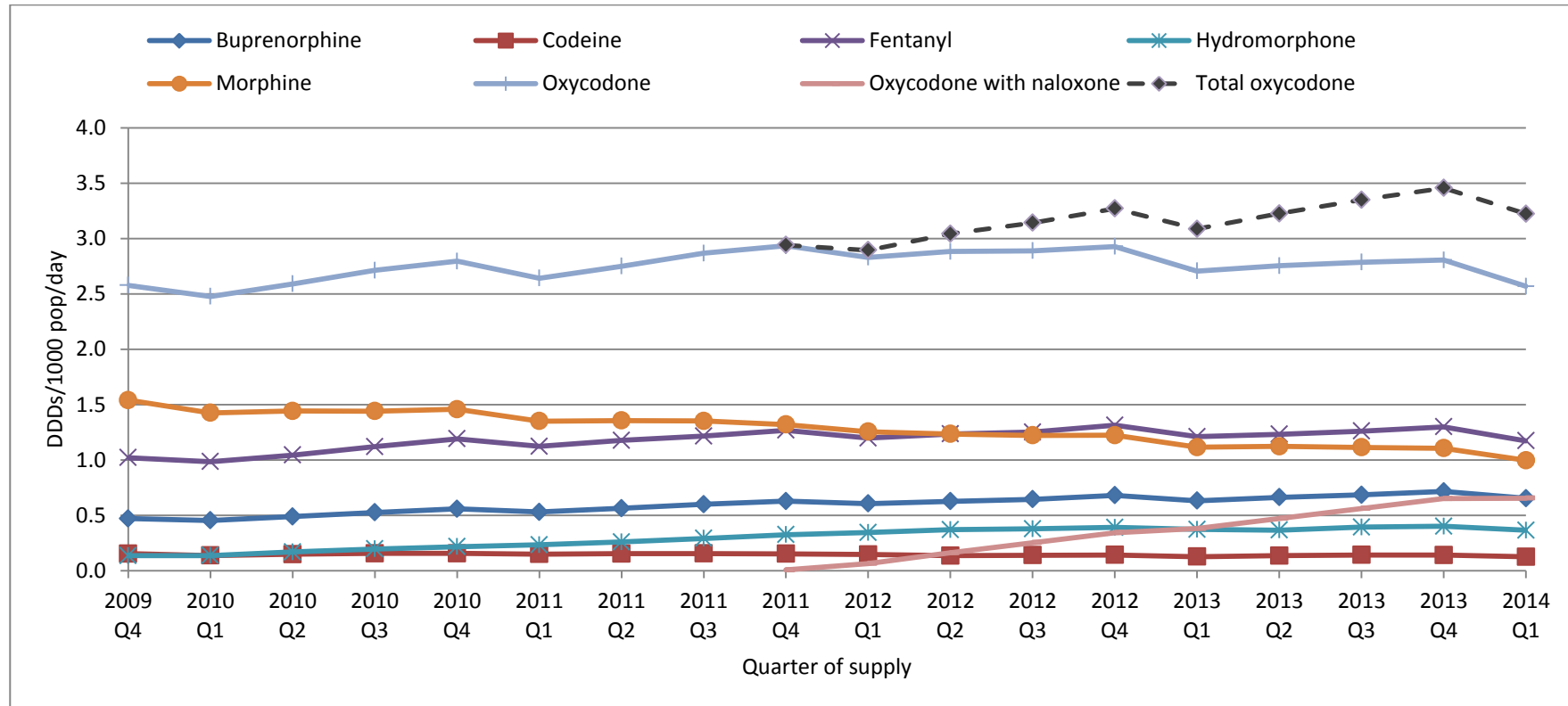
**Figure 3: R/PBS opioid utilisation in DDDs/1000 population/day by drug**

Source: DUSC Database, extracted August 2014

Paracetamol with codeine and tramadol were the most commonly supplied opioids for most of the data period. Since 2013, oxycodone has become the second most commonly used opioid. This appears to have occurred both due to increased oxycodone utilisation and decreased tramadol utilisation. The DUSC noted that based on a patient level analysis oxycodone would probably be the most commonly used opioid because the DDD for oxycodone and other strong opioids are much higher than the commonly used doses for chronic non-

cancer pain. The DUSC noted however, that there is a lack of historical data needed to make this type of analysis possible, unless a particular cohort of patients is selected (e.g. concessional only).

Figure 4 presents the data in Figure 3, excluding paracetamol with codeine and tramadol.

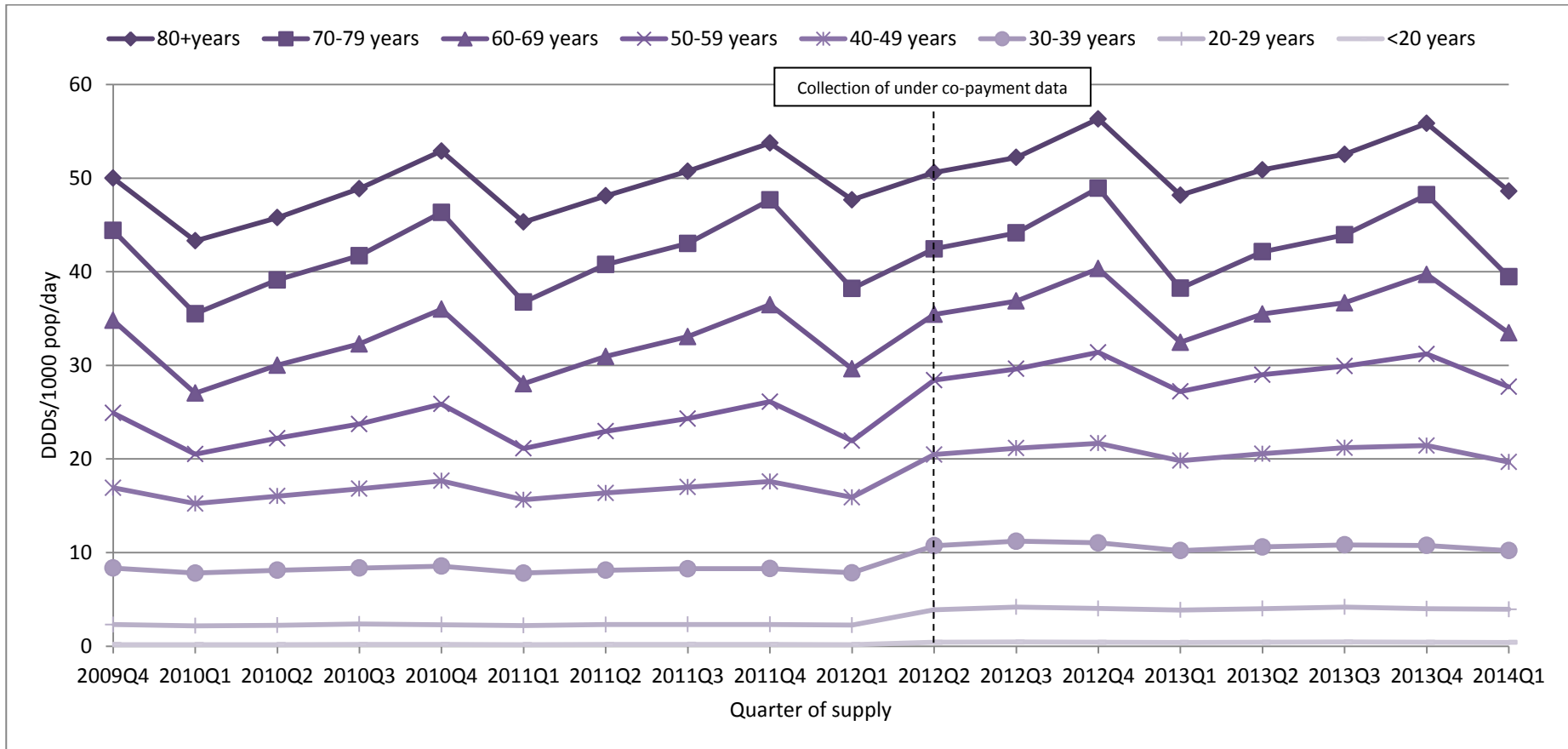


**Figure 4: R/PBS opioid utilisation in DDDs/1000 population/day by drug (excluding paracetamol with codeine and tramadol)**

Source: DUSC Database, extracted August 2014

The utilisation of morphine is decreasing, while utilisation of fentanyl, buprenorphine, oxycodone with naloxone and hydromorphone is increasing.

Figure 5 presents the total utilisation of opioids by DDD and age.



**Figure 5: R/PBS opioid utilisation in DDDs/1000 population/day by age**

Source: DHS Supplied Prescriptions Database, extracted August 2014. ABS population estimates

