

Opioid Analgesics

Drug utilisation sub-committee (DUSC)

February 2020

Abstract

Purpose

DUSC requested a review of the utilisation of Pharmaceutical Benefits Scheme (PBS)-listed opioid analgesics, including the combined use of pregabalin and opioid analgesics.

Data Source / methodology

Data were extracted from the Department of Human Services (DHS) Supplied Prescriptions database based on Anatomic Therapeutic Classification codes.

Key Findings

- Pregabalin had become the most supplied analgesic in the opioid and pregabalin analgesic market (see Figure 1a).
- Pregabalin and tapentadol were the only two drugs in this market currently not decreasing in utilisation. Tapentadol was increasing and pregabalin had plateaued and may have been starting to decrease (see Figures 1a and 7).
- The up-scheduling by the Therapeutic Goods Administration (TGA) of low dose codeine combination products to Schedule 4 Prescription Only on 1 February 2018 had a minor upward impact on the utilisation of PBS listed high dose codeine (i.e. 30mg) combination products (see Figures 1a and 7). The low dose codeine combination products were not PBS listed, so had to be supplied as private prescriptions. This may have provided a financial incentive to substitute low dose codeine private prescriptions with high dose PBS subsidised prescriptions.
- Prescriptions from the palliative care schedule accounted for only 0.8% of the opioid market in 2019 Q3 (see Figure 2). However prescriptions for palliative care patients accounted for at least 7.1% of the opioid market and 5.0% of the pregabalin market in the same period (see Figure 3).

The patient drug regimen analysis showed that;

- The listing of pregabalin for neuropathic pain in March 2013 coincided with the start of an increase in both two product and more than two product drug regimens (see Figure 13).
- Currently (as at August 2019) 5 of the 10 most common two-product regimens contain pregabalin and 8 of the 10 most common three-product regimens contain pregabalin (see Figures 9 and 10).

- At the time of reporting, 79%, 17% and 4% of patients were on a one, two or more than two product drug regimens respectively (see Figure 12).
- The number of patients on two or more than two product drug regimens had started to decrease (see Figure 13).

Purpose of analysis

To assess the utilisation of PBS listed opioid analgesics, including the combined use of pregabalin and opioid analgesics.

Scope

Committee-in-confidence

[Redacted content]

[Redacted content]

[Redacted content]

End committee-in-confidence

The analyses examine the use of opioids for analgesia on the Pharmaceutical Benefits Scheme (PBS) and the Repatriation PBS (RPBS) from April 2012 (the start of the collection of under copayment prescriptions) to the end of September 2019. This includes both single ingredient opioid analgesics and combination products; such as paracetamol with codeine and oxycodone with naloxone combinations. The analysis will not consider the use of non-PBS listed opioids or over-the-counter opioid preparations.

Background

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: μ , κ and δ (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 analgesic indications of opioids and gabapentinoids listed on the PBS.

Table 1: TGA analgesic indications of PBS listed opioids and gabapentinoids

Drug	Indication
Buprenorphine	Moderate to severe pain
Codeine	Mild to moderate pain (includes fixed-dose combinations with aspirin, ibuprofen, paracetamol)
Fentanyl	Moderate to severe acute or chronic pain. Breakthrough pain in patients stabilised on opioid analgesia for cancer pain (lozenge, buccal and sublingual tablets)
Hydromorphone	Moderate to severe pain
Methadone	Severe chronic pain
Morphine	Moderate to severe pain
Oxycodone	Moderate to severe pain
Oxycodone and naloxone	Moderate-to-severe chronic pain when opioid-induced constipation is refractory to optimised regular laxatives
Tapentadol	Moderate to severe chronic pain
Tramadol	Moderate to severe pain
Pregabalin	Neuropathic pain
Gabapentin	Neuropathic pain

Source: TGA Product Information and Australian Medicines Handbook online, accessed 2/12/2019, (<https://amhonline.amh.net.au/>)

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

The recommended dosages of these medicines are complex and vary widely within a medicine depending on use as acute/chronic treatment, mode of administration (i.e. intravenous (IV)/subcutaneous (SC)/oral/transdermal/rectal) and rate of release (immediate or controlled). Detailed dosing information can be found in the Australian Medicines Handbook online¹ and in the TGA Product Information.

PBS listing details (as at 1 December 2019)

Table 2 presents an overview of opioid analgesics listed on the PBS. Current PBS listing details are available from the PBS website.

Table 2: PBS restrictions for opioid analgesics and gabapentinoids

Drug and form	Restrictions (abridged)
Buprenorphine	
Buprenorphine patches	Chronic severe disabling pain
Codeine	
Codeine tablets	Unrestricted Benefit
Fentanyl	
Fentanyl patches	Severe disabling pain
Fentanyl lozenge & sublingual tablet	Breakthrough pain (palliative care)
Hydromorphone	
Hydromorphone tablets (standard release)	Severe disabling pain
Hydromorphone tablets (modified release)	Chronic severe disabling pain
Hydromorphone injection	Unrestricted benefit
Hydromorphone oral liquid	Severe disabling pain
Methadone	
Methadone tablet	Severe disabling pain
Methadone oral liquid	Chronic severe disabling pain (palliative care)
Methadone injection	Severe disabling pain
Morphine	
<i>Standard release tablets</i>	
Morphine sulfate tablet (10,20 or 30mg, 0 repeats)	Severe disabling pain
Morphine sulfate tablet (10 or 20mg with 2 repeats)	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 disabling 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 disabling severe pain

¹ <https://amhonline.amh.net.au/>

Drug and form	Restrictions (abridged)
Morphine controlled release granules for oral suspension (200mg)	Chronic severe disabling pain due to cancer
<i>Injections</i>	
Morphine sulphate injections	Unrestricted benefit
Oxycodone	
Oxycodone tablet or capsule (standard release)	Severe disabling pain
Oxycodone tablet (modified release)	Chronic severe disabling pain
Oxycodone oral liquid	Severe disabling pain
Oxycodone suppository	Severe disabling pain
Oxycodone + naloxone	
Oxycodone + naloxone tablet	Chronic severe disabling pain
Paracetamol + codeine	
Paracetamol 500mg + codeine phosphate 30mg – 20 tablets	Unrestricted benefit
Paracetamol 500mg + codeine phosphate 30mg – 60 tablets (Authority Required listing)	Severe disabling pain
Tramadol	
Tramadol capsule 50mg (standard release)	Acute pain not responding to aspirin and/or paracetamol Dose titration in chronic pain not responding to aspirin and/or paracetamol (50mg strength)
Tramadol tablet (modified release)	Pain not responding to aspirin and/or paracetamol
Tramadol oral drops	Pain not responding to aspirin and/or paracetamol
Tramadol injection	Unrestricted benefit (Doctor's bag) Short-term treatment of acute pain
Tapentadol	
Tapentadol tablet (modified release)	Chronic disabling pain
Gabapentinoids	
Pregabalin	Neuropathic pain
Gabapentin	Refractory neuropathic pain (RPBS only).

Source: December 2019 PBS Schedule

Changes to PBS listing

Since the October 2014 DUSC analysis the main change has been to the prescribing environment, not the PBS listings. That is, there was an up-scheduling by the TGA of low dose codeine combination products to Schedule 4 Prescription Only on 1 February 2018. These products (containing less than 30 mg of codeine) are not PBS listed, so they will have been supplied on private prescriptions after this change. This may have provided a financial incentive to substitute low dose codeine with higher dose PBS-subsidised prescriptions (e.g. 30 mg codeine in combination with 500 mg paracetamol).

Previous reviews by the DUSC

The DUSC previously reviewed opioid use at its October 2014 meeting where it examined PBS opioid use from October 2009 to March 2014. The key findings were:

- 2,968,733 people received at least one PBS-listed opioid analgesic in the 12 months from April 2013 to March 2014. Of these individuals, approximately 5% (approximately 150,000 people) accounted for 61% of opioid use over the year.
- Total use of opioids, in terms of prescriptions and DDDs/1000 population/day had continued 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 was increasing. The utilisation of morphine and tramadol appeared to be decreasing.

The DUSC also reviewed opioids at its February 2008 and February 2010 meetings. In addition, a 24 month predicted versus actual analysis of pregabalin was considered at the October 2015 DUSC meeting. The key findings were:

- There were 294,747 and 433,324 patients treated with PBS-subsidised pregabalin in the first two years of listing, respectively. This was [REDACTED] than predicted in both years. The number of actual patients in Year 2 [REDACTED] the number of patients predicted for Year 5.
- The total number of prescriptions of pregabalin supplied in Year 1 (1,396,766) was [REDACTED] to predicted, however utilisation in Year 2 (2,435,807 prescriptions) was [REDACTED] than predicted.
- The [REDACTED] than predicted number of patients and prescriptions in Year 2 did not translate to [REDACTED] than predicted government expenditure because there was:
 - a [REDACTED] than expected discontinuation rate after the first prescription leading to [REDACTED] than expected number of prescriptions per patient; and
 - [REDACTED] than expected expenditure per prescription due to [REDACTED] than expected average daily dose and [REDACTED] than expected average patient copayment (due to [REDACTED] than expected proportion of non-concessional patients).
- Prescribing of pregabalin in clinical practice may not be optimal. A large number of patients did not have the dose of pregabalin up-titrated and persistence to therapy was poor.

Methods

The analysis examines the use of opioids and pregabalin for analgesia on the PBS and RPBS from April 2012 (the start of the collection of under copayment prescriptions by the Department of Human Services (DHS)) to September 2019 (the most recent data available).

Data were extracted from the DHS Supplied Prescriptions database based on Anatomic Therapeutic Classification (ATC) codes. Data were extracted for:

- N02A (analgesics – opioids)
- N02BG (Other analgesics and antipyretics) - pregabalin, gabapentin and methoxyflurane. The number of methoxyflurane and gabapentin prescriptions are included in Figure 1a. Thereafter they are excluded as they are non-opioid and not a substantial proportion of the market.
- R05DA04 (codeine – cough suppressant) – PBS item 1214X (tablet containing codeine phosphate hemihydrate 30 mg) only. This was included as this item is also listed under N02AA (Natural opium alkaloids), but there is no way to distinguish if the item was supplied as a cough suppressant or an analgesic. It was assumed that the tablet is more likely to be used as an analgesic, thus all prescriptions for 1214X were assumed to be for analgesia in this report. Codeine linctus (Item 7530H) was assumed to be used as a cough suppressant and so excluded from the analysis.

In the previous DUSC analysis of opioid analgesics considered at the October 2014 DUSC meeting, the amount of drug supplied was standardised using defined daily doses (DDDs). DDDs provide an estimate of the number of people on treatment, assuming a standard dose. As a result of DUSC feedback from the October 2014 meeting, an additional analysis was undertaken² to refine the calculation of DDDs using oral morphine equivalents. As a long time series of patient level data are now available, this report counted the actual number of people on treatment and so analyses by DDDs were not included.

Estimated patient drug regimen analysis

The drug regimen analysis was undertaken for the opioid medicines using prescriptions supplied from April 2012 to the end of September 2019. Drug regimens are estimated weekly for each patient. A patient can be deemed to be on treatment with a drug or combination of drugs in a week without having a prescription supply for that drug(s) in that week. For more details see Appendix A: Detailed methodology to estimate drug regimens and regimen transitions.

The weekly drug regimens are only shown from the week beginning 16/9/2012 to the week beginning 28/7/2019 in figures 9 to 13 because the regimen estimates at the very start and the end of the period can be inaccurate. Drug regimens require a “run in” period to stabilise because some prescriptions are infrequent and the true drug regimen is only evident after prescriptions of all the drugs in the regimen have been supplied. Also the estimated drug regimens are inaccurate near the end of the data period (i.e. August and

² included in the Public Release Document, <http://www.pbs.gov.au/info/industry/listing/participants/public-release-docs/opioids/opioid-analgesics-overview>

September 2019) because there is greater uncertainty in this period whether or not patient treatment is on-going after their last recorded script in the period.

