

Attention Deficit Hyperactivity Disorder: Utilisation Analysis

Drug utilisation sub-committee (DUSC)

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Abstract

Purpose

To review the utilisation of the Pharmaceutical Benefits Scheme (PBS) and Repatriation PBS (R/PBS) listed medicines used in the management of attention deficit hyperactivity disorder (ADHD). This includes a predicted versus actual analysis of guanfacine in the first 24 months of R/PBS listing. Guanfacine was first R/PBS-listed for this indication on 1 September 2018.

Date of listing on the PBS

- Dexamfetamine - 1 December 1973
- Methylphenidate immediate release (IR) - 1 August 2005
- Methylphenidate modified release (MR) (Concerta®) - 1 April 2007
- Methylphenidate modified release (MR) (Ritalin LA®) - 1 April 2008
- Atomoxetine - 1 July 2007 requiring authority approval. On 1 August 2014, the restriction was simplified and changed to streamlined authority
- Lisdexamfetamine - 1 September 2015 requiring authority approval
- Guanfacine – 1 September 2018 requiring streamlined authority approval

Subsidy of lisdexamfetamine, atomoxetine and the two modified-release forms of methylphenidate (Ritalin LA and Concerta) is limited to patients diagnosed between the ages of 6 and 18 years of age inclusive. In addition, for modified-release methylphenidate, patients need to have demonstrated a response to immediate-release methylphenidate with no emergence of adverse events. Lisdexamfetamine and Concerta are for patients requiring coverage over 12 hours. Ritalin LA is for patients requiring coverage over 8 hours.

Atomoxetine and guanfacine are subsidised for patients unable to take dexamfetamine or methylphenidate due specific circumstances set out in the PBS restriction. Patients need to have been diagnosed by a paediatrician or psychiatrist according to the DSM-5 criteria.

Data Source / methodology

The analysis used data from Services Australia supplied prescriptions database.

Key Findings

Over the seven year period 2014-2020:

- The number of prevalent patients treated with R/PBS medicines for ADHD has risen at a yearly average growth rate of 12.43%, however this rate does not give the full picture. From 2014-2017 the yearly average growth rate was 9.75%, whereas from 2018-2020 the yearly growth rate was 16%. The substantial increase since 2018 is likely to be due to the listing of guanfacine in September 2018.
- The number of prescriptions also increased at similar growth rates, from 2014-2017 the yearly average growth rate was 10.25%, whereas from 2018-2020 the yearly growth rate was 17.67%.
- The most commonly used medicine in terms of prevalent patients is the modified-release formulation of methylphenidate.
- For all age groups more males than females were treated. For >6 year olds, 76% of prevalent patients were boys and for 6-12 year 72% of prevalent patients were boys.
- Of all prevalent patients treated with R/PBS listed ADHD medicines:
 - children under 6 years old account for 2% of patients
 - children aged 6-12 years old account for 43% of patients
 - adolescents aged 13-18 account for 22%
 - adults aged 19+ account for 33%.

An analysis of medicine use in 2020 shows that:

- The majority of prescriptions were written by paediatricians or psychiatrists.
- The initial prescription of methylphenidate, lisdexamfetamine and dexamfetamine for the treatment of ADHD is generally restricted to specialists in most Australian states and territories.
- Rates of prescribing vary across states and territories, reflecting the different jurisdictional laws about stimulant prescribing. The rates of treatment in >6 year olds was highest in Tasmania (Tas) and lowest in the Australian Capital Territory (ACT), while rates in school-aged children (6-12 years old) were highest in Queensland (QLD) and Tas, and lowest in South Australia (SA). Rates of treatment for 13-18 year olds was highest in ACT and lowest in SA, while rates of treatment in adults were highest in Western Australia (WA).

Guanfacine:

- The listing of guanfacine in September 2018 has contributed towards an increase in the use of ADHD medicines. The listing of guanfacine has not resulted in substitution of ADHD medicines and thus a corresponding reduction in the use of other ADHD medications.
- 18,030 and 25,580 prevalent R/PBS patients were treated with guanfacine in 2019 and 2020 respectively.
- The total number of guanfacine prescriptions supplied in Year 1 (74,725) was more than double the predicted number (111%) with an even higher increase in Year 2 (177,301) which was an increase of 255% over the predicted amount.
- A closer look at the distribution of the number of prescriptions per patient in the 12 months after initiation found that 11% of patients had one supply, while on average patients received 9.48 prescriptions in the first year of therapy.
- The expected cost offset from substitution of other ADHD medicines to guanfacine has not been realised.

Purpose of analysis

To review the utilisation of R/PBS-listed medicines used in the management of attention deficit hyperactivity disorder (ADHD). This includes a predicted versus actual analysis of guanfacine in the first 24 months of R/PBS listing (September 2018).

The ADHD medicines considered in this analysis are:

- dexamfetamine
- methylphenidate (immediate release (IR) and modified release (MR) forms)
- atomoxetine
- lisdexamfetamine
- guanfacine

This analysis also examines the use of clonidine (which has a specific registered indication as a cardiovascular drug) as a treatment for ADHD.¹

Background

Clinical situation

ADHD is characterised by a persistent pattern of inattentiveness, hyperactivity and/or impulsiveness that is associated with learning, behavioural and emotional impairment.

In 2013-2014, the prevalence of ADHD in Australian children and adolescents aged 4-17 was estimated to be 7.4%.² The prevalence of ADHD is higher in males than females at 10.4% compared to 4.3% of females having ADHD.¹ Many children with ADHD continue to have symptoms as adults.²

Comorbid psychiatric conditions are also common in patients with ADHD including anxiety disorders and mood disorders.³

The most current ADHD guidelines by the NHMRC² in 2012 and Therapeutic Guidelines⁴ in 2021 recommend an individualised multimodal management plan for the management of ADHD. Behavioural and educational interventions may be used as non-pharmacological management of ADHD symptoms, either alone or in combination with medicines. In young

¹ Australian Medicines Handbook January 2021. Accessed 15 April 2021.

<https://amhonline.amh.net.au/chapters/cardiovascular-drugs/antihypertensives/other-antihypertensives/clonidine-cardiovascular>

² Lawrence D, Johnson S, Hafekost J, Boterhoven De Haan K, Sawyer M, Ainsley J, Zubrick SR 2015. The Mental Health of Children and Adolescents. Report on the second Australian Child and Adolescent Survey of Mental Health and Wellbeing. Canberra: Department of Health

³ National Health and Medical Research Council (2012), Clinical Practice Points on the diagnosis, assessment and management of Attention Deficit Hyperactivity Disorder in children and adolescents. Canberra.

⁴ Attention deficit hyperactivity disorder. Therapeutic Guidelines Ltd (eTG March 2021 edition) [Internet]. Published March 2021. Accessed 13 April 2021. <https://tgldcdp.tg.org.au/viewTopic?topicfile=attention-deficit-hyperactivity-disorder&guidelineName=Psychotropic&topicNavigation=navigateTopic>

children, it is recommended to start on non-pharmacological interventions. This report focuses on pharmacological management.

In Australia, psychostimulants are considered the first-line pharmacological treatment for ADHD.^{2,3,5} Therapeutic Guidelines recommend that, with rare exceptions, stimulants (dexamfetamine, lisdexamfetamine and methylphenidate) should not be used in children aged younger than 6 years.³ Atomoxetine, a non-stimulant drug, is approved for use in children (over six years old), adolescents and adults with ADHD where treatment with stimulants is not suitable or tolerated.^{3,4} Guanfacine, a non-stimulant drug, is approved for children (over six years old) and adolescents (up to the age of 18).

In August 2017, guanfacine was registered for the management of ADHD in children 6-17 years old, as monotherapy where psychostimulants or atomoxetine are not suitable, not tolerated or have been shown to be ineffective; or as adjunctive therapy to psychostimulants (where there has been a sub-optimal response to psychostimulants).⁶

Dexamfetamine, lisdexamfetamine and methylphenidate are Schedule 8 medicines under the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP). Schedule 8 medicines have a high potential for abuse and dependence. The prescribing and supply of Schedule 8 medications are tightly regulated, and regulations vary between each state and territory.

Most Australian states and territories restrict the prescribing of psychostimulants for the treatment of ADHD to specialist medical practitioners, including psychiatrists, neurologists and paediatricians. These specialist prescribers are generally required to obtain prior authorisation from the relevant state or territory regulatory body for each patient. Prescribing of psychostimulants to patients under the age of 2 years is generally prohibited, and there are additional regulatory requirements to prescribe psychostimulants to patients aged between 2 to 3 years old.

State and territory government health pages should be checked for the most up to date regulatory information regarding psychostimulant prescribing.⁷

Previous utilisation analysis undertaken by DUSC did not consider the use of bupropion, modafinil, tricyclic antidepressants or clonidine as these medicines are not specifically TGA-indicated or R/PBS-subsidised for the treatment of ADHD. The utilisation of clonidine has been included in this analysis as the mechanism of action is similar to guanfacine and it is frequently used for the management of ADHD.⁸

⁵ Tonge, B. (2013). 'Principles for managing attention deficit hyperactivity disorder'. Australian Prescriber, 36:162-5.

⁶ Shire Australia Pty Ltd (2017), Product Information: Intuniv (Guanfacine hydrochloride). Approved 22 August 2017. Most recent amendment 26 March 2021. Accessed on: 13 April 2021, at: <https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2017-PI-02254-1&d=2018022716114622483>

⁷ A consolidated ADHD stimulant prescribing regulation and authorities overview can be found at <https://aadpa.com.au/adhd-stimulant-prescribing-regulations-authorities-in-australia-new-zealand>

⁸ Australian Medicines Handbook January 2021. Accessed 16 April 2021.

<https://amhonline.amh.net.au/chapters/cardiovascular-drugs/antihypertensives/other-antihypertensives/clonidine-cardiovascular>

Pharmacology

The exact mechanism of action of ADHD medications is not fully established but is thought to be due to modification of dopaminergic and noradrenergic activity in the brain.

Dexamfetamine, lisdexamfetamine and methylphenidate hydrochloride are central nervous system stimulants.^{5,9,10} Lisdexamfetamine¹¹ is a prodrug of dexamfetamine and is broken down into active dexamfetamine after ingestion.⁵ Atomoxetine is a selective noradrenaline reuptake inhibitor.¹² Guanfacine⁶ is a selective α_{2A} -adrenergic receptor agonist and was ATC classified as a cardiovascular drug similar to clonidine.¹³

Therapeutic Goods Administration (TGA) approved indications and PBS restrictions

Table 1 shows the TGA indications and PBS restricted uses of medicines used to manage ADHD.

Table 1: TGA indications and PBS restricted uses for ADHD medicines¹⁴

Drug	TGA indications	PBS restricted uses
Dexamfetamine	<ul style="list-style-type: none"> • Hyperkinetic behaviour disorders in children • Narcolepsy 	<ul style="list-style-type: none"> • ADHD • Narcolepsy
Methylphenidate IR	<ul style="list-style-type: none"> • ADHD • Narcolepsy 	<ul style="list-style-type: none"> • ADHD
Methylphenidate MR	<ul style="list-style-type: none"> • ADHD 	<ul style="list-style-type: none"> • ADHD in a patient diagnosed between ages 6 to 18, who require continuous coverage and has demonstrated a response to IR methylphenidate.
Atomoxetine	<ul style="list-style-type: none"> • ADHD as defined by the DSM-IV criteria for people aged ≥ 6 years. 	<ul style="list-style-type: none"> • ADHD as defined by the DSM-V criteria, diagnosed by a paediatrician or psychiatrist, in patients diagnosed between ages 6 to 18, who are contraindicated to or intolerant of stimulant treatment.

⁹ Aspen Pharma Pty Ltd, Product Information: Aspen Dexamfetamine Tablets. Approved 14 October 1991. Most recent amendment 10 December 2019. Accessed on: 13 April 2021, at:

<https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2017-PI-01667-1>

¹⁰ NOVARTIS Pharmaceuticals Australia Pty Limited, Product Information: RITALIN® 10/RITALIN® LA (methylphenidate). Approved 02 August 1991. Most recent amendment 14 August 2020. Accessed on: 13 April 2021, at:

<https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-03175-3>

¹¹ Takeda Pharmaceuticals Australia Pty Ltd, Product Information: VYVANSE (Lisdexamfetamine dimesilate) tablets. Approved 22 July 2013. Most recent amendment 29 October 2020. Accessed on: 16 April 2021.

<https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/PICMI?OpenForm&t=&q=lisdexamfetamine>

¹² Eli Lilly Australia Pty Limited (2018), Product Information: STRATERA® (atomoxetine hydrochloride). Approved 27 January 2004. Most recent amendment 06 May 2020. Accessed on: 13 April 2021, at:

<https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-04269-3>

¹³ Clonidine product information.

<https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/PICMI?OpenForm&t=&q=clonidine>

¹⁴ Sources: Therapeutic Goods Administration, Australian Register of Therapeutic Goods. Accessed 16 April 2021. Department of Health (2021) Schedule of Pharmaceutical Benefits. Effective 1 April 2021. Accessed 16 April 2021.

Drug	TGA indications	PBS restricted uses
Lisdexamfetamine	<ul style="list-style-type: none"> • ADHD treatment commenced by specialist • Moderate to severe Binge Eating Disorder in adults when non-pharmacological treatment is unsuccessful or unavailable. Must be commenced and managed by specialist. 	<ul style="list-style-type: none"> • ADHD in a patient diagnosed between ages 6 to 18, who require continuous coverage over 12 hours.
Guanfacine	<ul style="list-style-type: none"> • ADHD in children and adolescents aged 6-17 years old, as monotherapy (when stimulants or atomoxetine are not suitable, not tolerated or have been shown to be ineffective) or as adjunctive therapy to psychostimulants. 	ADHD as defined by the DSM-V criteria, diagnosed by a paediatrician or psychiatrist, in patients diagnosed between ages 6 to 17, who are contraindicated to or intolerant of stimulant treatment.