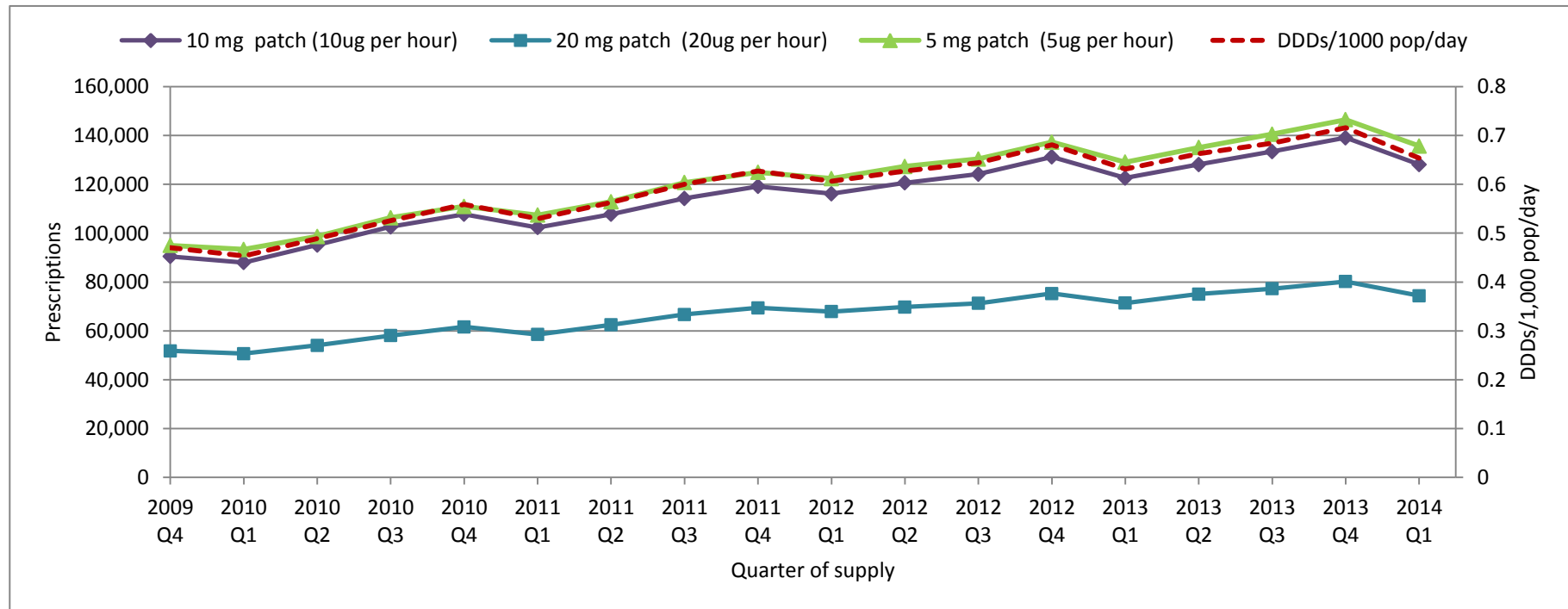
Utilisation across the ages has remained relatively consistent over time based on DDDs. The DUSC considered that utilisation will have increased more than it appears over time, because the doses used for chronic pain are much lower than the doses that were used to

calculate the WHO DDDs (the doses used to calculate the DDDs being those doses used to treat cancer pain). The DUSC noted that it would be interesting to look at the utilisation data using morphine equivalents.

The following figures present additional utilisation data on buprenorphine, fentanyl, morphine, oxycodone and tramadol.

**Buprenorphine**

Figure 6 presents the utilisation of buprenorphine patches by strength.

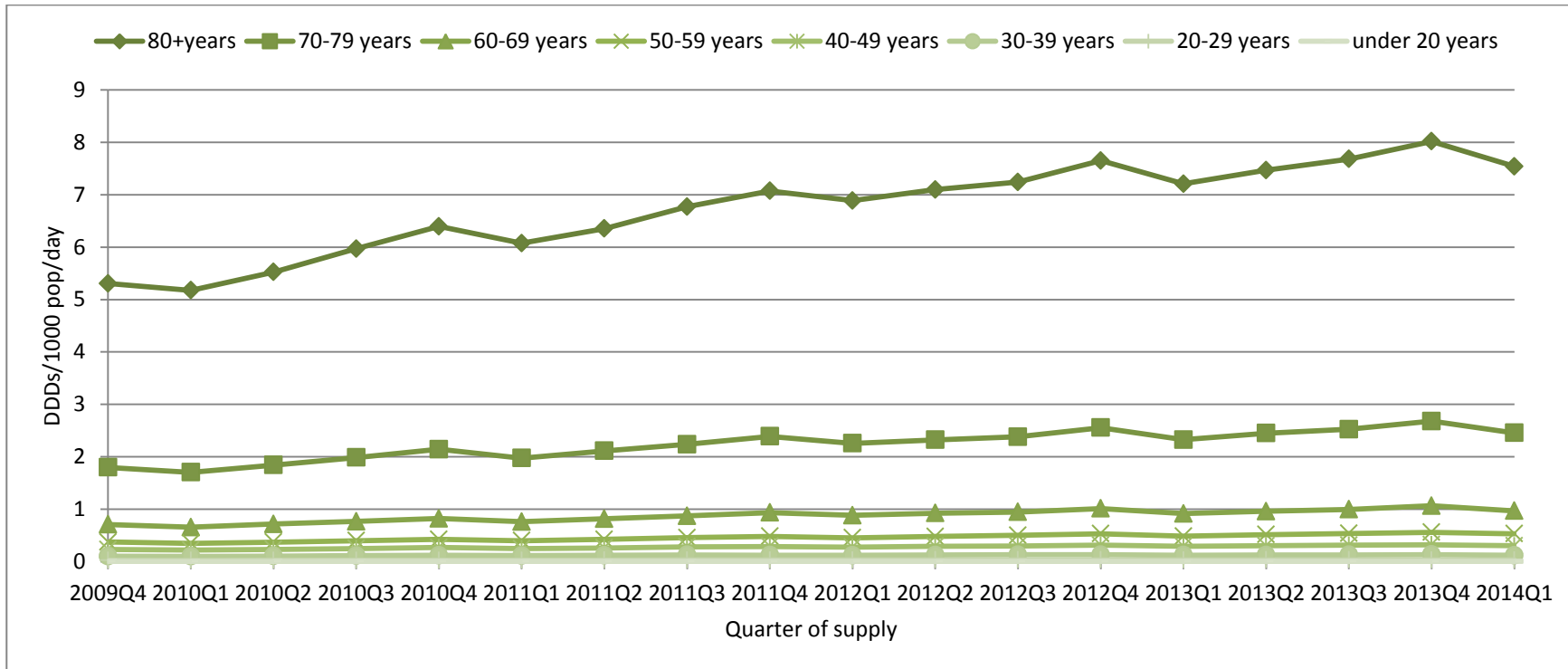


**Figure 6: Buprenorphine utilisation by strength**

Source: DUSC Database, extracted August 2014

The utilisation of buprenorphine patches has increased since 2009. The 5mcg and 10mcg patches continue to be the most frequently supplied strengths.

Figure 7 presents the utilisation of buprenorphine by age.



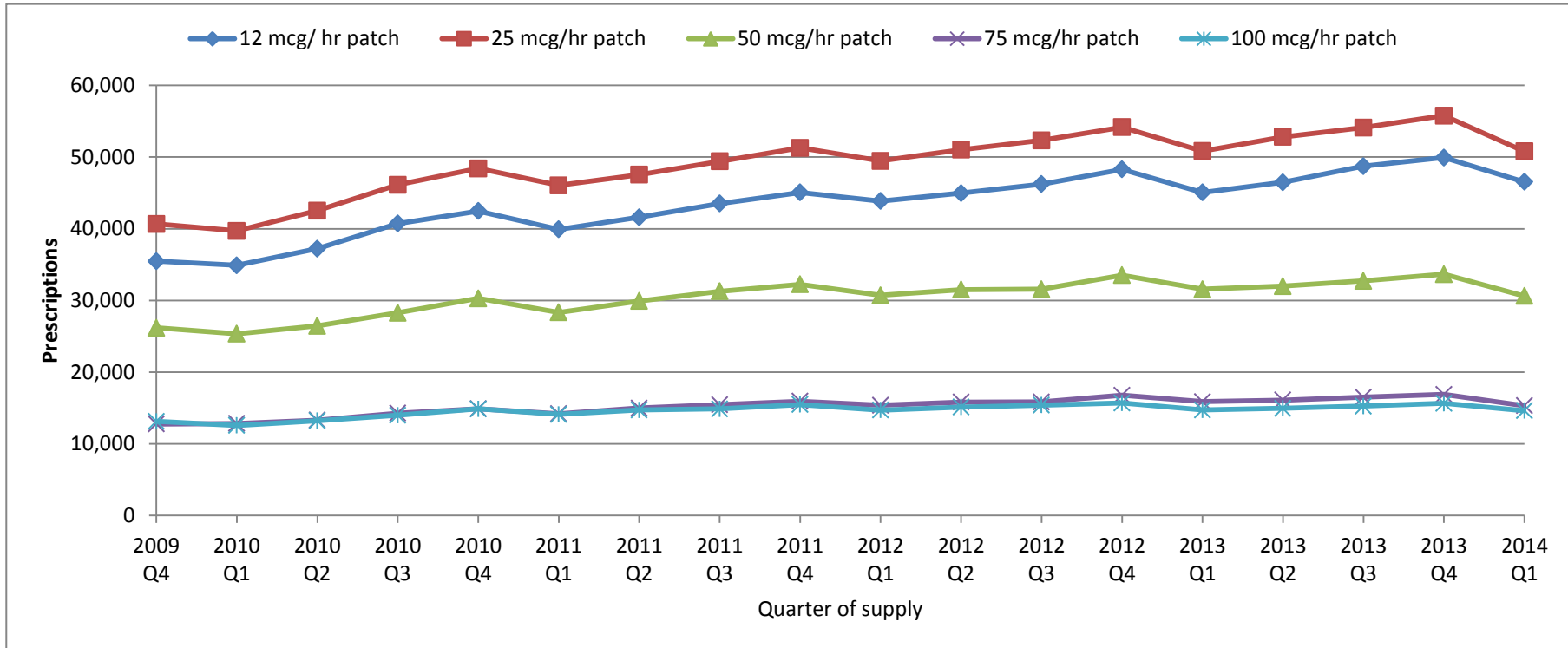
**Figure 7: Buprenorphine utilisation in DDDs/1000 population/day by age**

Source: DHS Supplied Prescriptions Database, extracted August 2014. ABS population estimates

The utilisation of buprenorphine is substantially higher in patients aged 70 years and over compared to younger age groups. During this time period, 65% of buprenorphine DDDs were supplied to patients aged 70 years and over.

## Fentanyl

Figure 8 presents the utilisation of fentanyl patches by strength.