Caveat on comparing date of supply with date of processing data

As all the above described analyses are based on date of supply, there may be small differences when compared with publicly available date of processing data on the Medicare Australia Statistics website³. In addition, medicines supplied to general patients costing less than the general patient contribution do not receive a PBS benefit (i.e. under-copayment prescriptions) and are not included in Medicare Australia Statistics website data.

Results

Number of prescriptions

Figure 1a shows the utilisation of PBS prescriptions for opioids and other selected analgesics by drug.

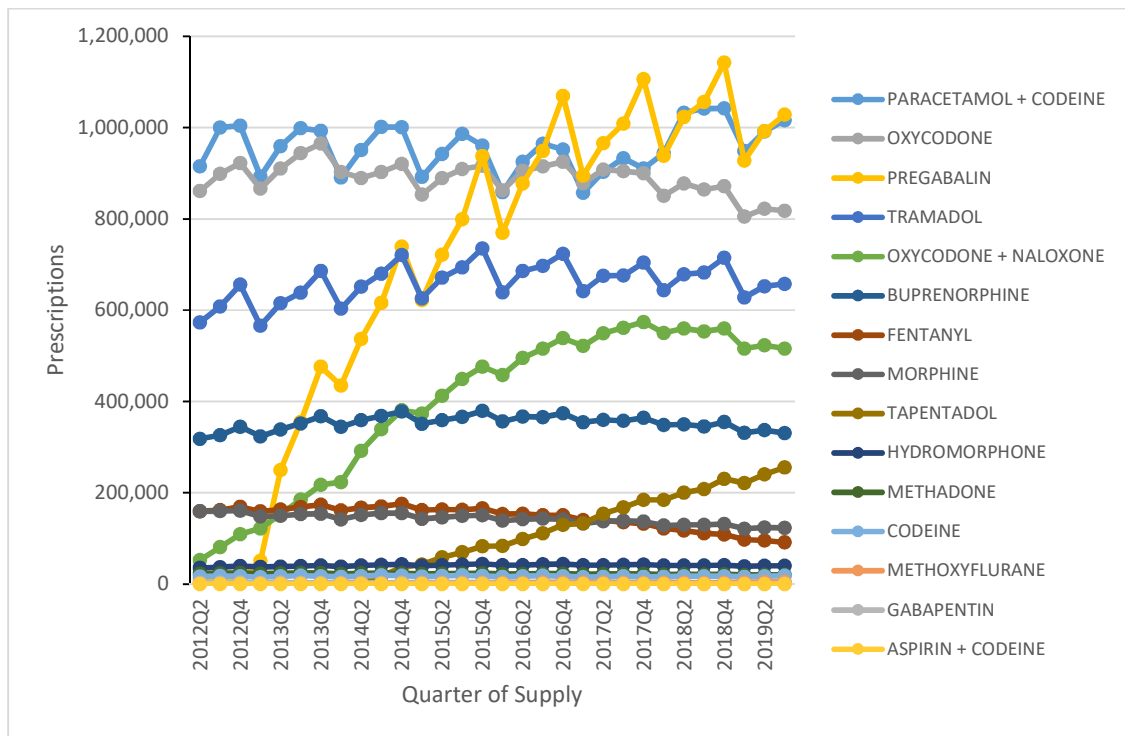


Figure 1a: PBS prescriptions for opioids and other selected analgesics by drug

Source: DHS prescription database (accessed 29 October 2019)

³PBS statistics. Australian Government Department of Human Services Medicare. Canberra. Available from http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp

Figure 1a shows that:

- Pregabalin has become the most supplied analgesic in this market.
- The number of prescriptions for the other non-opioid drugs, gabapentin and methoxyflurane, are small in the context of this market and so were excluded from all following analyses.
- Pregabalin and tapentadol are the only two drugs currently not decreasing in utilisation.
- The use of PBS-listed high dose codeine (i.e. 30 mg or more) in combination products (i.e. paracetamol + codeine) increased slightly in quarter 1 2018, which coincided with the up-scheduling of low dose codeine combination products to Schedule 4 Prescription Only by the TGA on 1 February 2018. Figure B.1 in Appendix B shows prescriptions for paracetamol + codeine by PBS item code. It shows that the increase in 2018 Q1 was due to an increase in item 1215Y (paracetamol 500mg + codeine 30mg). This item is Unrestricted. Two other items of the same form and strength did not noticeably increase. These were 8785J (Authority Required) and 3316M (for prescribing by dentists).

Figure 1b shows the total PBS prescriptions for opioids and pregabalin.

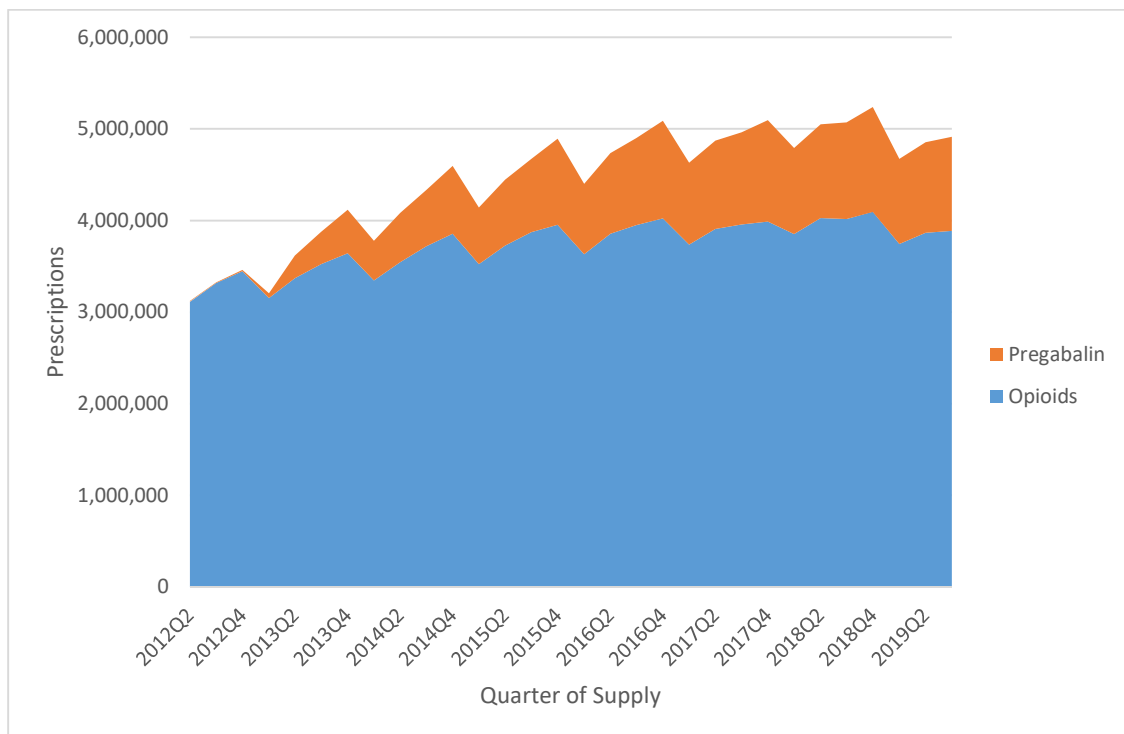


Figure 1b: Total PBS prescriptions for opioids and pregabalin

Figure 1b shows that the combined PBS opioid and pregabalin prescription market expanded until 2018 and may be starting to decrease.

Figure 2 shows the prescriptions in Figure 1b broken down by whether or not the PBS item is from the palliative care schedule.

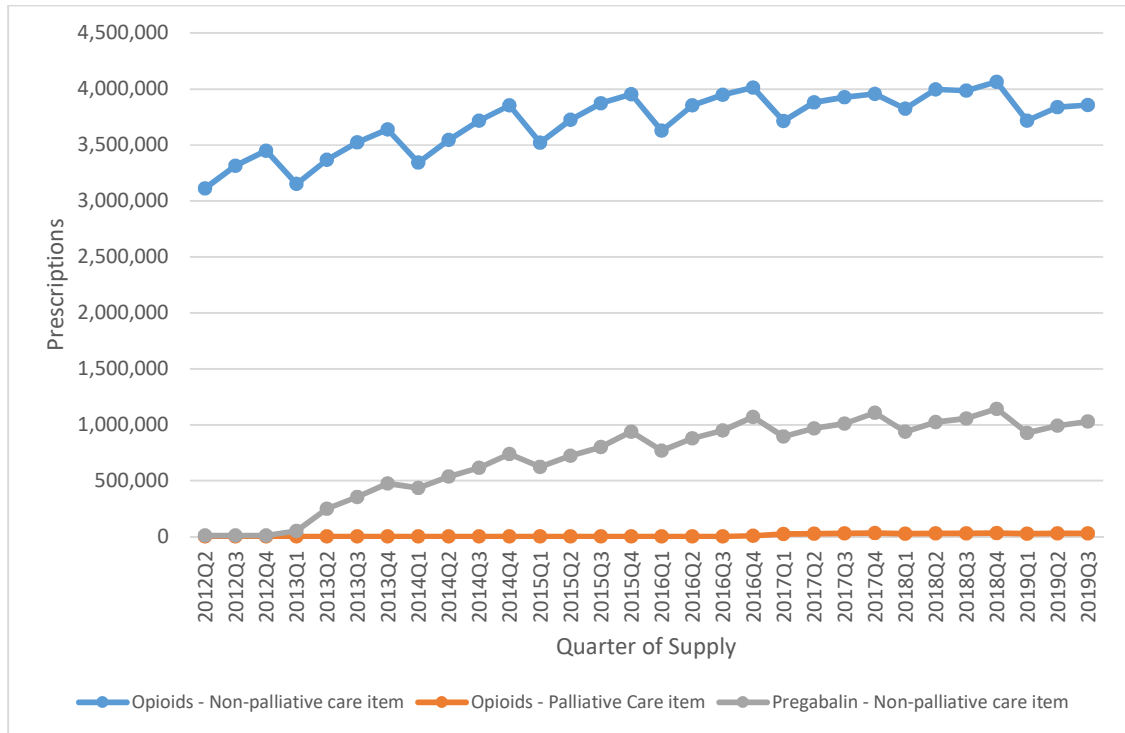


Figure 2: PBS prescriptions for opioids and pregabalin by whether or not the item is from the palliative care schedule

Figure 2 shows that prescriptions for palliative care items are a small proportion (0.8% in 2019 Q3) of the opioid market. However, it is possible for palliative care patients to be prescribed opioids using non-palliative care items (e.g. items from the General Schedule). The products on the palliative schedule are often replicated in the General Schedule, but with lower maximum quantities and repeats.

Figure 3 shows prescriptions supplied to palliative care patients. Palliative care prescriptions were defined as all opioid prescriptions supplied to a patient subsequent to their first opioid prescription supply from the palliative care schedule.