TGA product information box warnings

Dexamfetamine, lisdexamfetamine and methylphenidate have box warnings concerning drug dependence. They should be used cautiously in people with a history of drug or alcohol dependence. Chronic abuse may lead to tolerance, psychological dependence and abnormal behaviour.^{9,10,11} Supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

Atomoxetine has a box warning to monitor patients for suicidal thoughts and behaviours. Short-term placebo-controlled studies showed a positive signal for suicidal thoughts and behaviours in children aged 12 years and under.^{12,15}

Safety alerts

The TGA issued a safety alert for atomoxetine in November 2011 advising that the medication can cause clinically significant increases in heart rate and blood pressure in some patients and that its use is contraindicated in patients with symptomatic cardiovascular diseases, moderate to severe hypertension, or severe cardiovascular disorders, whose condition would be expected to deteriorate if they experienced increases in blood pressure or in heart rate.¹⁶

The TGA issued another safety alert for atomoxetine in October 2013¹⁷ advising the risk of suicidal ideation and behaviour in children and adolescents. The advice reinforced that while the risks of suicidal ideation and behaviour are well known, it is important that health

¹⁵ Therapeutic Goods Administration (2013), Atomoxetine and suicidality in children and adolescents. Accessed on: 09 February 2018, at: <https://www.tga.gov.au/publication-issue/medicines-safety-update-volume-4-number-5-october-2013#atomoxetine>

¹⁶ Therapeutic Goods Administration (2011), Atomoxetine (STRATTERA) - risk of increased blood pressure and/or heart rate. Accessed on 16 April 2021, at <https://www.tga.gov.au/alert/atomoxetine-strattera-risk-increased-blood-pressure-and-or-heart-rate>

¹⁷ Therapeutic Goods Administration (2013), Atomoxetine and suicidality in children and adolescents. Accessed on: 16 April 2021, at: <https://www.tga.gov.au/publication-issue/medicines-safety-update-volume-4-number-5-october-2013#atomoxetine>

professionals adequately inform parents and caregivers of the risks of suicidal ideation and behaviour in children and adolescents taking atomoxetine.

In October 2014, the TGA issued a safety alert advising health professionals that in very rare cases, treatment with methylphenidate may potentially lead to prolonged and sometimes painful erections.¹⁸

Dosage and administration

Treatment is usually commenced on dexamfetamine, lisdexamfetamine or the immediate release (IR) formulation of methylphenidate. Doses are started low and then up-titrated weekly to optimal doses.³

Patients taking methylphenidate IR may switch to long-acting methylphenidate once responsive and dose stabilised. Alternative treatments should be considered if the maximum stimulant dose has been reached and significant improvement in symptoms has not occurred after a month or unacceptable side effects have developed.⁴

There are no established guidelines for the length of time a child should be maintained on stimulants.

Full details on dosing and titration schedules can be found in the Product Information. The current Product Information (PI) and Consumer Medicine Information (CMI) are available from [the TGA \(Product Information\)](#) and [the TGA \(Consumer Medicines Information\)](#).

Date of listing on R/PBS

The dates of listing and changes to listing for these medicines are available in [Appendix A](#).

Current R/PBS listing and restriction details are available from the [PBS website](#).¹⁹

Relevant aspects of consideration by the Pharmaceutical Benefits Advisory Committee (PBAC)

The PBAC recommendations for all ADHD medicines listed prior to 2018 are provided in Appendix B. Most medicines have been recommended on a cost-minimisation basis to existing therapies.

Guanfacine (Intuniv®)

In July 2017, the PBAC recommended the listing of guanfacine on a cost-minimisation basis with atomoxetine for the treatment of patients diagnosed with ADHD between the ages of 6 and 17 years inclusive who are contraindicated or intolerant to stimulant therapy. The PBAC did not recommend the listing of guanfacine as monotherapy in patients who have failed to

¹⁸ Therapeutic Goods Administration (2014), Methylphenidate and priapism. Accessed on: 16 April 2021, at: <https://www.tga.gov.au/publication-issue/medicines-safety-update-volume-5-number-5-october-2014-0#methylphenidate>

¹⁹ Schedule of Pharmaceutical Benefits (Volume 1 – General Schedule). Accessed on: 15 April 2021 <https://www.pbs.gov.au/publication/schedule/2021/04/2021-04-01-general-volume-1.pdf> p.879

achieve an adequate response to stimulants as the evidence presented did not support a listing in that population.

The PBAC recommended that the indications for guanfacine should be the same as those of atomoxetine and that guanfacine should be a streamlined authority.

The PBAC advised that guanfacine should not be treated as interchangeable on an individual basis with any other drugs and that it is not suitable for prescribing by nurse practitioners.²⁰

In July 2018, the PBAC recommended the listing of guanfacine, as a General Schedule Authority Required (Streamlined) benefit, as add-on therapy in conjunction with optimised stimulant therapy, for ADHD in patients experiencing residual moderate to severe ADHD symptoms. The PBAC was satisfied that guanfacine (as add-on therapy) provides, for some patients, a significant improvement in efficacy over placebo in patients receiving optimised stimulant therapy and who are experiencing residual symptoms.

The PBAC noted the requested restriction and sponsor comments in its Pre-PBAC response, and considered it would be appropriate for the restriction to allow some flexibility for clinicians to individually evaluate patient responses to stimulant therapy and determine whether they may benefit from guanfacine add-on therapy. Therefore, the PBAC considered the proposed criteria defining ADHD symptoms was appropriate as requested.

The PBAC noted the resubmission offered a lower price for the add-on setting, which resulted in a lower ICER of \$15,000/QALY - \$45,000/QALY. The PBAC considered the ICER was high for this population; however was acceptable based on the clinical need for additional therapies in patients who experience residual symptoms whilst on optimised stimulant therapy.

The PBAC considered there was some uncertainty in the utilisation and financial estimates, in particular concerning the off-label use of clonidine in ADHD and of the extent of potential substitution. The PBAC agreed a risk share arrangement (RSA) with a hard cap on PBS expenditure based on the submission estimates would be a reasonable method to mitigate the risk of higher than expected use of guanfacine.²¹

In February 2021, the DUSC noted that guanfacine has been ATC classified as a cardiovascular drug but is TGA registered only for ADHD. DUSC also noted that utilisation of guanfacine has been higher than predicted.

Copies of the PBAC Meeting Outcomes and Public Summary Documents are available on the [PBAC Meetings](#) website.

Previous reviews by the DUSC

DUSC reviewed this therapeutic area in October 2010, as part of the 24 month Predicted versus Actual (PvA) review of atomoxetine. DUSC noted that there was lower than expected utilisation of atomoxetine, which may have been influenced by the listing of Concerta® three

²⁰ <https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2017-07/files/guanfacine-hydrochloride-psd-%20july-2017.pdf>

²¹ <https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2018-07/files/guanfacine-psd-july-2018.pdf>

months before the listing of atomoxetine and possible over-estimation of the number of patients with the required contraindications to stimulants to meet the restriction.²²

DUSC reviewed ADHD medicines in June 2012, with further analyses requested by DUSC considered in October 2012.²³ When considering all people treated with ADHD medicines, highest use was in children aged 10 years. DUSC noted that there was steady growth in the utilisation of ADHD medicines between January 2005 and October 2011. PBS benefits paid for ADHD medicines in November 2010–October 2011 totalled around \$24.6 million, up 4.2% from the previous year. The highest cost medicine to the PBS was Concerta® at \$11.2 million, followed by atomoxetine at \$6.2 million, despite its low utilisation.¹⁸

The DUSC reviewed ADHD medicines in June 2015,²⁴ finding that there was steady growth in the utilisation of ADHD medicines between 2010 and 2014. Over 875,000 prescriptions were dispensed at a cost to the PBS of approximately \$30 million in 2014, with methylphenidate being the most commonly used medication. Rates of prescribing varied across states and territories, with rates of treatment in school-aged children being highest in the ACT, NSW and Queensland. Rates of treatment in adults were highest in Western Australia. The majority of prescriptions were written by a specialist, usually a paediatrician or psychiatrist as most Australian states and territories restrict the prescribing of methylphenidate and dexamfetamine for the treatment of ADHD to specialist medical prescribers.

The DUSC reviewed ADHD medicines again in May 2018.²⁵ Key findings over the five year period of 2013-2017 were:

- The number of patients treated with R/PBS medicines for ADHD increased at a yearly average growth rate of 9.9%, with the number of prescriptions increasing at similar rates.
- The most commonly used medicine in terms of prevalent patients is the modified-release formulation of methylphenidate.
- More males than females were treated, although the ratio is decreasing over time.
- Children aged 6-12 years old account for over 40% of R/PBS ADHD medicines supplied.

A snapshot of medicine use in 2017 shows the same picture as the June 2015 review with:

- Rates of prescribing varying across states and territories, with rates of treatment in school-aged children being highest in the ACT, NSW and Queensland. Rates of treatment in adults were highest in Western Australia.

²² Drug Utilisation Sub-Committee. DUSC Predicted versus Actual analysis of atomoxetine. Canberra: Australian Department of Health: 2010. Unpublished.

²³ Drug Utilisation Sub-Committee. DUSC Reviews of ADHD Drugs June and October 2012. Canberra: Australian Department of Health: 2010. Unpublished.

²⁴ Drug Utilisation Sub-Committee. ADHD Utilisation Analysis October 2015. Canberra: Australian Department of Health. Accessed on 25 March 2021, at: <http://www.pbs.gov.au/pbs/industry/listing/participants/public-release-docs/2015-06/attention-deficit-hyperactivity-disorder-2015-06-prd>

²⁵ Drug Utilisation Sub-Committee. ADHD Utilisation Analysis May 2018. Canberra: Australian Department of Health. Accessed on 25 March 2021, at: <https://www.pbs.gov.au/pbs/industry/listing/participants/public-release-docs/2018-05/attention-deficit-hyperactivity-disorder>

- The majority of prescriptions were written by paediatricians or psychiatrists as most Australian states and territories restrict the prescribing of methylphenidate, lisdexamfetamine and dexamfetamine for the treatment of ADHD to specialists.

Methods

PBS and RPBS (R/PBS) prescription data for PBS-listed ADHD medicines (dexamfetamine, methylphenidate, atomoxetine, lisdexamfetamine and guanfacine) and clonidine (Unrestricted PBS listing) were extracted from the Services Australia prescription database for the period April 2012 to February 2021 inclusive, based on the date that the prescription was supplied. Data for this period includes all R/PBS supplies regardless of whether a subsidy was paid; i.e. both over co-payment and under co-payment. As dexamfetamine is PBS-listed for both ADHD and narcolepsy, the prescription data for dexamfetamine was merged with the authority approvals database and limited by the ADHD authority restriction number to obtain only the supplies related to ADHD.

The R/PBS prescription data were used to determine the number of prescriptions supplied, R/PBS expenditure, age, sex, state/territory of residence and prescriber type. These prescription data were also used to count the number of patients, both incident (new to pharmacological treatment) and prevalent (number treated) in each time period. The number of prevalent patients was determined by counting the number of people supplied at least one PBS prescription using person-specific numbers (non-identifying) in the data for the specified time periods. Patient initiation date was defined as the date of supply of the first PBS or RPBS prescription of the ADHD medicine (since April 2012).

An analysis of scripts per patient in the 12 months after initiation of PBS guanfacine was also performed. This analysis was limited to patients that initiated from September 2018 to the end of February 2020, as this cohort of patients had at least 12 months of follow-up data after initiation.

Clonidine was included in the data extract to examine if it was being used to treat ADHD.

As these analyses use date of supply prescription data, there may be small differences compared with publicly available Services Australia Medicare date of processing data. These data only include subsidised R/PBS prescriptions with prescriptions under the patient co-payment not included.

Results

Analysis of drug utilisation

Overall utilisation

The number of R/PBS prescriptions for ADHD medications supplied per calendar year since 2013 is shown in Figure 1.

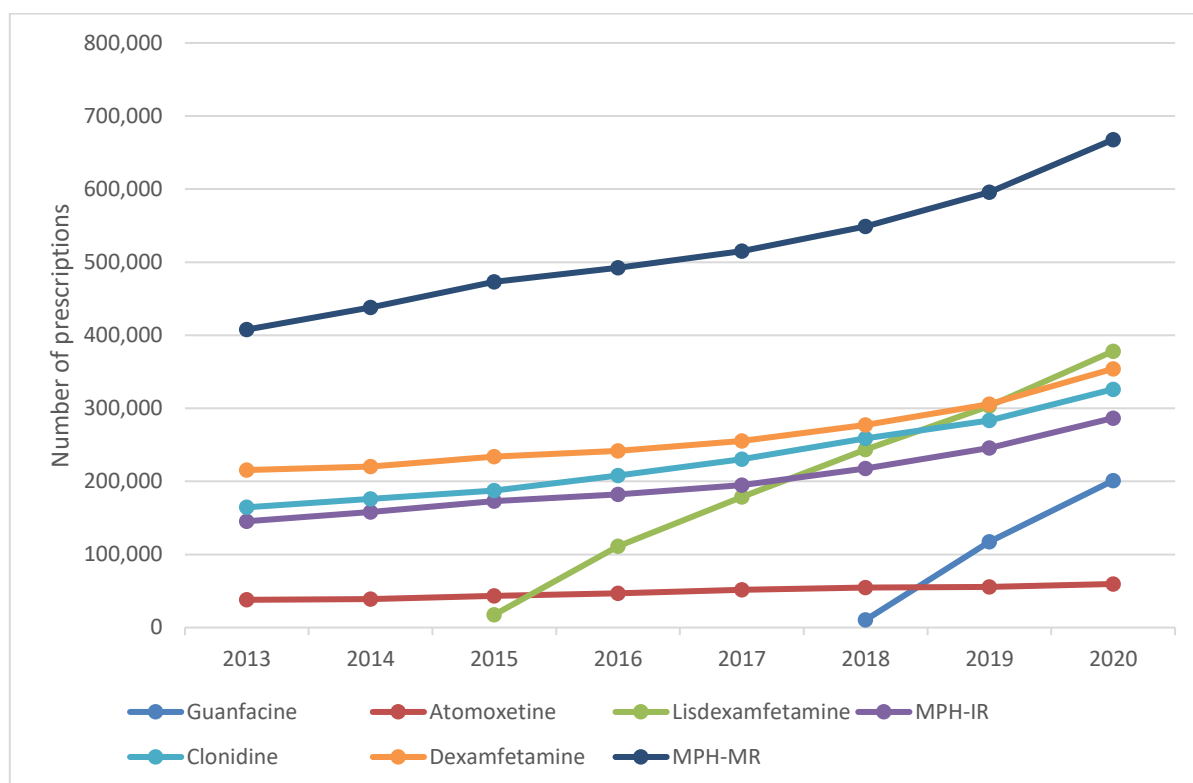


Figure 1: Number of PBS/RPBS ADHD prescriptions supplied per year

Source: Services Australia prescriptions database, extracted March 2021

*MPH-MR consists of both Concerta® and Ritalin LA®

Figure 1 shows an overall increase in the rate of growth in R/PBS ADHD prescriptions supplied during 2013 to 2020. The average annual growth rate during this period was 14%, however the growth rate from 2018-2019 and 2019-2020 increased to 20% (Table 1). This substantial increase might be due to the addition of guanfacine on the R/PBS in September 2018. Figure 1 includes the prescription count of clonidine however the prescription count of clonidine includes prescriptions for non-ADHD related indications.