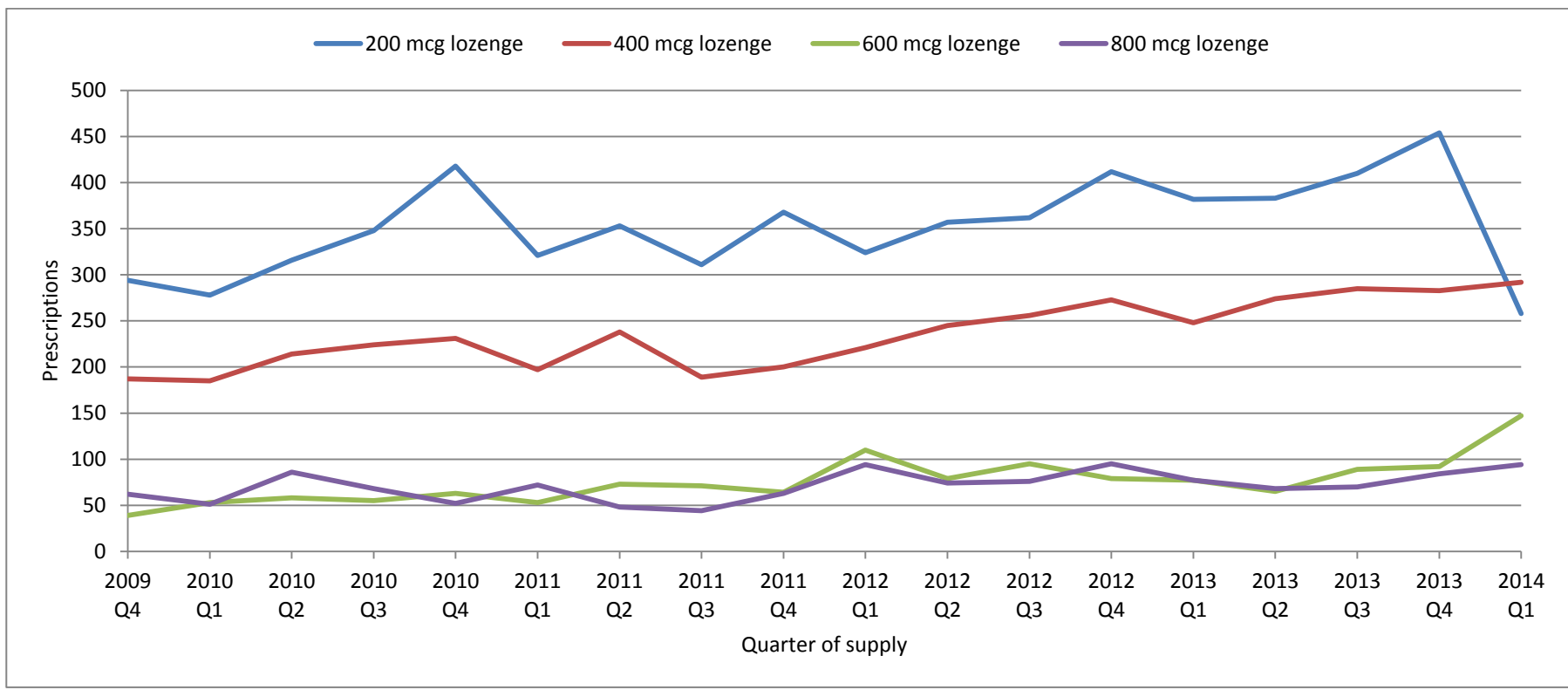


**Figure 8: Fentanyl patch utilisation by strength**

Source: DUSC Database, extracted August 2014

The number of fentanyl patch prescriptions supplied has increased since 2009.

Figure 9 presents the utilisation of fentanyl lozenges by strength. Fentanyl lozenges are available in pack sizes of 9 or 30 lozenges. Figure 9 combines prescriptions for the same strength of fentanyl.

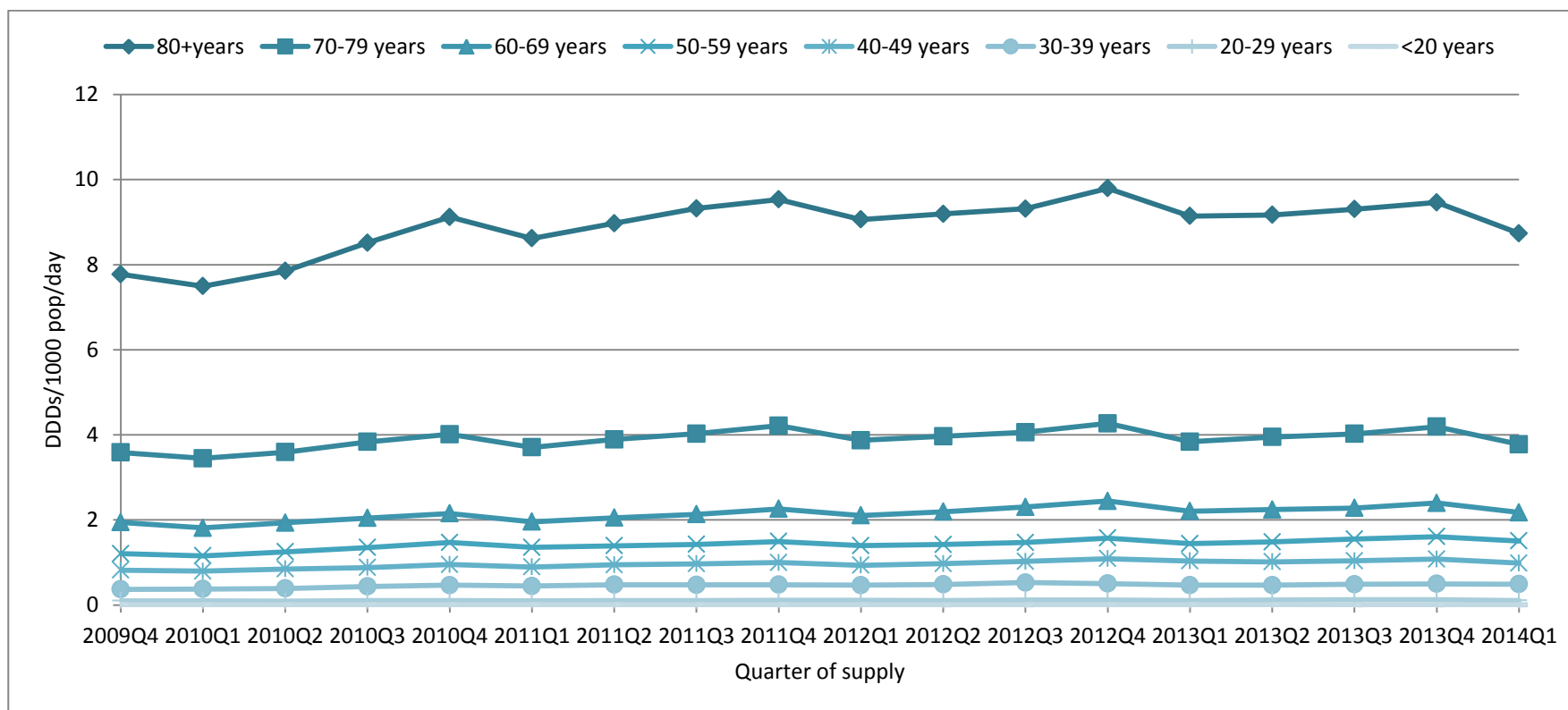


**Figure 9: Fentanyl lozenge utilisation by strength**

Source: DUSC Database, extracted August 2014

The utilisation of fentanyl lozenges has increased since 2009. The data for the 1200mcg and 1600mcg have not been presented due to small numbers of prescriptions supplied each quarter. From September 2009 to March 2014, 376 prescriptions for fentanyl 1200mcg lozenge and 336 prescriptions for fentanyl 1600 mcg lozenge were supplied. Fentanyl lozenges are only subsidised for palliative care.

Figure 10 presents the utilisation of fentanyl products by patient age. This includes both the transdermal patch and lozenges.

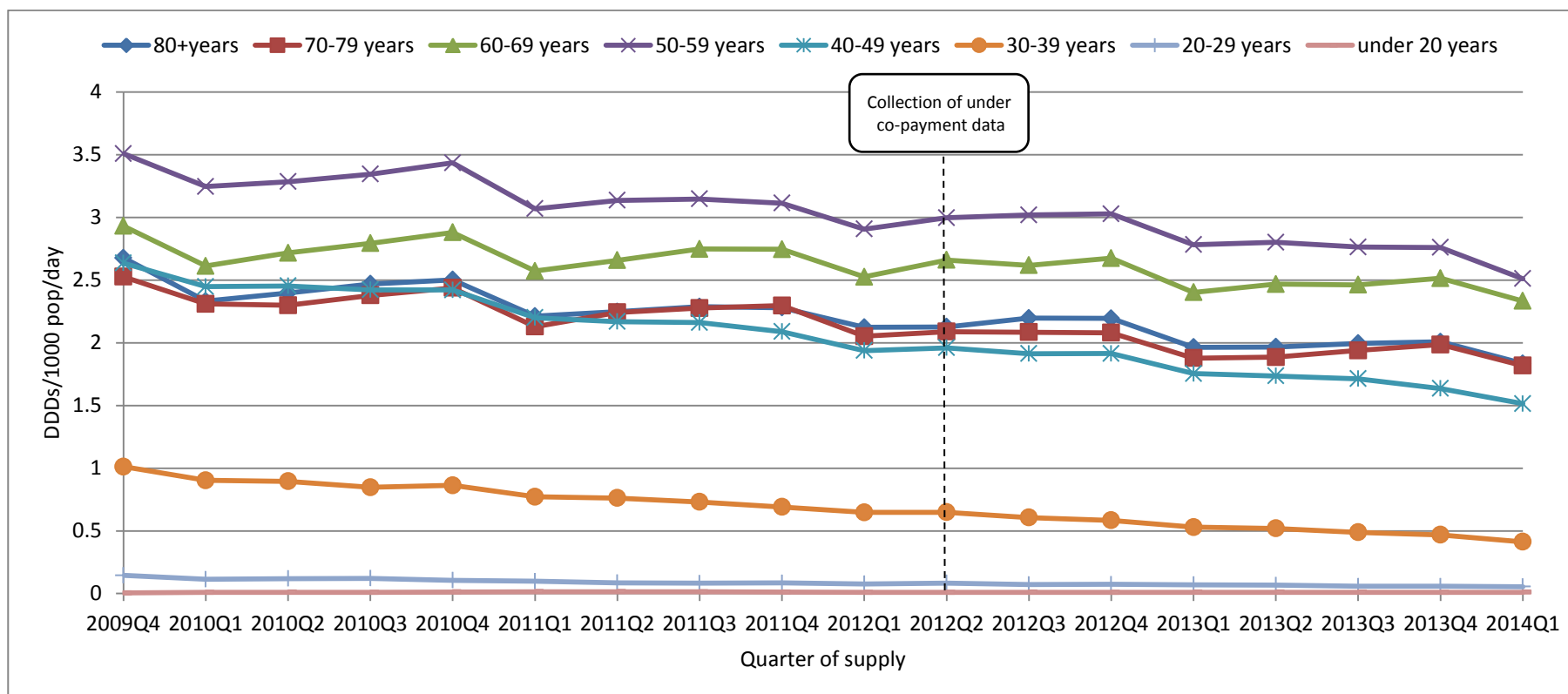


**Figure 10: Fentanyl utilisation in DDDs/1000 population/day by age**  
 Source: DHS Supplied Prescriptions Database, extracted August 2014. ABS population estimates

Fentanyl utilisation is substantially higher in patients aged 70 years and over. Utilisation has increased substantially in patients aged 80 years and older. From October 2009 to March 2014, 48% of total fentanyl DDDs supplied were for patients aged 70 years and over.