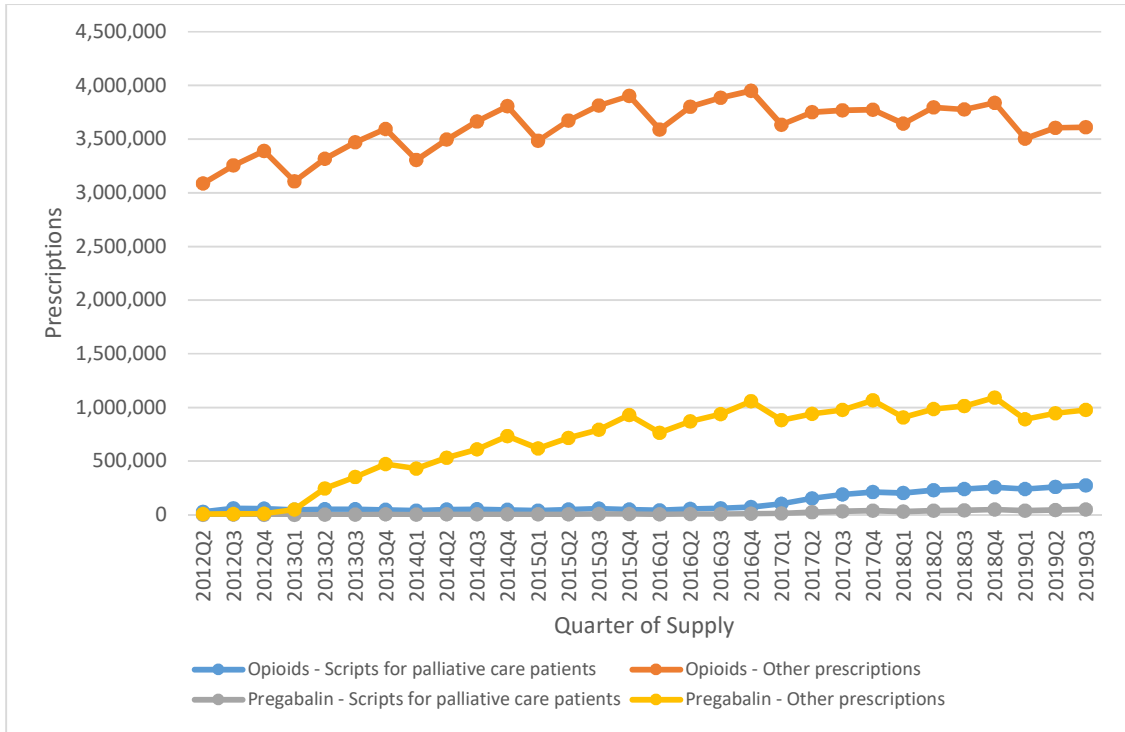


Figure 3: PBS prescriptions for opioids and pregabalin by whether or not they are for a palliative care patient

Figure 3 shows that there are many more opioid prescriptions for palliative care patients, than from the palliative care schedule (Figure 2). In 2019 Q3, prescriptions for palliative care patients were 7.1% of the opioid market and 5.0% of the pregabalin market. These may be an underestimates, as some palliative care patients may only be supplied opioid prescriptions from the General Schedule and would not be identified by this method.

Figure 4 show the drug breakdown of the palliative care item prescriptions in Figure 2 and Figure 5 shows the drug breakdown of the palliative care patient prescriptions in Figure 3.

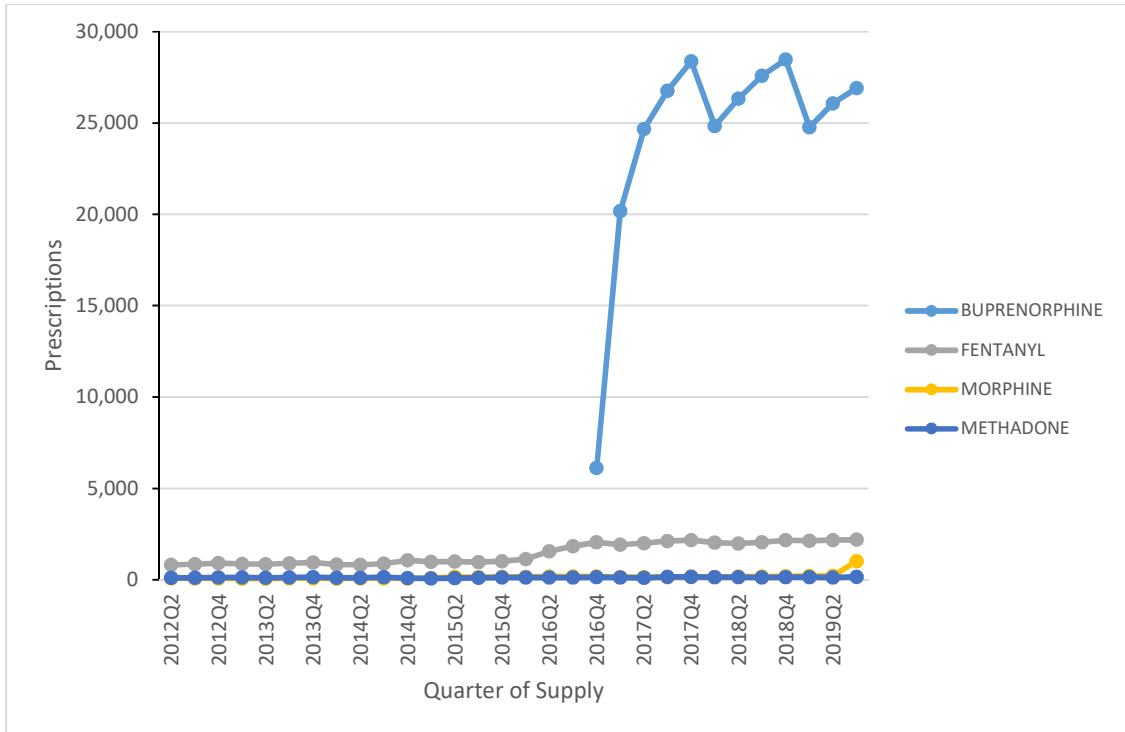


Figure 4: PBS opioid prescriptions supplied from palliative care schedule by drug

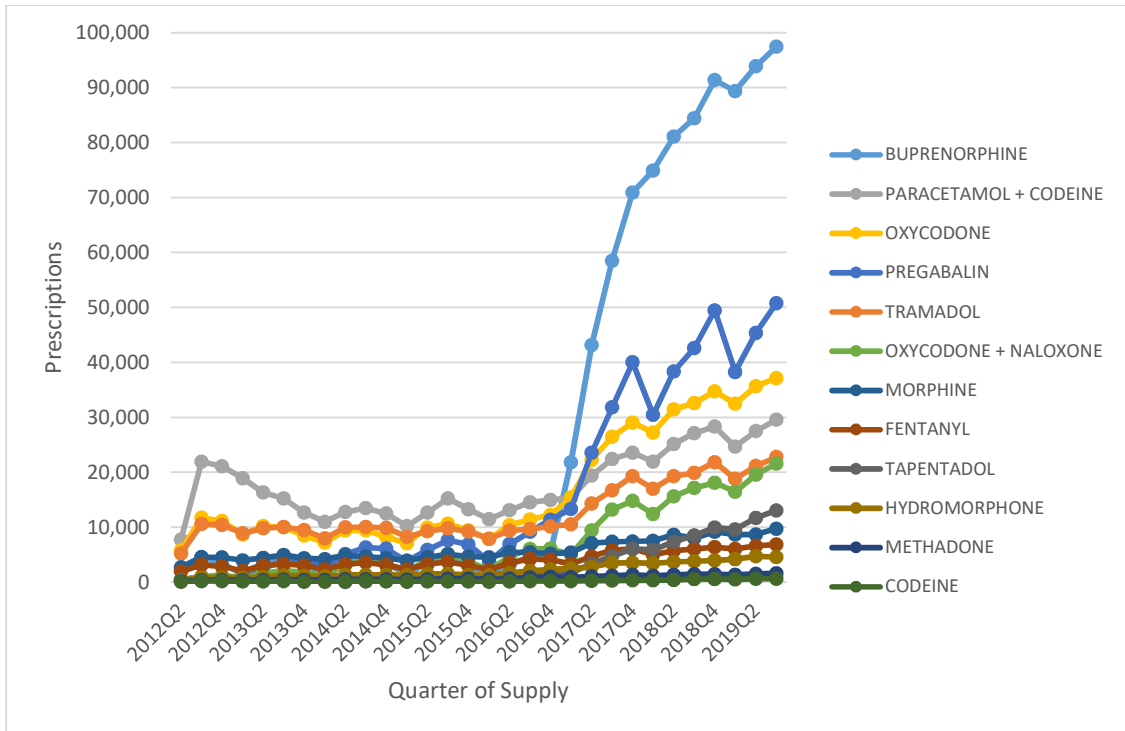


Figure 5: PBS opioid and pregabalin prescriptions for palliative care patients by drug
 Note: ASPIRIN + CODEINE is not shown as some quarters have 5 or less prescriptions.

Comparing Figures 4 and 5 shows that a large majority of buprenorphine and fentanyl prescriptions for palliative care patients are supplied using PBS items from the General

Schedule, not the palliative care schedule. Buprenorphine patches are Authority Required on the palliative care schedule and Restricted Benefit on the General Schedule. Thus ease of prescribing may be a factor in the buprenorphine prescribing pattern. For fentanyl, the patches are on the General Schedule only (as Restricted Benefit) and the lozenges and tablets are on the palliative care schedule only (as Authority Required).

Number of patients

Figure 6 shows the number of patients prevalent to and initiating treatment with opioids or pregabalin.

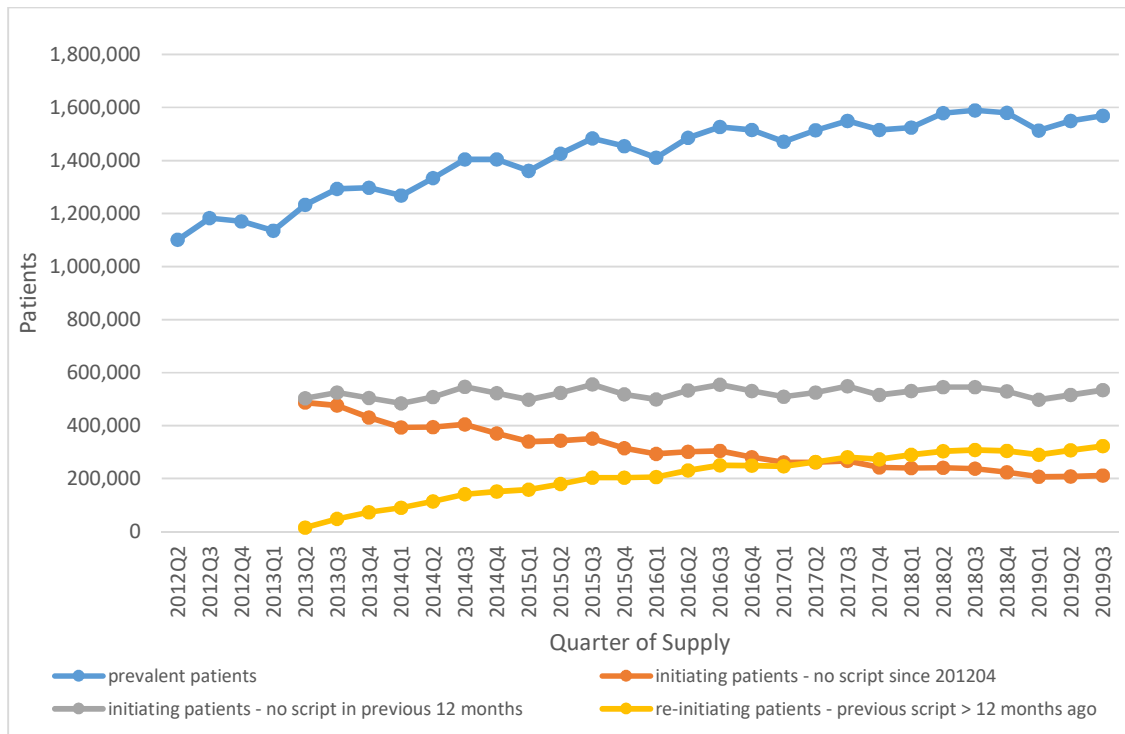


Figure 6: Patients prevalent to and initiating treatment with opioids or pregabalin

Figure 6 shows that the number of prevalent patients grew until 2018 and appears to have plateaued. The number of initiating patients (based on no prescription in the previous 12 months) has been very consistent since 2013.

