Australian Government
Department of Health
Therapeutic Goods Administration

Antidepressant utilisation and risk of suicide in young people

Safety investigation

Version 2.0, April 2021

TGA Health Safety Regulation

Contents

1. Executive summary

This safety investigation was conducted by the Therapeutic Goods Administration (TGA) in response to a review article by Whitely, Raven, and Jureidini, in July 2020 that identified a decade long pattern of increasing antidepressant use and increasing rate of suicide in young Australians. Whitely, et al., postulated that increased antidepressant use may have contributed to the rising rate of youth suicide in Australia they identified.[1]

The aims of this safety investigation were to assess:

1. The strength of the current evidence for a causal association between prescribing of antidepressants and rates of youth suicide;
2. The international regulatory landscape with respect to use of antidepressants in children and adolescents and risk minimisation;
3. The current role of antidepressants in clinical practice for the treatment of psychiatric and developmental disorders in young people in Australia; and
4. Whether the current risk minimisation measures in place in Australia are adequate.

Clinical worsening of depression and suicidality in the early phases of antidepressant treatment in young people is a recognised potential risk identified in clinical trials. However, young people with depression may experience worsening of their depressive symptoms and/or the emergence of suicidality whether or not they are taking antidepressant medications and this risk may persist until significant remission occurs.

Whitely, et al., compared changes in Pharmaceutical Benefits Scheme (PBS) antidepressant dispensing from 2003 to 2018 for young Australians (aged <28 years) with youth suicide rates (for people aged <25 years) from the Australian Bureau of Statistics (ABS). They found that Australian youth suicide rates have trended upwards in the previous two decades and there has been an increase in antidepressant dispensing in youths in the same period. Whitely et al state that "*there is clear evidence that more young Australians are taking antidepressants, and more young Australians are killing themselves and self-harming…*".

A number of limitations of the Whitely, et al. article, were identified by the TGA and the authors themselves. These include uncontrolled confounding and conclusions drawn from imperfect data. A TGA analysis of PBS dispensing data confirms a steady increase in the rate of antidepressant prescribing to young people in Australia, both male and female, between 2013 and 2019. Rates of suicide of young people in Australia have also increased but with a more complex trajectory, with male and female suicide rates showing differing trends.

As part of this investigation, the TGA sought advice from the Advisory Committee on Medicines (ACM). The ACM advised that there is a valid and important role for selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs) in current clinical practice in treating moderate-to-severe depression in children and adolescents, supported by professional guidelines. The ACM noted that psychological therapies are recommended as the first line treatment for depressive disorders in children and adolescents. The ACM also noted that access to publicly funded psychological therapies for young Australians is often limited. The ACM expressed concern around the increasing use of antidepressants in young people in the absence of other alternatives and recommended the development of further clinical guidance to support the safe prescribing of antidepressants to young people in whom antidepressant therapy is clinically appropriate.

While the increasing use of antidepressants in young people is a concern, the strength of the current evidence is insufficient to conclude that a causal relationship exists between prescribing of antidepressants and increasing rates of youth suicide. Analysis of linked PBS data and suicide data is required to further explore any potential causal relationship between antidepressants and increased rates of youth suicide in Australia.

Based on the findings of this safety investigation, the TGA will:

1. Liaise with the relevant professional colleges regarding the outcomes of our review and ACM advice, and, in particular, the need for additional clinical guidelines for general practitioners around the management of depression and prescribing of antidepressants to children, adolescents and young people. Letters have already been sent from the TGA to the Royal Australian College of General Practitioners, the Royal College of Physicians and the Royal Australian and New Zealand College of Psychiatrists, to advise them of the ACM advice and request that these bodies work collaboratively towards providing additional guidance for pharmacological management of depression in young people.
2. Explore potential analysis of linked PBS, Medicare Benefits Schedule (MBS), hospital and death data to further investigate the clinical journeys of young people prescribed antidepressants in Australia and the relationship between antidepressants and rates of youth suicide. In addition there will be consideration of the utility of established datasets held by the Australian Bureau of Statistics and the Australian Institute of Health and Welfare. This work will commence in early 2021 subject to access to data.

2. Introduction and background

2.1 Introduction

Concerns about an association between antidepressant use and increased risk of suicide first emerged in the 1990s.[2] Product Information (PI) and Consumer Medicine Information (CMI) documents for antidepressants in Australia contain warnings about the risk of worsening depression and emerging suicidality, and advise patients and caregivers to closely monitor for worsening symptoms and suicidal thoughts.

In a review article published in July 2020, Whitely, Raven and Jureidini postulated that increased antidepressant use by young Australians may be contributing to the apparent rise in youth suicide.[1] Whitely, et al., highlighted that PBS antidepressant dispensing to people aged less than 28 years and suicide rates in people aged less than 25 years had both increased between 2009 and 2018. The authors acknowledged that correlation does not prove causation, and reflected on the multiplicity of risk factors associated with suicide.

In response to this review article, the TGA has undertaken an investigation to consider:

- the strength of the current evidence for the association between antidepressants and youth suicide;
- the international regulatory landscape with respect to antidepressants and youth suicide;
- the current role of antidepressants in clinical practice for the treatment of psychiatric and developmental disorders in children, adolescents and young adults in Australia; and
- whether the current risk minimisation measures in place in Australia are adequate.

The TGA investigation considered a number of sources of information including:

- available clinical guidelines;
- adverse event data;
- peer-reviewed literature;
- dispensing and death data; and
- advice from the ACM.

2.2 Products, registered indications and PBS status

There are several different classes of medicine that fit within the umbrella term antidepressant. The active ingredients entered on the Australian Register of Therapeutic Goods (ARTG) in each class for the treatment of depression are listed in Table 1. Many of these medicines have additional indications for the treatment of other mental health conditions, such as various anxiety disorders, obsessive-compulsive disorder, and pre-menstrual dysphoric disorder.

The majority of these antidepressants are registered for use only in adults, with the exception of sertraline and fluvoxamine products, which have an indication for treatment of obsessive-compulsive disorder (OCD) in children aged 6 or 8 years and over respectively. With the exception of these approved indications for the treatment of OCD, use of antidepressants in individuals under the age of 18 is considered "off-label" in Australia. Off-label prescribing is very common in paediatric populations because the clinical trials on which approved indications are based are usually conducted in adults.

Most antidepressants available in Australia are subsidised under the Pharmaceutical Benefits Scheme (PBS), with the exception of vortioxetine and agomelatine. Amitriptyline, dosulepin, doxepin, imipramine and tranylcypromine are included on the General Schedule without any restriction on prescribing to receive PBS reimbursement. All other antidepressants are listed as a Restricted Benefit, meaning that they can only be prescribed for the listed indication(s) in order to receive PBS reimbursement. There is no restriction on age group for PBS prescriptions of antidepressants.

Appendix 1 lists antidepressant medicines entered on the ARTG, their approved indications and their PBS status in Australia.