**Morphine**

Figure 11 presents the utilisation of morphine by patient age.



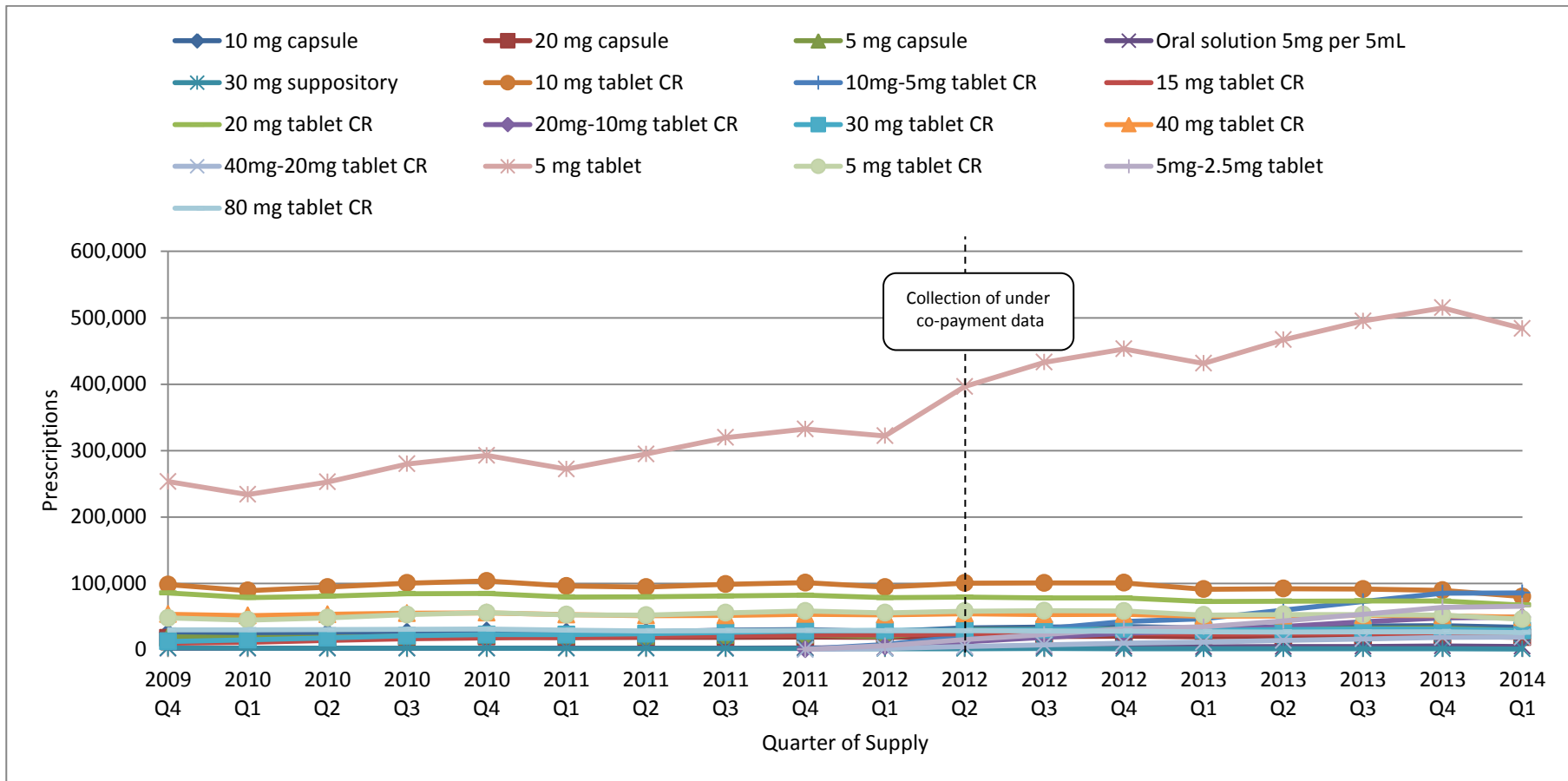
**Figure 11: Morphine utilisation in DDDs/1000 population/day by age**

Source: DHS Supplied Prescriptions Database, extracted August 2014. ABS population estimates

There are higher rates of morphine utilisation in patients aged 50-69 years than other age groups. The utilisation of morphine appears to be decreasing across most age groups.

### **Oxycodone**

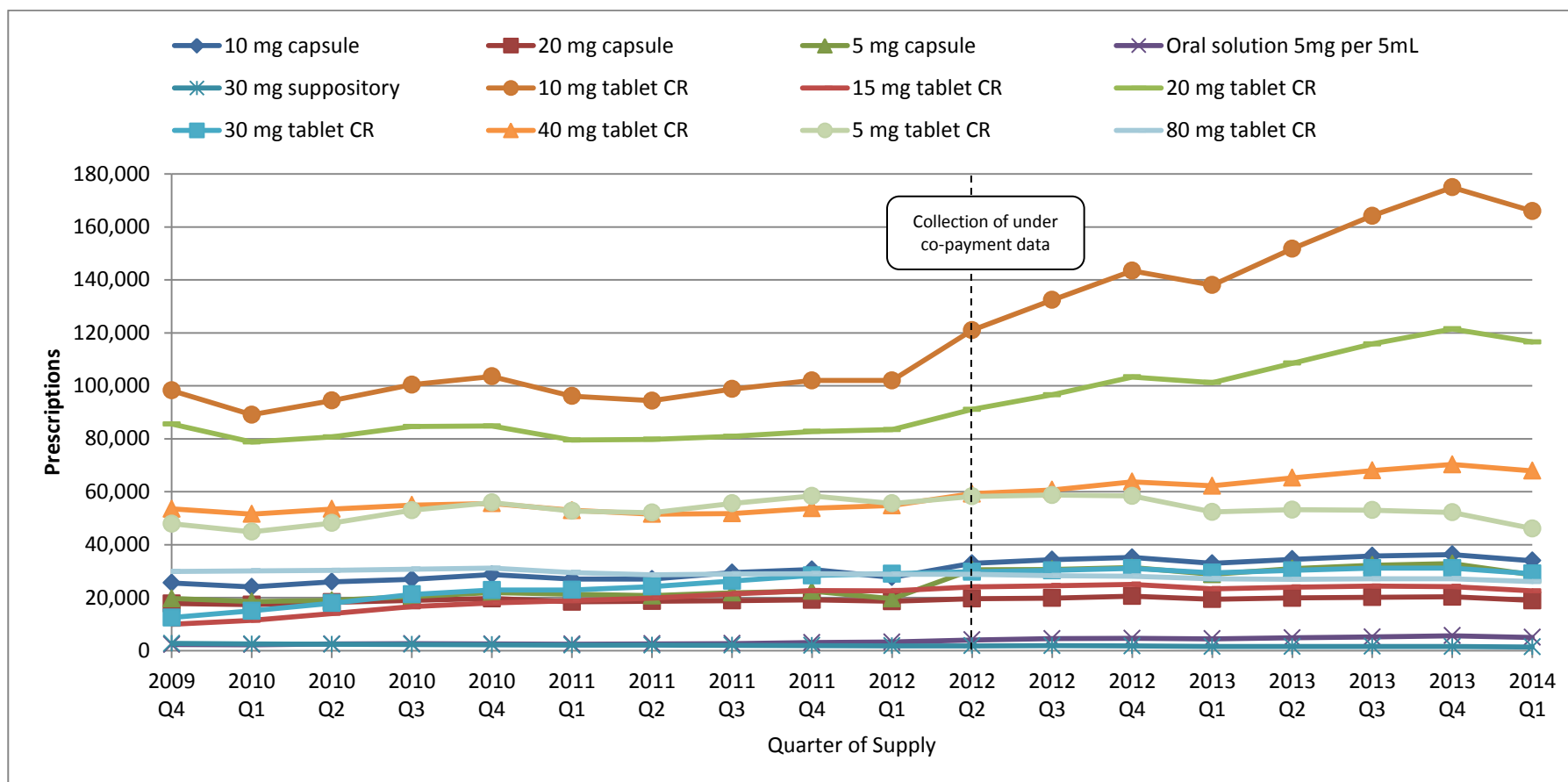
Figure 12 presents the utilisation of oxycodone products by strength.