Estimated use of clonidine for ADHD

In 2019, 50,814 patients initiated ADHD medication therapy. Of these patients, 7,325 (14.4%) also initiated clonidine at some time up until the end of February 2021 (either as the first medication or subsequently). In addition there were 20,497 patients that initiated clonidine in 2019 and had no ADHD medicines up until the end of February 2021. Of these patients, 4,079 were ≤ 19 years and so likely to be ADHD patients even though they were not on any medicines that were R/PBS-listed for ADHD.

It appears that clonidine is being used in significant numbers as an ADHD medication.

Table 1: ADHD drug prescription count by year.

Drug Name / Prescription Count	2013	2014	2015	2016	2017	2018	2019	2020	Total
Guanfacine						10,490	117,409	201,200	329,099
Atomoxetine	38,010	39,169	43,404	46,811	51,697	54,779	55,524	59,649	389,043
Lisdexamfetamine			17,635	111,438	178,853	243,491	303,277	378,237	1,232,931
MPH-IR	145,479	158,092	172,920	182,395	194,836	217,797	245,912	286,698	1,604,129
Dexamfetamine	215,548	220,287	233,804	241,615	255,218	277,246	305,920	354,139	2,103,777
MPH-MR	407,798	438,178	472,911	492,472	515,290	548,959	595,728	667,803	4,139,139
Total	806,835	855,726	940,674	1,074,731	1,195,894	1,352,762	1,623,770	1,947,726	9,798,118
Growth from previous year (%)		6%	10%	14%	11%	13%	20%	20%	

Source: Services Australia prescriptions database, extracted March 2021

Patients initiating and prevalent to ADHD therapy

The total number of new patients starting ADHD medicines (initiating) and the number of patients treated with R/PBS-listed ADHD medicines each quarter (prevalent) are shown in Figure 2.

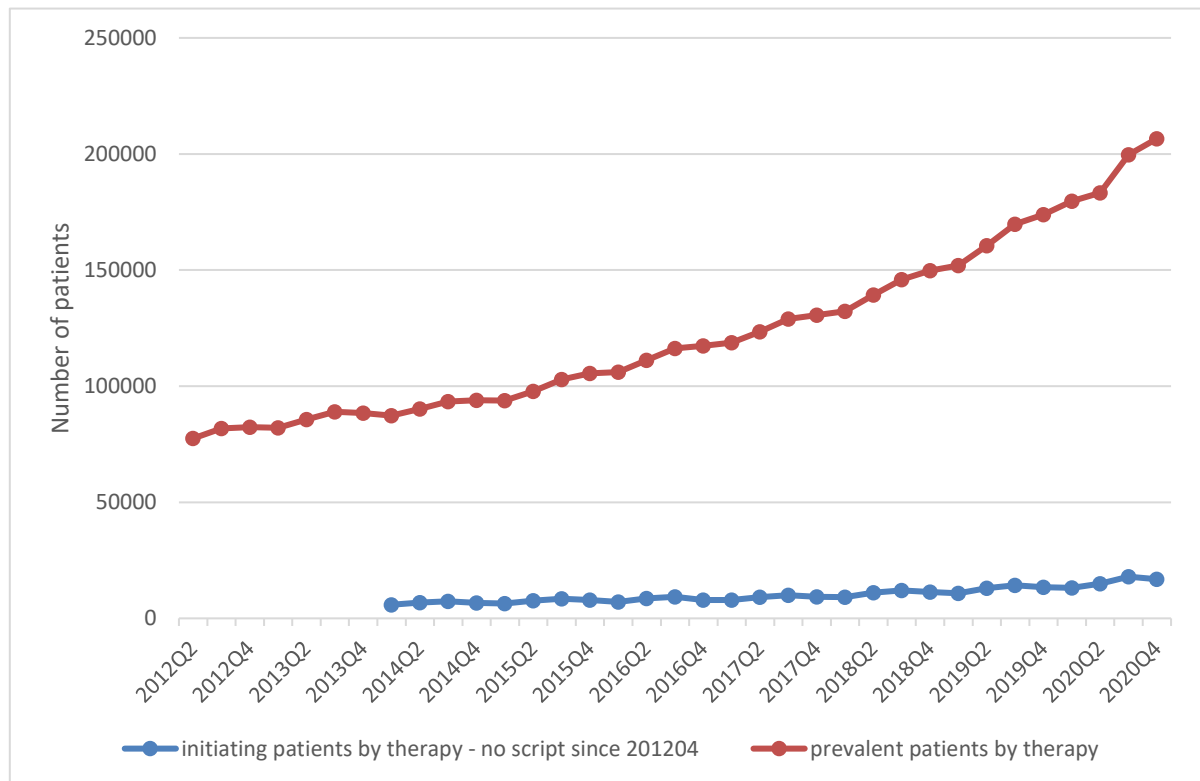


Figure 2: Prevalent and initiating patients receiving ADHD therapy per quarter

Source: Services Australia prescriptions database, extracted March 2021

The number of new patients tends to increase during the year reaching a peak in the third quarter of each year.

The total number of patients on ADHD medicines has increased over time. The average annual growth rate from 2013 to 2020 was 12.6%, while the number of initiating patients had an average annual growth rate of 15.5% over 2014 to 2020.

Figure 3 shows the number of initiating patients per quarter by their first ever R/PBS-subsidised ADHD medicine supplied in 2014 to 2020.

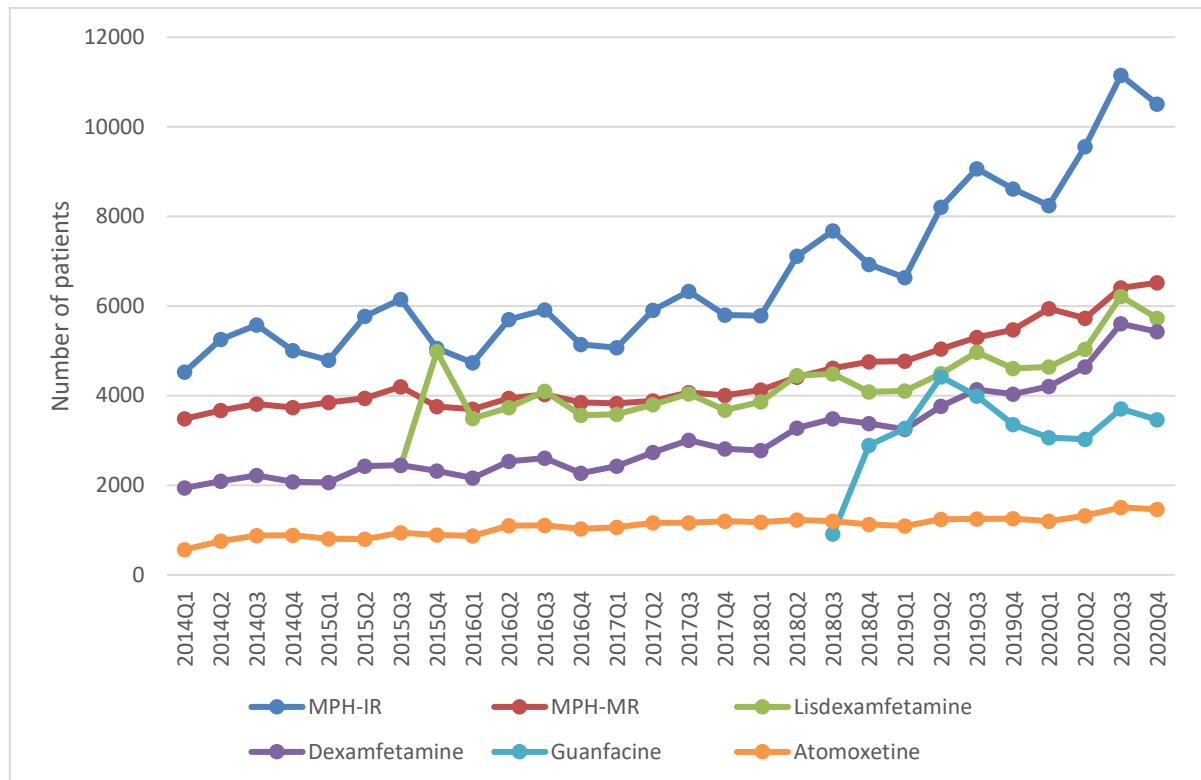


Figure 3: Number of patients initiating ADHD therapy by initiating medicine (i.e. first ever prescription for an ADHD medicine, not including clonidine)

Source: Services Australia prescriptions database, extracted March 2021. Initiating patients are determined as having no ADHD prescriptions since April 2012.

*MPH-MR Consists of both Concerta® and Ritalin LA®

The majority of initiating patients (Figure 3) commence R/PBS ADHD therapy with short-acting medicines, particularly short-acting methylphenidate. There has been considerable uptake in lisdexamfetamine since its R/PBS listing in September 2015. Guanfacine has overtaken atomoxetine as the first initiated non-stimulant initial ADHD medication. In 2019 and 2020, guanfacine accounted for approximately 14% and 11% of initial ADHD medicines supplied to new patients respectively.

Figure 4 depicts the number of prevalent patients per quarter for each ADHD medicine supplied from 2012 to 2020. In Figure 4, a patient may be supplied more than one ADHD medicine in the same quarter.

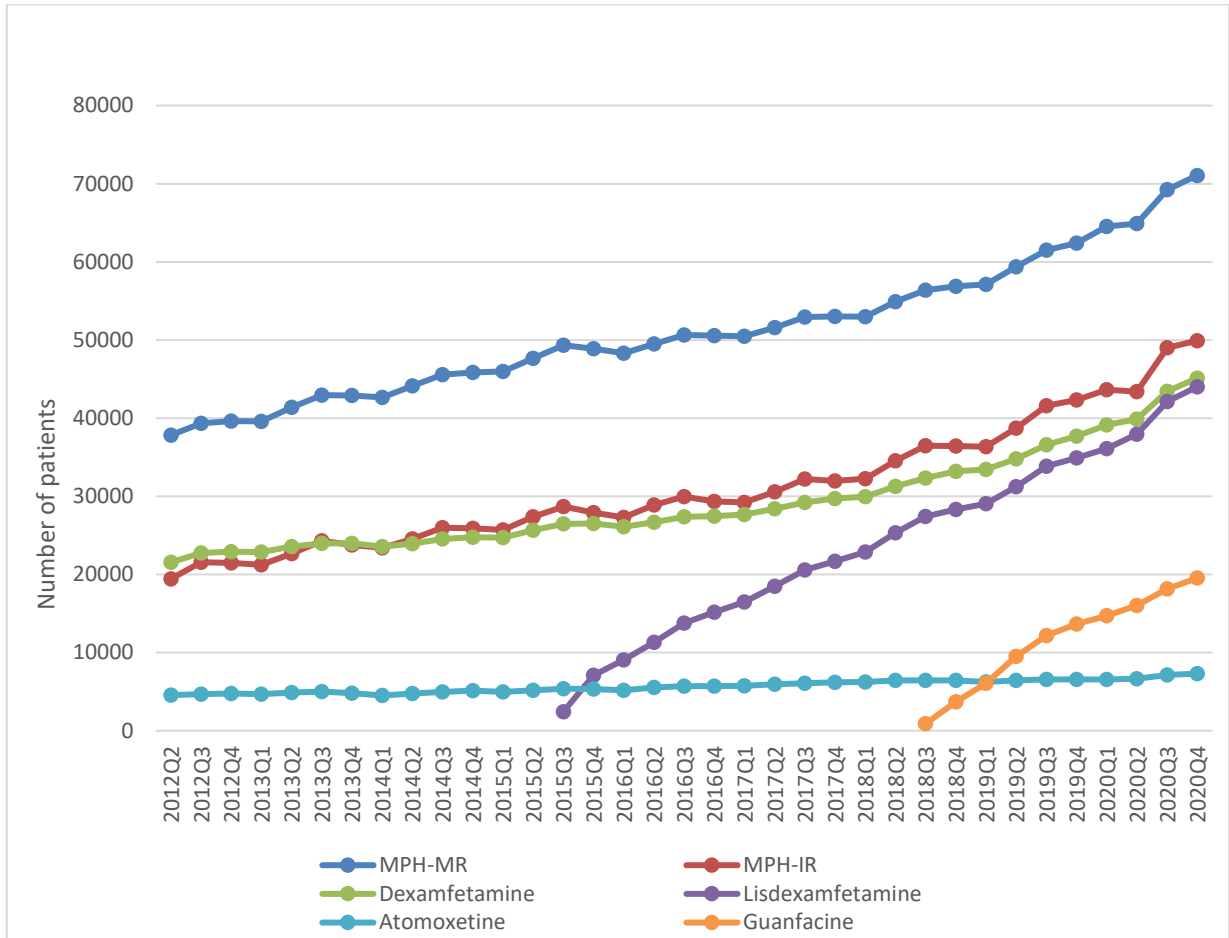


Figure 4: Prevalent patients treated with each ADHD medicines per quarter

Source: Services Australia prescriptions database, extracted March 2021

*MPH-MR Consists of both Concerta® and Ritalin LA®

When considering the number of prevalent patients treated across all years (Figure 4 and Table 2), long-acting methylphenidate was the most commonly used ADHD medicine. Atomoxetine is used in a small proportion of patients and has shown very low growth, which is surprising considering the substantial uptake of guanfacine since its R/PBS listing in September 2018. Overall, the data shows a steady increase in the number of ADHD patients, with a much higher increase starting from 2019, with a growth rate of 19% over 2019 and 2020. This indicates that the listing of guanfacine on the R/PBS has added to the use of ADHD medications and not substituted for prescribed medications. As expected, the patient growth rates correlates to the prescriptions growth rate (Table 1).