Table 1: Antidepressants approved in Australia (ATC code N06A*)

Medicine class	Active ingredients
Selective serotonin reuptake inhibitors (SSRIs)	• Citalopram • Escitalopram • Fluoxetine • Fluvoxamine • Paroxetine • Sertraline
Serotonin and noradrenaline reuptake inhibitors (SNRIs)	• Desvenlafaxine • Duloxetine • Venlafaxine
Tricyclic antidepressants (TCAs)	• Amitriptyline • Clomipramine • Dosulepin • Doxepin • Imipramine • Nortriptyline

* The Anatomical Therapeutic Chemical (ATC) classification is a hierarchy of drug classification that is used internationally to ensure consistency of research in drug utilisation. See: https://www.whocc.no/atc/structure_and_principles/

Medicine class	Active ingredients
Monoamine oxidase inhibitors (MAOIs)	• Phenelzine • Tranylcypromine
Other	• Agomelatine • Mianserin • Mirtazapine • Moclobemide • Reboxetine • Vortioxetine

2.3 Previous actions by the TGA

The TGA has previously investigated the issue of antidepressants and suicidality a number of times. A warning and precaution statement about the risks of clinical worsening and suicide was then added to all antidepressant PIs in 2004 and 2005 following consideration of the issue by the Australian Adverse Drug Reactions Advisory Committee (ADRAC – now part of the Advisory Committee on Medicines). This warning statement includes details of potential symptoms experienced and recommendations for monitoring behaviour. As a result, the TGA approved PI documents for all antidepressants registered in Australia include warnings about these risks and specifically mention children, adolescents and young adults. This information is also conveyed in the CMIs for these products.

Adverse Drug Reactions Advisory Committee – Use of SSRI antidepressants in children and adolescents

The ADRAC considered the safety and efficacy of SSRI antidepressants and venlafaxine in children and adolescents in 2004, including review of the 2003 evaluation by the UK Committee on Safety of Medicines (CSM)[3] and briefing papers considered by the US FDA. ADRAC also sought advice from the Royal Australian and New Zealand College of Psychiatrists (RANZCP) and the Royal Australasian College of Physicians (RACP) Division of Paediatrics & Child Health. Of note, the CSM advised against the use of venlafaxine or SSRIs (with the exception of fluoxetine) in children and adolescents aged <18 years, following concerns about their possible association with an increased risk of suicide and suicidal behaviour.[4]

ADRAC noted that no antidepressants were approved in Australia for the treatment of major depressive disorder (MDD) in children and adolescents and found that assessment of the published and unpublished data available for SSRI use in children and adolescents indicated that there was some evidence of an increased risk of suicidality, including suicidal ideation, suicide attempts and self-harm events, associated with SSRIs.

ADRAC also identified evidence that fluoxetine was beneficial for the treatment of depression in adolescents with moderate to severe symptoms of MDD and that treatment with fluoxetine plus cognitive behaviour therapy was more beneficial and decreased suicidal ideation compared with placebo by the end of the treatment period.

ADRAC noted that, in general, clinical trials of SSRIs in children and adolescents have excluded severely depressed patients and have not adequately monitored participants for self-harm or suicide-related events. Other non-SSRI antidepressants have been subjected to less scrutiny, and may be inefficacious and also associated with suicidality, as well as having other undesirable effects such as the toxicity in overdose of the tricyclics.

Overall, ADRAC considered that the data at the time were not conclusive regarding the efficacy and safety of SSRIs in MDD in children and adolescents and with this in mind, recommended:

1. Any SSRI use in children and adolescents with MDD should be undertaken only within the context of comprehensive management of the patient, as outlined in the NHMRC Clinical Practice Guidelines for Depression in Young People (1997). Such management should include careful monitoring for the emergence of suicidal ideation and behaviour.
2. The choice of an SSRI for children or adolescents with MDD should be made only after taking into account the recent evaluations of clinical trial data and the PI. Note that the current Australian PI for paroxetine and venlafaxine recommends **against** their use in children and adolescents.
3. Children and adolescents who are currently being treated for MDD with an SSRI should not have their medication ceased abruptly.[5]

Report of the Psychiatric Drug Safety Expert Advisory Panel

In August 2008 the TGA established an independent panel of psychiatrists and epidemiologists, the Psychiatric Drug Safety Expert Advisory Panel (PDSEAP), to undertake a specific review of the safety of SSRIs and atypical antipsychotic medicines.

The PDSEAP concluded that the risk-benefit balance for each of these medicines remained positive and that they are an effective part of treatment regimens for patients with certain psychiatric conditions.[6]

The PDSEAP undertook a scientific review of a series of case reports submitted to the TGA by a psychiatrist with a special interest in forensic and medico-legal psychiatry. Most of the reports described complicated medication and adverse event histories, in which numerous psychotropic medications had been administered over considerable time periods.

The PDSEAP also undertook extensive literature reviews, with a view to examining the current state of knowledge for a number of topics, including SSRI antidepressants and suicidal mortality, and reconciling this with the appropriateness of information in existing Australian prescribing information documents, including the TGA-approved PI.

The PDSEAP reviewed evidence on the association between SSRI antidepressants and suicide mortality deriving from meta-analyses of randomised controlled trials (RCTs), observational studies and ecological studies, commenting that each type of study has its strengths and weaknesses. For example, meta-analyses of RCTs are able to increase statistical power by aggregating the number of participants from smaller RCTs, but are limited by short study periods and uncertainty about the validity of using suicidal ideation as a surrogate for suicide risk. Observational studies tend to be larger than RCTs and are able to observe risks in the real world context, but are significantly limited by confounding by indication (higher risk patients being more likely to receive antidepressant treatment). In addition, completed suicide is a relatively rare event in the population, which means an often unfeasibly large number of participants would be required to have the statistical power to detect a difference between groups in an observational study. Ecological studies may be able to identify small effects aggregated over a large exposed population, but are also limited by confounding by indication, and have limited capacity to test alternative explanations for an observed change in suicide rates (e.g. the impact of economic circumstances, or other suicide risk factors).

The PDSEAP found that children and adolescents were not well represented in the larger observational and ecological studies of the risk of suicide associated with antidepressants. Inconsistent results between studies were noted, with some studies finding that an increased risk of suicide among adolescents prescribed an SSRI was no longer significant after adjustment for confounding by indication. The PDSEAP also noted that evidence of efficacy is less convincing in adolescents than in adults because there have been many fewer placebo controlled RCTs of SSRIs in adolescents than in adults.

The PDSEAP's report was published in December 2009 and concluded that Australian PIs contained extensive precautions regarding the risk of suicidality which were consistent across the class, and with FDA warning statements. The PDSEAP found that due to the prominence of the existing warnings, an update to PIs to include a boxed warning was not necessary.[7]

2.4 Regulatory status in other countries

The status of SSRIs and SNRIs for comparable overseas regulators is similar to Australia. The PI equivalents in the UK, US, Canada and Europe for all antidepressants contain some version of a warning statement regarding the risk of clinical worsening and suicidality very similar to that in Australia. Some notable differences, particularly of indications, have been outlined below.

A significant difference between the Australian PIs for antidepressants and the UK and US equivalents is the lack of dosing information for the paediatric population. This is because this information has not been submitted to the TGA for consideration as part of a registration of indication for this population.

United Kingdom

- Fluoxetine is indicated for the treatment of "*Moderate to severe major depressive episode, if depression is unresponsive to psychological therapy after 4-6 sessions*" in children and adolescents aged 8 years and above.[8]

United States

- Fluoxetine is approved for use for MDD in children 8 years and over.[9]
- Fluoxetine, sertraline, fluvoxamine and clomipramine are approved for used for OCD in children 6, 7, 8 and 10 years and over respectively.[9-12]
- All SSRI and SNRI products contain a boxed warning that outlines the risk of increased suicidality in children, adolescents and young adults (see Figure 1 below).[13] This was introduced announced in 2004 in response to clinical trials data that highlighted a potential suicide risk with these products.[14]

Figure 1: US Food & Drug Administration boxed warning for antidepressant medications

DRUG NAME

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of [Insert established name] or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. [Insert Drug Name] is not approved for use in pediatric patients. [The previous sentence would be replaced with the sentence, below, for the following drugs: Prozac: Prozac is approved for use in pediatric patients with MDD and obsessive compulsive disorder (OCD). Zoloft: Zoloft is not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD). Fluvoxamine: Fluvoxamine is not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD).] (See Warnings: Clinical Worsening and Suicide Risk, Precautions: Information for Patients, and Precautions: Pediatric Use)

Source: FDA[13]

Canada

- The indications for all SSRI and SNRI products contain wording that states "*Not indicated for use in patients below the age of 18 years*".

