Medicines for Alzheimer disease

# Drug utilisation sub-committee (DUSC)

## February 2016

## Abstract

## Purpose

To review the utilisation of medicines for the treatment of Alzheimer disease 24 months after changes to their Pharmaceutical Benefits Scheme (PBS) restrictions arising from the Post‑Market Review of Anti-dementia drugs. The changes were implemented on
1 May 2013.

## Date of listing on the Pharmaceutical Benefits Scheme (PBS)

The three acetylcholinesterase inhibitors - donepezil, rivastigmine, and galantamine - were first listed on the PBS in 2001. Memantine was listed in 2008. The changes from the post‑market review were implemented on 1 May 2013. The main change was a broadening of the eligibility criteria for patients to continue treatment.

## Data Source / methodology

The analysis used PBS prescription claims data from the Department of Human Services (DHS). The analysis used data from January 2003 to September 2015. The analysis relates mainly to the utilisation of these medicines from January 2009 to September 2015.

## Key Findings

* The number of patients supplied medicines to treat Alzheimer disease has increased. In 2009, 43,619 patients were supplied an anti-dementia medicine. In 2014, 52,012 patients were supplied an anti-dementia medicine, and of these 13,745 patients were new to treatment.
* Donepezil is the market leader and its utilisation continues to grow.
* Approximately 70% of people who start an acetylcholinesterase inhibitor and 64% of people who start memantine treatment continue treatment beyond 6 months. Continuation rates before and after the changes to the PBS restrictions are similar.
* In 2014, the Australian Government spent $31,771,611 subsidising anti-dementia medicines. The annual cost to Government of subsidising these medicines has almost halved since 2012 due to price reductions arising from the post‑market review, generic competition and price disclosure.

#### Purpose of analysis

To review the utilisation of medicines for the treatment of Alzheimer disease 24 months after changes to their PBS restrictions arising from the Post‑Market Review of Anti-dementia drugs. The changes were implemented on 1 May 2013.

#### Background

### Post‑market review

At its March 2012 meeting, the PBAC requested a review of all anti-dementia medicines listed on the PBS for the treatment of Alzheimer disease. This was as a result of a DUSC analysis, which found that these medicines were being used in a much larger population and for longer periods of time than originally considered cost-effective by the PBAC. Refer to [Previous Reviews by the DUSC](#_Previous_reviews_by).

The PBAC considered the findings of the post‑market review at its December 2012 meeting. The review updated the utilisation data and confirmed that approximately 60% of patients who start treatment with an acetylcholinesterase inhibitor (AChEI) or memantine continued treatment beyond 6 months (measured as a being supplied a seventh prescription). Approximately 30% of all patients dispensed an AChEI were also dispensed medicines with anticholinergic effects. Of veterans who started an AChEI or memantine, 19% did so in a residential aged care facility.

The review found there were only a small number of new trials assessing the effectiveness of these medicines since listing. This more recent evidence was consistent with evidence previously considered by the PBAC. There was no evidence to suggest one drug is more effective than another. The review found the Standardised/Mini-Mental State Examination (S/MMSE) to be a valid measure of cognition but the relationship between changes in the S/MMSE and activities of daily living and quality of life to be highly variable. The validity of S/MMSE as a surrogate outcome for final outcomes such as quality of life, overall survival, care-giver time (and quality of life) or time to nursing home placement was unknown. The review concluded that there needs to be caution in interpreting small changes in the S/MMSE because the results may be due to measurement error, regression to the mean or the effect of repeated testing.

The PBAC recommended replacing the use of S/MMSE or the Alzheimer disease Assessment Scale - Cognition (ADAS-Cog) tools and using a clinical assessment of response to treatment at 6 months. The PBAC also recommended the Department seek a 40% price reduction on these medicines to re-establish their cost-effectiveness.

For further details on the review, refer to the [Review of Anti-Dementia Drugs](http://www.pbs.gov.au/info/reviews/anti-dementia-drugs/).

For further details on the PBAC recommendation, refer to the [Minutes of the December 2012 Special PBAC meeting](http://www.pbs.gov.au/info/reviews/pbac-minutes-alzheimers).

### PBS listing details

## Date of listing on PBS

Donepezil, rivastigmine, and galantamine were listed on the PBS in 2001. Memantine and rivastigmine patches were listed on the PBS in 2008.

## Changes to listing

In November 2011, the restrictions for AChEIs and memantine were changed to allow the diagnosis to be made by or in consultation with a specialist. Previously, a specialist had to confirm the diagnosis.

In May 2013, the changes to the restrictions arising from the post‑market review were implemented. The changes included:

* Removal of the requirement for patients to achieve a 2 point increase in their S/MMSE, or either a 4 point decrease in their ADAS-Cog score, or a rating of "very much improved" or "much improved" in the Clinicians Interview Based Impression of Change (CIBIC) Scale for patients unable to achieve a S/MMSE for reasons other than their Alzheimer disease;
* Patients are able to receive continuing treatment as long as they have a clinically meaningful response to initial treatment; and
* The continuing treatment restrictions were changed to streamlined authorities. Previously, an initial written authority was required for the first continuing approval and telephone approval was required for subsequent approvals.

Rivastigmine oral liquid was delisted on 1 September 2015. Rivastigmine 13.3 mg/24 hours patches were listed on 1 December 2015.