**Figure 12: Oxycodone prescription utilisation by strength**

Source: DUSC Database, extracted August 2014

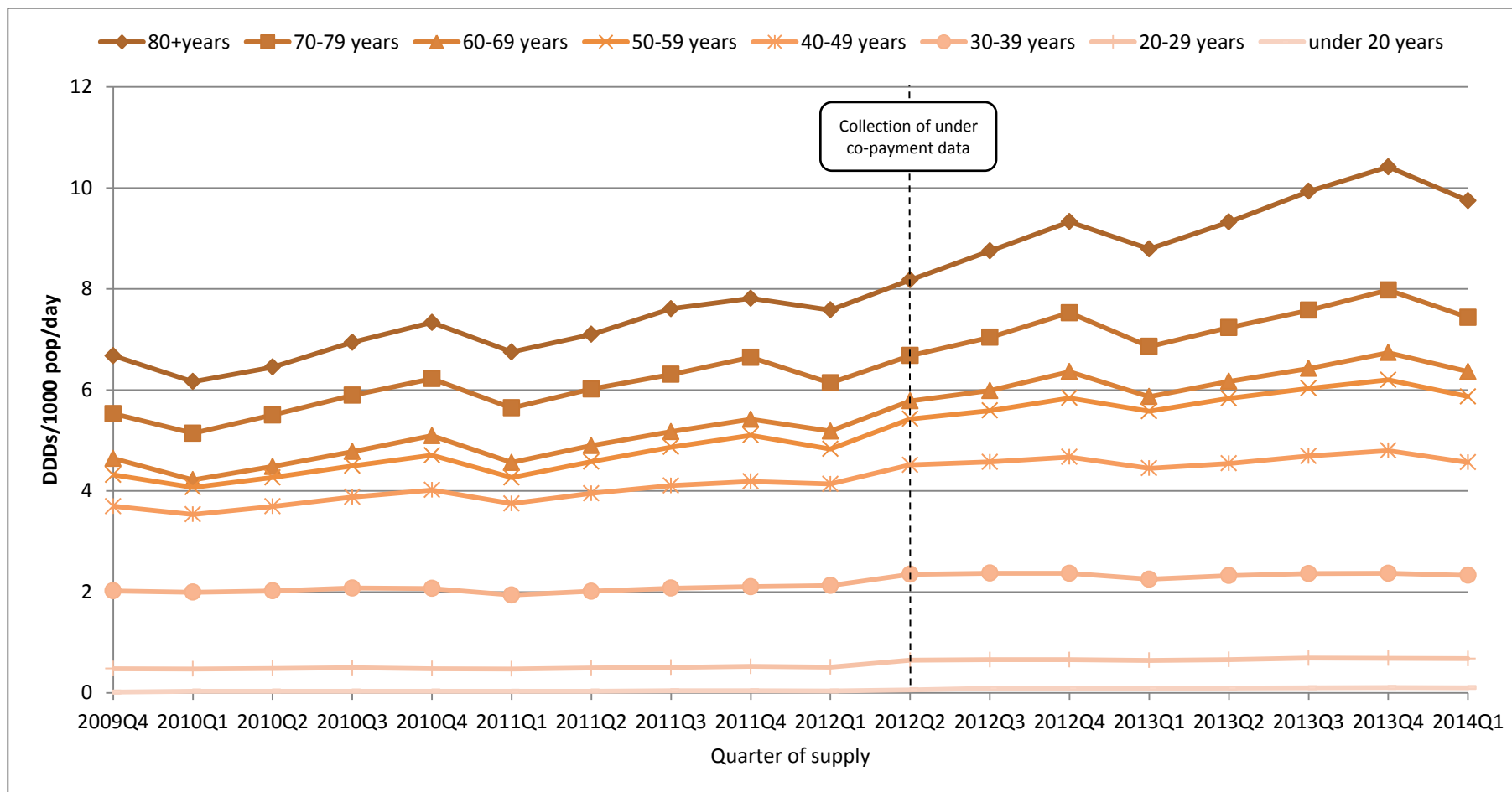
The oxycodone 5mg immediate release formulation dominates the prescription market and use is increasing substantially. Figure 13 presents oxycodone utilisation by strength, excluding the 5mg immediate release tablet. The graph combines oxycodone with naloxone with plain oxycodone by oxycodone content. Utilisation of 10mg, 20mg and 40mg controlled release oxycodone products have increased considerably.



**Figure 13: Oxycodone utilisation by strength (excluding 5mg immediate release tablets)**

Source: DUSC Database, extracted August 2014. Note: Oxycodone with naloxone has been combined with plain oxycodone by oxycodone strength.

Figure 14 presents the utilisation of oxycodone, including combinations with naloxone, by age. The increase is most evident for older age groups, particularly patients 80 years and older. However unlike buprenorphine and fentanyl, which are predominantly supplied to patients over 70 years of age, 62% of total DDDs of R/PBS oxycodone is for patients aged 40-69 years.

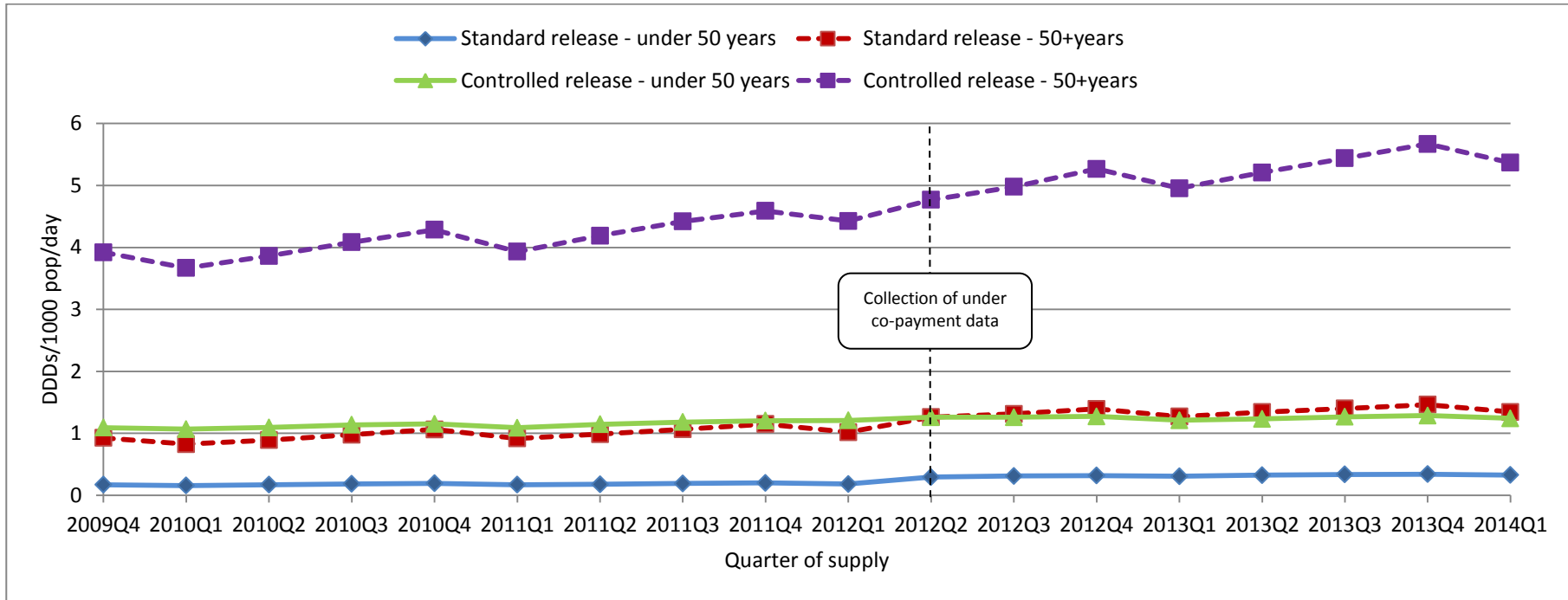


**Figure 14: Oxycodone utilisation in DDDs/1000 population/day by age**

Source: DHS Supplied Prescriptions Database, extracted August 2014. ABS population estimates

While prescription volumes for the most commonly supplied oxycodone standard release and modified release strengths have grown at similar rates (see Figures 12 and 13), the largest contribution to growth in DDDs/1000 population/day is attributed to the modified release formulation. From 2010 to 2013, the DDDs/1000 population/day increased by 0.18 for the standard release formulation and 0.61 for the

modified release formulation. Figure 15 presents the utilisation of oxycodone including combinations with naloxone by standard release and controlled release formulation and patient age.



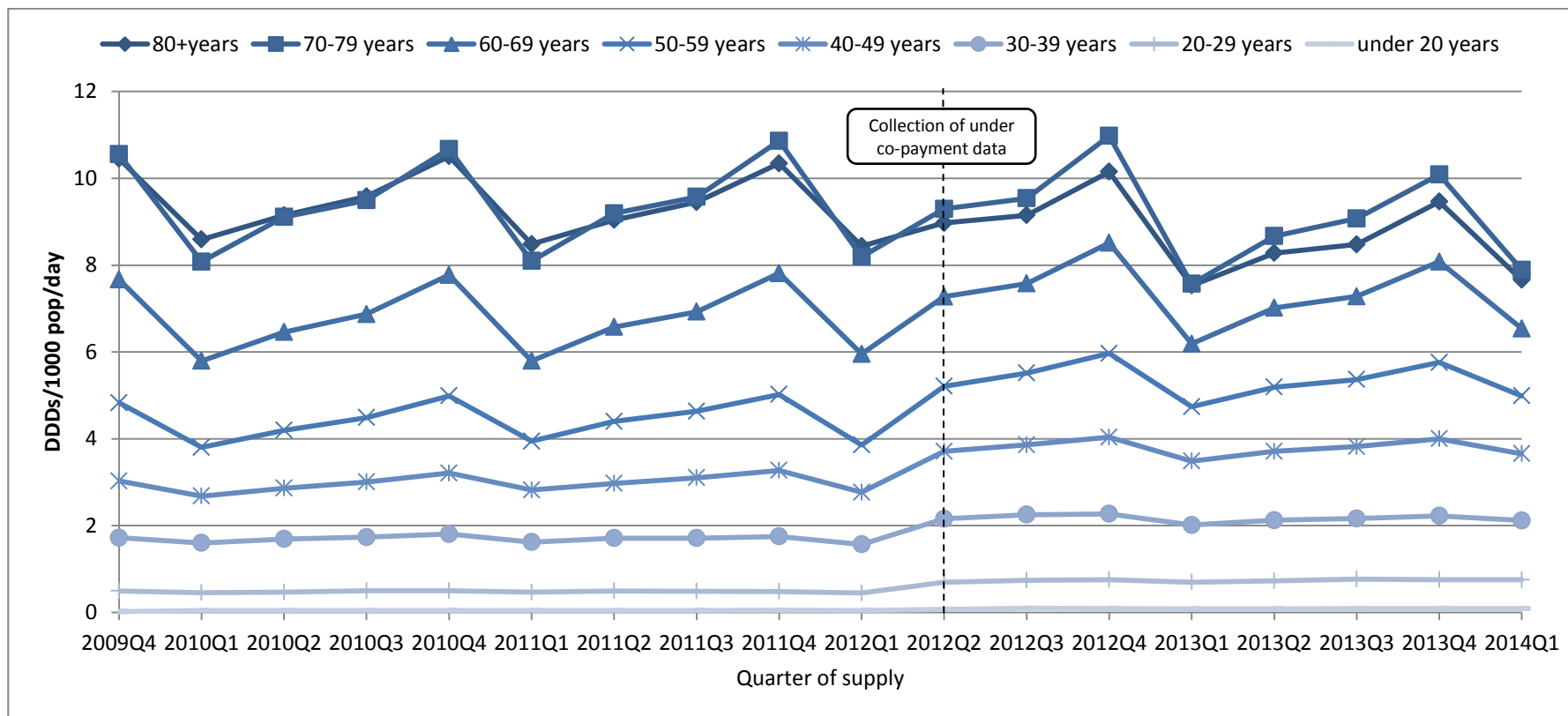
**Figure 15: Oxycodone utilisation by formulation and patient age**