Europe

- The European Medicines Agency 2005 review of SSRIs and SNRIs in children and adolescents concluded that they should not be used in children and adolescents except in their approved indications.
  - "Most of these products are approved for the treatment of depression and anxiety in adults in the European Union, but are not licensed Europe-wide for the treatment of these conditions in children or adolescents. Some of these products are however licensed for paediatric use for the treatment of obsessive-compulsive disorder and one of them for the treatment of attention deficit/hyperactivity disorder."[15]

Fluoxetine is available in a 10mg strength in the above overseas jurisdictions, which aids appropriate dosing in the paediatric population.

3. TGA investigation

3.1 The current role of antidepressants in clinical practice for the treatment of children, adolescents and young people in Australia

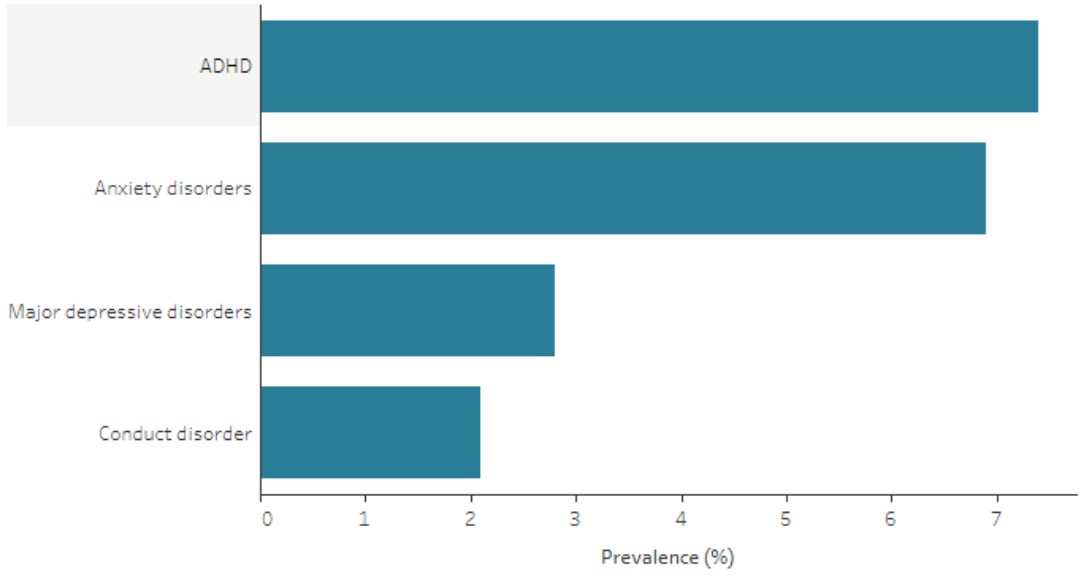
3.1.1 Epidemiology of depression in young people in Australia

The Australian Child and Adolescent Survey of Mental Health and Wellbeing, a national household survey, was conducted for the second time in 2013–14 (also referred to as the 'Young Minds Matter' survey). The survey found that mental health disorders were common in children and adolescents aged 4-17 years, with almost 14% of the population in this age group experiencing a mental health disorder in the preceding 12 months. Comorbidity of mental health conditions was also relatively common – almost one third of those with a disorder experienced two or more mental disorders at some time in the previous 12 months, equivalent to 4.2% of all 4-17 year olds. Attention Deficit Hyperactivity Disorder (ADHD) was the most common mental disorder (7.4% of all children and adolescents, or about 315,000 based on the estimated 2017 population), followed by anxiety disorders (6.9% or about 293,000), MDD (2.8% or about 119,000) and conduct disorder (2.1% or about 89,000)— see Figure 2. The survey also indicated prevalence did not differ significantly with age for boys, but that it was slightly higher in 12-17 year-old girls at 12.8% compared with 4-11 year-old girls at 10.6%.[16]

The 2007 National Survey of Mental Health and Wellbeing found that the prevalence of mental health disorders in adults (aged 16-85 years) was 1 in 5 over the previous 12 months, which is higher than the prevalence in children that was demonstrated in the Australian Child and Adolescent Survey of Mental Health and Wellbeing. The NSMHW estimated that almost half (45%) of the Australian adult population would experience a mental disorder at some time in their life. Anxiety disorders (such as social phobia) were the most prevalent, afflicting 1 in 7 (14.4%) of the population, followed by Affective disorders (such as depression) (6.2%), and Substance use disorders (such as alcohol dependence) (5.1%).

The Intergenerational Health and Mental Health Study is scheduled to be undertaken from 2020 by the Australian Bureau of Statistics (ABS). The Mental Health Study will measure the prevalence of mental illnesses for the first time since the 2007 National Survey of Mental Health and Wellbeing. It will provide updated statistics and insights into the impact of mental, behavioural, and other chronic conditions on Australians and the use of health services and barriers to accessing them, as well as other health topics.[17]

Figure 2: Prevalence of mental disorders in the past 12 months (from 2013-14) among 4-17 year olds



Source: Lawrence, et al., 2015[15]

3.1.2 Clinical practice guidelines

In the absence of registered indications for the use of antidepressants in children and adolescents, clinical guidelines provide clinicians with guidance in determining the appropriate treatment of depression in these age groups, including recommendations about pharmacological therapy. The 'Royal Australian and New Zealand College of Psychiatrists (RANZCP) clinical practice guidelines for mood disorders'[18] recommend fluoxetine as second line treatment for moderate to severe major depressive disorder in children and adolescents. Psychological interventions are the recommended first line treatment. These guidelines state that of the SSRIs, fluoxetine has the most consistent evidence of efficacy over placebo, and is recommended as the first line antidepressant for young people in the UK National Institute for Health and Care Excellent (NICE) treatment guidelines[19]. The RANZCP guideline also recommends that clinicians advise young patients and their families of the small chance of suicidal thoughts emerging during the early phase of treatment with SSRIs and monitor all patients for the emergence or worsening of suicidal thoughts during the first 2–4 weeks of treatment.[18]

The NICE treatment guidelines, last updated in 2019, recommend that antidepressant medication should not be used for the initial treatment of children and young people with mild depression, and that antidepressant medication should only be offered to a child or young person with moderate to severe depression in combination with a concurrent psychological therapy. The NICE guidelines state that fluoxetine is the only antidepressant for which clinical trial evidence shows that benefits outweigh the risks. Sertraline or citalopram are included as potential second-line medications in certain circumstances including if a fair trial of fluoxetine and psychological therapy has not resulted in improvement. The NICE guidelines also include recommendations about the dosage and duration of pharmacological treatment, specifically that for fluoxetine, the starting dose should be 10mg daily (or less in children of lower body weight), which is half the starting dose for adults.[19]

3.2 The strength of current evidence for an association between antidepressants and youth suicide

3.2.1 Evidence from peer-reviewed literature

While Whitely, et al., have included ecological data looking at population rates of prescribing and suicide in their paper, the question of particular concern to the TGA as a medicines regulator is one of causality between antidepressants and the risk of suicide in young people. The limitations of different types of evidence noted by the PDSEAP discussed in section 2.3 remain unchanged. We therefore undertook a limited literature search to identify if additional high level evidence published in recent years has advanced the subject further since the previous TGA investigation, focussing particularly on meta-analyses of RCTs and observational studies. Our review ultimately has not identified additional literature that can definitively answer the question of causality between the use of antidepressants and risk of suicide in young people. The available literature can however inform our exploration of this issue, in particular the complexities of risk.