Other minor changes to the listings (such as the introduction of controlled release galantamine) occurred prior to the previous DUSC analysis of these medicines.

Current PBS listing details are available from the [PBS website](http://www.pbs.gov.au/pbs/home).

## PBS listing details (as at 1 December 2015)

Table 1 presents the PBS listings of medicines to treat Alzheimer disease as at 1 December 2015. Initial treatment with an AChEI or memantine requires an initial written authority approval. Up to two months initial treatment may be authorised through a telephone authority. The balance of the six month supply is then authorised when the written application is received. Continuing treatment for AChEIs and memantine is through an Authority Required (STREAMLINED) listing. Nurse practitioners can prescribe continuing therapy for AChEIs and memantine.

Table 1: PBS listing of medicines to treat Alzheimer disease

| Item | Name, form & strength, pack size | Max. quant.  | Rpts  | DPMQ | Brand name and manufacturer |
| --- | --- | --- | --- | --- | --- |
| 8496E (init.)2479L (cont.) | donepezil hydrochloride 10 mg tablet, 28 | 1 | 5 | $29.33 | Numerous brands and manufacturers |
| 8495D (init.)2532G (cont.) | donepezil hydrochloride 5 mg tablet, 28 | 1 | 5 | $29.33 | Numerous brands and manufacturers |
| 8770N (init.)2463P (cont.) | galantamine 8 mg capsule: modified release, 28 capsules | 1 | 5 | $38.63 | Numerous brands and manufacturers |
| 8771P (init.)2537M (cont.) | galantamine 16 mg capsule: modified release, 28 capsules | 1 | 5 | $44.92 | Numerous brands and manufacturers |
| 8772Q (init.)2531F (cont.) | galantamine 24 mg capsule: modified release, 28 capsules | 1 | 5 | $51.54 | Numerous brands and manufacturers |
| 8497F (init.)2475G (cont.) | rivastigmine 1.5 mg capsule, 56 | 1 | 5 | $91.71 | Exelon® Novartis Pharmaceuticals Australia Pty Ltd |
| 8498G (init.)2493F (cont.) | rivastigmine 3 mg capsule, 56 | 1 | 5 | $91.71 | Exelon® Novartis Pharmaceuticals Australia Pty Ltd |
| 8499H (init.)2494G (cont.) | rivastigmine 4.5 mg capsule, 56 | 1 | 5 | $91.71 | Exelon® Novartis Pharmaceuticals Australia Pty Ltd |
| 8500J (init.)2526Y (cont.) | rivastigmine 6 mg capsule, 56 | 1 | 5 | $91.71 | Exelon® Novartis Pharmaceuticals Australia Pty Ltd |
| 9161E (init.)2477J (cont.) | rivastigmine 4.6 mg/24 hours patch, 30 | 1 | 5 | $97.51 | Exelon® Patch 5 Novartis Pharmaceuticals Australia Pty Ltd |
| 9162F (init.)2551G (cont.) | rivastigmine 9.5 mg/24 hours patch, 30 | 1 | 5 | $97.51 | Exelon® Patch 10 Novartis Pharmaceuticals Australia Pty Ltd |
| 10541T (init.)10538P(cont.) | rivastigmine 13.3 mg/24 hours patch, 30 | 1 | 5 | $97.51 | Exelon® Patch 15 Novartis Pharmaceuticals Australia Pty Ltd |
| 2492E (init.)1956Y (cont.) | memantine hydrochloride 10 mg tablet, 56 | 1 | 5 | $57.42 | Numerous brands and manufacturers |
| 2513G (init.)9306T (cont.) | memantine hydrochloride 20 mg tablet, 28 | 1 | 5 | $57.42 | Numerous brands and manufacturers |

Source: December 2015 PBS Schedule (refer to [PBS website](http://www.pbs.gov.au/pbs/home))
Note: The price of donepezil decreased below the general patient co-payment in October 2015.

## Restrictions (abridged)

**AChEIs – Initial therapy**

* Mild to moderately severe Alzheimer disease;
* Confirmed by, or in consultation with, a specialist or consultant physician (including a psychiatrist);
* Must have a S/MMSE of 10 or more:
	+ If this score is 25-30 points, the result of a baseline Alzheimer disease Assessment Scale, cognitive sub-scale (ADAS-Cog) may also be specified.
* Patients who are unable to score 10 or more on the S/MMSE due to the following reasons may be assessed by the CIBIC scale. Such patients must meet one or more of the following criteria:
	+ Lack of competence in English;
	+ Limited education (less than 6 years) or are illiterate or innumerate;
	+ Aboriginal or Torres Strait Islanders unable to complete the test due to cultural factors;
	+ Intellectual disability;
	+ Significant sensory impairment precluding test completion; or
	+ Prominent dysphagia out of proportion to cognitive and functional impairment.

The treatment must be the sole PBS-subsidised therapy for Alzheimer disease.

**AChEIs – continuing therapy**

The continuing treatment criteria require patients to have received six months of initial therapy with the drug and to have demonstrated a clinically meaningful response to initial treatment. A clinically meaningful response is demonstrated in the following areas:

* Patient's quality of life including but not limited to level of independence and happiness;
* Patient's cognitive function including but not limited to memory, recognition and interest in environment; and
* Patient's behavioural symptoms, including but not limited to hallucination, delusions, anxiety, marked agitation or associated aggressive behaviour.