Source: DHS Supplied Prescriptions Database, extracted August 2014. ABS population estimates

The increasing utilisation of oxycodone appears to be due to increasing utilisation of the modified release formulation in patients 50 years of age and older. Utilisation of oxycodone in younger patients and use of standard release oxycodone in patients over 50 years is relatively stable.

### Tramadol

Figure 16 presents the utilisation of tramadol by age.



**Figure 16: Tramadol utilisation in DDDs/1000 population/day by age**

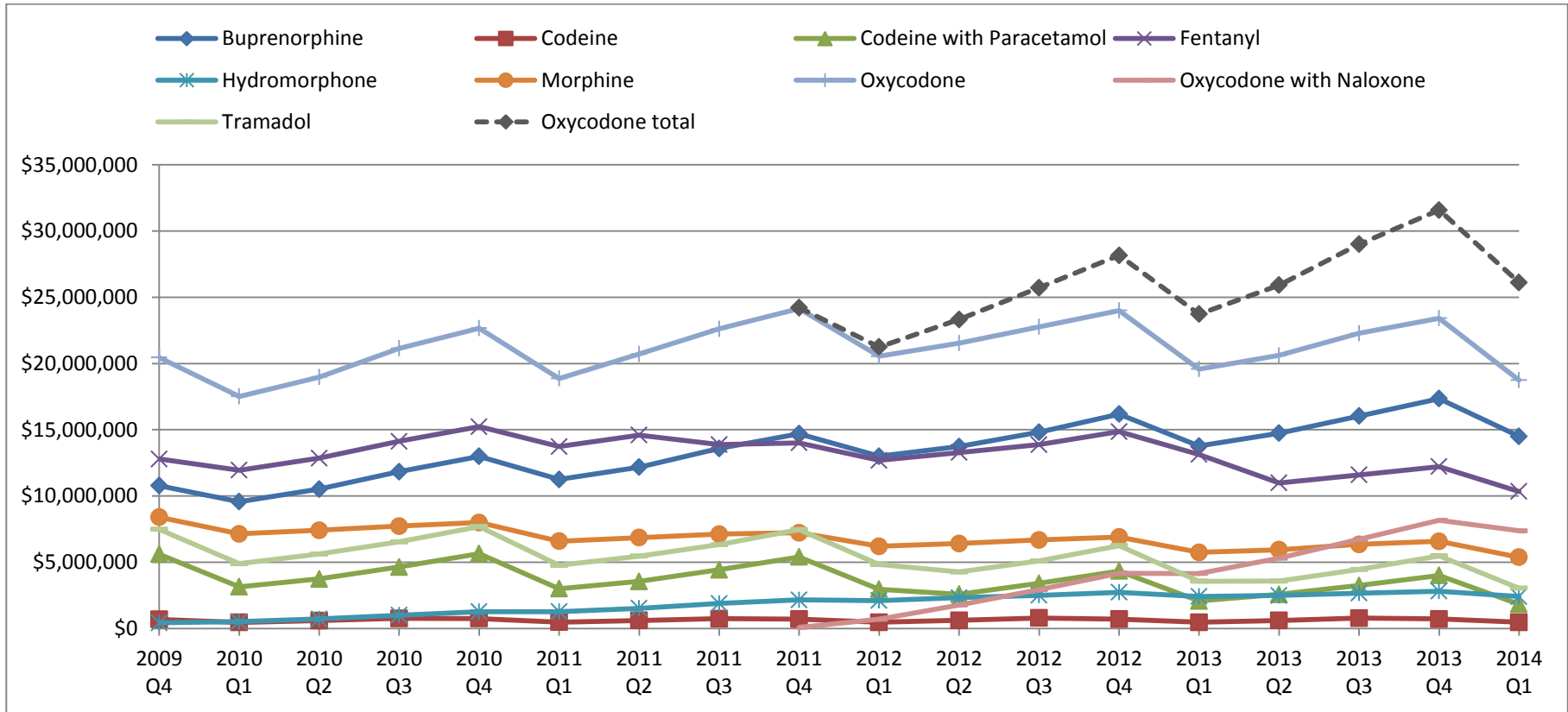
Source: DHS Supplied Prescriptions Database, extracted August 2014. ABS population estimates

Tramadol utilisation increases with age, however utilisation in the 70-79 year age group is similar to that of the 80+ years age group. Tramadol utilisation appears to be decreasing, particularly in patients aged 70 years and older.

## Analysis of expenditure

Figure 17 presents an overview of R/PBS expenditure on opioids.

As DUSC analyses are usually based on date of supply, this should be noted as there may be small differences between publicly available Medicare Australia date of processing data



**Figure 17: Opioid expenditure by drug based on date of supply**

Source: DUSC Database, extracted August 2014

Oxycodone products continue to be the most costly opioid on the PBS. Expenditure on single ingredient oxycodone formulations appear to have stabilised from 2012 onwards. Buprenorphine is the next most costly opioid. Fentanyl expenditure has decreased, likely due to the availability of generic products and price disclosure price reductions. Expenditure on morphine, tramadol and paracetamol with codeine has decreased. Tramadol and paracetamol with codeine have also been subject to price disclosure price decreases.

## Discussion

The utilisation of opioid analgesics continues to increase, both in terms of DDDs/1000 population/day and prescription numbers. The rolling annual average of DDDs/1000 population/day supplied increased from 15.7 to 17.1 in the data period. The DUSC considered measuring DDDs/1000 population/day to underestimate the extent and growth of strong opioid utilisation. The DDDs for strong opioids such as oxycodone, fentanyl and morphine were developed when the main use of strong opioids was for end-of-life cancer pain. In contrast, most of the use of strong opioids in Australia is for chronic non-cancer pain where lower doses are used. The DUSC considered that using DDDs to measure increasing utilisation of opioids, particularly strong opioids, may mask a large and rising number of patients being treated with lower doses of strong opioids. The DUSC considered that in the context of increasing use of strong opioids such as oxycodone and fentanyl and slower growth of weaker opioids such as tramadol and codeine products, an assessment of utilisation taking into account relative analgesic potency may be informative.

The increasing utilisation of opioids is mainly due to increasing utilisation of oxycodone, fentanyl and buprenorphine. The utilisation of hydromorphone is also increasing. The utilisation of other opioid analgesics is stable or decreasing. Since 2013, oxycodone products are the second most utilised opioid analgesic on the PBS, exceeding the utilisation of tramadol. The DUSC considered that overall, the increasing use of oxycodone during this period appears to be the result of increasing utilisation of the modified release formulations, including in combination with naloxone, in patients aged 50 years or more. Overall utilisation of single ingredient preparations appears to have stabilised, however increasing use of the combination with naxolone continues to increase total oxycodone utilisation.

The additional analyses undertaken for buprenorphine, fentanyl, morphine, oxycodone and tramadol show the different patterns of use between opioid analgesics. There was higher morphine utilisation in patients aged 50-69 years than older age groups. The utilisation of morphine was decreasing across most age groups. Buprenorphine and fentanyl were predominantly used in patients aged 70 years and older. The majority of oxycodone use, measured as a proportion of total DDDs, is for patients aged 40-69 years. However, patients aged 70 years and older were supplied oxycodone at higher rates than younger patients based on DDDs/1000 population/age.

Oxycodone products continue to have the highest PBS expenditure of all opioid analgesics on the PBS, followed by buprenorphine and fentanyl.

## DUSC actions

- The DUSC requested that the report be referred to the PBAC for information.
- The DUSC requested the report and minutes be referred to the Post-market Review of Authority Required PBS Listings for information. The DUSC noted that while Authority approvals for increased quantities and/or repeats constituted a large administrative burden for prescribers, there are quality use of medicines issues that need to be considered for this group of medicines.
- The DUSC requested that a copy of the report be provided to the NPS MedicineWise.
- The DUSC requested that a copy of the report be provided to the Department of Human Services Prescription Shopping Program area.
- The DUSC recommended presenting the information in the form of DDDs/1000 population/day and also alternate measures of opioid utilisation to better understand use in persistent non cancer pain (refer to additional analysis below).

## Additional analysis

### Purpose of analysis

To assess opioid utilisation on the PBS taking into account relative analgesic potency.