Suicide is a complex outcome with many interacting factors.[20-23] The features of suicidality in children and adolescents are different from those occurring in adults and while depression is a factor strongly associated with suicidality in this population, it is not present in all cases.[21] A systematic review by Carballo, et al., in 2019 found that the majority of publications reviewed indicated that young people with suicidal behaviour had significant psychiatric problems, mainly depressive disorders and substance use disorders. They further state that the evidence clearly highlights the complexity of suicidality and points towards an interaction of factors contributing to suicidal behaviour.[21] This statement is supported by an earlier systematic review by Beautrais in 2000[22] that found that risk factor domains which may contribute to suicidal behaviour include social and educational disadvantage; childhood and family adversity; psychopathology; individual and personal vulnerabilities; exposure to stressful life events and circumstances; and social, cultural and contextual factors. Beautrais surmises that suicidal behaviours in young people appear to be frequently a consequence of adverse life sequences in which multiple risk factors from these domains combine to increase risk of suicidal behaviour.

Activation syndrome is a side effect of antidepressants that is thought to carry a potentially increased risk of suicide, although the literature presents inconsistent findings from clinical studies.[24] Symptoms consist of irritability, mania, self-harm, akathisia, impulsivity, restlessness and/or insomnia and disinhibition.[24, 25] However, the incidence of activation syndrome has not been fully investigated and little has been reported on its predictors.[26] However, it does appear that higher plasma concentrations and rapid increases in plasma concentrations of SSRIs, may be a risk factor for emergence of activation-related adverse events. This may reflect high doses or rapid escalation of doses, but may also be related to other factors affecting drug concentration such as inter-individual variability in pharmacokinetics and polymorphisms in genes encoding cytochrome enzymes involved in drug metabolism.[24]

Zhou, et al.,[27] conducted a comprehensive systematic review and network meta-analysis of all available RCTs up to 1 January 2019 comparing active interventions (antidepressant treatment, psychotherapy, alone or in combination) with another active treatment or a control condition for the acute treatment of depressive disorders in children and adolescents. They based their final analysis on 71 RCTs, including 9510 children and adolescents with depressive disorders. They found that out of the active treatment conditions, only fluoxetine alone or in combination with cognitive behavioural therapy were significantly more efficacious than pill placebo. The authors also assessed suicidal behaviour within a network meta-analysis and found that venlafaxine was associated with a significantly increased risk of suicidal behaviour or ideation compared with pill placebo, and with 10 other active treatments (citalopram, escitalopram, fluoxetine, fluoxetine plus CBT, duloxetine, imipramine, family therapy, desvenlafaxine, CBT and pill placebo plus CBT). Other comparisons failed to achieve statistical significance. The reported odds ratio for fluoxetine compared with pill-placebo for suicidality was 1.11 (95% Credibility

Interval 0.74 to 1.75). The authors commented that comprehensive assessment of the risk of suicidality for all interventions was not possible, and noted that few psychotherapy trials report data on adverse events and suicidality. They urged prescribers to closely monitor suicide risk when children and adolescents take any antidepressant drugs, particularly at treatment initiation.

Ignaszewski and Waslick[28] performed a meta-analysis of seven randomised controlled trials published through to July 2016 that addressed antidepressant use in paediatric patients for the management of major depressive disorder. Within their cohort, the acute and extension trials exclusively utilized the Columbia Suicide Severity Rating Score (CSSR-S) to evaluate for treatment-emergent suicidality whereas the two relapse trials relied on safety outcomes evaluating adverse effects leading to medication discontinuation and self-report. Analysis revealed similar rates of treatment-emergent suicidality in patients on antidepressants as placebo in studies that used newer rating scales (ie. CSSR-C) however authors cautioned that there are relatively few studies using this CCSR-S methodology and higher sensitivity meta-analyses are not yet available.[28]

A 2016 systematic review by Xu, et al.,[29] examined four studies that addressed the risk of suicide related outcomes (defined as definitive suicidal ideation or behaviour) in children with major depressive disorder taking SNRIs. Whilst some studies demonstrated an increased risk of suicide-related outcomes for those receiving venlafaxine compared with placebo there were few suicide-related events and overall there was no statistical difference found in suicide-related risk outcome for those receiving SNRIs compared with those receiving placebo.[29]

Gibbons, et al.,[30] analysed two large US medical claims databases containing 221,028 patients between the ages of 5 and 17 with new episodes of depression, with and without antidepressant treatment during 2004-2009. They used marginal structural modelling to adjust for time-dependent modelling. They found that while a significantly increased risk of suicide attempts and self-injury were seen during antidepressant treatment episodes in the unadjusted and simple covariate-adjusted analyses, accounting for dynamic confounding in the treatment selection process resulted in non-significant odds ratios (MarketScan data: OR=1.21, 95% CI = 0.79, 1.88; LifeLink data: OR=1.05, 95% CI = 0.92, 1.19).[30] This suggests that the association seen in other observational studies is related to confounding by variables that change over time, and that accounting for these can reveal a more accurate measure of the strength of association between antidepressant treatment and suicidality.

3.2.2 Database of Adverse Event Notifications

Adverse event reports are one of the ways in which the TGA monitors the safety of medicines, including antidepressants. While this information is important, due to underreporting and lack of control for confounding, these reports do not provide evidence upon which a causal association can be established or refuted.

A search of the Database of Adverse Event Notifications (DAEN) on 19 November 2020 identified 167 suicide-related adverse event† reports for persons aged under 25 years of age listing antidepressant medications as suspected medicines recorded in the TGA DAEN (see Appendix 2 for search strategy). These reports were received between 1993 and July 2020. Reports received by the TGA contain suspected associations that reflect the observations of an individual reporter, however causality has not usually been established.

Table 2 shows the total number of reports for each antidepressant class and the number of reports where an antidepressant medicine was reported as the sole-suspected medicine.

† Search terms included completed suicide, suicidal attempt, suicidal ideation and suicidal behaviour.

Table 2: Number of total cases and sole suspected cases by antidepressant class

Antidepressant class	No. of patient cases*	No. of cases where sole suspected
SSRIs	106	68
SNRIs	54	37
TCAs	5	3
MAOIs	-	-
Other	15	10
TOTAL	**167**	**118**

* Of the 167 reports of suicide-related adverse events, 11 patients were reported to be taking more than one antidepressant medicine concurrently.

Of the 167 reports recorded in the DAEN, 78 were for children and adolescents (under 18 years of age). Twenty-four reports, received between 2005 and 2018, listed completed suicide as the adverse event (see Appendix 2 for full case line listing). Figure 3 provides a breakdown of reports completed suicides by age group. SSRI medicines were listed as the suspected medicine in 13 of the 24 reports of completed suicide, SNRI medicines were listed as the suspected medicine in seven reports, with TCAs and agomelatine listed as the suspected medicine in three reports and one report respectively.

The time from medication initiation to the outcome of completed suicide (time to onset) was not provided in 13 of the 24 reports (see Figure 4). Of the remaining 11 reports, one was a patient who was not taking an SSRI prior to the event and obtained an SSRI for the sole purpose of an intentional, multi-drug overdose. This report has not been included in Figure 4. Of the other 10 reports with a recorded time to onset, there was insufficient information to suggest the presence of activation syndrome. See section 3.2.2 for more detail on activation syndrome.