Re-assessments for a clinically meaningful response are required to be undertaken and documented every six months. The restriction states that treatment should cease if there is no agreement of benefit as there is always the possibility of harm from unnecessary use. The treatment must be the sole PBS-subsidised therapy for Alzheimer disease.

**Memantine**

Memantine is listed for the treatment of moderately severe Alzheimer disease. Patients are a required to have S/MMSE of 10 to 14. Where patients are unable to achieve an S/MMSE score of 10 to 14 due to the aforementioned reasons, they may be assessed by the CIBIC scale. All other aspects of the restrictions are consistent with the AChEI restrictions.

For details of the current PBS listing refer to the [PBS website](http://www.pbs.gov.au/pbs/home).

## Changes to PBS prices

The prices of the four medicines were reduced by 40% on 1 April 2013. This reduction was recommended by the PBAC at its December 2012 consideration of the post‑market review. Also on 1 April 2013, the prices of donepezil and galantamine were reduced by a further 16% due to statutory price reductions and 10.12% due to price disclosure reductions, respectively.

In October 2014, the prices of donepezil and galantamine were reduced through price disclosure reductions. In October 2015, the prices of donepezil, galantamine and memantine were further reduced through price disclosure reductions.

### Pharmacology

Donepezil,1 galantamine2 and rivastigmine3 are AChEIs, which inhibit the enzyme that breaks down acetylcholine. Alzheimer disease causes a decrease in the activity of cholinergic neuronal pathways in the brain that are known to be involved in cognition3. It is believed increasing the availability of acetylcholine in the brain will improve cognitive function.

Memantine4 is an N-methyl-D-aspartate (NMDA) receptor antagonist. NMDA receptors are glutamate receptors. It is believed increased levels of glutamate released in the brain can lead to the symptoms and disease progression in dementia.

### Therapeutic Goods Administration (TGA) approved indications

Donepezil is indicated for the treatment of mild, moderate and severe Alzheimer disease.1

Galantamine2 and rivastigmine3 are indicated for the treatment of mild to moderately severe Alzheimer disease.

Memantine4 is indicated for the treatment of symptoms of moderately severe to severe Alzheimer disease. There is clinical trial evidence showing the addition of memantine to stable donepezil treatment improved cognition in patients with moderate to severe Alzheimer disease.5

### Dosage and administration

Table 2 presents the dosing and administration information on medicines for Alzheimer disease.

Table 2: Dosage and administration of anti-dementia medicines

| Drug  | Dose and frequency of administration  |
| --- | --- |
| Donepezil1 | 5 mg dailyCan increase to 10 mg daily if tolerated after 4 weeks treatment with 5 mg dose.  |
| Galantamine2 | Starting dose: 8 mg daily. Increase to 16 mg after 4 weeks. Can increase to 24 mg if patient deteriorates after a good response |
| Rivastigmine (oral)3 | Effective dose from trials: 3-6 mg twice daily (6-12 mg per day)Maintenance dose: 1.5-6 mg twice dailyDose Titration:Week 1-2: 1.5 mg twice daily Week 3: 3 mg twice daily Week 5 onwards: further increases to 4.5 mg and 6 mg twice daily can be undertaken every two weeks.  |
| Rivastigmine (transdermal)6 | Dose titration: One Exelon 5 patch (4.6 mg daily dose) daily for 4 weeks then increase to one Exelon 10 patch (9.5 mg daily dose) daily.Patients with moderate or severe disease may be increased to Exelon 15 patch (PBS-listed on 1 December 2015) |
| Memantine | Maintenance dose: 20 mg daily Dose Titration: Week 1: 5 mg orally dailyWeek 2: 5 mg twice daily Week 3: 10 mg in the morning and 5 mg in the eveningWeek 4 onwards: 10 mg twice daily.  |

Source: Donepezil Product Information, Galantamine Product Information, Rivastigmine (oral) product information). Rivastigmine (transdermal patch) Product Information, Memantine Product information.

The current Product Information (PI) and Consumer Medicine Information (CMI) are available from [the TGA (Product Information)](http://tga.gov.au/hp/information-medicines-pi.htm) and [the TGA (Consumer Medicines Information)](http://www.tga.gov.au/consumers/information-medicines-cmi.htm).

### Guidelines

The draft Clinical Practice Guidelines for Dementia in Australia was released for public consultation in early 2015. The draft guidelines used the National Institute for Health and Care Excellence (NICE) dementia guidelines as its basis. The draft guidelines made the following recommendations7:

* Any one of the three AChEIs can be considered for managing mild-to-moderate as well as severe Alzheimer disease;
* Memantine is the recommended option for people with moderate-to-severe Alzheimer disease who are intolerant to or have a contraindication to AChEIs;
* Any one of the AChEIs can be considered for managing the symptoms of Lewy Bodies dementia, Parkinson’s Disease dementia, vascular dementia or mixed dementia;
* Patients prescribed a AChEI or memantine should be assessed within six months to determine whether there is a clinically meaningful response to treatment; and
* AChEIs should not be prescribed for people with mild cognitive impairment.

The draft guidelines note that its recommendations to prescribe AChEIs for patients with severe Alzheimer disease and other types of dementia are outside the current PBS listings. For further information, refer to the [Draft Clinical Practice Guidelines for Dementia in Australia](http://sydney.edu.au/medicine/cdpc/documents/about/Dementia-Guideline-Draft-for-Public-Consultation.pdf).