### Background

At the October 2014 meeting, DUSC examined the utilisation of opioid analgesics listed on the PBS. The DUSC considered that using DDDs to measure increasing utilisation of opioids, particularly strong opioids, may mask a large and rising number of patients being treated with lower doses of strong opioids. The DUSC considered that in the context of increasing use of strong opioids such as oxycodone and fentanyl and slower growth of weaker opioids such as tramadol and codeine products, an assessment of utilisation taking into account relative analgesic potency may be informative.

### Methods

PBS analgesic supply was converted to oral morphine equivalents. The conversion factors for estimating oral morphine equivalents were sourced predominantly from the National Drug and Alcohol Research Centre publication 'Comparing opioids: A guide to estimating oral morphine equivalents in research'<sup>4</sup> and the ANZCA Faculty of Pain Medicine guidance

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<sup>4</sup> Nielsen, S., Degenhardt, L., Hoban, B. and Gisev, N. (2014). Comparing opioids: A guide to estimating oral morphine equivalents (OME) in research. Technical Report No. 329 Sydney: National Drug and Alcohol Research Centre, University of NSW.

for calculating oral morphine equivalents.<sup>5</sup> These conversion factors were checked for consistency with the Australian Medicines Handbook. The conversion factors for fentanyl and buprenorphine patches were adjusted due to the DUSC database reporting total dose delivered, not hourly dose delivered.

The conversion factors used in the analysis are presented in Table 4.

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<sup>5</sup> Australian and New Zealand College of Anaesthetists. Opioid Dose Equivalence - Calculation of Oral Morphine Equivalent Daily Dose (oMEDD). Melbourne: Australian and New Zealand College of Anaesthetists; 2014. Available from: <<http://www.fpm.anzca.edu.au/resources/professional-documents/OPIOID%20DOSE%20EQUIVALENCE.pdf>>

**Table 4: Oral morphine conversion factors**

Drug and Route of Administration	DUSC database unit	Conversion factor (DUSC)	NDARC	ANZCA	Comments
<b>BUPRENORPHINE</b> Transdermal	mg	85	2.5	2	Modified due to differences in reporting
<b>CODEINE</b> Oral	mg	0.13	0.13	0.13	
<b>CODEINE with PARACETAMOL</b> Oral	mg	0.13	0.13	0.13	
<b>FENTANYL</b> Buccal/Sublingual	mg	100	0.1	0.1	Multiplied by 1000 due to reporting in mg. 600mcg fentanyl = 60mg oral morphine <sup>a</sup>
Transdermal	mg	100	3	0.1	
<b>HYDROMORPHONE</b> Oral	mg	5	5	5	
Parenteral	mg	15	15	15	
<b>MORPHINE</b> Oral	mg	1	1	1	
Parenteral	mg	3	3	3	
<b>OXYCODONE</b> Oral	mg	1.5	1.5	1.5	
Parenteral	mg	3	3	3	
Rectal	mg	1.5	1.5	1.5	
<b>OXYCODONE with NALOXONE</b> Oral	mg	1.5	1.5	1.5	

Drug and Route of Administration	DUSC database unit	Conversion factor (DUSC)	NDARC	ANZCA	Comments
<b>TRAMADOL</b>					
Oral	g	200	0.2	0.2	multiplied by 1000 due to reporting in grams
Parenteral	g	167	-	-	120mg oral tramadol = 100mg parenteral tramadol <sup>a</sup>

Source: National Drug and Alcohol Research Centre, 2014. Faculty of Pain Medicine, Australian and New Zealand College of Anaesthetists, 2014.

<sup>a</sup> Eastern Metropolitan Region Palliative Care Consortium (Victoria) Opioid Conversion Ratios - Guide to Practice 2013

The conversion factor for buprenorphine patches has been adjusted from the factors published by NDARC and ANZCA. The DUSC database reports the total amount of buprenorphine delivered by each patch supplied over its seven day duration of use. This value is reported in milligrams. Doses of buprenorphine patches are typically reported as a number of micrograms of buprenorphine delivered per hour. The conversion factors published by NDARC and ANZCA allow for conversion to oral morphine equivalents based on hourly doses. This has been adjusted so the factor is appropriate for reporting in the DUSC database. A conversion factor for parenteral tramadol was derived from the oral to parenteral tramadol dosing equivalents published in an Australian palliative care guideline<sup>6</sup> and the oral tramadol to oral morphine conversion factor published by NDARC and ANZCA.

For the purposes of the analysis, 30mg of oral morphine was considered a standard daily dose for chronic pain. This value was based on a British publication examining the use of opioid in general practice.<sup>7</sup> This publication found the mean annual DDD of oxycodone used was 0.28, equating to 21 mg of oxycodone daily or 31.5 mg of oral morphine daily.

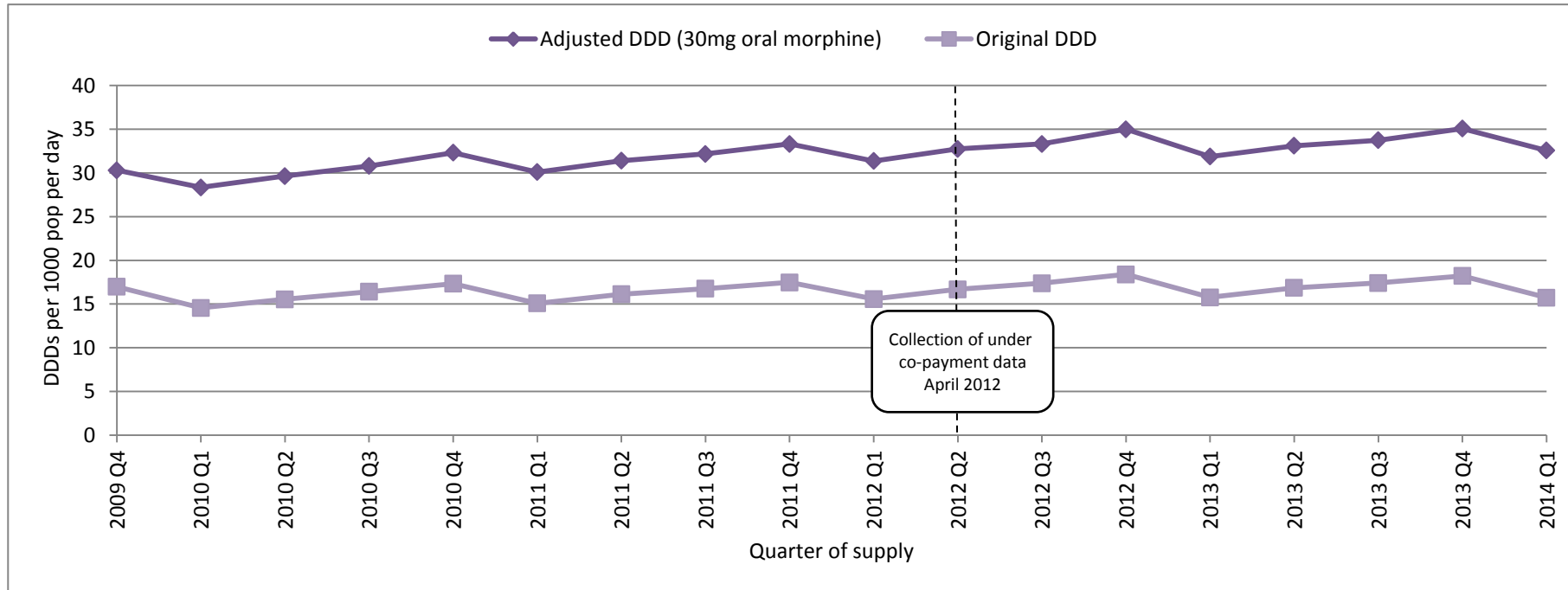
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<sup>6</sup> Eastern Metropolitan Region Palliative Care Consortium (Victoria). Opioid Conversion Ratios - Guide to Practice 2013. Rangeview: Eastern Metropolitan Region Palliative Care Consortium; 2013. Available from < <http://centreforallcare.org/assets/uploads/EMRPCC%20Opioid%20Conversion%20Ratios%20131023.pdf>>

<sup>7</sup> Zin CS, Chen LC, Knaggs RD. Changes in trends and pattern of strong opioid prescribing in primary care. Eur J Pain 2014. 18: 1343-1351.