Figure 7 shows the number of patients prevalent to opioids by drug.

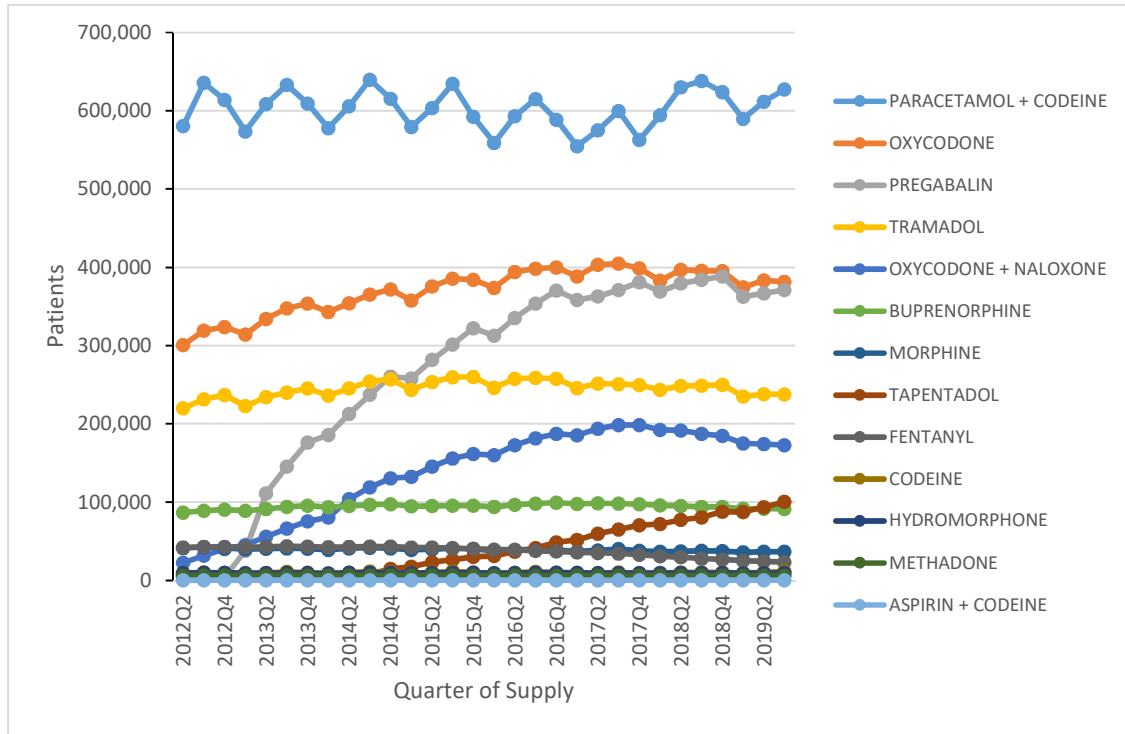


Figure 7: Patients prevalent to opioids and pregabalin by drug.

Comparing Figures 7 and 1a shows that pregabalin is supplied more frequently per patient in a quarter than paracetamol + codeine. That is, even though the number of prescriptions supplied per quarter for these two drugs is approximately the same (see Figure 1a), there were considerably fewer prevalent patients supplied pregabalin than paracetamol + codeine. The median time to re-supply was calculated for all drugs (see Table A.1 in Appendix A) and was 28 days for pregabalin and 37 days for paracetamol + codeine. This reflects the fact that pregabalin is taken chronically while paracetamol + codeine can be prescribed acutely.

Like Figure 1a, Figure 7 shows a changed trend in paracetamol + codeine use in 2018, which coincided with the TGA up-scheduling of low dose non-PBS codeine combination products on 1 February 2018. The seasonality of the paracetamol + codeine time series (low in Q1 and high in Q3) was broken in 2018 Q1 (i.e. it is a step up rather than a step down) and 2018 Q3 was a large step up compared with 2017 Q3.

Figure 8 shows the number of patients initiating (based on no prescription in previous 12 months) to opioids or pregabalin by drug.

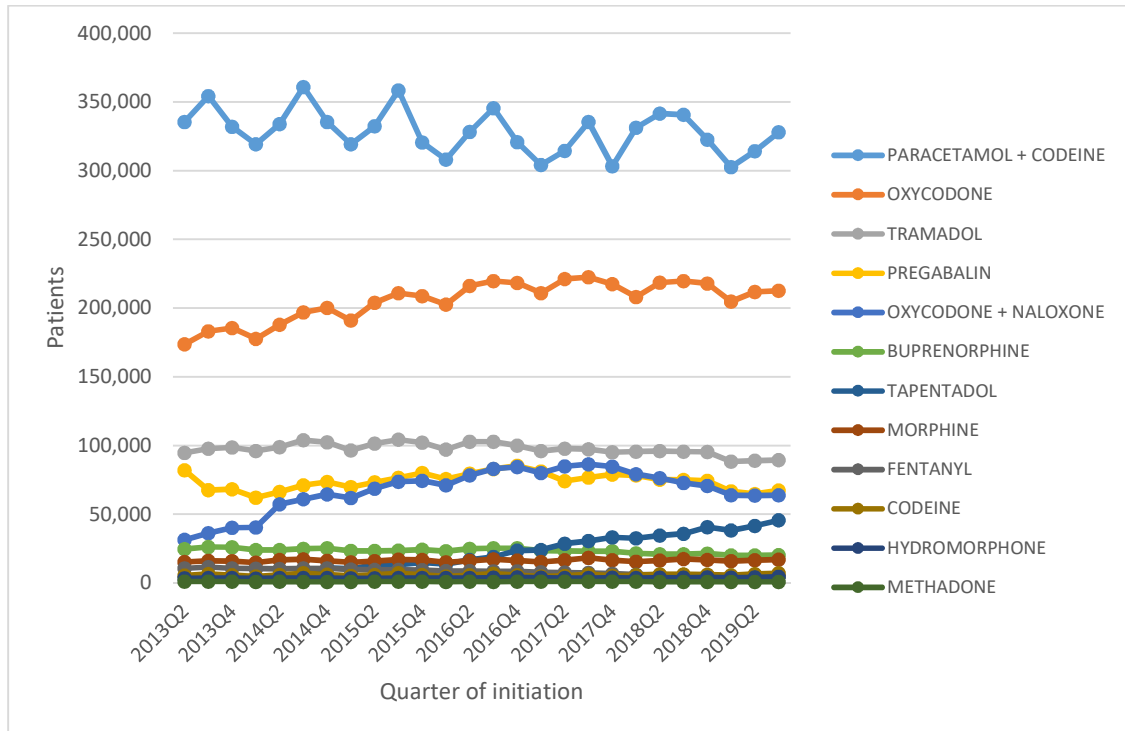


Figure 8: Patients initiating opioids or pregabalin by drug.

Note: ASPIRIN + CODEINE is not shown as some quarters have 5 or less patients.

Figure 8 shows that the only drug with an increasing number of initiators is tapentadol. It also shows that the number of initiators to pregabalin is relatively low, even though the number of prevalent patients is relatively high (i.e. the same as oxycodone, see Figure 7). This suggests that patients persist with treatment on pregabalin longer than on oxycodone. This again reflects the fact that pregabalin tends to be used chronically while oxycodone can be used acutely.

Patient drug regimen analysis

The week by week opioid drug regimens for all patients are shown in Figures 9 to 13. As there are too many regimens to show in a single figure, they have been split in the following way;

Figure	Regimen description
9	Includes 2 products (this can be more than 2 drugs if one or more of the products is a combination product)
10	Includes >2 products
B.2	Only includes 1 product (included in Appendix B for completeness)
11a	Includes pregabalin
11b	Includes pregabalin and > 1 product
12	Total 1, 2 and >2 product regimens
13	2 and >2 product regimens

To further limit the number of regimens displayed and so improve readability of the figures, only the top 10 (based on patient numbers) are displayed in each figure.

The names of the drugs have been modified slightly from those shown in previous figures. This is because the estimation of drug regimens at any point in time relies on an estimate of standard coverage days (SCD) for each prescription. It was found that SCD varied significantly with mode of administration (MoA) within drugs (see Appendix A, Table A.1), thus MoA-specific SCDs were used in the estimation of drug regimens. This required that drug names were modified to include the MoA if a drug had more than one MoA. Otherwise the drug name was not modified. This applied only to the following drugs;

	Modified drug name (includes MoA)
Fentanyl	fentanyl_buccal
	fentanyl_sublingual
	fentanyl_transdermal
Hydromorphone	hydromorphone_injection
	hydromorphone_oral
Methadone	methadone_injection
	methadone_oral
Morphine	morphine_injection
	morphine_oral
Oxycodone	oxycodone_oral
	oxycodone_rectal
Tramadol	tramadol_injection
	tramadol_oral

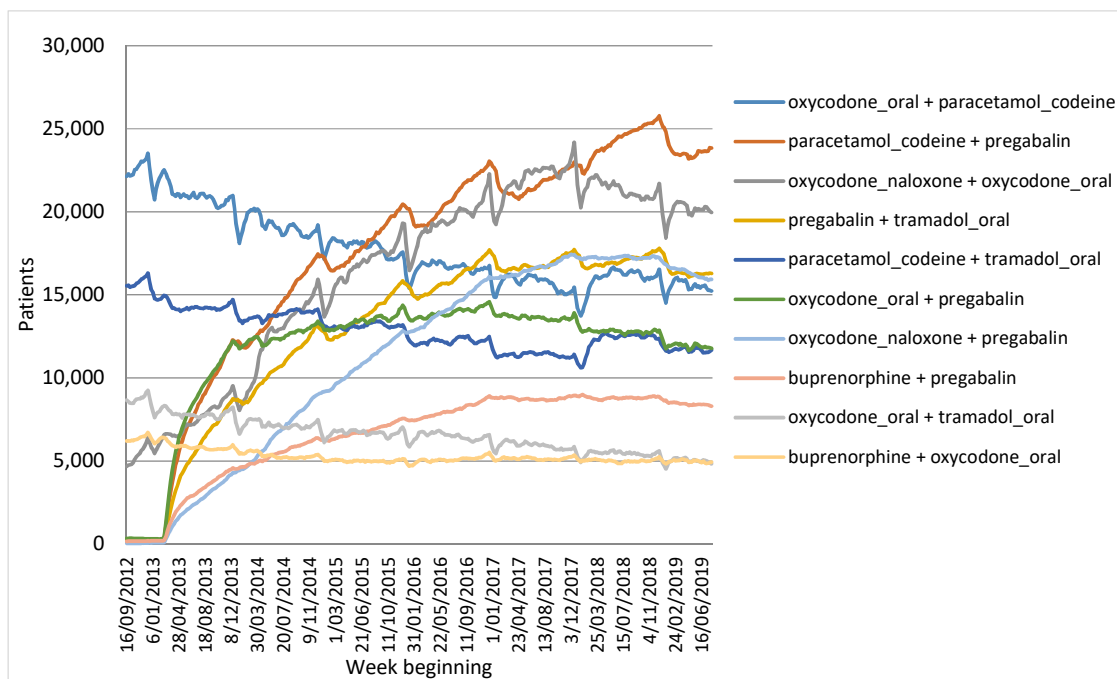


Figure 9: Opioid drug regimens, 2 products

Note: Only top 10 regimens are shown.