Table 2: Prevalent patients treated with each ADHD medicines per year

Drug Name / Patient Count	2013	2014	2015	2016	2017	2018	2019	2020
MPH-MR	54,395	58,059	62,694	65,395	68,101	72,930	79,821	90,253
MPH-IR	42,343	45,583	50,233	52,584	56,535	64,412	73,997	87,735
Dexamfetamine	32,003	33,200	35,704	37,634	40,620	45,358	51,567	61,784
Lisdexamfetamine			7,424	20,809	29,230	37,899	45,972	57,021
Atomoxetine	7,434	7,516	8,151	8,996	9,900	10,436	10,735	11,628
Guanfacine						3,805	18,030	25,580
Therapy Total*	112,605	119,561	132,204	147,310	163,831	186,411	215,858	334,001
Growth from previous year (%)		6%	11%	11%	11%	14%	16%	18%

Source: Services Australia prescriptions database, extracted March 2021

* Therapy total is less than the sum of components as patients are only counted once even if they are prevalent to more than one ADHD medication.

Number of patients by age and gender

The number of patients treated with R/PBS-listed medicines for ADHD is shown in Figure 5 and Tables 2, 3 and 4. The data is presented as the number of patients initiating R/PBS ADHD therapy (Table 3) from 2014 to 2020 and prevalent patients (Table 4) from 2013 to 2020 by age group and gender. Figure 5 shows a snapshot of the prevalent patient distribution by age group and sex in 2020.

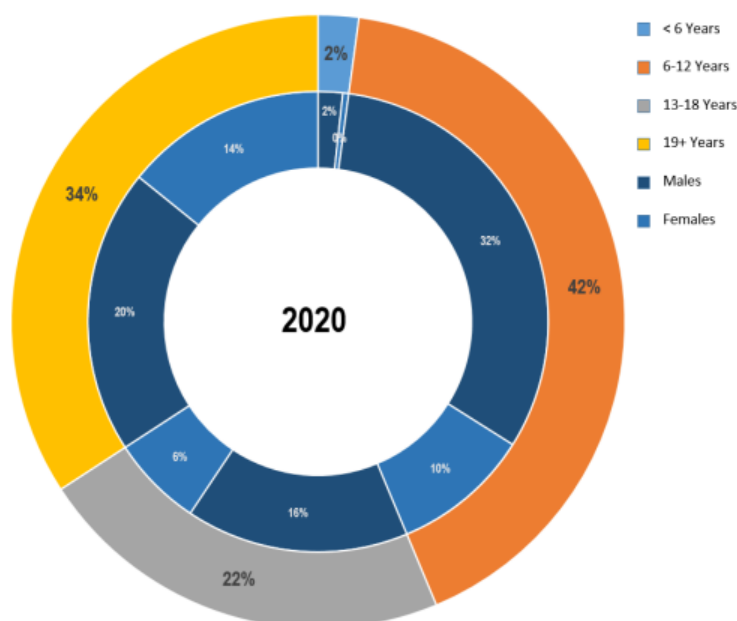


Figure 5: Prevalent patients treated with R/PBS-listed ADHD medicines in 2020 by age group and sex.

Source: Services Australia prescriptions database, extracted March 2021.

Table 3. Number of patients initiating R/PBS-listed ADHD medicine therapy by age group and gender per calendar year

	2014	2015	2016	2017	2018	2019	2020
<6 years male	1,603	1,646	1,796	1,990	2,435	2,820	3,131
<6 years female	357	451	471	499	513	691	817
6-12 years male	9,957	11,719	12,608	13,616	16,174	18,477	20,151
6-12 years female	2,930	3,388	3,753	4,310	5,375	6,326	7,461
13-18 years male	2,536	2,712	2,719	3,041	3,539	4,392	5,344
13-18 years female	1,209	1,341	1,434	1,637	2,177	2,840	4,373
19+ years male	5,007	5,510	6,166	6,573	7,878	9,007	11,482
19+ years female	3,034	3,568	3,970	4,564	5,412	6,864	10,100
Unknown	17	8	5	<5	<5	-	6
Total New patients	26,650	30,343	32,922	36,234	43,505	51,417	62,866
% growth from previous year		14%	8%	10%	20%	18%	22%

Source: Services Australia prescriptions database, extracted March 2021. Unknown denotes age and sex not available in the data. Table 4. Number of prevalent patients treated with R/PBS-listed ADHD medicines by age group and gender per calendar year.

Table 4. Number of prevalent patients treated with PBS-listed ADHD medicines by age group and gender per calendar year

	2013	2014	2015	2016	2017	2018	2019	2020
<6 years male	2,226	2,277	2,334	2,518	2,807	3,319	3,873	4,395
<6 years female	521	516	620	654	676	682	894	1,055
6-12 years male	38,216	40,869	45,506	50,727	55,878	63,239	71,894	81,209
6-12 years female	9,716	10,472	11,672	13,312	15,197	17,897	21,113	24,857
13-18 years male	20,914	21,385	22,893	24,520	26,893	29,750	34,273	39,984
13-18 years female	6,074	6,364	7,032	7,785	8,740	10,214	12,473	16,450
19+ years male	21,899	23,498	26,144	29,727	32,980	37,518	43,012	51,032
19+ years female	12,962	14,107	15,923	18,051	20,627	23,748	28,295	36,204
Unknown	77	73	80	16	32	44	31	21
Total patients	112,605	119,561	132,204	147,310	163,831	186,411	215,858	255,208
% growth from previous year	-	6%	11%	11%	11%	14%	16%	18%

Source: Services Australia prescriptions database, extracted March 2021. Unknown denotes age and sex not available in the data.

Children aged 6-12 years constituted 42% of all patients treated with ADHD medicines from 2013 to 2020. In addition, over the same period, approximately two thirds of patients supplied R/PBS ADHD medicines were less than 18 years of age.

The ratio of males to females receiving an ADHD medicine varied across the age brackets with the least difference in treatment rates occurring in adults (19+).

Figure 6 depicts the age distribution of patients new to R/PBS-subsidised ADHD therapy in 2020 by the first ever ADHD medicine they were supplied. Figure 7 shows the age distribution

for all patients supplied an ADHD medicine in 2020 by medicine. In Figure 7, patients may be double counted if they are supplied more than one ADHD medicine in the same year.

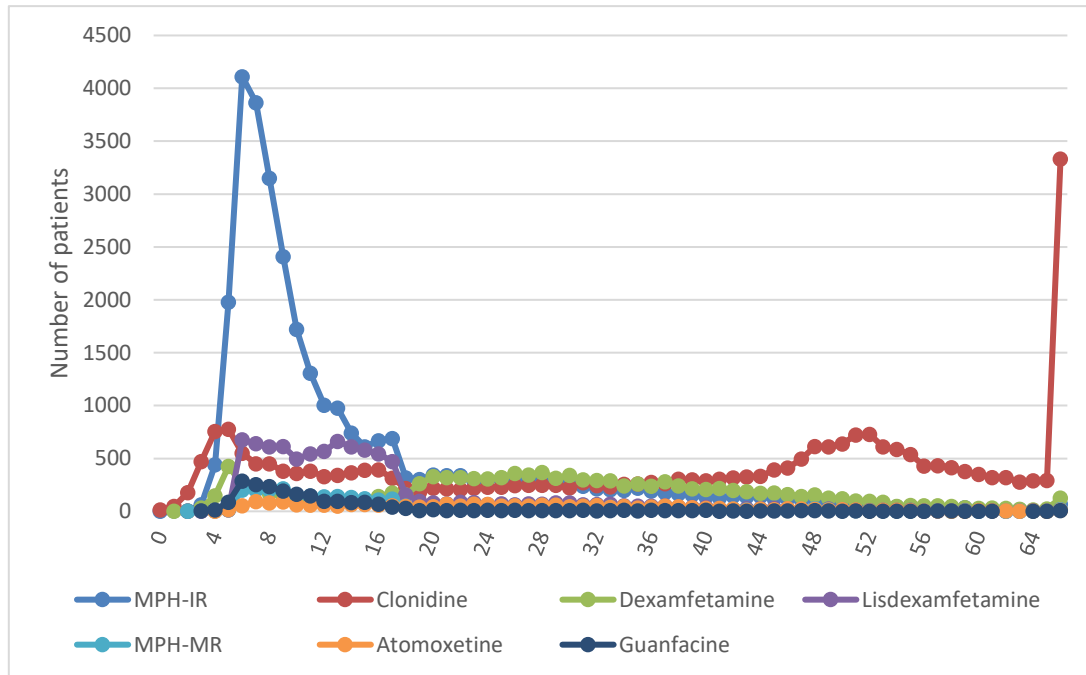


Figure 6: Age distribution of patients new to ADHD therapy by first ever ADHD medicine or clonidine supplied in 2020

Source: Services Australia prescription database, extracted March 2021. Initiating patients are determined as having no ADHD prescriptions since April 2012.

*MPH-MR Consists of both Concerta® and Ritalin LA®

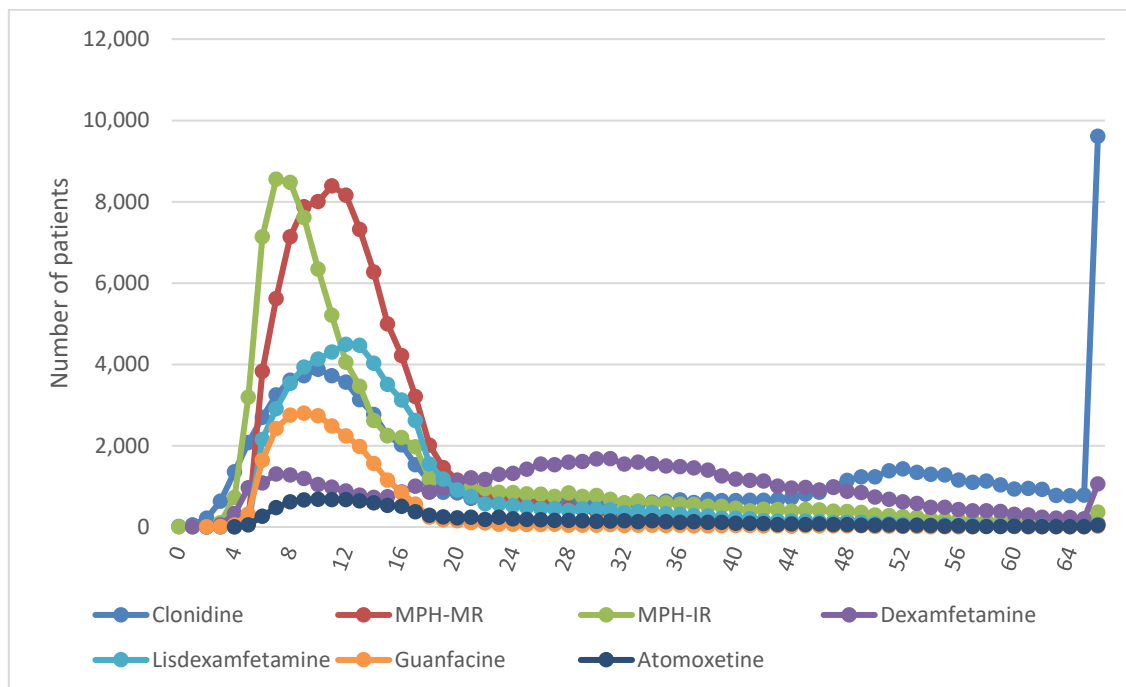


Figure 7: Age distribution of prevalent patients by ADHD medicine or clonidine in 2020

Source: Services Australia prescriptions database, extracted March 2021

*MPH-MR Consists of both Concerta® and Ritalin LA®

In children and adolescents, the most common initiating medicine for ADHD is short-acting methylphenidate followed by clonidine and lisdexamfetamine (Figure 6). The use of clonidine in younger patients is a good indication of off-label use to treat ADHD. Both short-acting methylphenidate and long-acting methylphenidate formulations are the most common continuing ADHD treatments in school-aged children (Figure 7). This indicates that children either switch therapy from short-acting to long-acting formulations or that long-acting formulations are added to short-acting therapy. Similar to initiating patients, clonidine use remains high in continuing patients.

In adults commencing R/PBS-subsidised therapy for the first time, dexamfetamine is the most common medicine, followed by short-acting methylphenidate (Figure 6). Dexamfetamine is most commonly used in all adults receiving ADHD therapy over the age of 21 (Figure 7).

Prescribers

Each State and Territory law stipulates the conditions under which medical practitioners are able to prescribe ADHD medicines.¹

Figure 8 shows the type of prescribers for the initiating prescription for each R/PBS ADHD medicine or clonidine supplied in 2020.