## Results

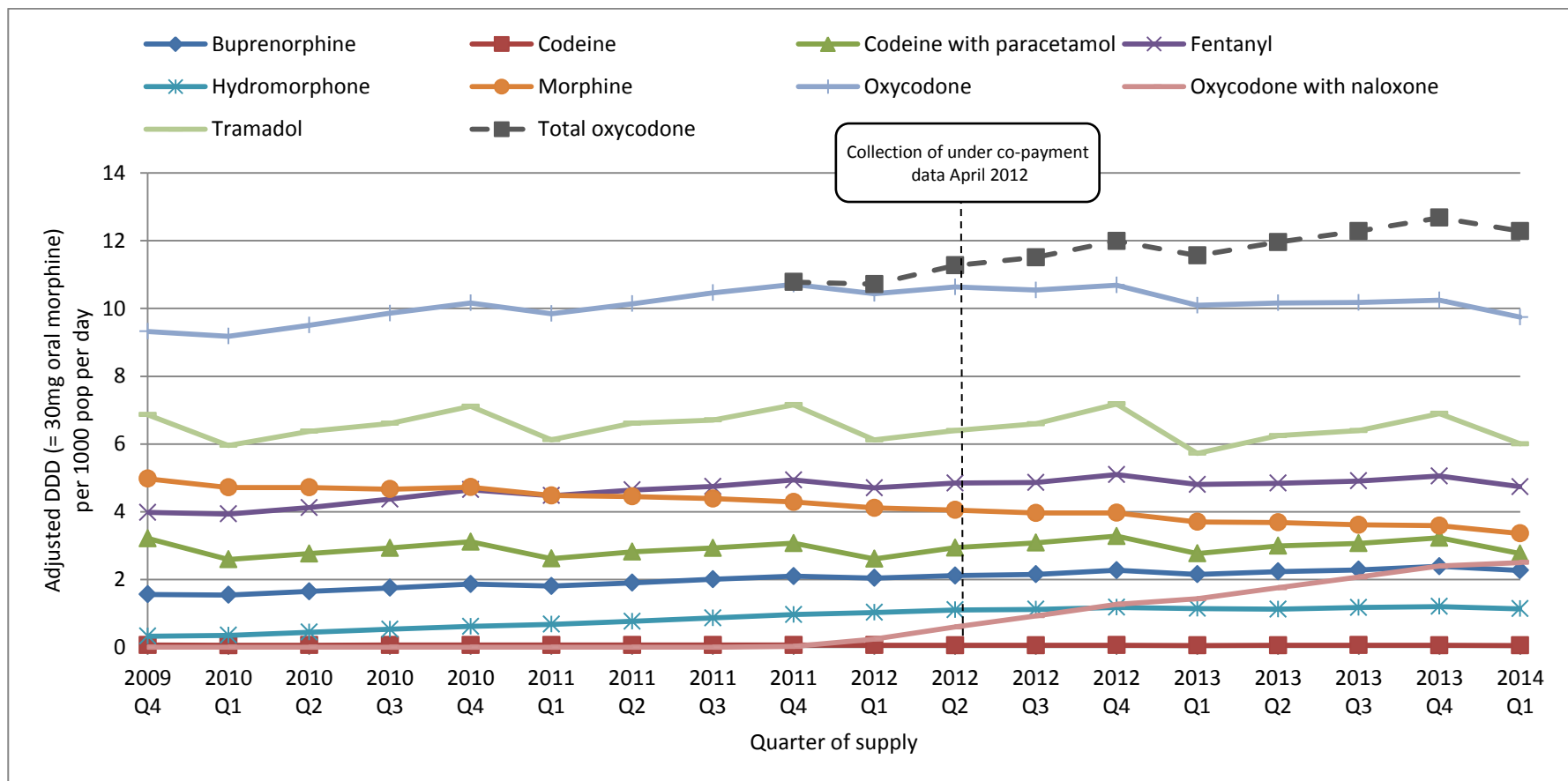
Figure 18 presents the results of potency adjusted analysis where 1 DDD equates to 30 mg of oral morphine.



**Figure 18: Overall R/PBS opioid utilisation - potency adjusted to 30mg oral morphine**

Source: DUSC Database, extracted August 2014

The potency adjusted analysis shows gradual growth in utilisation over the period. Figure 19 presents the results of the potency adjusted analysis by drug.

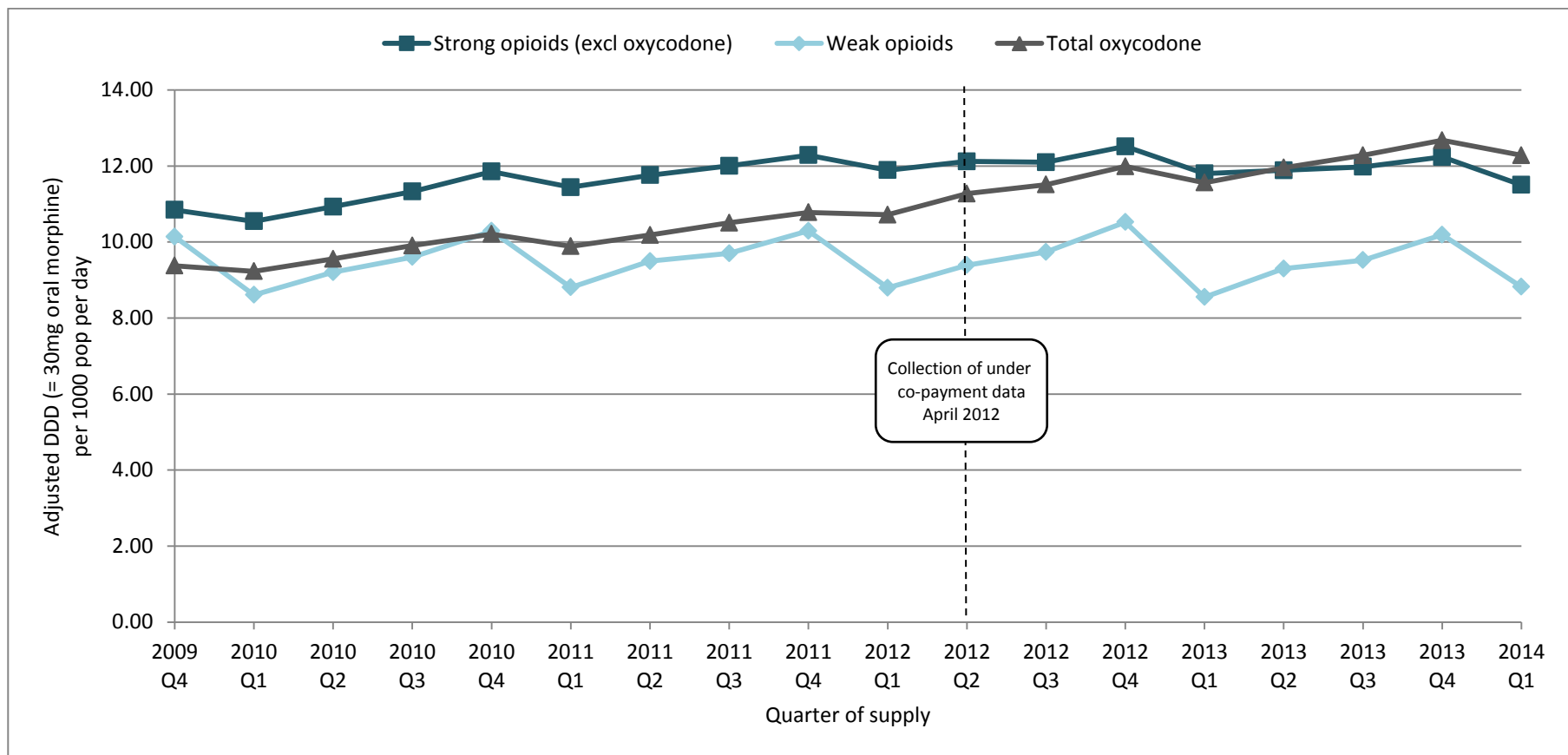


**Figure 19: R/PBS opioid utilisation by drug - potency adjusted to 30mg oral morphine**

Source: DUSC Database, extracted August 2014.

The results show oxycodone has the highest utilisation in terms of analgesic potency adjusted utilisation. This contrasts with the original analysis, presented in Figure 3, where codeine with paracetamol has the highest utilisation in terms of DDDs/1000 pop/day. The use of oxycodone products (plain and in combination) continues to increase at a magnitude higher than other opioids.

Figure 20 presents the potency adjusted use of strong opioids (excluding oxycodone), weak opioids and oxycodone. For this analysis, codeine and tramadol products were considered weak opioids and all other PBS-listed opioids were considered strong opioids.



**Figure 20: R/PBS opioid utilisation of oxycodone compared to strong and weak opioids - potency adjusted to 30mg oral morphine**

Source: DUSC Database, extracted August 2014.

The figure shows oxycodone utilisation surpassing all weak opioids early in the data period and all other strong opioids in the later quarters.

## **Further Discussion**

Oxycodone has the highest level of utilisation in terms of opioid potency, followed by tramadol. Increasing utilisation of fentanyl and decreasing utilisation of morphine results in fentanyl becoming the third most utilised opioid in term of opioid potency. Despite its higher potency compared to morphine, oxycodone utilisation is higher than all other strong opioids combined from 2013-Q3 onwards. The high and increasing use of oxycodone products may be reflective of clinical preference for oxycodone for both moderate and severe pain.

## **Context for analysis**

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

## **Sponsors' comments**

Actavis Pty Ltd: The sponsor has no comment.

Alphapharm Pty Ltd: The sponsor has no comment.

Apotex Pty Ltd: The sponsor has no comment.

Aspen Pharma Pty Ltd: The sponsor has no comment.

bioCSL (Australia) Pty Ltd: The sponsor has no comment.

Fawns and McAllan Proprietary Limited: The sponsor has no comment.

Generic Health Pty Ltd: The sponsor has no comment.

Hospira Pty Limited: The sponsor has no comment.

Janssen-Cilag Pty Ltd: The sponsor has no comment.

Mayne Pharma International Pty Ltd: The sponsor has no comment.

Medis Pharma Pty Ltd: The sponsor has no comment.

Mundipharma Pty Limited:

A key driver is use in the elderly, and this is not necessarily surprising given that Australia has an aging population and the prevalence of both cancer pain and chronic non-cancer pain is highest in this group. The number of Australians aged above 65 is growing at a rate of 3.5% p.a. according to recent ABS analysis and the growth in use is consistent with this. Another finding of relevance to Mundipharma, but not flagged as a key finding by the DUSC, was that 5% of people using opioids accounted for 61% of opioid use. This suggests that there is a relatively small population for which there may be an issue with misuse or abuse of opioids. This is significant, because it suggests that intervention should be targeted.

Prescription opioid analgesics have an established role in modern pain management. When used responsibly, prescription opioid analgesics are safe and effective; adverse effects are generally manageable; and they are considered valuable in reducing the suffering of many patients who would otherwise experience a greatly diminished quality of life. Mundipharma supports the initiatives outlined in the National Pharmaceutical Drug Misuse Framework for Action (2012-2015).

Orphan Australia Pty Ltd: The sponsor has no comment.

Pharmacor Pty Limited: The sponsor has no comment.

Sandoz Pty Ltd: The sponsor has no comment.

Sanofi-Aventis Australia Pty Ltd: The sponsor has no comment.

The Trustee for Virgo Unit Trust (trading as Phebra): The sponsor has no comment.

## **Disclaimer**

The information provided in this report does not constitute medical advice and is not intended to take the place of professional medical advice or care. It is not intended to define what constitutes reasonable, appropriate or best care for any individual for any given health issue. The information should not be used as a substitute for the judgement and skill of a medical practitioner.

The Department of Health (DoH) has made all reasonable efforts to ensure that information provided in this report is accurate. The information provided in this report was up-to-date when it was considered by the Drug Utilisation Sub-committee of the Pharmaceutical Benefits Advisory Committee. The context for that information may have changed since publication.

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