The 2012 Guidelines published in the Journal of the American Board of Family Medicine recommend the use of an AChEI in combination with memantine for moderate to severe Alzheimer disease.8

### Previous reviews by the DUSC

The DUSC reviewed the utilisation of anti-dementia medicines for Alzheimer disease in June 2010. The findings of the report were published in the Australasian Journal of Ageing in 2012.9 The key findings were:

* 57.3% of patients received more than 6 prescriptions of cholinesterase inhibitors;
* 12.2% of patients who received a first prescription did not have subsequent prescriptions;
* The median duration of treatment was 17 months; and
* Persistence was 54% at 1 year, 43% at 2 years and 33% at 3 years.

#### Methods

The analysis used PBS prescription claims data from the Department of Human Services (DHS) from January 2003 to September 2015. This report predominantly presents data from January 2009 to June 2015, inclusive. The time to re-supply analysis included data from July 2008 to June 2015. Patient count data where patients are classified as initiating patients and re-initiating patients used data from January 2003. The transition analysis used data to September 2015. All four medicines cost more than the general patient co-payment for the period of the analysis and are expected to be included in the database. This database does not include private prescriptions that are supplied outside of the PBS.

The number of prevalent patients was determined by counting the number of people supplied at least one PBS prescription in a given period. Unique patients were counted using non-identifying personal identification numbers. Patients were considered to be new patients (initiators) if they had not received a prescription for any of the anti‑dementia medicines since 2003. Patients were considered re-initiators if they had no supply for the stated number of months but had received an earlier supply. An analysis of re-initiators was undertaken based on six and 12 months without treatment. It was calculated as follows:

Re-initiators (no script in X months) = Initiators (lookback of X months) - Initiators (no script since Jan 2003).

The DHS Authority approvals database was used to compare the number of authority approvals for new patients with the number of new patients supplied their first prescription. A longer lookback period of 18 months was used to identify new patients in the authority approvals database. This was because there may be delays between authority approval to first supply and because approvals are only required every six months.

As this analysis uses date of supply prescription data, there may be small differences compared with publicly available Department of Human Services (DHS) Medicare date of processing data.10

Memantine treatment transition analysis

An analysis was undertaken to assess the use of AChEIs around the time of memantine initiation. It assessed drug regimens used by patients who initiated treatment with memantine between May 2013 and April 2014, inclusive. This cohort was chosen because these patients started treatment following the restriction changes arising from the post‑market review. Each patient’s PBS prescription history was assessed, giving 78 weeks of data before starting memantine and 73 weeks after starting memantine. This analysis only assessed anti-dementia medicines listed on the PBS.

For more details see Appendix A: Detailed methodology to estimate drug regimens and regimen transitions.

#### Results

### Analysis of drug utilisation

## Overall utilisation

Table 3 presents the total number of patients who received an anti-dementia medicine each year and the number of new patients that started treatment each year. The figures for 2015 are complete to September 2015.

Table 3: Patients treated with dementia medicines

| Year  | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015a |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Prevalent patients | 43,619 | 45,005 | 46,267 | 47,979 | 49,563 | 52,012 | 49,936 |
| Initiating patients | 12,147 | 12,583 | 12,518 | 13,127 | 13,531 | 13,745 | 10,172 |

Source: DHS Supplied Prescriptions database, extracted December 2015
a Complete to September 2015

The number of patients receiving dementia medicines on the PBS has steadily increased at a rate of 3.6% per year between 2009 and 2014. The number of patients starting treatment has generally increased each year, except in 2011, when 65 fewer patients started treatment than in the preceding year.

Figure 1 presents the number of patients starting anti-dementia medicines by the first medicine they received. These patients have not received any anti-dementia medicines since 2003.

Figure 1: Patients starting dementia medicines by drug
Source: DHS Supplied Prescriptions database, extracted December 2015.

Most patients start treatment with donepezil. The number of patients who start treatment with galantamine is decreasing.

Figures 2 and 3 present the number of patients re-starting anti-dementia medicines. Alzheimer disease is a chronic disease and as such, these medicines are intended to be used chronically until treatment cessation. These figures identify patients who are having breaks in treatment. These figures use data from 2003 to 2015 to identify patients who stop treatment for 12 months and six months, respectively. The analyses look at breaks in therapy (not individual medicines) and counts patients who switch medicines with a break of the specified number of months.

Figure 2: Patients re-starting anti-dementia medicines (12 month break by re-initiating drug)
Source: DHS Supplied Prescriptions database, extracted December 2015.
Note: Values in earlier data periods are suppressed due to small numbers.

Figure 3: Patients re-starting anti-dementia medicines (6 month break by re-initiating drug)
Source: DHS Supplied Prescriptions database, extracted September 2015.

The number of patients defined as re-initiators is sensitive to the definition of a treatment break. The number of patients defined as re-initiators doubles when the definition of a break in treatment is decreased from 12 months to six months. Overall, the number of patients classified as re-initiators is small relative to the large number of patients using these medicines.

Figure 4 presents the number of anti-dementia prescriptions supplied each year.

Figure 4: Prescriptions for anti-dementia medicines by drug
Source: DHS Supplied Prescriptions database, extracted September 2015.