Figure 3: Number of DAEN reports of completed suicides by age group and gender in persons under 25 years

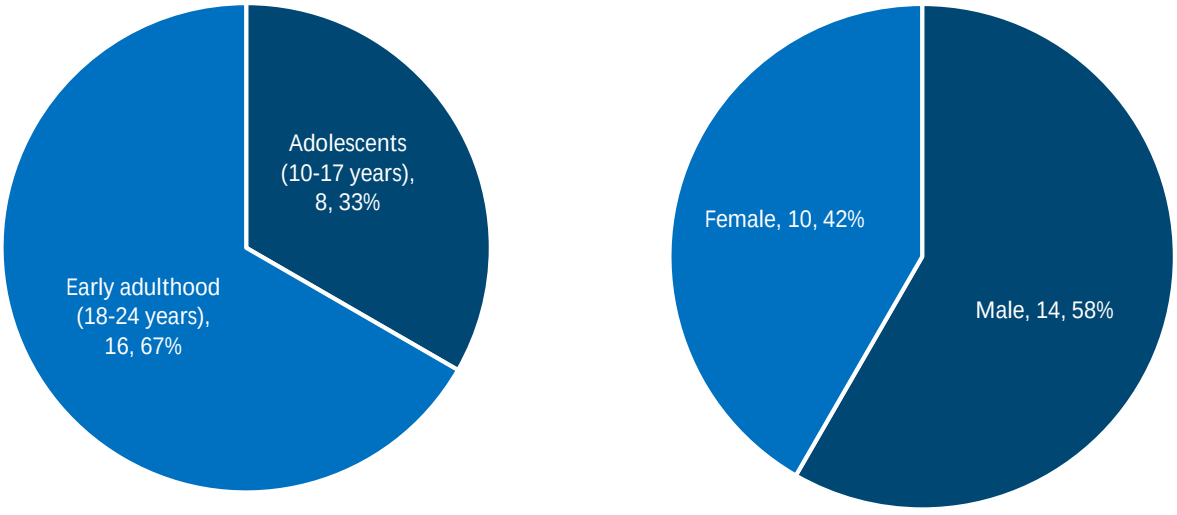


Figure 4: Time from medication to completed suicide in persons under 25 years

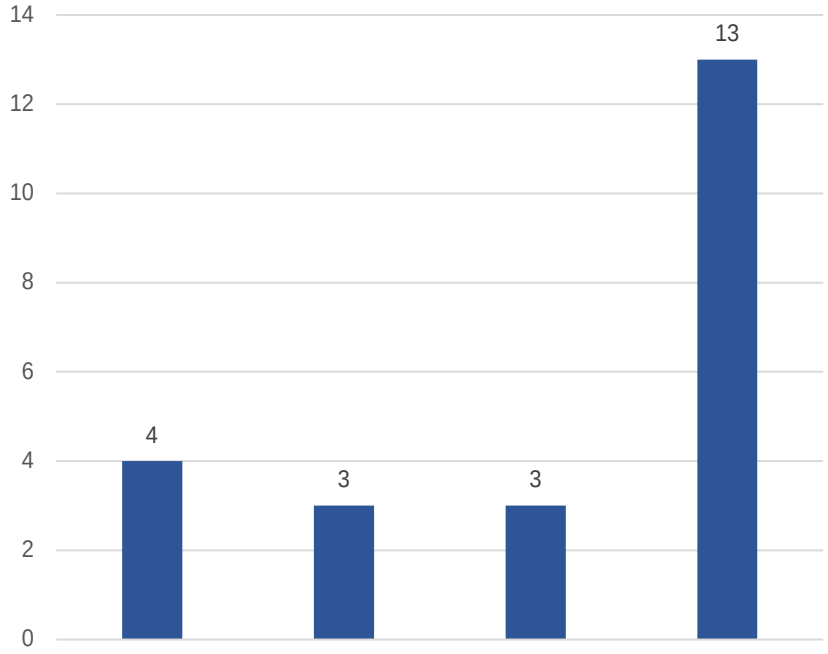


Figure 5 shows the aggregate number of reports to the DAEN of suicide-related adverse events for people aged under 25 years according to the active ingredient in the antidepressant listed as a suspected medicine.

Figures 6 through 8 provide a summary of suicide-related adverse events stratified by suspected antidepressant medicine and age group.

Figure 5: Suicide-related adverse events reported in persons under 25 years of age by suspected antidepressant medicine

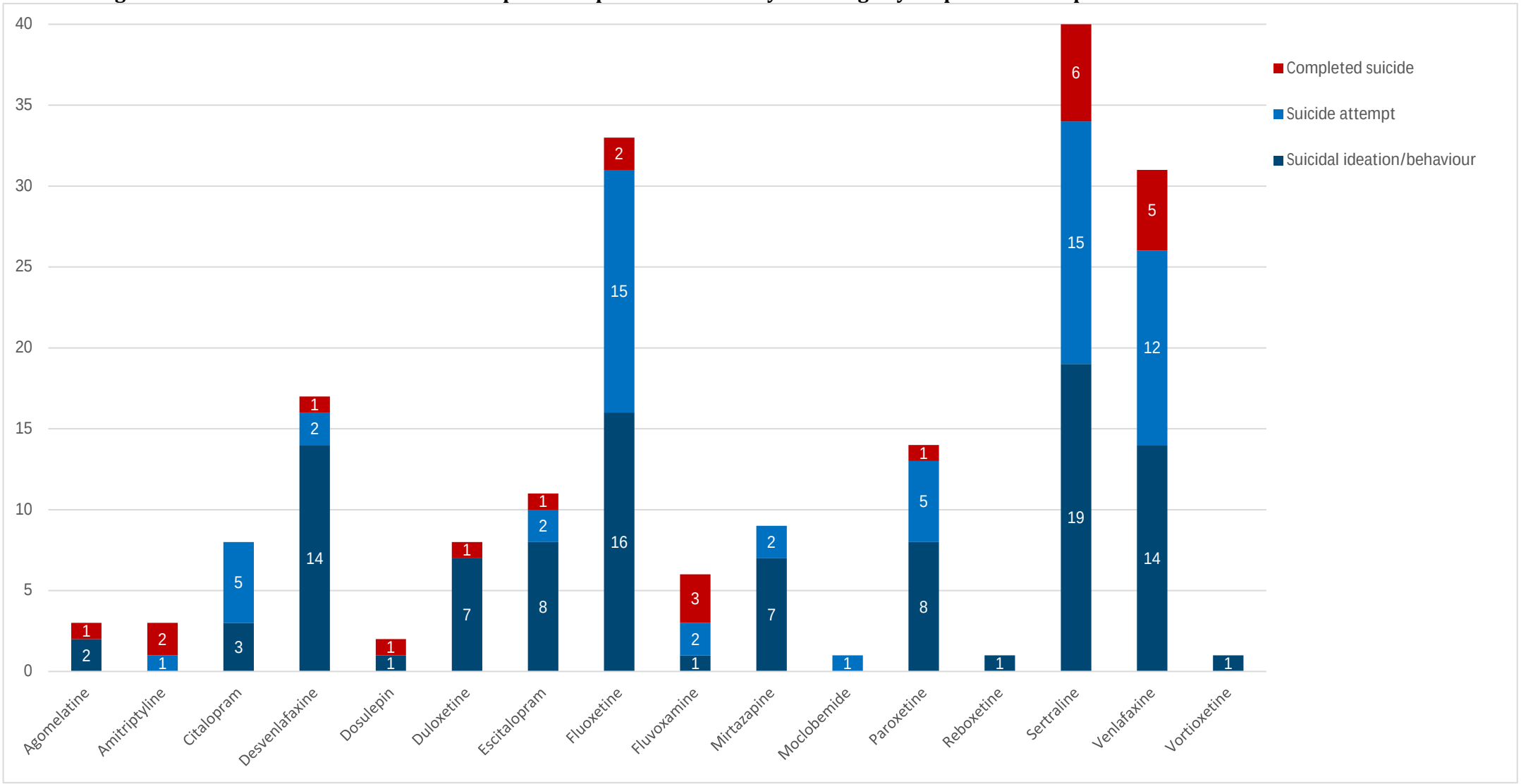


Figure 6: Suicide-related adverse events reported in young adults aged 18 to 24 years by suspected antidepressant medicine