The most common two-product regimen has changed from oxycodone_oral + paracetamol_codeine in 2012 to paracetamol_codeine + pregabalin in 2019. For a period starting in March 2017, oxycodone_naloxone + oxycodone_oral became the most common two-product regimen. However, after the TGA up-scheduling of low dose non-PBS codeine combination products on 1 February 2018, this regimen began to decrease and paracetamol_codeine + pregabalin became the most common. This may not indicate an increase in this regimen in the Australian population, but instead an increase in the utilisation of PBS paracetamol_codeine (as noted in Figures 1a and 7). This effect can also be seen in the uptick in utilisation of the oxycodone_oral + paracetamol_codeine and paracetamol_codeine + tramadol_oral regimens at February 2018.

All 2 product regimens appear to be currently declining or steady. 5 of the 10 most common 2 product regimens contain pregabalin.

Note that the order of the drugs in the regimens is alphabetical, not order of supply. One reason for this is because using order of supply would increase (double in this case) the number of regimens.

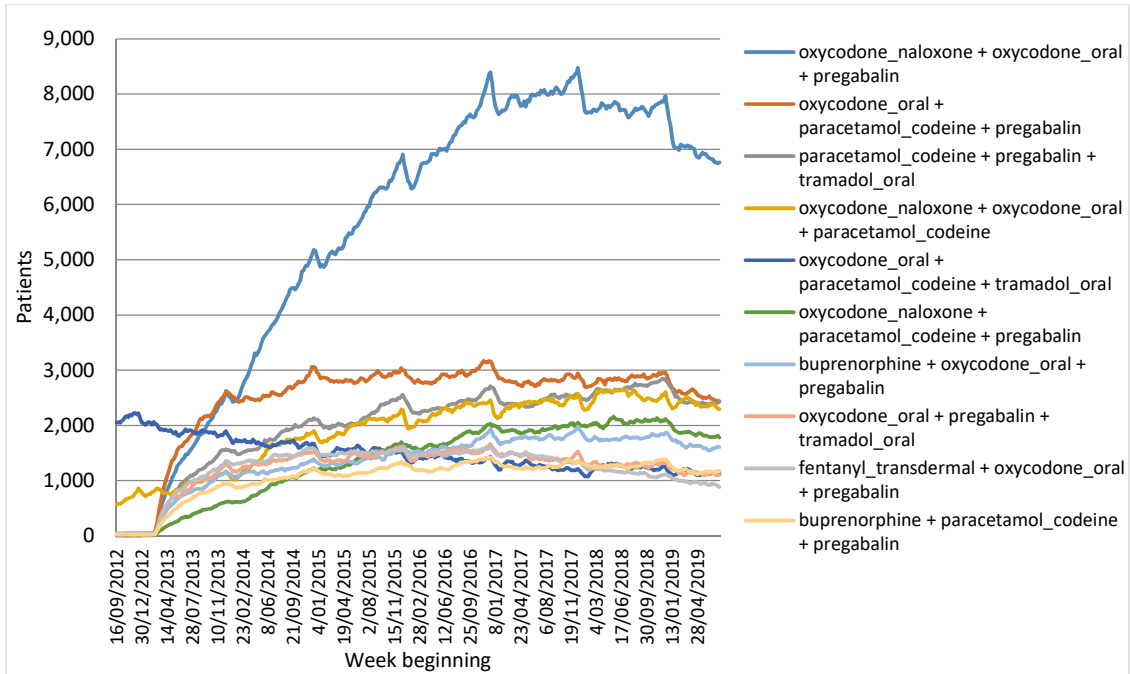


Figure 10: Opioid drug regimens, >2 products

Note: Only top 10 regimens are shown.

The 10 most common >2 product regimens are all 3 product regimens. The most common 3 product regimen, by a large margin, is oxycodone_naloxone + oxycodone_oral + pregabalin. 8 of the 10 most common 3 product regimens contain pregabalin.

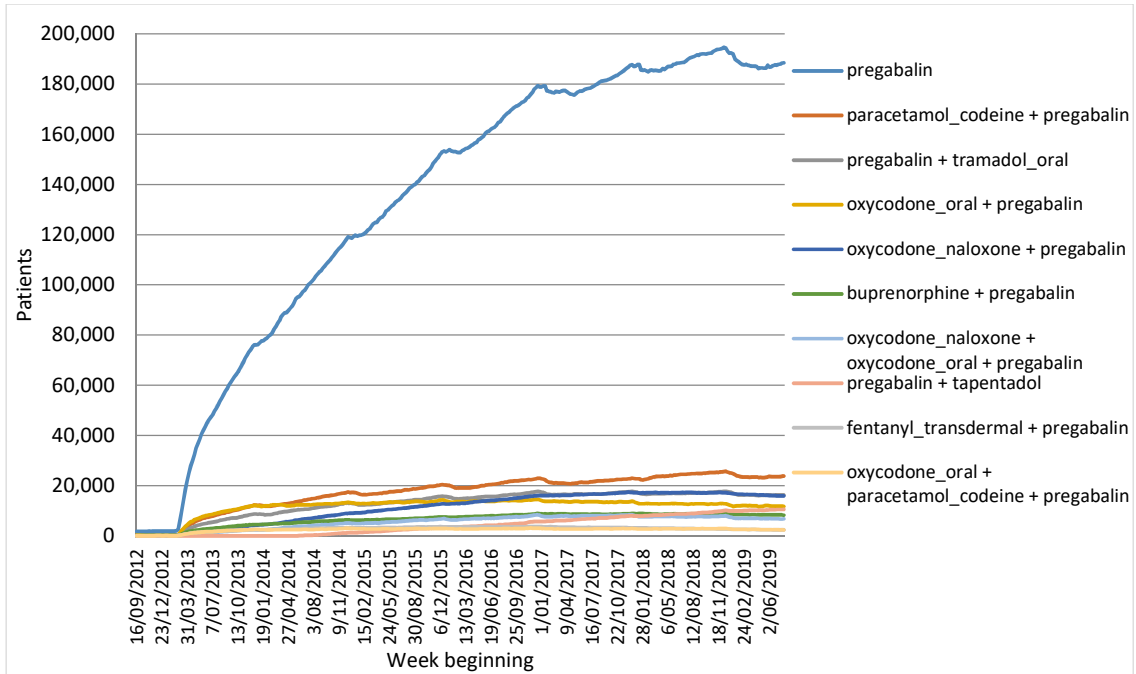


Figure 11a: Opioid drug regimens including pregabalin

Note: Only top 10 regimens are shown.

Figure 11a shows the relative magnitude of the utilisation of pregabalin monotherapy compared to pregabalin regimens with more than one product. Figure 11b is similar to Figure 11a except that pregabalin monotherapy is excluded so that the details of the other regimens are more visible.

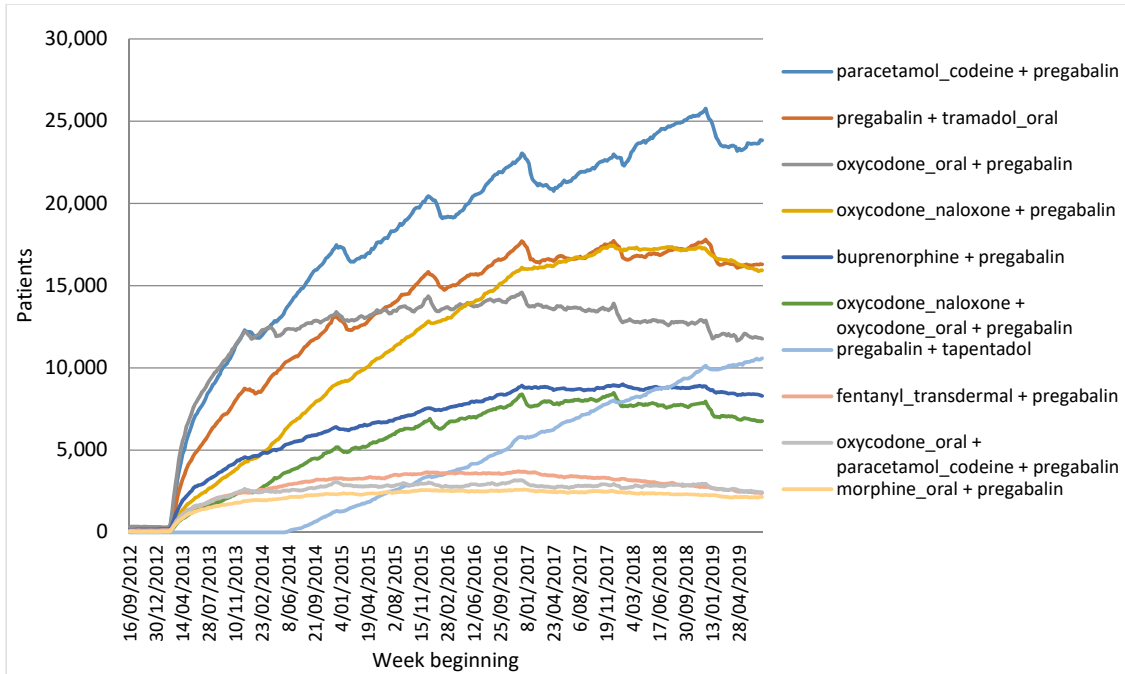


Figure 11b: Opioid drug regimens including pregabalin, excluding pregabalin monotherapy

Note: Only top 10 regimens are shown.

Figure 11b shows that all regimens containing pregabalin are currently decreasing, except pregabalin + tapentadol. The most common regimen containing pregabalin is paracetamol_codeine + pregabalin. However, if the oxycodone containing regimens were combined (i.e. oxycodone_oral + pregabalin, oxycodone_naloxone + pregabalin, oxycodone_naloxone + oxycodone_oral + pregabalin and oxycodone_oral + paracetamol_codeine + pregabalin) then this would become the most common regimen.

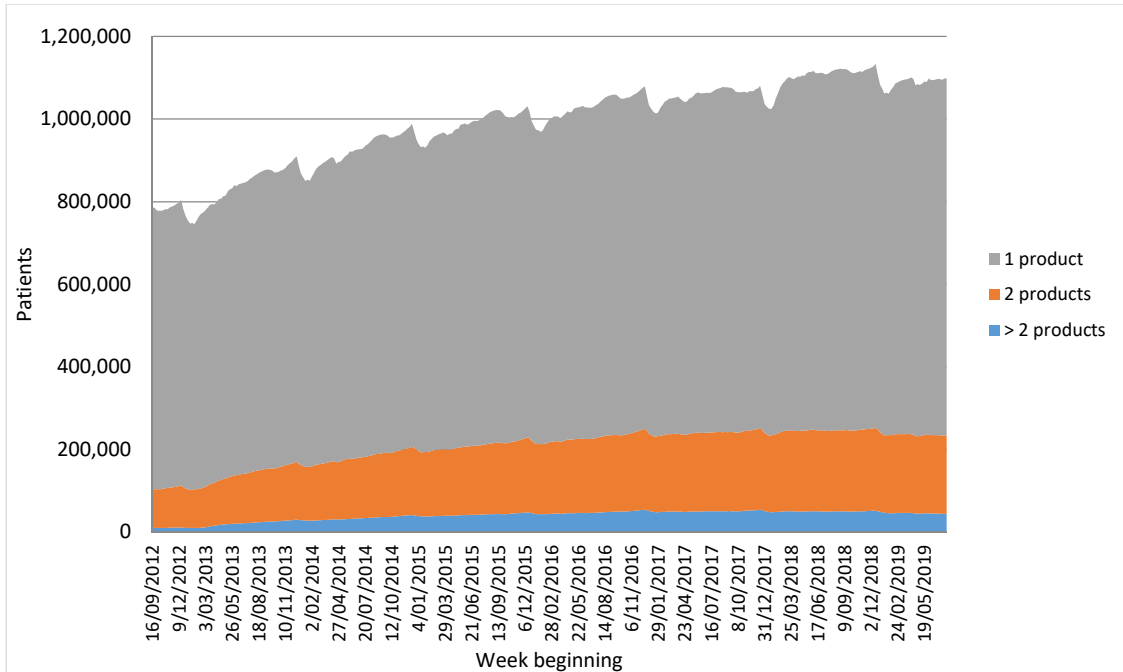


Figure 12: Opioid patients by the number of products in the regimen (cumulative)

Figure 12 shows that (as at the most recent week in the figure, 28/7/2019) there were 864,661, 188,545, 45,487 patients on 1, 2 and >2 product regimens, respectively. This represents 79%, 17% and 4% of the 1,098,693 patients, respectively. This compares to the first week (i.e. 16/9/2012) when there were 87%, 12% and 1% of patients on 1, 2 and >2 product regimens, respectively.