The number of prescriptions supplied each year has increased more rapidly in the later years. Between 2009 and 2012, the number of prescriptions increased at 3-4% per year. From 2012 to 2013 and 2013 to 2014, the number of prescriptions increased by 5% and 7%, respectively.

Figure 5 shows the time to re-supply for anti-dementia medicines by drug. This analysis combines the data for rivastigmine oral dose forms with the transdermal patch. One pack of rivastigmine capsules provides 28 days supply whereas one pack of rivastigmine patches provides 30 days supply.

Figure 5: Days to next supply by drug
Source: DHS Supplied Prescriptions database, extracted September 2015. Includes data from January 2008 to June 2015 inclusive.
Note: The figure has been truncated at 120 days. 1% of repeat prescriptions are supplied more than 120 days after the previous prescription.

The median time to the next supply, excluding same day supply, was 28 days for donepezil, galantamine and memantine and 30 days for rivastigmine. The average time to the next supply was 31 days for donepezil, 30 days for galantamine and 35 days for both memantine and rivastigmine. These figures also exclude same day supply which account for 2.6% of repeat prescriptions. These findings are consistent with findings from previous DUSC and post-market review analyses which found approximately 55% of prescriptions are supplied at or before 28 days.

## Continuation analysis

Figure 6 presents data on the rates of continuation for AChEIs, up to the twelfth supply, in three cohorts. Patients who started treatment between January 2011 and September 2012, inclusive are the “Before change” cohort. Patients starting between October 2012 and April 2013 are the “Overlap” cohort and patients starting between May 2013 and June 2014 are the “After change” cohort. The data present the proportion of the cohort who received the stated number of prescriptions.

Figure 6: Treatment continuation of AChEIs by cohort.
Source: DHS Supplied Prescriptions database, extracted September 2015.

Overall, the rates of continuation are similar across the three cohorts. The “Before changes” cohort had a slightly higher level of discontinuation before receiving a seventh prescription. 66% of the patients in the “Before change” cohort received a seventh prescription compared to 70% of the “Overlap” and “After change” cohorts. The rates of continuation at the 11th and 12th prescriptions are similar across the cohorts.

Figure 7 presents the continuation data for AChEIs by drug for the “Before” and “After” cohorts.

Figure 7: Treatment continuation of AChEIs by drug
Source: DHS Supplied Prescriptions database, extracted September 2015.

The results for the individual medicines show a pattern similar to the class. Before the changes, there was a small but noticeable reduction in continuation to receive a seventh prescription. Following the changes, the reduction at the seventh prescription does not occur however continuation rates for the 11th and 12th prescription are similar to that before the changes.

Figure 8 presents the continuation data for memantine.

Figure 8: Treatment continuation of memantine by cohort
Source: DHS Supplied Prescriptions database, extracted September 2015.

In the “Before change” cohort, 56% of patients received a seventh memantine prescription, compared to 64% of the “overlap” and “After change” cohorts. Similar to the AChEIs, there is a noticeable decrease in continuation to receive a seventh memantine prescription in the “Before change” cohort that is not visible in the “Overlap” and “After change” cohorts. However, the differences in continuation between the “Before change” and “After change” cohorts are minimal (4%) by the 11th prescription.

The proportion of patients supplied a seventh prescription are similar to those seen in the post-market review and earlier DUSC analysis.

## Treatment transition to memantine

A transition analysis was undertaken assessing whether patients were starting memantine as monotherapy, in accordance with the PBS restriction, or as combination therapy added to an AChEI. Evidence relating to the concomitant use of memantine with an AChEI was considered in the post-market review. The evidence was found to be conflicting, with two trials11, 12 reporting no incremental benefit and one reporting a benefit.5

The analysis examined the patterns of anti-dementia medicines use in patients who started memantine between May 2013 and April 2014 inclusive. The analysis assessed utilisation 78 weeks before the start of memantine and for 73 weeks afterwards. Figure 9 presents the results of the analysis. Anti-dementia medicines taken prior to the initiation of memantine are referred to as “Pre-init” and anti-dementia medicines taken after the initiation of memantine are referred to as “Post-init”, including where memantine was ceased and the patient received no anti-dementia medicines (“Post-init None”).


Figure 9: Treatment transition to memantine (n=1,387)
Source: DHS Supplied Prescriptions database, extracted December 2015.
Init = initiation
Note: Some treatment regimens were suppressed due to small patient numbers. All suppressed regimens had multiple AChEIs co-administered.

No dementia treatment was the most common regimen in the 78 weeks before starting memantine. At treatment initiation, the most common treatment regimen is memantine monotherapy. Approximately 14% of regimens after the initiation of memantine are in combination with an AChEI. This decreases to 11% five weeks after initiation. At week 52, 7% of regimens are in combination with an AChEI.

## Operation of Authority Restriction

Figure 10 presents the data on patients who are being given initial authority approvals (Authority initiators) for anti-dementia drugs from the authority approvals database compared to the total number of patients who are being supplied their first prescription of an anti-dementia medicine (Supply initiator).

Figure 10: Patients starting dementia medicines: first supply vs first authority approval
Source: DHS Supplied Prescriptions database and DHS Authority approvals database, extracted September 2015.
Note: This analysis used a 12 month lookback period to identify supply initiators.