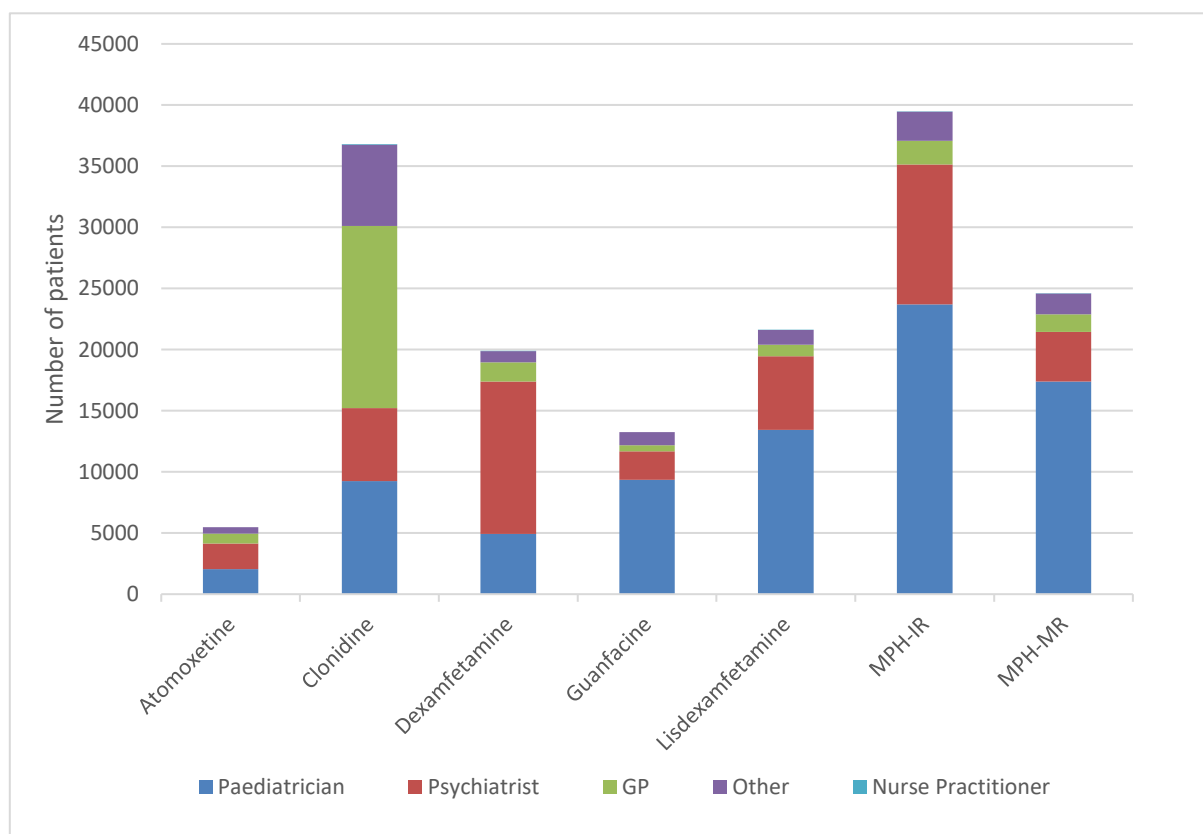


Figure 8: Prescriber type for patients initiating ADHD medicines or clonidine in 2020

Source: Services Australia prescriptions database, extracted April 2021

*MPH-MR Consists of both Concerta® and Ritalin LA®

^a initial prescription = first prescription for patients who received their first R/PBS ADHD medicine in 2020

The initial prescriber for commencing an ADHD medicine is influenced by state and territory regulations. The initial prescriber type for initiating ADHD medicines is also influenced by the age of the patient.

For first prescriptions of lisdexamfetamine, methylphenidate and guanfacine, a large proportion of initial prescribers were paediatricians. Clonidine also had a large proportion of paediatricians as the initial prescribers. As the age distribution of lisdexamfetamine and methylphenidate use were more common in adults under 18 years (Figure 6), paediatricians are more likely to be involved in the management of ADHD.

First prescriptions of dexamfetamine were more commonly prescribed by psychiatrists. As the age distribution of dexamfetamine use were more common in adults over 18 years (Figure 6), psychiatrists are more likely to be involved in the management of ADHD.

Utilisation by State/Territory

Figure 9 shows the number of people supplied ADHD medicines (excluding clonidine) per 1,000 population by therapy in 2020, broken down by age and patient state/territory. Figure 9 does not double count patients who are on more than one ADHD medication.

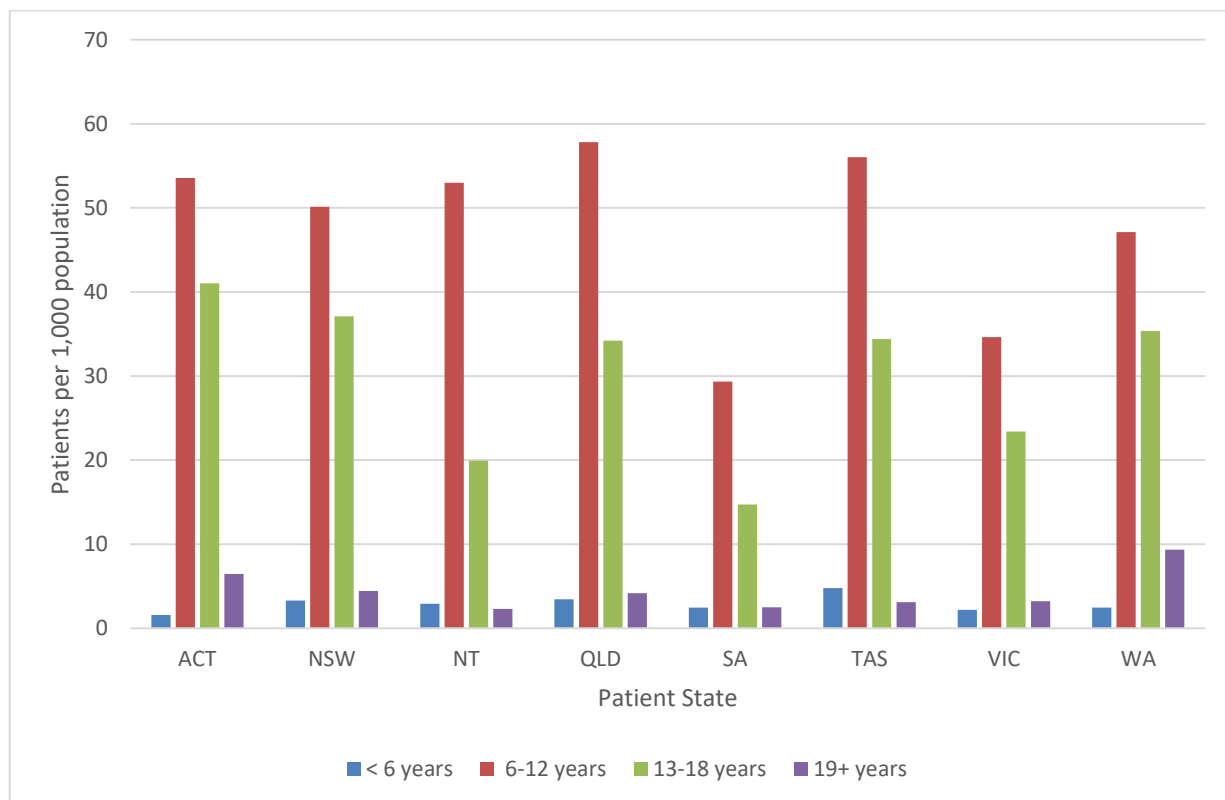


Figure 9: Number of people supplied an ADHD medicine (excluding clonidine) per 1000 population in 2020 by patient state/territory and age group (age group specific rate)

Source: Services Australia prescriptions database, extracted March 2021, based on 2020 ABS estimated residential population data

Table 5. Number of people supplied an ADHD medicine (excluding clonidine) per 1000 population by state/territory and age group 2014-2020

Age Group	State / Territory	2014	2015	2016	2017	2018	2019	2020
< 6 years	ACT	1	1.04	0.84	0.91	1.3	1.48	1.6
	NSW	1.9	1.97	2.02	2.1	2.41	2.91	3.28
	NT	0.87	1.35	1.43	1.48	2.03	2.83	2.92
	QLD	1.86	2	2.1	2.35	2.53	2.96	3.46
	SA	1.1	1.05	0.92	1.2	1.24	1.75	2.44
	TAS	2.12	1.7	1.81	3.17	3.17	3.78	4.79
	VIC	1.06	1.12	1.27	1.34	1.7	1.99	2.18
	WA	1.03	1.16	1.44	1.53	1.76	2.08	2.46
6-12 years	ACT	26.71	29.15	32.46	34.43	39.83	47.25	53.56
	NSW	30.45	32.7	34.93	36.78	40.35	44.69	50.14
	NT	15.52	17.88	24.04	30.38	36.33	42.18	52.98
	QLD	32.43	35.33	38.54	41.62	46.36	51.98	57.81
	SA	13.84	14.76	16.02	17.79	20.91	24.38	29.33
	TAS	26.33	27.79	30.63	34.56	39.77	46.72	56.03
	VIC	17.18	19.07	21.16	23.32	26.62	30.64	34.64
	WA	22.4	25.46	28.87	32	36.43	41.63	47.12
13-18 years	ACT	15.57	17.58	19.55	23.15	28.07	33.09	41.02
	NSW	21.34	22.8	24.23	25.83	27.94	31.97	37.09
	NT	8.62	9.52	9.93	11.08	13.43	16.9	19.94
	QLD	17.31	19.06	20.41	22.29	25.01	28.67	34.21
	SA	7.27	7.29	7.97	8.87	9.97	11.57	14.74
	TAS	17.69	18.3	20.2	22.14	24.45	28.52	34.39
	VIC	10.94	11.89	13.03	14.68	16.54	19.39	23.4
	WA	16.57	17.97	19.69	21.64	25.14	29.32	35.34
19+ years	ACT	2.67	2.82	3.07	3.46	4.09	4.92	6.47
	NSW	2.07	2.28	2.55	2.83	3.23	3.73	4.45
	NT	1.13	1.27	1.36	1.54	1.87	2.08	2.3
	QLD	1.89	2.14	2.46	2.77	3.1	3.5	4.17
	SA	1.22	1.29	1.49	1.62	1.8	2.01	2.48
	TAS	0.99	1.17	1.54	1.94	2.04	2.39	3.12
	VIC	1.27	1.42	1.61	1.82	2.11	2.53	3.21
	WA	5.43	5.87	6.36	6.74	7.3	8.07	9.35

Source: Services Australia prescriptions database, extracted March 2021, based on 2020 ABS estimated residential population data

Table 5 and Figure 10 show the increase use of ADHD medication since 2014 across all state and territories and age groups.

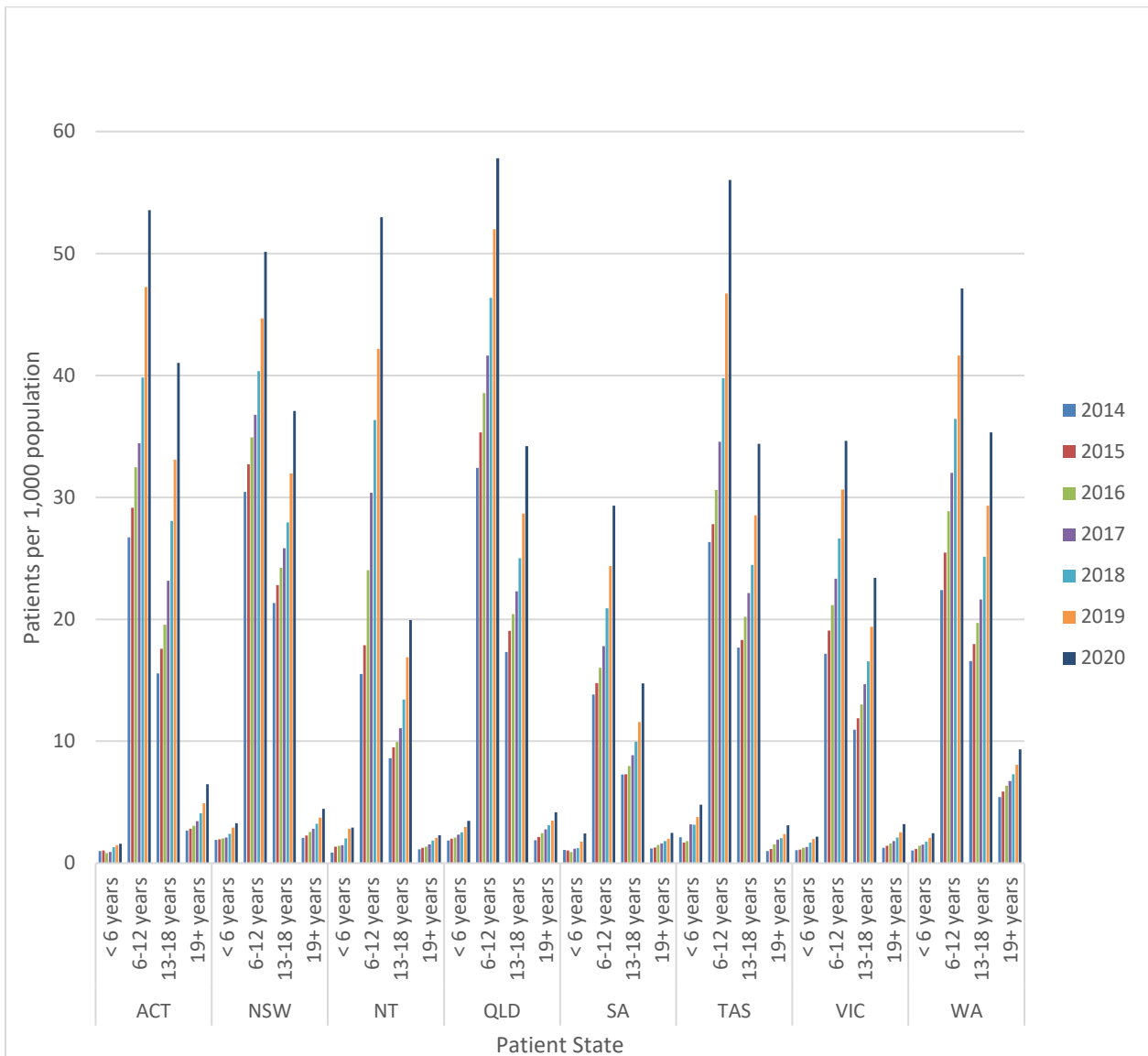


Figure 10: Number of people supplied an ADHD medicine (excluding clonidine) per 1000 population by state/territory and age group 2014-2020

Source: Services Australia prescriptions database, extracted March 2021, based on 2020 ABS estimated residential population data

For children under 6 years, the rate of ADHD medicine supply was low, ranging from 1.6/1000 population in the ACT to 4.79/1000 population in Tas.

The rate of ADHD medicine supply in the 6-12 year age group was highest in QLD (57.81/1000 population), closely followed by Tas (56.03/1000 population), with SA having the lowest rate amongst this age group (29.33/1000 population). The rate of ADHD medicine supply in adolescents (13-18 year olds) was highest in the ACT (41.02/1000 population) and lowest in SA (14.74/1000 population). For adults, the rate of supply of ADHD medicine was much higher in WA (9.35/1000 population) than all other states and territories, which ranged from 2.3-6.47/1000 population. This was consistent with the findings in previous DUSC reports.