Comparing the patients numbers in Figure 12 to those in Figure 6 (in 2019 Q3 the prevalent and incident patients were 1,568,683 and 533,907, respectively) shows that there is a difference. This can be explained by the fact that Figure 6 shows prevalence over a quarter, whilst Figure 12 is estimating prevalence at the weekly level.

It can be estimated from Figure 6 that the number of patients prevalent in 2019 Q3 that were continuing from 2019 Q2 was 1,568,683 total - 533,907 initiating = 1,034,776. As the prevalence in the most recent quarters in Figure 6 is approximately constant, then it can be assumed that the number of patients ceasing treatment is approximately equal to the number initiating treatment (i.e. 533,907). As each quarter is on average 13 weeks, then the number of patients initiating and ceasing each week is approximately 41,000. Thus the weekly prevalence could be estimated from the Figure 6 data as approximately 1,034,776 + 41,000 initiating + 41 ceasing = 1,116,776 patients. This is consistent with the patient count in Figure 12.

Figure 13 is similar to Figure 12 except the 1 product regimens have been removed to show more detail of the multi-product regimens.

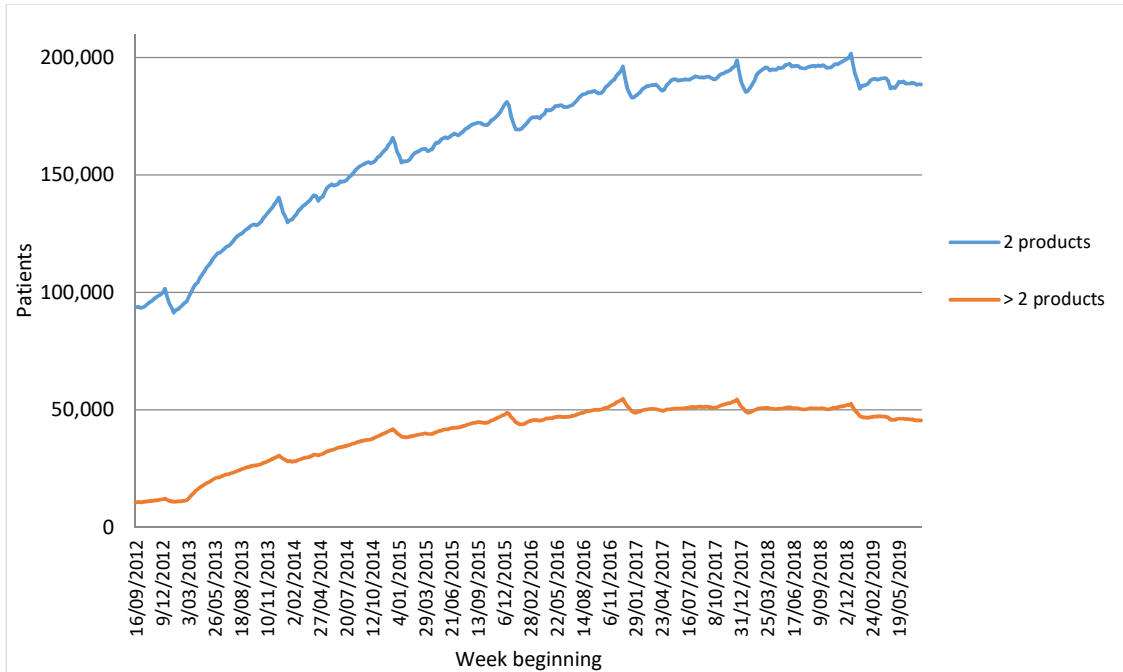


Figure 13: Opioid patients by the number of products in the regimen (excluding 1 product regimens)

Figure 13 shows that number of 2 and >2 regimens have increased since the listing of pregabalin in March 2013. Comparing the last (28/7/2019) with the first (16/9/2012) displayed week, the number of opioid patients on a 2 and >2 product regimen has increased by 101% and 325% respectively. Over the same period the number of patients on 1 product regimens increased by 27%.

Recent data show the number of patients supplied 2 and >2 product regimens has started to decrease.

Analysis of expenditure

Figure 14a presents R/PBS expenditure on opioids by drug.

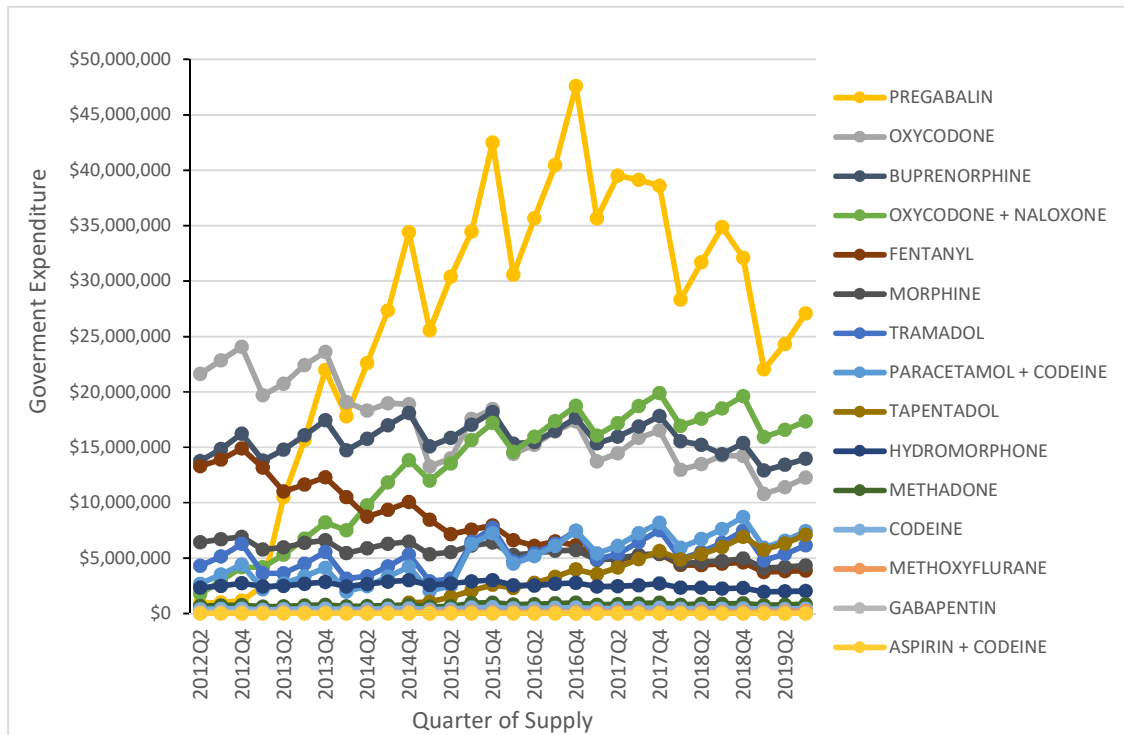


Figure 14a: Government expenditure for opioids and other selected analgesics by drug
Source: DHS prescription database (accessed 29 October 2019)

Comparing figures 14a and 1a shows that the expenditure on pregabalin was proportionally greater than its share of the prescription market. The relative difference has decreased since 2016 Q4 due to price reductions which have been applied to pregabalin. Table 3 shows a summary of the main PBS price reductions for these drugs over the analysis period.

Table 3: Summary of main PBS price decreases

Date	Drug(s)	Details
December 2014	Oxycodone	16% price reduction for listing of generic brand ⁴
April 2016	fentanyl, tramadol	Price Disclosure Reductions ⁵
	hydromorphone, buprenorphine	5 year anniversary 5% price reduction ⁶
October 2016	Fentanyl	Price Disclosure Reductions
April 2017	fentanyl, tramadol	Price Disclosure Reductions
August 2017	Pregabalin	16% price reduction for listing of generic brand
June 2018	buprenorphine	16% price reduction for listing of generic brand of patch
October 2018	pregabalin, oxycodone	Price Disclosure Reductions
August 2019	hydromorphone	25% price reduction for listing of generic brand of injection

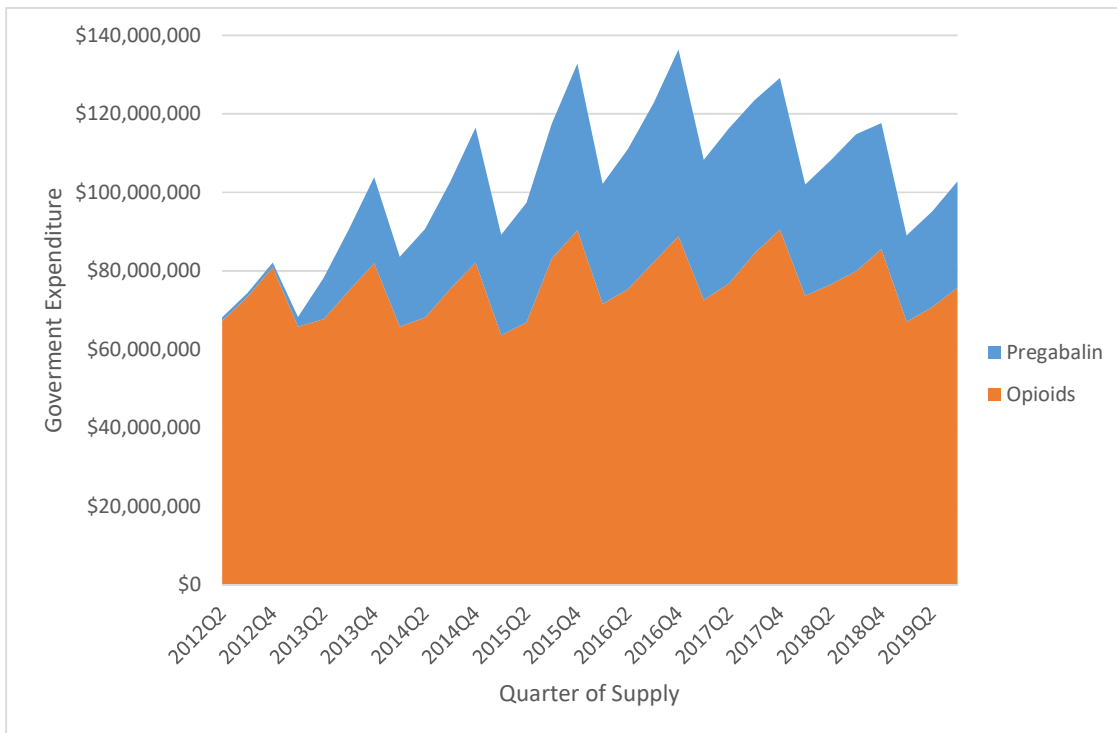


Figure 14b: Total PBS expenditure for opioids and pregabalin (i.e. all prescriptions shown in Figure 1b)

Figure 14b shows that total PBS expenditure on opioids and pregabalin peaked in 2016 Q4 and has been decreasing since. Figure 1b showed that prescriptions utilisation has recently plateaued and may be starting to decrease.