Prior to the second quarter of 2013, the number of first authority approvals for patients starting an anti-dementia medicine was slightly higher than the number of patients being supplied their first anti-dementia medicine. From 2013-Q4 onwards, the number of patients receiving their first anti-dementia medicine has generally been higher than the number of initial authority approvals for these medicines. A written authority approval is required for the first prescription of this group of medicines. Continuing treatment can be prescribed as a streamlined authority. Currently, there are no arrangements to ensure continuing streamlined prescribing can only be done for patients who have previously received a written authority approval. That is, it relies on the prescriber following the restriction to initiate therapy with a written approval rather than using the streamlined listing for the first supply.

In the period before the introduction of the streamlined continuing authority, the number of “supply initiators” in the fourth quarter of every year, except 2011, was higher than the number of “authority initiators”.

### Analysis of expenditure

Figure 11 presents the changes in expenditure for anti-dementia drugs by quarter of supply.

Figure 11: Anti-dementia medicine expenditure

Source: DHS Supplied Prescriptions database, extracted September 2015.

The overall cost to Government of anti-dementia medicines has decreased substantially. In 2014, the cost to Government of anti-dementia medicines was $31,771,611, almost half of the $61,194,255 spent in 2012. The PBS prices of anti-dementia medicines decreased by 40% in April 2013 following the post‑market review. Also on 1 April 2013, the prices of donepezil and galantamine were reduced by a further 16% due to statutory price reductions and 10.12% due to price disclosure reductions, respectively. The prices of donepezil and galantamine were reduced in October 2014 through price disclosure price reductions.

#### Discussion

The main change to the restrictions for anti-dementia medicines following the post-market review was to broaden the continuation criteria and change the continuing restriction from a written authority approval to a streamlined authority. These changes do not appear to have resulted in any major changes to treatment continuation. The proportion of patients supplied a seventh prescription following the changes is similar to the rates seen in the post-market review analysis and the previous DUSC analysis. The post-market review analysis found continuation rates of 55-69% in patient cohorts who started AChEIs or memantine between 2004 and 2010. The previous DUSC analysis found a continuation rate of 62.8% for patients who started AChEI treatment in 2004.This is similar to the continuation rates of 70% for AChEIs and 64% for memantine in patients who started treatment between May 2013 and April 2013.

The changes appear to have resulted in a slightly lower proportion of patients discontinuing treatment before receiving a seventh prescription but a similar proportion of patients who receive 11 or 12 prescriptions. The small decrease in continuation before receiving a seventh prescription (continuing approval) under the previous restrictions may suggest that the written Authority criteria only had a small impact on the decision to cease treatment.

The Australian Institute of Health and Welfare estimated there were 298,000 people with dementia in Australia in 2011. This was expected to increase to 332,000 in 2014. The AIHW estimated the prevalence of dementia would increase between 3-4.5% per year between 2011 and 2015.13 This is similar to the increase in the prevalent patient numbers treated on the PBS. However, it should be noted, the AIHW figures refer to all types of dementia whereas the PBS listing is specific for Alzheimer disease.

There has been a small increase in the number of patients restarting anti-dementia medicines following the changes to the restriction and authority level. Some patients may have previously stopped treatment because they were not eligible under the previous continuation criteria, but may have been achieving a clinically meaningful response. Such patients may have re-started treatment following the changes to the continuation criteria allowing for patients with a meaningful response to continue treatment. The number of patients restarting anti-dementia medicines is small relative to the total number of patients using these medicines.

A transition analysis was undertaken to identify patterns of treatment leading up to and after memantine treatment. This analysis found the most common treatment transition was from no dementia treatment to memantine. The analysis also found that there may be some use of memantine with AChEIs. A small proportion of regimens after starting memantine include an AChEI. The proportion of memantine + AChEI regimens decreased from 14% at memantine initiation to 7% at week 52. The figure of 14% combination use is likely to be an overestimate because patients may have been dispensed an AChEI shortly before switching to memantine. The proportion of donepezil + memantine decreases noticeably around week 4 of memantine treatment, suggesting the higher value may be artefactual. There is some evidence to suggest the combination of an AChEI with memantine produces better outcomes in cognition and other domains.5 The combination of AChEI and memantine was recommended in the 2012 Guidelines published in the Journal of the American Board of Family Medicine8. The PBS restrictions specify use of memantine and AChEIs as the sole PBS-subsidised therapy for this condition.

There is some known variation in the rates of AChEIs supply across Australia. The Australian Commission on Safety and Quality in Health Care Atlas of Health Care Variation found rates of PBS supply to vary 15.3 fold in the highest area to the lowest area.14 Much of this variation was due to more extreme values in 25 of 323 geographical areas. There was a 3.7 fold variation between the remaining 298 areas. For further details, refer to Chapter 6 of the [Australian Atlas of Healthcare Variation](http://www.safetyandquality.gov.au/atlas/).

An analysis examining the co-administration of anticholinergic medicines for patients taking anti-dementia medicines was not undertaken. There have been numerous studies examining issues surrounding the use of anticholinergic medicines in dementia patients as well as older people more broadly.15-18 Additionally, assessing the use of anticholinergic medicines in PBS data would underestimate anticholinergic medicine use as a number of such medicines are available over-the-counter. Additionally, the NPS has undertaken a number of initiatives in 2014 focusing on medicines use in older people, including the use of anticholinergics.19

Government expenditure on anti-dementia medicines has decreased due to the price reductions from the post‑market review and price disclosure price reductions.