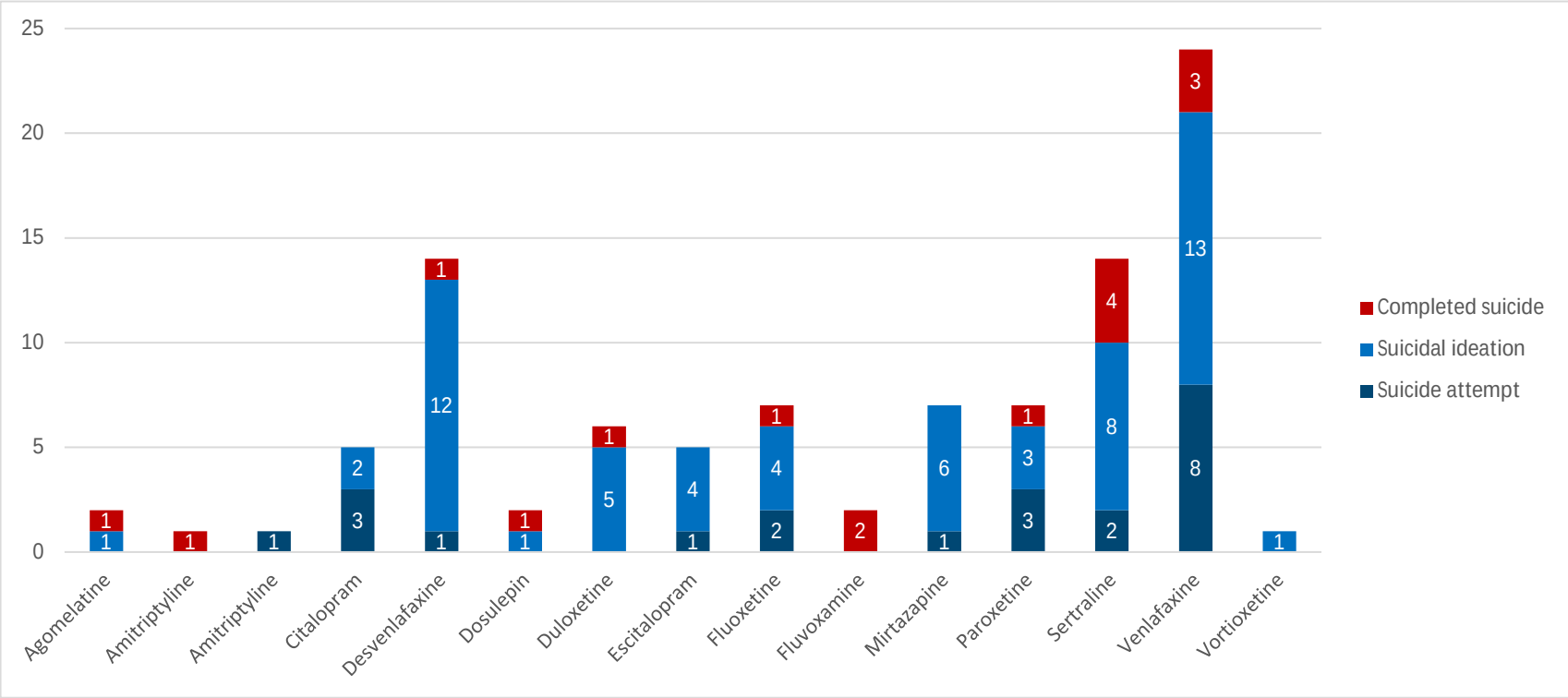


Figure 7: Suicide-related adverse events reported in adolescents aged 13 to 17 years by suspected antidepressant medicine

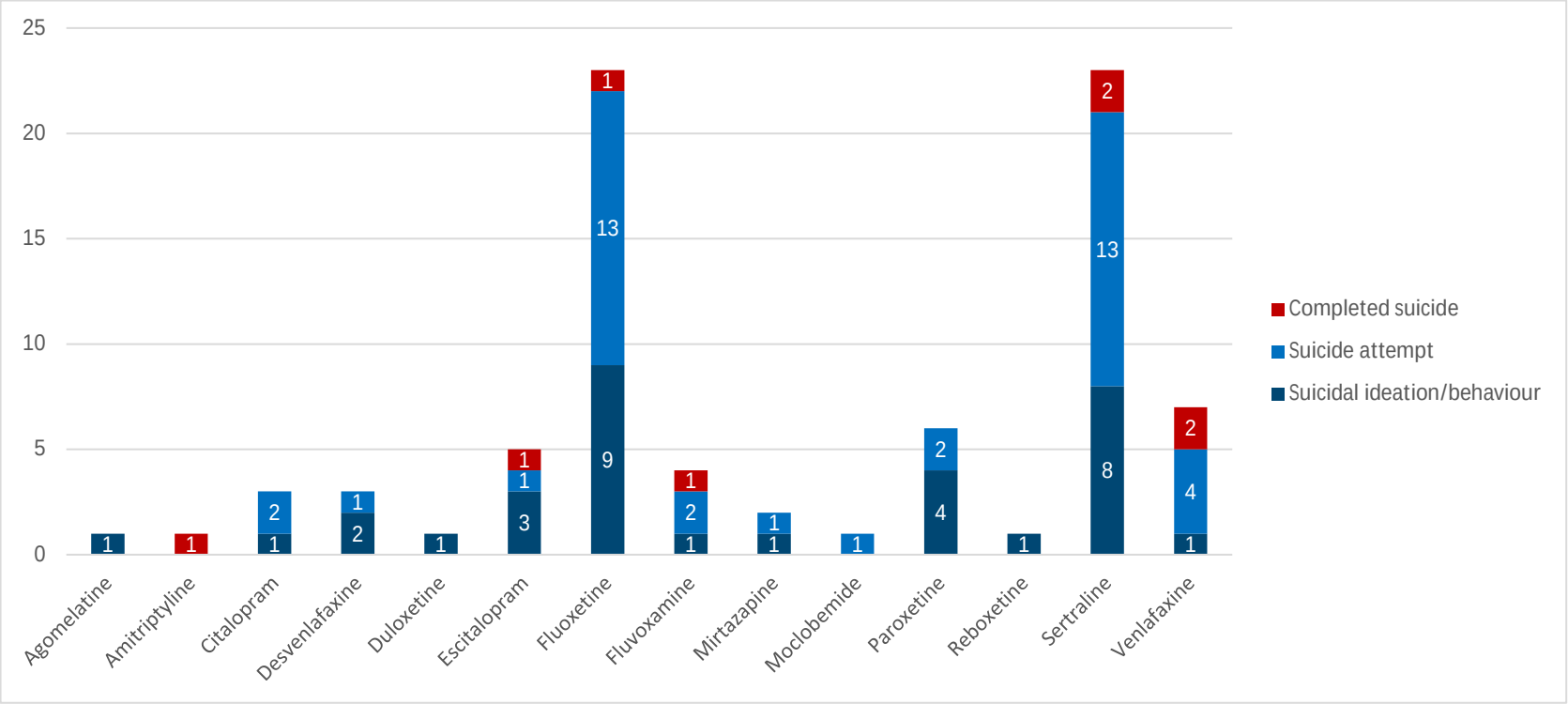
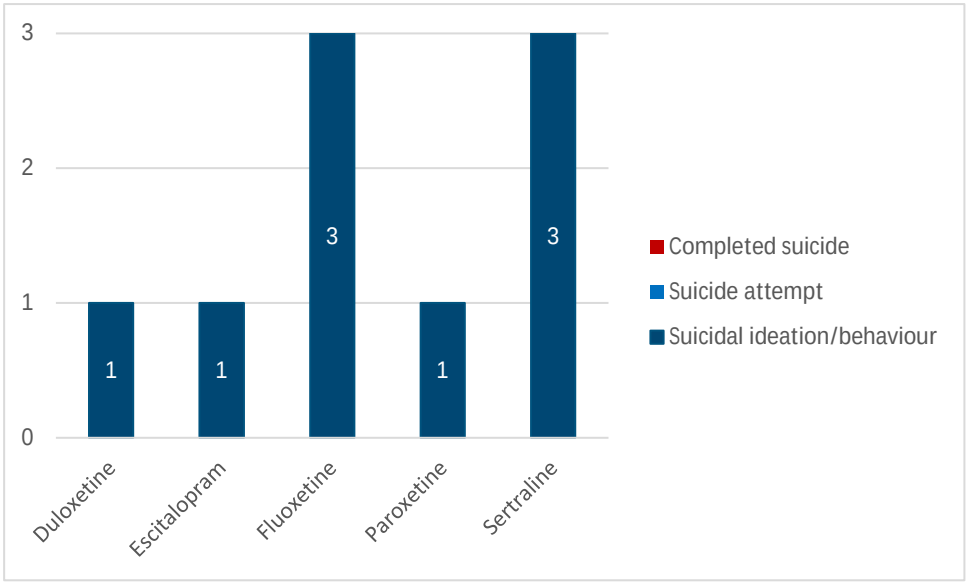