Figures 11 and 12 depict the number of people supplied ADHD medicines per 1,000 population in 2020 for patients under the age of 19 and those 19 and over, respectively. The figures are presented by medicine and patient state/territory, and are adjusted to account for the population size and age distribution in each state/territory in 2020. The high use of clonidine in the under 19 age group (Figure 11) indicates an even greater proportion of young people are being treated for ADHD or side effects of ADHD medications, than what is currently recognised.

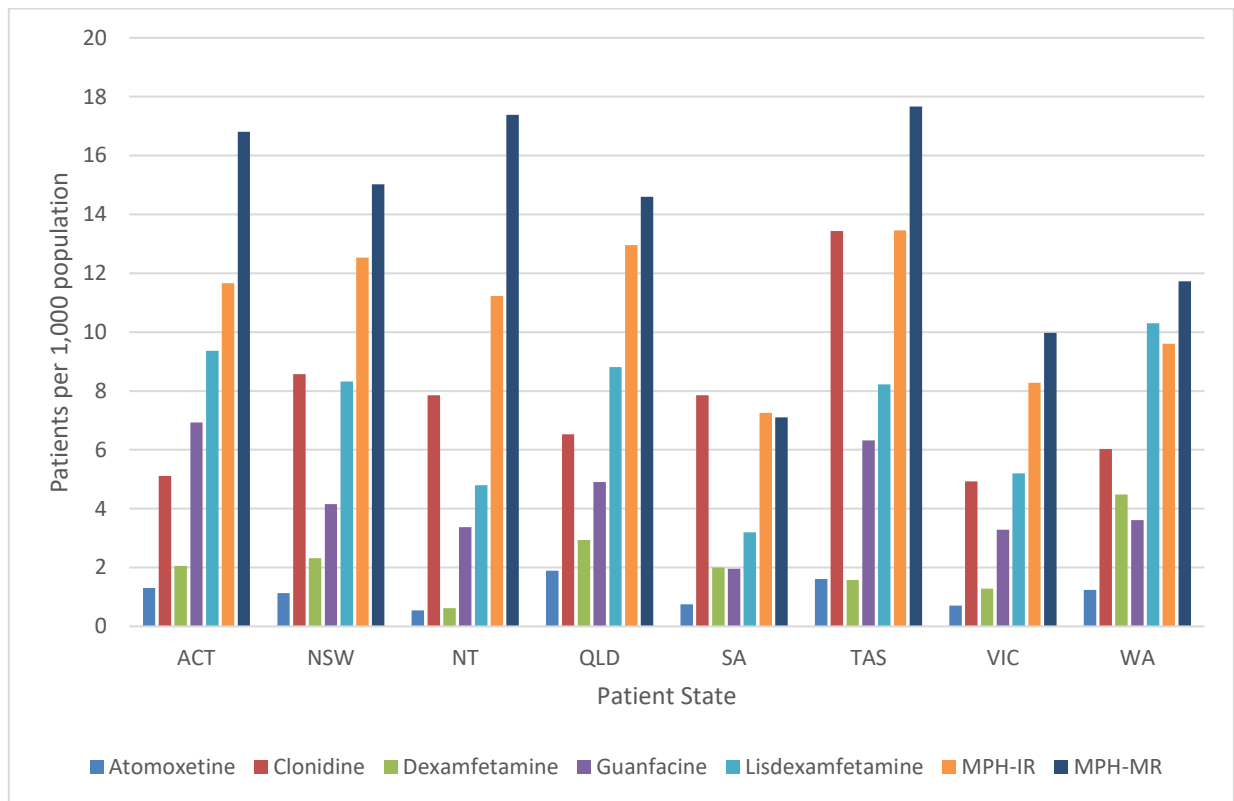


Figure 11: Number of people aged ≤18 years supplied an ADHD medicine or clonidine per 1,000 population in 2020 by patient state/territory and medicine (age group specific rate)

Source: Services Australia prescriptions database, extracted March 2021, based on 2020 ABS estimated residential population data

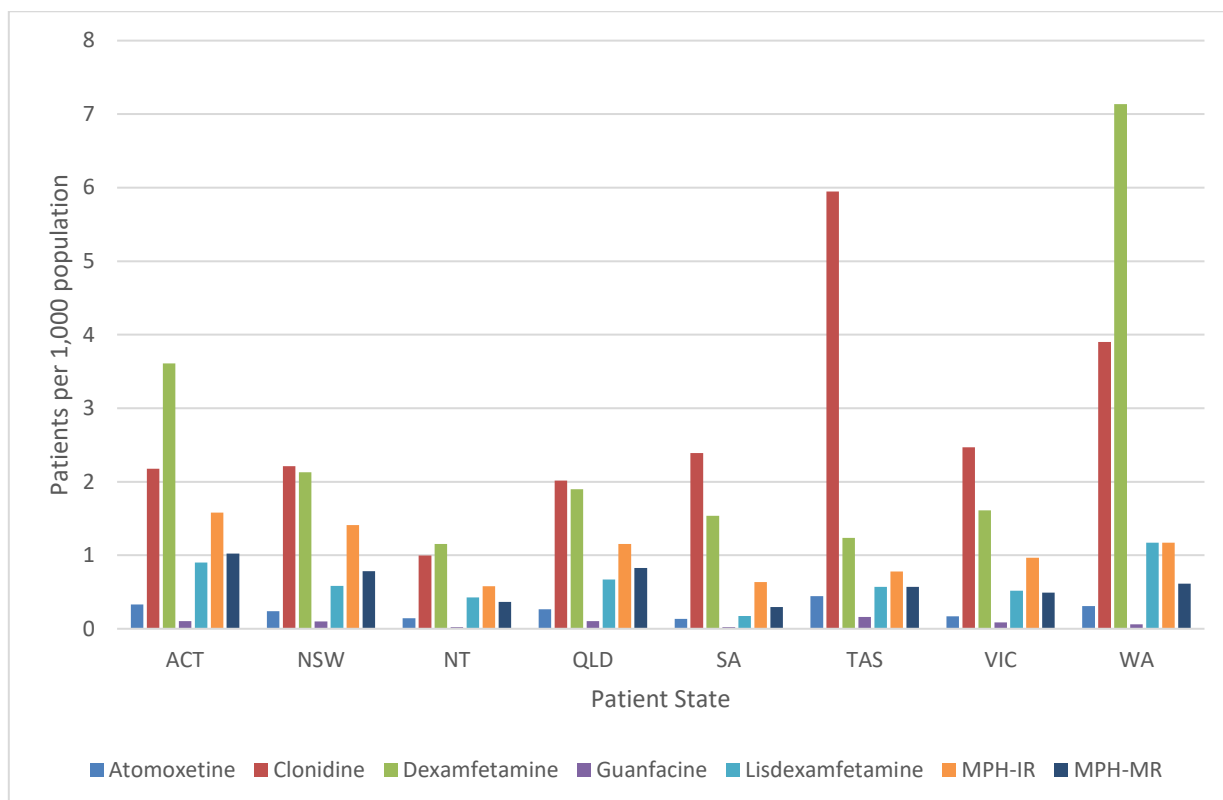


Figure 12: Number of people aged >18 years supplied an ADHD medicine or clonidine per 1,000 population in 2020 by patient state/territory and medicine (age group specific rate)

Source: Services Australia prescriptions database, extracted March 2021, based on 2020 ABS estimated residential population data

The pattern of ADHD medicines use varied across the states and territories. In age groups (under 19s and those 19 and older), the rate of patients supplied dexamfetamine and lisdexamphetamine is higher in Western Australia compared to other states and territories.

Tasmania had the highest rate of supply to under 19 year olds for short-acting methylphenidate, long-acting methylphenidate, clonidine and the second highest rate of lisdexamphetamine. The rate of supply of clonidine to under 19 year olds in Tasmania is almost double compared to other states and territories.

Conversely, South Australia had the lowest rate of supply in patients aged under 18 years for ADHD medicines (lisdexamphetamine, short-acting methylphenidate, long-acting methylphenidate and guanfacine).

Guanfacine predicted versus actual analysis

Approach taken to estimate utilisation

A market share approach was used to inform the utilisation and financial estimates of guanfacine. Guanfacine was assumed to substitute for the following PBS listings: atomoxetine; clonidine; methylphenidate; and lisdexamfetamine.

The script volumes for the substituted drugs were obtained from the Services Australia (formerly Medicare Australia) Pharmaceutical Benefits Schedule Item reports, available at: http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp. The script data was extracted based on the date of processing.

Clonidine was an unrestricted listing. Clonidine was assumed to be used for ADHD if the script was dispensed for:

- persons aged 6 to 17 years; and
- there was a switch from a stimulant to clonidine; or
- a stimulant was used as add on to clonidine; or
- a switch from atomoxetine to clonidine; or
- the patient commenced on clonidine and remained on this therapy.

Of clonidine scripts identified as being used for ADHD, it was assumed that 51.7 percent of this use would be in persons eligible for guanfacine.

The following treatment uptake assumptions were applied to all substituted drugs:

Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)	Year 6 (2023)
■	■	■	■	■	■

The estimated offset from drug substitutions is presented in the following table.

Year 1 (2018) (\$m)	Year 2 (\$m)	Year 3 (\$m)	Year 4 (\$m)	Year 5 (\$m)
■	■	■	■	■

Note: Figures are based on calendar years.

It was estimated that there would be 15.52 scripts of guanfacine per year. This was calculated as $365.25 \times (1.19 \text{ units per day} / 28 \text{ units per pack})$.

Analysis of actual versus predicted utilisation

Table 6 presents the predicted versus actual utilisation of guanfacine. The results presented are based on date of supply. As a result, there may be small differences between publicly available Services Australia dates of processing data.

Table 6. Guanfacine: actual versus predicted utilisation

Parameter	Difference	Year 1 (Sept 2018 – Aug 2019)	Year 2 (Sept 2019 – Aug 2020)	Year 3 YTD (Sept 2020 – Aug 2021)
Number of scripts dispensed	Predicted (P)	35,335	49,926	██████
	Actual (A)	74,725	177,301	Incomplete data
	Difference (%) $((P-A)/P) \times 100$	111%	255%	-

Note: The estimated figures are based on the agreed financial estimates model. The estimated figures are adjusted for the listing date of 1 September and presented in listing years. e.g. The first listing year figures for September 2018 to August 2019 are calculated as: $4/12 \times 2018$ calendar year + $8/12 \times 2019$ calendar year.

In the first year of listing, the number of prescriptions dispensed for guanfacine was much higher (2.1 fold) than the number predicted.

In the second year of listing, the number of prescriptions dispensed was also substantially higher at 3.6 fold above the expected number.

Prescriptions per patient

The number of prescriptions per patient in the 12 months after initiation was calculated for guanfacine patients that initiated from September 2018 to the end of January 2020 (n=19,647) to allow for 12 months of follow-up for each patient.

Table 7 Distribution prescription per patient

Drug	Patient count	Mean	Median	Mode
Guanfacine	19,647	9.48	11	14

Out of the 19,647 patients starting on guanfacine, 11% received no further prescriptions in the 12 month period (Table 7). On average, patients received 9.48 prescriptions per year in the first year of therapy. The most frequent amount of prescriptions dispensed in the first year was 14.

First prescriptions of guanfacine were largely prescribed by paediatricians, followed by psychiatrists (Figure 13).

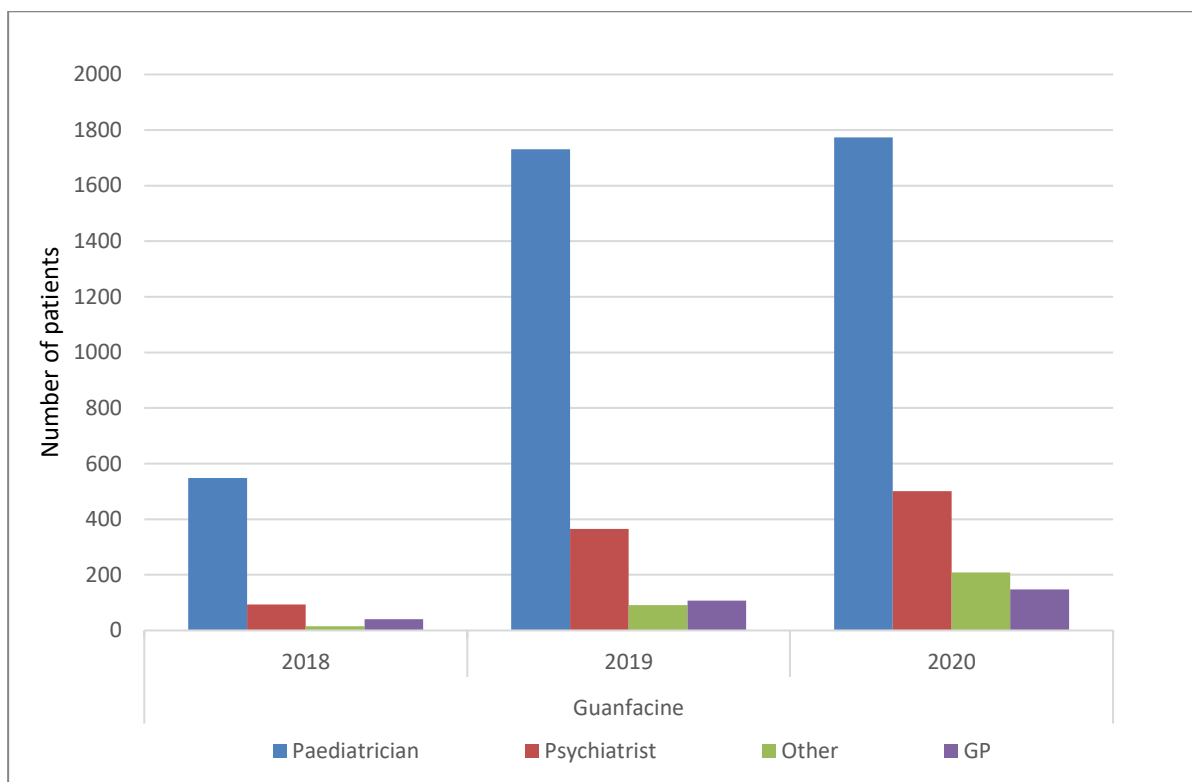


Figure 13: Prescriber type for patients initiating ADHD therapy on guanfacine by year

Source: Services Australia prescriptions database, extracted April 2021

Figure 13 depicts the prescriber type for patients initiating ADHD therapy on guanfacine since R/PBS listing.