#### DUSC consideration

The main change to the restrictions for anti-dementia medicines following the post-market review was to broaden the continuation criteria and change the continuing restriction from a written authority approval to a streamlined authority. These changes do not appear to have resulted in any major changes to treatment continuation. DUSC agreed that there has been only a small step-up in utilisation of anti-dementia medicines since changes arising from the post-market review.

DUSC noted the peaks in the time to next supply analysis at 28 days indicates that most people take their anti-dementia medicine regularly and likely reflects use of these medicines in settings such as residential aged care facilities where administration and supply are controlled or for patients who have dose administration aids where date of dispensing is also likely to be controlled. DUSC noted for memantine there is a peak in the days to next supply at 56 days. This may reflect ongoing once daily dosing of 10mg, for example in patients with renal impairment.

DUSC considered that QUM issues remain with anti-dementia medicines. Of particular concern to DUSC was the likely continuation on anti-dementia medicines for long periods of time where there may be little or no benefit, and co-administration of anticholinergic medicines with cholinesterase inhibitors. An analysis examining the co-administration of anticholinergic medicines for patients taking anti-dementia medicines was not undertaken in the current review as there have been numerous studies examining the use of anticholinergic medicines in dementia patients as well as older people more broadly. DUSC considered that recent studies highlight an ongoing problem with simultaneous use of cholinergic and anticholinergic medicines. DUSC considered that a reinforcement of the QUM message may be of value.

#### DUSC actions

The DUSC requested that the report be provided to the PBAC for noting.

#### 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

Janssen-Cilag Pty Ltd: Janssen consider these analyses performed by the DUSC demonstrate that the anti-dementia drugs, including galantamine, are being used correctly for the chronic treatment of Alzheimer’s disease, in line with PBS restrictions and in the appropriately defined patient population.

Numerous other sponsors: 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.

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

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#### References

1. Aricept (Donepezil). Australian Approved Product Information. West Ryde: Pfizer Australia Pty Ltd. Approved 30 March 1998. Updated 16 November 2012. Available from: <https://www.tga.gov.au/product-information-pi>.

2. Reminyl (Galantamine). Australian Approved Product Information. Macquarie Park: Janssen-Cilag Pty Ltd. Approved 14 July 2010. Updated 14 January 2015. Available from: <https://www.tga.gov.au/product-information-pi.>.

3. Exelon (Rivastigmine). Australian Approved Product Information. North Ryde: Novartis Pharmaceuticals Australia Pty Limited. Approved 6 June 2000. Updated 22 August 2015. Available from: <https://www.tga.gov.au/product-information-pi>.

4. Ebixa (Memantine). Australian Approved Product Information. North Ryde: Lundbeck Australia Pty Limited. Approved 17 April 2003. Updated 8 February 2013. Available from: <https://www.tga.gov.au/product-information-pi>.

5. Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. JAMA. 2004;291:317-24.

6. Exelon Patch (Rivastigmine). Australian Approved Product Information. North Ryde: Novartis Pharmaceuticals Australia Pty Limited. Approved 12 March 2008. Updated 7 April 2015. Available from: <https://www.tga.gov.au/product-information-pi>.

7. National Health and Medical Research Council Cognitive Decline Partnership Centre. Clinical Practice Guidelines for Dementia in Australia - Public Consultation Draft. 2015.

8. Sadowsky CH, Galvin JE. Guidelines for the management of cognitive and behavioral problems in dementia. J Am Board Fam Med. 2012;25:350-66.

9. Le Couteur DG, Robinson M, Leverton A, Creasey H, Waite L, Atkins K, et al. Adherence, persistence and continuation with cholinesterase inhibitors in Alzheimer disease. Australas J Ageing. 2012;31:164-9.

10. PBS statistics. Australian Government Department of Human Services Medicare. Canberra. Available from <<http://www.medicareaustralia.gov.au/provider/pbs/stats.jsp>>.

11. Choi SH, Park KW, Na DL, Han HJ, Kim EJ, Shim YS, et al. Tolerability and efficacy of memantine add-on therapy to rivastigmine transdermal patches in mild to moderate Alzheimer disease: a multicenter, randomized, open-label, parallel-group study. Curr Med Res Opin. 2011;27:1375-83.

12. Porsteinsson AP, Grossberg GT, Mintzer J, Olin JT. Memantine treatment in patients with mild to moderate Alzheimer disease already receiving a cholinesterase inhibitor: a randomized, double-blind, placebo-controlled trial. Curr Alzheimer Res. 2008;5:83-9.

13. Australian Institute of Health and Welfare. Dementia in Australia. Cat. no. AGE 70. Canberra: 2012.

14. Australian Commission on Safety and Quality in Health Care. Australian Atlas of Healthcare Variation. Sydney, Australia: Australian Commission on Safety and Quality in Health Care; 2015. p. 342.

15. Parkinson L, Magin PJ, Thomson A, Byles JE, Caughey GE, Etherton-Beer C, et al. Anticholinergic burden in older women: not seeing the wood for the trees? Med J Aust. 2015;202:91-4.

16. Gnjidic D, Hilmer SN, Hartikainen S, Tolppanen AM, Taipale H, Koponen M, et al. Impact of high risk drug use on hospitalization and mortality in older people with and without Alzheimer disease: a national population cohort study. PLoS One. 2014;9:e83224.