⁴ <http://www.pbs.gov.au/info/industry/pricing/pbs-items/first-new-brand-price-reductions>

⁵ <http://www.pbs.gov.au/pbs/industry/pricing/price-disclosure-spd>

⁶ <http://www.pbs.gov.au/info/industry/pricing/anniversary-price-reductions/5-year-anniversary>

Discussion

Pregabalin has become the most supplied analgesic in the opioid and pregabalin analgesic market (see Figure 1a). All the drugs in this market, except pregabalin and tapentadol, are declining in prescription and patient utilisation (see Figures 1a and 7).

The patient drug regimen analysis showed that the listing of pregabalin for neuropathic pain in March 2013 coincided with the start of an increase in both 2 product and >2 product drug regimens (see Figure 13). Currently (as at August 2019) 5 of the 10 most common 2 product regimens contain pregabalin and 8 of the 10 most common 3 product regimens contain pregabalin (see Figures 9 and 10).

The use of PBS-listed high dose codeine (i.e. 30 mg) in combination products increased slightly in quarter 1 2018, which coincided with the up-scheduling of low dose codeine combination products to Schedule 4 Prescription Only by the TGA on 1 February 2018 (see Figures 1a & 7). The low dose codeine combination products are not PBS listed and thus, since the up-scheduling, can only be supplied as private prescriptions. This may have provided a financial incentive to substitute low dose codeine private prescriptions with high dose codeine PBS-subsidised prescriptions in some cases.

Currently 79%, 17% and 4% of patients are on a 1, 2 or >2 product drug regimen respectively (see Figure 12). This distribution had less multi-product regimens at the beginning of the analysis period, (i.e. 16/9/2012) when there were 87%, 12% and 1% of patients on 1, 2 and >2 product regimens respectively. The current proportion of multi product regimens is 21% (i.e. 17% + 4%), however this was higher from September 2016 to December 2018, when it was 23% (18% 2 product and 5% >2 product regimens). Thus the proportion of multi-product regimens is currently decreasing.

Prescriptions from the palliative care schedule accounted for only 0.8% of the opioid market in 2019 Q3 (see Figure 2). However prescriptions for palliative care patients accounted for at least 7.1% of the opioid market and 5.0% of the pregabalin market in the same period (see Figure 3). The top 6 drugs (in order of prescription utilisation, from most to least in 2019 Q3) in this market supplied to palliative care patients are buprenorphine, pregabalin, oxycodone, paracetamol + codeine, tramadol and oxycodone + naloxone (see Figure 5).

DUSC consideration

DUSC considered that;

- The increase in use of PBS codeine combination products after the codeine up-scheduling by the TGA in February 2018 was approximately 100,000 prescriptions per quarter.
- The palliative care schedule may be under-utilised by palliative care patients. This may be due to the difference in the restriction level compared to the general schedule (i.e. Authority Required vs. Restricted Benefit). DUSC noted that compared to the palliative

care listings, only lower quantities are available in the general schedule listings which would require more prescriptions and patient copayments for palliative care patients to access.

- It would have been instructive to see total patient counts for all opioids and pregabalin separately as well as the combined patient count (Figure 6).
- The method for calculating standard coverage days (SCD, a key metric in the drug regimen method) could be further refined. Referring to the SCD data presented in Table A.1 in the report, it was noted that there was variance between the median and mode of the SCD for some drug and Mode of Administration (MoA) combinations. As such, DUSC considered it may be more accurate to calculate and apply SCDs at a level lower than drug + MoA. (e.g. drug + MoA + rate of release or the PBS item level). A large difference between the mode and the median for SCD can indicate either intermittent use or that the products within that grouping have quite different times to re-supply. DUSC considered that sensitivity analyses could be used determine the impact of applying lower level SCD estimates on the results for the drug regimen analyses.
- It would be informative for future considerations of opioid use to include an analysis of:
 - Dose. This could be in the form of DDDs per patient per day or preferably in the form of Oral Morphine Equivalents (OMEs) per patient per day.
 - Persistence or time on treatment.
 - Age groups. DUSC noted from previous analyses of opioids the increasing utilisation by DDD by age analysis showed that the increase in opioid use is most evident for older age groups. It is of interest to see if this trend is continuing by Oral Morphine Equivalents (OME) per age group.
 - Linkage to hospital data if possible to assess the harms of opioid use.
 - Regional variation (e.g. by State or Territory). As there are real time monitoring systems for high-risk prescription medicines in the ACT, Tasmania and Victoria, it would be of interest to see if PBS utilisation of opioids in these states has changed since the introduction of these systems.

DUSC actions

DUSC requested that the report be provided to the PBAC for consideration.

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

None of the sponsors of products in this report had comments. The sponsors contacted for comment were Alphapharm, Apotex, Arrow Pharma, Aspen Pharmacare, Dr Reddy, Generic Health, Johnson and Johnson, Junopharm, Luminarie, Mayne pharma, Medis, Medsurge, Menariniapac, Mundipharma, Mylan, Pfizer, Pharmacor, Phebra, Sandoz, Sanofi, Seqirus, and Teva pharmaceuticals.

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.

To the extent provided by law, DoH makes no warranties or representations as to accuracy or completeness of information contained in this report.

To the fullest extent permitted by law, neither the DoH nor any DoH employee is liable for any liability, loss, claim, damage, expense, injury or personal injury (including death), whether direct or indirect (including consequential loss and loss of profits) and however incurred (including in tort), caused or contributed to by any person's use or misuse of the information available from this report or contained on any third party website referred to in this report.

Appendix A

Detailed methodology to estimate drug regimens and regimen transitions

Drug treatment regimens are estimated from prescription supply dates

The prescription data contains date of supply of each prescription, but no information on whether or not medicines should be (or were) co-administered. Thus co-administration was estimated from the data in the following way;

Step 1:

Determine the estimated medication coverage days for **each** drug or drug group. This mainly involves detecting breaks in treatment. The outcome is the start and estimated end date for each episode of treatment for each drug or drug group.

Step 2:

Determine the estimated medication coverage days **across all** drug and drug group episodes defined in Step 1. The outcome is an estimated treatment regimen for each patient for every day in the data period.

Similar methods have been used for assessing medicine use in Australian populations.^{7,8} Hallas⁹ describes the method and provides references to early variants.

Figure A.1 illustrates the method specified above. It addresses the scenario where the research question is concerned with the drug regimens before and after initiation to a third line agent (Drug C in this example). However the method of determining a patient's drug regimen at any point in time is the same for other scenarios (e.g. when the regimens are estimated in each calendar weeks rather than in weeks relative to an initiation event). The standard coverage days (SCD) for each drug A, B & C have been shortened to 5 days to enable the figure to fit on one page. The Step 1 process results in the production of the episodes (pink bars) and the Step 2 process results in the production of the treatment regimen (blue bar). The days in this illustration are days from initiation (applicable to an incident patient analysis) but they can also be calendar days (applicable to a prevalent patient analysis).

In this illustration, a break in treatment is defined as a coverage gap of 2 or more SCDs (i.e. the patient has not received re-supply at three consecutive expected refill dates. The first gap in drug A coverage (from days -39 to -35) is not deemed to be a break in the drug A Episode 1 as the estimated gap in coverage is only 1 x SCD. The second gap in drug A

⁷ Pratt N, Roughead EE, Ramsay E, Salter A, Ryan P 2011 "Risk of hospitalization for hip fracture and pneumonia associated with antipsychotic prescribing in the elderly: a self-controlled case-series analysis in an Australian health care claims database" *Drug Saf.* 34(7):567-75. doi: 10.2165/11588470-000000000-00000.

⁸ Vitry AI, Roughead EE, Preiss AK, Ryan P, Ramsay EN, Gilbert AL, Caughey GE, Shakib S, Esterman A, Zhang Y, McDermott RA 2010 "Influence of comorbidities on therapeutic progression of diabetes treatment in Australian veterans: a cohort study" *PLoS One.* 5(11):e14024. doi: 10.1371/journal.pone.0014024.

⁹ Hallas J. 2005 "Drug utilization statistics for individual-level pharmacy dispensing data" *Pharmacoepidemiol Drug Saf.* 14:455-463. doi: 10.1002/pds.1063.

coverage from days -29 to -20 is deemed to be a break in treatment and the end of Episode 1 because the gap in estimated coverage is 2 x SCD.

The two prescriptions for drug B supplied on day -9 are interpreted as dose escalation of drug B, if each prescription is for a different strength. The two prescriptions are deemed to be necessary to supply one SCD period and not used to extend the drug coverage period. If each prescription of drug B were for the same strength then this would be interpreted as “stockpiling” and assumed to extend the drug coverage period (see Details of Methodology below for details)

Drug C is a third line agent and initiated on day 0 (by definition). The basic method imputes a short period of B+C, but a refinement of the method includes the calculation of an adjusted treatment regimen which removes short periods of overlap when it is likely that a switch has occurred before the prior medicine is deemed to be fully used.

The final method for estimating the drug treatment regimen includes several refinements which are explained in below. Briefly they are:

1. Calculation of the treatment regimen on a weekly rather than daily basis.
2. Calculation of drug treatment regimen transitions – including an adjustment to allow for switching when the prior medication is not fully used.
3. Adjustment to allow for stockpiling of medication, both same-day supply and supplies on different days.
4. Change in the rules for prescriptions whose coverage spans the initiation date;
- removal of the stockpiling rule
5. Estimating if a patient is continuing or stopping treatment after their last script

Details of Methodology

1. Calculation of the treatment regimen

Drug treatment regimens are estimated from prescription supply dates in the following way;

Step 1:

Determine the estimated medication coverage days for **each** drug or drug group. This mainly involves detecting breaks in treatment. The outcome is the start and estimated end date for each episode for each drug or drug group.

Step 2:

Determine the estimated medication coverage days **across all** drug and drug group episodes defined in Step 1. The outcome is an estimated treatment regimen for each patient for every day in the data period.

Step 2 above was modified so that the treatment regimen was estimated on a weekly rather than daily basis. This modification was deemed necessary to keep the data volume at a manageable level. This modification means that if the a medication coverage start date falls in a particular calendar week (for prevalent patient analysis) or week since initiation (for initiation analysis) then the medication is deemed to cover that week. The same rule was applied to the medication coverage end date.

2. Drug regimen transitions - including an adjustment to allow for switching when the prior medication is not fully used

Once estimated drug regimens have been determined for every week, then transitions can be computed.

These are useful for determining patient behaviour upon initiation of a drug; e.g. $A \rightarrow A+B$ (adding to existing therapy), $A \rightarrow B$ (switching) or $\text{None} \rightarrow A$ (starting therapy).

Every drug regimen transition is assessed as to whether or not it is likely to be a real change, or an apparent addition of a drug that is really a substitution of another drug (i.e. a switch of drugs). An apparent addition occurs when a patient has not consumed all of the prior drug before starting a new drug. As the coverage of the prior drug is based on when the script was supplied and the SCD for that drug, there may be apparent overlap of coverage of the two drugs that does not occur in reality.