As clonidine was used as a market comparator for guanfacine it is useful to compare the utilisation of both medicines (Figures 14, 15 and 16).

Figure 14 depicts the prescriber type for initiating guanfacine or clonidine patients and Figure 15 depicts the prescriptions by paediatrician or psychiatrist for guanfacine or clonidine by month. Figure 16 shows the total prescription count for guanfacine and clonidine by month. Of interest is that the rate of increase in clonidine appear consistent despite guanfacine becoming available in September 2018, indicating that paediatricians and psychiatrists have continued to prescribe clonidine.

A noticeable dip can be seen in Figure 15 over April 2020, this is most likely attributed to specialists' availability to see new patients over the covid-19 shut-down period. Interestingly, over the same month, there is a noticeable increase in the number of prescriptions dispensed for guanfacine and clonidine (Figure 16).

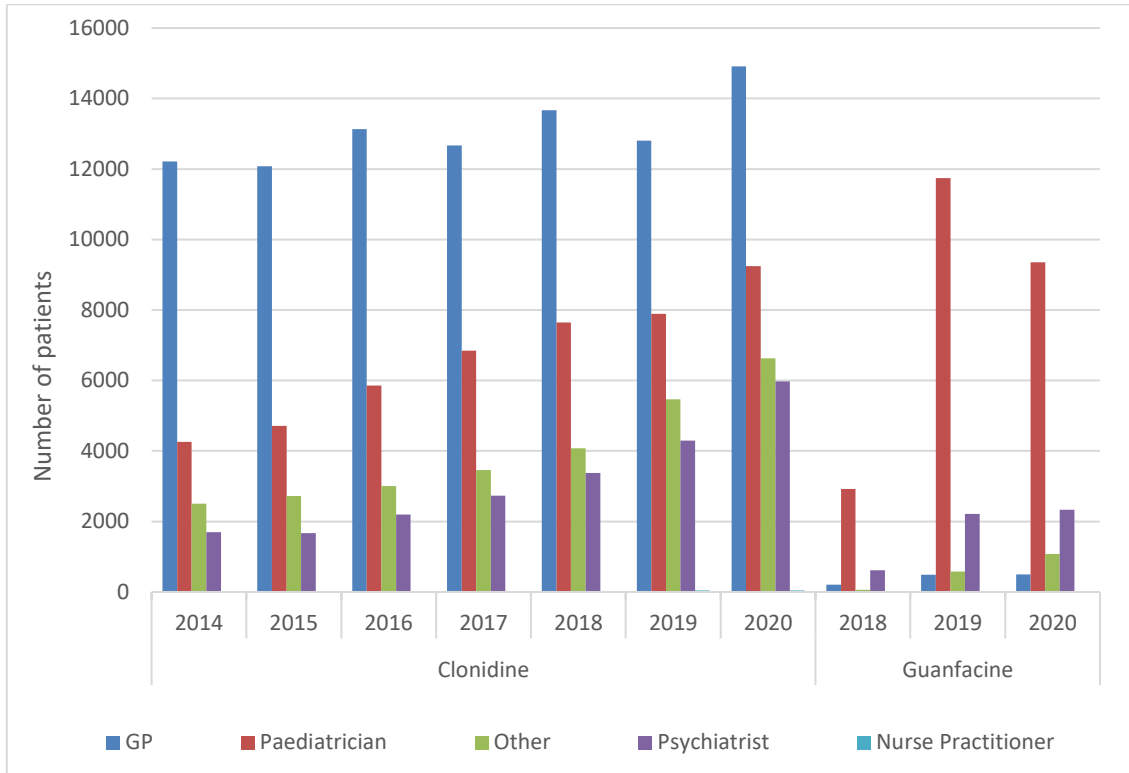


Figure 14: Prescriber type for patients initiating guanfacine or clonidine by year

Source: Services Australia prescriptions database, extracted April 2021

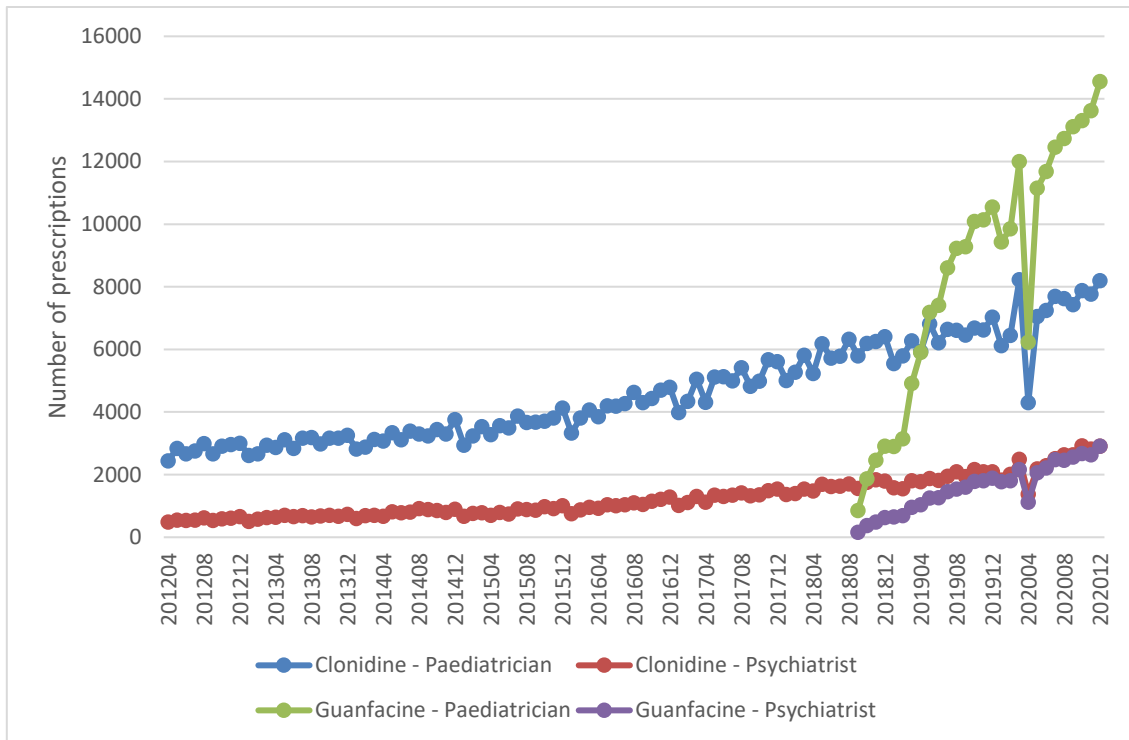


Figure 15: Prescriptions by paediatrician or psychiatrist for guanfacine or clonidine by month.

Source: Services Australia prescriptions database, extracted April 2021

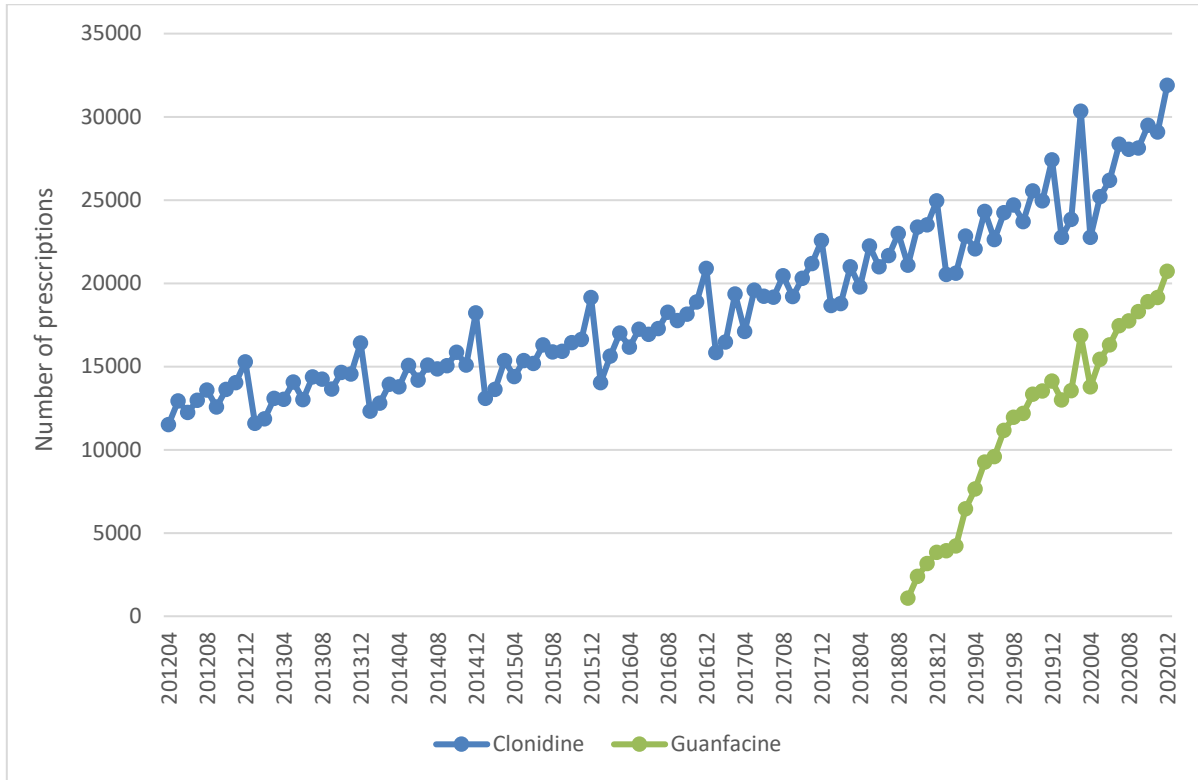


Figure 16: Total prescriptions for guanfacine and clonidine by month.

Source: Services Australia prescriptions database, extracted April 2021

Changes in the use of other medicines for ADHD

The rate of growth in prescriptions for other medicines supplied for ADHD were largely unchanged by the listing of guanfacine, indicating that the listing of guanfacine has resulted in growth of the overall R/PBS ADHD medicine market.

Discussion

This ADHD utilisation report examines the use of clonidine as a medication prescribed for ADHD. While definitive results are difficult to establish, it is estimated that clonidine is being used as an ADHD medication across all age groups. There is a high level of confidence that clonidine is being prescribed for patients 18 years and under, as this age group would not usually be prescribed clonidine for other diseases/disorders. As a result of this analysis, it appears that the ADHD market, and corresponding number of patients is potentially significantly larger than previously reported.

Overall, the utilisation of ADHD medicines listed on the R/PBS increased between 2014 and 2020. This trend is consistent for prescriptions and patient data over this period.

Children aged 6-12 years old continue to be the highest percentage (42%) of patients treated with ADHD medicines. Males continue to be treated at much higher rates than females across all age groups. The rate of ADHD medicine supply per 1000 population shows that Tas has the highest rate of supply for under 6 year olds (4.79), while the ACT has the lowest (1.6). Rates in the 6-12 year old group were highest in QLD (57.81) and Tas (56.03), while SA had a much lower rates of 29.33 per 1000 population respectively. It is unknown what the reason for this difference is, however if the trend prevails it might be worth exploring in a future analysis.

The greater rate of dexamfetamine supplied to adults in WA compared with other states was consistent in 2014, 2017 and 2020. A higher rate of dexamfetamine supply was also observed in WA patients 18 years and under. Tas had the highest supply rates of short and long acting methylphenidate in 18 year olds and under, as well as having a much higher rate of supply to this age group of clonidine (13.43/1000 population), compared to the other states and territories with the next highest rate being 8.57/1000 population in NSW. Guanfacine was prescribed in higher rates in ACT and Tas in patients 18 years and under.

The sponsor of guanfacine anticipated substitution of other ADHD treatments and considered that the listing would not cause growth in the market. However, there is a distinct increase in the prescriptions supplied and prevalent patients from 2018, indicating that the listing of guanfacine has increased the rate of growth beyond the previous trend.

In the first two years of guanfacine being listed on the R/PBS, the total number of patients has been much higher than the number projected. In the first year of listing the number of patients supplied guanfacine has been more than double the predicted number (111% increase), and this rate has more than quadrupled in the second year of listing (an increase of 255% over the predicted amount).

A breakdown of total prescriptions by medicine did not show substitution of guanfacine for other ADHD treatments. Therefore, the drug cost offsets estimated in the submission have not been realised.

Actions undertaken by the DUSC Secretariat

A copy of the report was sent to the sponsor of guanfacine.

DUSC Consideration

DUSC noted this was the first time DUSC had investigated ADHD utilisation which included clonidine as a medication prescribed for ADHD. While definitive results are difficult to establish, it was estimated that clonidine was being used as an ADHD medication across all age groups. There was a high level of confidence that clonidine was being prescribed for patients 18 years and under, as this age group would not usually be prescribed clonidine for other diseases/disorders. DUSC considered that clonidine may be used as a sedative in children and adolescents due to the side effects of psychostimulant medications used to treat ADHD. As a result of this analysis, it appeared that the ADHD market, and corresponding number of patients was potentially significantly larger than previously reported.

Overall, the utilisation of ADHD medicines listed on the R/PBS increased between 2014 and 2020. This trend was consistent for prescriptions and patient data over this period. DUSC noted that the prevalence of ADHD medications did not appear saturated and considered that patients are beginning therapy and not stopping.

Children aged 6-12 years old continued to be the highest percentage (42%) of patients treated with ADHD medicines. Males continued to be treated at much higher rates than females across all age groups. The rate of ADHD medicine supply per 1000 population showed that Tas had the highest rate of supply for under 6 year olds (4.8), while the ACT had the lowest (1.6). Rates in the 6-12 year old group were highest in QLD (57.8) and Tas (56.0), while SA had a much lower rates of 29.3 per 1000 population respectively. It was unknown what the reason for this difference was, however if the trend prevails it might be worth exploring in a future analysis. DUSC noted that there was regional variability in prescribing and prevalence. DUSC noted that it is common to see low rates of medicine use in NT however this data indicates similar use of ADHD medications to the rest of Australia. DUSC considered that this may be due to overdiagnosis in some groups of children in NT and may need further investigation. DUSC was also interested in the how Australia compared to the rest of the world regarding the prevalence of ADHD. DUSC noted a review done by Sayal et al. 2018²⁶ where administrative prevalence of ADHD in children and adolescents was between 2-7% with an average of 5%. Administrative prevalence was described as the number of people with a diagnosis or recording of ADHD either in clinical notes or through prescription data. The data from Australian sources indicated the administrative prevalence ranged from 1.24-2.4%.