17. Gnjidic D, Le Couteur DG, Pearson SA, McLachlan AJ, Viney R, Hilmer SN, et al. High risk prescribing in older adults: prevalence, clinical and economic implications and potential for intervention at the population level. BMC Public Health. 2013;13:115.

18. Mate K, Kerr K, Pond D, Williams E, Marley J, Disler P, et al. Impact of Multiple Low-Level Anticholinergic Medications on Anticholinergic Load of Community-Dwelling Elderly With and Without Dementia. Drugs Aging. 2015;32:159-67.

19. NPS MedicineWise. Older people and medicines 2013 [cited 2015 28 September]. Available from: <http://www.nps.org.au/topics/ages-life-stages/for-individuals/older-people-and-medicines>.

### 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.[[1]](#footnote-1),[[2]](#footnote-2) Hallas[[3]](#footnote-3) describes the method and provides references to early variants.

Figure B.1 illustrates the method specified above. 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 two 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 2nd gap in drug A 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 3rd 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 prior medicine is deemed to be fully used.

The final method for estimating the drug treatment regimen includes several refinements which are explained 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 data;
- removal of stockpiling rule
5. Estimating if a patient is continuing or stopping after their last script



**Figure A.1 Diagrammatic representation of the methodology used to determine treatment regimen**

**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🡪A+B (adding to existing therapy), A🡪B (switching) or None🡪A (starting therapy).

The transitions can be;

1. previous drug regimen 🡪drug regimen at week x, or
2. drug regimen at week -1 🡪drug regimen at week x

Option A has the advantage that it can be calculated at any week, whereas Option B can only be calculated after initiation (i.e. from week 0). The main advantages of Option B are that it can easily be used to adjust the drug regimen in the first few weeks after initiation to allow for switching when the prior medication is not fully used. That is, if a patient switches from A to B, in the first few weeks after initiation to drug B the drug regimen may be incorrectly estimated to be A+B if the patient still has drug A “on hand” (i.e. some is unused) when drug B is initiated.

The regimen transitions are adjusted so that if a regimen transition corresponding to a switch (e.g. A🡪B) is detected within the first X weeks after initiation (e.g. at week Y), then all weeks between the initiation (i.e. week 0) and week Y are modified to the switch transition (i.e. A-B). This means some instances of "A🡪A+B" (apparent co-administration after a switch) are modified to "A🡪B" from week 0 to week Y (where Y ≤ X). The value of X is the 1 week + SCD (expressed in weeks) for the drug or drug group that is being substituted.

This means that if drug A was supplied 1 day before an initiation to drug B and then there were no further supplies of drug A, then there would be apparent co-administration of A and B from week 0 to week X-1. Then in week X the drug regimen would be drug B only and considered a switch. Thus the regimens from weeks 0 to X-1 would be modified to be drug B only. If a switch is first detected in week X +1 then the A script would have been supplied in week 0 (i.e. at or after initiation to drug B) and this would mean that the transition was not a switch, but an add. Thus the logic is only applied to weeks 0 to X.

A transition is considered a switch if a drug in the regimen prior to initiation (the week=-1 regimen) is not in the regimen post initiation (i.e. the week=0 regimen).

After this transition adjustment, the drug regimens can also be adjusted by using the regimen after the arrow in the adjusted regimen transition. That is, if a transition gets adjusted from A🡪A+B to A🡪B in week Y then the adjusted drug regimen for week Y changes from A+B to B. Thus even though the drug regimen is calculated first, its adjustment is dependent on both the regimen transition and adjusted regimen transition. Thus the sequence of calculations is;

1. drug regimens
2. drug regimen transitions around initiation
3. adjusted drug regimen transitions
4. adjusted drug regimens

The above adjustment process is reliant on having regard to drug initiations. If the analysis is for prevalent drug regimens only (i.e. regimens by calendar week and not relative to an initiation date) then the above adjustment is not possible. This is not a major problem as the overestimation of co-administration (e.g. A🡪A+B instead of A🡪B) is greatest in the month after initiation. In a prevalent patient analysis, patient initiations (to any and all drugs) are spread out in time (i.e. all patients do not generally initiate in the same week), and so the overestimation is also spread out over time and so minimised. In an initiating patient analysis, all over-estimations occur at the same time (as time is relative to the initiation week) and so the overestimation is significant and so needs to be adjusted for. In theory, in a prevalent patient analysis, it is possible to do an initiation analysis for every drug and so find adjusted drug regimens that can then be re-expressed in calendar weeks. In practice this is too resource intensive and is unlikely to be make a significant difference to the prevalent patient drug regimens.

**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 refill date of the previous 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 x SCD; and,
* the actual refill date of the previous prescription plus n x 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).

**4. Change in the rules for prescriptions whose coverage spans the initiation data; - 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 rules were 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 a 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 patients 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 patients script history plus 1 x SCD.

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

| **Drug**  | **Standard Coverage Days(i.e. Median time to re-supply by any item of the same drug)** |
| --- | --- |
| Donepezil | 28 |
| Galantamine | 28 |
| Memantine | 28 |
| Rivastigmine | 30 |

1. 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. [↑](#footnote-ref-1)
2. 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. [↑](#footnote-ref-2)
3. Hallas J. 2005 “Drug utilization statistics for individual-level pharmacy dispensing data” Pharmacoepidemiol Drug Saf. 14:455–463. doi: 10.1002/pds.1063. [↑](#footnote-ref-3)