This is assessed by noting the composition and length of the current, prior and post drug regimens. For example, if the regimen being assessed is $A+B$ and the prior regimen is A , the post regimen is B and the length of the $A+B$ regimen is less than or equal to the SCD of prior regimen (i.e. A) then the $A+B$ regimen is deemed to have not occurred and the regimen is changed to the post regimen (i.e. B). Thus before adjustment the regimen sequence would have been $A \rightarrow A+B \rightarrow B$ and after adjustment the sequence is $A \rightarrow B \rightarrow B$ which is the same as $A \rightarrow B$. In this way all apparent overlaps, which are really switches, are corrected for.

If the prior regimen contains multiple drugs (e.g. A+B+C) then the minimum period overlap of regimens required for the transition to be deemed real, and not apparent, is equal to the longest SCD of the drugs in the prior regimen (e.g. if A & B have a SCDs of 5 weeks and C has and SCD of 9 weeks then the overlap period needs to be 9 weeks).

Further criteria for defining a switch are;

- all drugs in the prior and post regimen are in the current regimen; and
- the prior and post regimens are different

3. Adjustment to allow for stockpiling of medication, both same-day supply and supplies on different days

The two step methodology outlined in point 1 and refined by logic in point 2 above did not take into account the phenomenon of stockpiling. This often occurs towards the end of the calendar year when a Safety Net card holder fills prescriptions more frequently than expected, so as to stockpile the medicine and avoid a higher co-payment in the next calendar year when they lose Safety Net eligibility. Stockpiling can also occur at other times of the year. Step 1 can impute higher rates of breaks in episodes around February. This is likely to be due to the stockpiling effect and not due to genuine breaks in treatment. Thus the rule to estimate the prescription coverage end date was modified to be the greater of;

- the predicted coverage end date of the previous prescription plus the standard coverage days (SCD); and,
- the actual supply date of the prescription plus the SCD.

This way of calculating the prescription coverage end date takes into account medication stockpiling (i.e. early supply). The logic of the break rule remained unchanged, that is;

- a break was where a prescription was supplied 2 x SCD or more after the coverage end date of the previous prescription for the same drug or drug group.

Application of this refinement results in the reduction of the extent of seasonality in the number of breaks in episodes.

If multiple prescriptions of the same drug (but not the same strength) or drug group are supplied on the same day, it was assumed that these were necessary for the prescribed dose for the SCD and not for an extension of coverage.

If multiple prescriptions of the same drug are supplied it is generally for two different strengths to enable the prescribed dose to be administered. If two prescriptions for the same strength (as opposed to increased quantity for a single script) are supplied, the method assumes this is similar to stockpiling (i.e. same day stockpiling) and the predicted coverage end date is extended to be the greater of;

- the predicted coverage end date of the previous prescription plus $n \times$ SCD; and,
- the actual supply date of the prescription plus $n \times$ SCD

where n = number of prescriptions on the same day.

A special case of multiple prescriptions being supplied on the same day is Regulation 24 prescriptions.

If the original and repeat prescriptions were supplied under Regulation 24 on the same day, then this was assumed to extend the coverage period (i.e. coverage period = prescriptions x SCD).

There is a danger that patients who consistently consume their medicine in less than the SCD period for a particular drug, will be deemed to be stockpiling (when they are not) and the coverage end date for a prescription will get unrealistically ahead of the supply date. To reduce this risk, the stockpiling rule was modified to limit the stockpiling to 3 extra SCD periods of coverage.

**4. Change in the rules for prescriptions whose coverage spans an initiation date;
- removal of stockpiling rule**

It was found that the stockpiling rule could result in the script coverage end date getting considerably ahead of the script supply date. This is the intent of the rule, however when a new drug B was initiated the stockpiling rule was resulting in the imputation that the new drug B was being added to an existing drug A, when in all probability it was substituting drug A. To correct for this, the script coverage rule was changed so that if the script coverage period for a drug A script included the initiation date for drug B, then the stockpiling rule would not apply to the drug A script (i.e. its coverage would be from its supply date to the supply date + SCD). The rationale for this change is that even if patient has a lot of drug A on hand, the decision by the prescriber to initiate a new drug means that a switch could have occurred.

5. Estimating if a patient is continuing or stopping after their last script

If the last script in a patient's script history is supplied within 2 x SCD of the end of the data period then the treatment is estimated to be continuing at the end of the data period (i.e. the episode coverage end date is set to the end date of the data period). Otherwise the treatment episode is estimated to have stopped and the episode coverage end date is equal to the last script in a patient's script history plus 1 x SCD.

Table A.1: Standard Coverage Days used in this analysis

Drug + MoA*	Days to re-supply		Chronic or Acute treatment**	Standard Coverage Days (SCD)***
	Mode	Median		
aspirin_codeine	28	38	Chronic	38
buprenorphine	14	16	Chronic	16
codeine	28	28	Chronic	28
fentanyl_buccal	14	22	Acute	14
fentanyl_sublingual	14	21	Acute	14
fentanyl_transdermal	14	16	Chronic	16
hydromorphone_injection	1	4	Acute	1
hydromorphone_oral	14	16	Chronic	16
methadone_injection	1	5	Acute	1
methadone_oral	28	23	Chronic	23
morphine_injection	1	4	Acute	1
morphine_oral	28	21	Chronic	21
oxycodone_naloxone	14	19	Chronic	19
oxycodone_oral	7	19	Chronic	19
oxycodone_rectal	28	19	Chronic	19
paracetamol_codeine	28	37	Chronic	37
pregabalin	28	28	Chronic	28
tapentadol	14	23	Chronic	23
tramadol_injection	2	7	Chronic	7
tramadol_oral	7	21	Chronic	21

*MoA = Mode of Administration. This is only included if the drug has more than one MoA

** Treatment is deemed to be chronic if more than 50% of all prescriptions have been resupplied. Otherwise it is deemed to be acute treatment.

*** SCD is the median days to re-supply if the treatment is chronic and the mode days to re-supply if the treatment is acute.

If the drug regimens are display by calendar week instead of weeks relative to initiation, then towards the end of the data period there may be some obvious “end effect” artefacts in some of the regimen time series. This is because the true continuation rate may not be well estimated by the continuation logic described above (i.e. If the last script is supplied within 2 x SCD of the end of the data period then the treatment is estimated to be continuing at the end of the data period). If this is the case then there will be a trend change close to the end of the regimen time series plot. One solution to this problem is to not display approximately the last 2 x SCD portion of the time series.

Appendix B

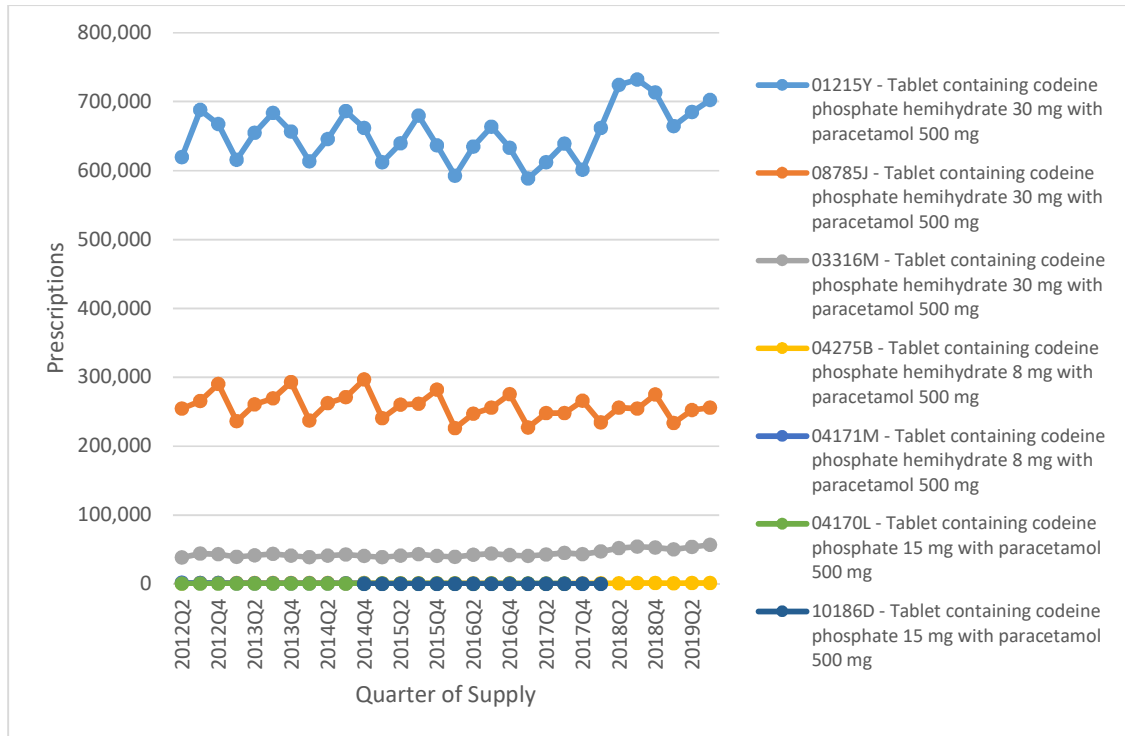


Figure B.1: Prescriptions for paracetamol + codeine products

Note: Item 1215Y is Unrestricted, 8785J is Authority Required and 3316M is for prescribing by Dentists

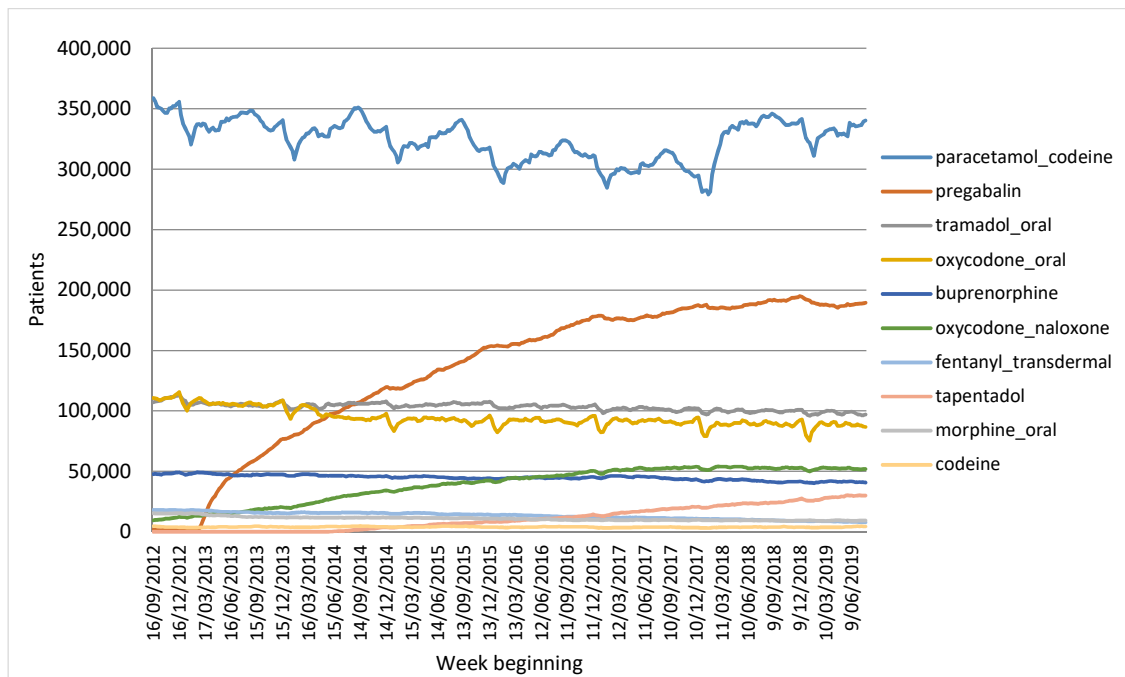


Figure B.2: Opioid drug regimens, only 1 product

Note: only top 10 regimens are shown