The greater rate of dexamfetamine supplied to adults in WA compared with other states was consistent in 2014, 2017 and 2020. A higher rate of dexamfetamine supply was also observed in WA patients 18 years and under. Tas had the highest supply rates of short and long acting methylphenidate in 18 year olds and under, as well as having a much higher rate of supply to this age group of clonidine (13.4/1000 population) compared to the other states and territories with the next highest rate being 8.6/1000 population in NSW. Guanfacine was prescribed in higher rates in ACT and Tas in patients 18 years and under. DUSC noted that

²⁶ Sayal K, Prasad V, Daley D, Ford T, Coghill D. ADHD in children and young people: prevalence, care pathways, and service provision. *Lancet Psychiatry*. 2018 Feb;5(2):175-186. doi: 10.1016/S2215-0366(17)30167-0. Epub 2017 Oct 9. PMID: 29033005.

clonidine use was greater than expected and considered that clonidine may be initiated by GPs due to access issues to psychiatrists/paediatricians.

The sponsor of guanfacine anticipated substitution of other ADHD treatments and considered that the listing would not cause growth in the market. However, there was a distinct increase in the prescriptions supplied and prevalent patients from 2018, indicating that the listing of guanfacine has increased the rate of growth beyond the previous trend.

In the first two years of guanfacine being listed on the R/PBS, the total number of patients had been much higher than the number projected. In the first year of listing the number of patients supplied guanfacine was more than double the predicted number (111% increase), and this rate had more than quadrupled in the second year of listing (an increase of 255% over the predicted amount). DUSC noted that guanfacine appeared to have grown the market.

A breakdown of total prescriptions by medicine did not show substitution of guanfacine for other ADHD treatments. Therefore, the drug cost offsets estimated in the submission had not been realised. DUSC considered that guanfacine was being used similar to clonidine where it was being added to existing regimens of treatment rather than being supplied as monotherapy. DUSC noted that paediatricians and psychiatrists had continued to prescribe clonidine at similar rates after the introduction of guanfacine.

DUSC noted that the prevalence of ADHD was increasing. DUSC considered that this may be due to an increasing awareness of ADHD in schools and by parents where symptoms were being identified and referred to doctors. DUSC noted that there is some controversy surrounding the over and underdiagnosis of ADHD particularly in children. DUSC noted a recent journal article by Kazda et al. 2021²⁷ which suggested that ADHD was overdiagnosed and overtreated in children and adolescents. The article stated that further research needed to be done on the long-term benefits and harms of treating mild ADHD symptoms with medications. DUSC noted in contrast that there is a negative stigma towards those with ADHD. DUSC noted this stigma could potentially cause underdiagnosis in children and adolescents as parents and carers actively avoid referrals to doctors. DUSC was concerned about the potential for polypharmacy in this group of patients.

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.

²⁷ Kazda L, Bell K, Thomas R, McGeechan K, Sims R, Barratt A. Overdiagnosis of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents: A Systematic Scoping Review. *JAMA Netw Open*. 2021;4(4):e215335. doi:10.1001/jamanetworkopen.2021.5335

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

The sponsor has no comment.

Disclaimer

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

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

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Appendix A: Key R/PBS listing dates for ADHD medicines and changes to listing dates

Table A.1: Date of listing of PBS medicines used in the treatment of ADHD

Date	Drug name	Brand name	Strength	Item
Dec 1973	Dexamfetamine	-	5 mg	1165H
Aug 2005	Methylphenidate IR	Ritalin 10	10 mg	8839F
Dec 2005	Methylphenidate IR	Attenta*	10 mg	8829F
April 2007	Methylphenidate MR	Concerta	18 mg	2387P
			36 mg	2388Q
			54 mg	2432B
July 2007	Atomoxetine	Strattera	10 mg	9092M
			18 mg	9093N
			25 mg	9094P
			40 mg	9095Q
			60 mg	9096R
Aug 2007	Methylphenidate MR	Concerta	27 mg	2172H
April 2008	Methylphenidate MR	Ritalin LA	20 mg	2276T
			30 mg	2280B
			40 mg	2283E
Dec 2008	Atomoxetine	Strattera	80 mg	9289X
			100 mg	9290Y
Aug 2010	Methylphenidate MR	Ritalin LA	10 mg	3440C
Sep 2015	Lisdexamfetamine	Vyvanse	30 mg	10486X
			50 mg	10474G
			70 mg	10492F
Sep 2018	Guanfacine	Intuniv	1 mg	11452R
			2 mg	11451Q
			3 mg	11440D
			4 mg	11441E

Notes: * The Attenta® brand of methylphenidate IR was delisted in March 2009.

Table A.2. Changes to R/PBS restrictions of ADHD medicines

Date	Drug name	Change to the restriction/s
Aug 2007	Methylphenidate MR (Concerta®)	Replacement of "...child or adolescent aged 6 to 18 years inclusive" with "...patient aged 6 to 18 years inclusive".
Nov 2008	Atomoxetine (all items)	<p>The restrictions were changed to remind prescribers that atomoxetine is not PBS subsidised for use with other ADHD medicines. "Initial treatment..." was replaced by "Initial sole PBS-subsidised treatment...", and "Continuing treatment..." was replaced by "Continuing sole PBS-subsidised treatment...".</p> <p>A note was also added, "No applications for increased maximum quantities and/or repeats will be authorised", as the listing of the 80 mg and 100 mg doses was considered to negate the need for increased maximum quantities.</p>
Oct 2009	Methylphenidate (modified release) (all items)	The restrictions were modified to extend the listing to the treatment of patients aged over 18 years who were diagnosed between ages 6–18. "Treatment of attention deficit hyperactivity disorder (ADHD) in a patient between the ages of 6 and 18 years inclusive" was changed to "Treatment of attention deficit hyperactivity disorder (ADHD) in a patient <i>diagnosed</i> between the ages of 6 and 18 years inclusive".
Aug 2014	Atomoxetine (all items)	The restriction was simplified and changed from Authority Required to Authority Required (STREAMLINED). The requirement for diagnosis using the DSM-IV criteria was updated to the DSM-V. The emphasis on "sole PBS-subsidised treatment" use was removed. References in the previous restriction to specific contraindications and adverse events were generally removed.
July 2016	Methylphenidate (modified release) (all items)	The restriction criteria remains the same but was contents were restructured to separately define population criteria and clinical criteria.
July 2016	Dexamfetamine 5mg, tablets	The restriction criteria remains the same but was contents were restructured to separately define the two criteria for prescribing.
July 2016	Atomoxetine (all items)	<p>The restriction was modified to account for the new listing of lisdexamfetamine. The criteria was further limited by adding the requirement for contraindication to lisdexamfetamine before prescribing.</p> <p>"* Patient must have a contraindication to dexamphetamine, methylphenidate or <i>lisdexamfetamine</i> as specified in TGA-approved product information;"</p>
Sept 2018	Atomoxetine (all items)	Change in the restriction from 'The condition must be or have been diagnosed by a paediatrician or psychiatrist according to the DSM-5 criteria...' to 'Treatment criteria: * Must be treated by a paediatrician or psychiatrist. Clinical criteria: * The condition must be or have been diagnosed according to the DSM-5 criteria...'
March 2019	Guanfacine (all items)	Addition of new listing for patients taking guanfacine simultaneously with maximum tolerated dose of other stimulants.

Appendix B: PBAC recommendations for listing of ADHD medicines (Prior to 2018)

Copies of the PBAC Meeting Outcomes and Public Summary Documents are available on the [PBAC Meetings](#) website.

Methylphenidate IR

At the March 2005 meeting, the PBAC recommended listing on a cost-minimisation basis compared to dexamfetamine sulfate, with the equi-effective doses being methylphenidate hydrochloride 10 mg and dexamfetamine sulfate 5 mg.²⁸ The PBAC was concerned over the possible extent of use of the product and requested that the DUSC monitor this.

Methylphenidate MR (Concerta®)

At the November 2006 meeting the PBAC recommended listing of methylphenidate MR (Concerta®) as an authority required benefit on a cost effectiveness basis over methylphenidate IR. Although the extent of any clinical benefit over methylphenidate IR remained uncertain, the Committee agreed that the likely improvements in compliance and in ease of administration, particularly in relation to the removal of the need for a dose of medication at school, were sufficient to justify listing.²⁹

In July 2012 the PBAC rejected a submission to extend the listing to include patients diagnosed with ADHD after the age of 18 years, on the basis of uncertain efficacy and safety in the proposed population, and high and highly uncertain cost to the PBS.³⁰

Methylphenidate MR (Ritalin LA®)

In November 2007, the PBAC recommended listing of methylphenidate hydrochloride modified release (Ritalin LA®) capsules on the PBS on a cost-minimisation basis compared with methylphenidate hydrochloride modified release tablets (Concerta®) at the same price per day, as reflected by the equi-effective doses.³¹

In March 2020, the PBAC recommended the listing of methylphenidate hydrochloride 60 mg modified release capsule capsule (Ritalin® LA 60 mg), under the same conditions as the currently listed Ritalin LA strengths (10 mg, 20 mg, 30 mg and 40 mg).³²

²⁸ Department of Health (2005), March 2005 PBAC Outcomes - Positive Recommendations. Accessed on: 27 February 2018, at: <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/2005-03/positive-recommendations>

²⁹ Department of Health (2007), PBAC Meetings Public Summary Documents: Methylphenidate Hydrochloride, extended release tablets, 18 mg, 36 mg and 54 mg, Concerta November 2006. Accessed on: 27 February 2018, at: <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2006-11/pbac-psd-methylphenidate-nov06>

³⁰ Department of Health (2012), PBAC Meetings Public Summary Documents: Methylphenidate hydrochloride, Tablets, 18 mg, 27 mg, 36 mg, and 54 mg,(extended release) Concerta® - July 2012 Accessed on: 27 February 2018, at: <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2012-07/methylphenidate-hydrochloride>

³¹ Department of Health (2007), November 2007 PBAC Outcomes - Positive Recommendations. Accessed on: 27 February 2018, at: <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/2007-11/positive-recommendations>

³² <https://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2020-03/methylphenidate-capsule-containing-methylphenidate>

Atomoxetine (Strattera®)

The PBAC recommended the listing of atomoxetine (Strattera®) 10 mg, 18mg, 25 mg, 40 mg and 60 mg in November 2006, on a cost-effectiveness basis over placebo. The PBAC considered that there was a clinical need for the product and that the proposed restriction targeted the appropriate population.³³

In July 2008, the PBAC recommended the listing of two additional strengths of atomoxetine (Strattera®), 80 mg and 100 mg, but rejected a submission to extend the use of atomoxetine to patients diagnosed with ADHD as adults due to insufficient evidence of clinical and cost-effectiveness. The submission claimed that the new strengths were unlikely to increase atomoxetine use or cost to the PBS.³⁴

In March 2014, the PBAC recommended that the current Authority required restriction for atomoxetine be changed to Authority Required (STREAMLINED).³⁵

Lisdexamfetamine (Vyvanse®)

In July 2014, the PBAC considered the resubmission and recommended the listing of lisdexamfetamine (Vyvanse®) 30mg, 50mg, 70mg on a cost-minimisation basis compared with long-acting methylphenidate. The PBAC considered that the evidence in the submission demonstrated non-inferiority to long-acting methylphenidate in terms of effectiveness, and inferiority to long-acting methylphenidate in terms of safety.

The resubmission presented cost minimisation analysis versus MPH-OROS in children aged 6 to 12, cost-utility analysis versus MPH-OROS in adolescents aged 13-17 and cost-utility analysis versus 'no pharmacological treatment' or 'placebo' as proxy for standard of care in patients who have failed MPH-OROS.

The PBAC recommended the proposed listing of LDX as an authority required benefit in patients diagnosed between the ages of 6 and 18 years (inclusive). For the restriction, PBAC considered that there should be no requirement for patients to demonstrate response to dexamfetamine, as use of dexamfetamine DEX does not give guidance of dose or tolerability of lisdexamfetamine.

The PBAC recommended that lisdexamfetamine should not be treated as interchangeable with any other drugs.³⁶

³³ Department of Health (2007), PBAC Meetings Public Summary Documents: Atomoxetine Hydrochloride, capsules, 10 mg, 18 mg, 25 mg, 40 mg and 60 mg, Strattera® November 2006. Accessed on: 15 April 2021, at: <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2006-11/pbac-psd-atomoxetine-nov06>

Department of Health (2008), PBAC Meeting Public Summary Documents: Atomoxetine hydrochloride, capsules, 80 mg and 100 mg,

³⁴ Strattera®, July 2008 Accessed on: 27 February 2018, at: <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2008-07/pbac-psd-atomoxetine-hydrochloride-july08>

³⁵ Department of Health (2014), March 2014 PBAC Outcomes - Positive Recommendations. Accessed on: 27 February 2018, at: <http://www.pbs.gov.au/info/industry/listing/elements/pbac-outcomes/pbac-outcomes/pbac-recommendations-march-2014>

³⁶ Department of Health (2014), PBAC Meeting Public Summary Document: LISDEXAMFETAMINE DIMESILATE, capsules, 30 mg, 50 mg & 70 mg, Vyvanse®, Shire Australia Pty Ltd, July 2014. Accessed on: 16 April 2021, at: <https://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2014-07/lisdexamfetamine-dimesilate-psd-07-2014>

In July 2019, the PBAC recommended the listing of three additional strengths of lisdexamfetamine (Vyvanse®), 20 mg, 40 mg and 60 mg.³⁷

In March 2020, the PBAC recommended expanding the listing of lisdexamfetamine to include treatment of patients with ADHD who are diagnosed after the age of 18.³⁸

³⁷ <https://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2019-07/lisdexamfetamine-capsule-containing-lisdexamfetamine-dimesi>

³⁸ <https://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2020-03/lisdexamfetamine-capsule-containing-lisdexamfetamine>