Figure 8: Suicide-related adverse events reported in children 12 years of age and under by suspected antidepressant medicine



3.2.3 Appraisal of Whitely et al publication

Whitely, et al., compared changes in PBS antidepressant dispensing to young Australians (aged <28 years) with youth suicide rates (aged <25 years) from the ABS.[1] They found that Australian youth suicide rates have trended upwards in the decade from 2009 to 2018 and there has been an increase in antidepressant dispensing in youths in the same period. The proportion of young Australians using antidepressants rose from 2.9% to 4.8% over 2008-09 to 2017-18 (a 66% increase). The suicide rate for Australians aged 9-24 years increased from 3.87 to 5.78 deaths per 100,000 (49.2% increase) between 2009 and 2018. Whitely et al state that "*there is clear evidence that more young Australians are taking antidepressants, and more young Australians are killing themselves and self-harming…*".

The authors acknowledged a number of limitations of their analysis including that:

- Many factors impact suicide rates and it is impossible to isolate the effects of specific factors.
- Data collection practices have changed over time, which can make interpretation of time trends difficult, especially before and after 2012 due to changes in the data to record low cost prescriptions.
- The analysis is complicated by the use of different age group and calendar year definitions in the dispensing and suicide outcomes ("*antidepressant dispensing data cover the age-range 0–27 years; however, suicide data cover ages 0–24 years. Also, antidepressant data are for financial years (July to June), but suicide data are for calendar years*)".[1]
- Correlation in observational studies is not sufficient to establish a causal association because of inherent uncontrolled confounding factors that influence youth suicide rates.

Additional limitations identified by the TGA's appraisal include that:

- The PBS data and ABS suicide data analysed in this study are not linked so it is not possible to tell whether the young people recorded as having completed suicide had actually been prescribed an antidepressant.
- It is not possible to identify the reason the antidepressants were prescribed, as PBS data does not include a diagnosis field and there are several conditions for which antidepressants are prescribed in children.

- The analysis was not stratified by sex, despite well-established sex differences in suicide risk.

Overall, while the rate of antidepressant prescribing to children and adolescents is of concern, the analysis presented by Whitely, et al., does not represent causal evidence that antidepressant use in these age groups increases the risk of suicidal behaviours.

3.2.4 TGA analysis of PBS and ABS data

In light of the limitations of the Whitely, et al., paper discussed in the previous section, the TGA conducted an analysis of antidepressant prescribing on the PBS and suicide rates in young age groups to explore rates of antidepressant prescribing and youth suicide in more detail.

Data sources and methods

The rate of suicide analysis used two sources of data published by the ABS: 1) annual number of male and female suicides between 2009 and 2019 at ages 0-14, 15-19 and 20-24 years[31, 32] and 2) annual mid-year populations for these ten years in one-year age intervals[33]. We combined the population estimates for the relevant ages to match the suicide data and calculate age-specific rates of suicide (per 100 000). We further combined all ages to calculate rates of suicide under age 25, and combined male and female data to analyse suicide rates for the two sexes combined.

As preliminary analysis indicated changes in the risk of suicide that varied over time, we divided the eleven years into three time intervals (2009-2012, 2013-2015 and 2016-2019) and calculated proportionate change between the time intervals as well as proportionate change over the entire period to summarise the suicide trends.

The number of suicides was small, and the mortality data were subject to considerable fluctuations. This is particularly the case in the age-specific analysis. The grouping of calendar years mitigated some of the annual fluctuations, allowing better evaluation of overall trends.

Although the quality of Australia's cause-of-death coding is good, delays in the coroner's investigation and finalising the cause of death may result in the underestimation of suicide deaths, adding additional uncertainty to the trends.[34]

Antidepressant dispensing data were extracted from the PBS, Australia's national program for government-subsidised prescription medicines. From April 2012 onwards, the PBS captures all dispensing for medicines listed on its schedules, including the transactions below the threshold for government subsidy. However, the PBS does not cover prescriptions in the private market or public hospital inpatients. In addition, medication dispensing does not fully capture the use of health services, in particular specialist services, as the patient may consult a healthcare provider without being prescribed medications.

For each dispensing, the PBS provides information on the demographic and residential characteristics of the patient, and the prescriber's specialty type as well as medication names and classifications. Our analysis used patient, prescriber and medication characteristics at the time of first dispensing.

Medications with the Anatomical Therapeutic Chemical (ATC) Classification code 'N06A' were included in the analysis. Antidepressants were further divided into four classes: monoamine reuptake inhibitors (4th-level ATC code N06AA), SSRI (N06AB), non-selective monoamine oxidase inhibitors and monoamine oxidase A inhibitors (N06AF and N06AG), and other antidepressants (N06AX).

For each year between 2013 and 2019, prevalent antidepressant users were defined as patients who were dispensed an antidepressant medication in that year. Patients were restricted to those aged under 25, further divided into three age groups of 0-14, 15-19 and 20-24 years to match the ABS suicide data. Rates of antidepressant dispensing were calculated as the number of patients divided by the ABS mid-year population. Dispensing rates were expressed as per 100 (rather than %) to avoid confusion with proportionate change (expressed as %) in the mortality analysis.

Prescriber type was analysed for the population of incident antidepressant users aged 5-17 years between 2015 and 2019. Incident use was defined as the first antidepressant dispensing over the five years and no antidepressant dispensing between 2012 and 2014 in the PBS. A minimum three-year look-back period has been used previously to study antidepressant use in paediatric patients.[35, 36] The incident user analysis was restricted to those aged 5-17 years, the patient population targeted by clinical guidelines recommending that initiation of antidepressants for treating major depression should follow assessment and diagnosis by clinicians with the specific experience and expertise of treating paediatric mental health conditions.[19, 37]

Incident male and female patients were categorised into three age groups: 5-11, 12-14 and 15-17 years. Prescribers were grouped into four types: paediatrician, psychiatrist, general practitioner, and other. When modelling the data, a binary variable of paediatrician/psychiatrist vs. all others was used.

The patient's postcode associated with the incident dispensing was used to determine the geographic remoteness and area-level socioeconomic status of the patient's residence. Using the correspondence between postcodes and remoteness areas generated by the ABS, five classes of remoteness areas were defined according to relative access to services: major cities, inner regional, out regional, remote and very remote.[38] The IRSAD socioeconomic status index was developed by the ABS, based on Census data about income, education, occupation, employment and housing.[39] Deciles of the IRSAD score were used in the analysis. Area-level characteristics were coded as missing if no postcode was listed or if the listed postcode was for the purpose of postal deliveries (e.g., post office boxes) with no defined geographic location.

The linear probability model was used to model the probability of specialist prescribing (that is, paediatrician/psychiatrist) vs. all others in relation to geographic remoteness and the demographic and social variables. The coefficients under the linear probability model can be directly interpreted as probabilities. The probability model was used instead of the logit model for ease of interpretation. However, a separate logistic regression analysis (not shown) found largely similar results.

Two models were estimated. Model 1 includes geographic remoteness, calendar year, age and sex. Model 2 adds the IRSAD deciles to the analysis. A comparison of coefficient estimates under the two models would show the extent to which variations in specialist prescribing across remoteness areas were explained by socioeconomic conditions. As more remote areas tend to have fewer social and economic resources, it was expected that remoteness area variations in specialist prescribing were at least partially of socioeconomic origin.

The ABS data were available in the public domain. The PBS data were extracted from the Enterprise Data Warehouse of the Department of Health on 8 July and 21 September 2020, using Teradata SQL. The statistical models were estimated in the R software (version 4.0.0).

Trends in suicide mortality

Suicide rates increased between 2009 and 2019, but the increase was smaller in the later than earlier years. For the two sexes combined, suicide mortality increased from 4.43 per 100 000 in 2009-2012 to 5.24 in 2013-2015 and 5.75 in 2016-2019, with a proportionate increase of 18% and 10% respectively (Table 3).

Table 3: Suicide rates under age 25 years, Australia 2009-2019

Age intervals (years)	Rates (per 100 000) 2009-12 (1)	2013-15 (2)	2016-19 (3)	Proportionate change (%) (2) vs. (1)	(3) vs. (2)	(3) vs. (1)
Two sexes						
0-14	0.28	0.43	0.45	50.6	4.0	56.7
15-19	8.05	9.94	11.11	23.4	11.8	38.0
20-24	12.04	13.95	15.44	15.8	10.7	28.2
All ages	4.43	5.24	5.75	18.3	9.7	29.7
Male						
0-14	0.24	0.41	0.51	69.1	24.9	111.2
15-19	10.71	13.32	15.53	24.4	16.6	45.0
20-24	17.43	20.75	23.23	19.0	11.9	33.3
All ages	6.12	7.36	8.32	20.2	13.0	35.8
Female						
0-14	0.33	0.45	0.37	36.3	-16.2	14.2
15-19	5.25	6.38	6.46	21.6	1.2	23.0
20-24	6.38	6.85	7.27	7.3	6.2	13.9
All ages	2.65	3.01	3.04	13.6	1.0	14.7

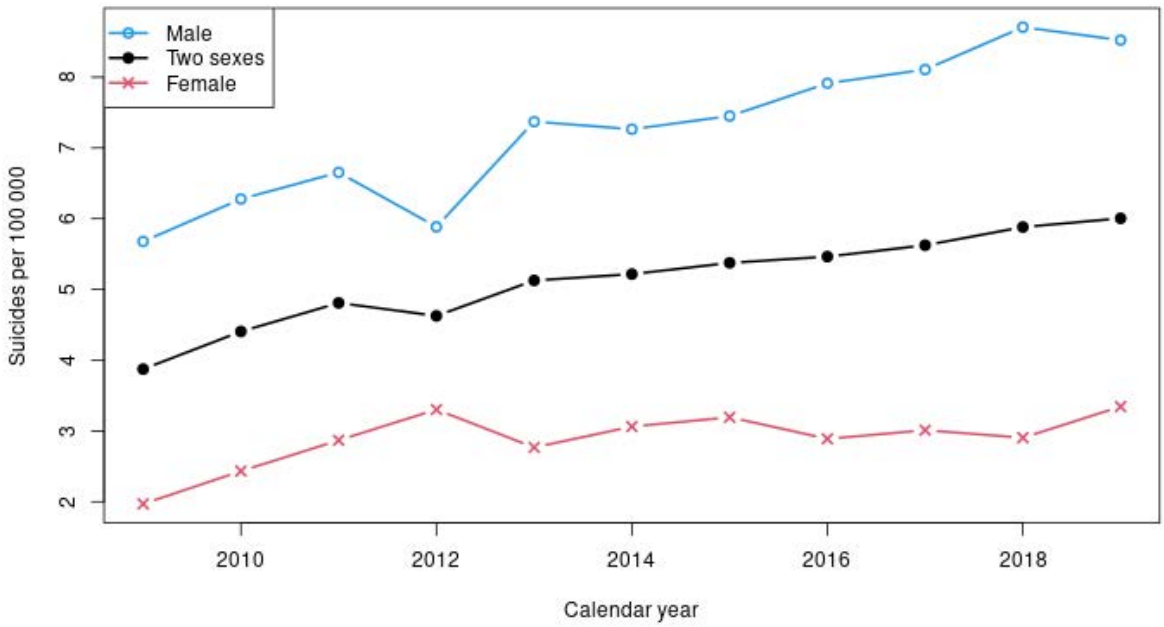
Source: ABS

There were substantial sex differences in the trends. The mortality increases were stronger for males, with an overall increase of 36% for males and 15% for females across the eleven years. The generally upward trend persisted over the eleven years for males only. Male suicide rates increased from 6.12 per 100 000 in 2009-2012 to 7.36 in 2013-2015 and 8.32 in 2016-2019, with a proportionate increase of 20% and 13%, respectively. In contrast, female suicide increased from 2.65 per 100 000 in 2009-2012 to 3.01 per 100 000 in 2013-2015, but did not change perceptibly afterwards and stayed at 3.04 per 100 000 in 2016-2019; the proportionate change was 14% and 1% in the respective sub-periods.

Age-specific suicide rates show similar sex-specific variations over time. From 2009-2012 to 2013-2015, male mortality increased by 69%, 24% and 19% at ages 0-14, 15-19 and 20-24 years, respectively. From 2013-2015 to 2016-2019, the corresponding increases were reduced to 25%, 17%, 12% respectively. In comparison, female suicide rates increased by 36%, 22% and 7% at the respective ages in the earlier years, but in the later years decreased by 16% at ages 0-14, and increased by 1% and 6% at ages 15-19 and 20-24, respectively.

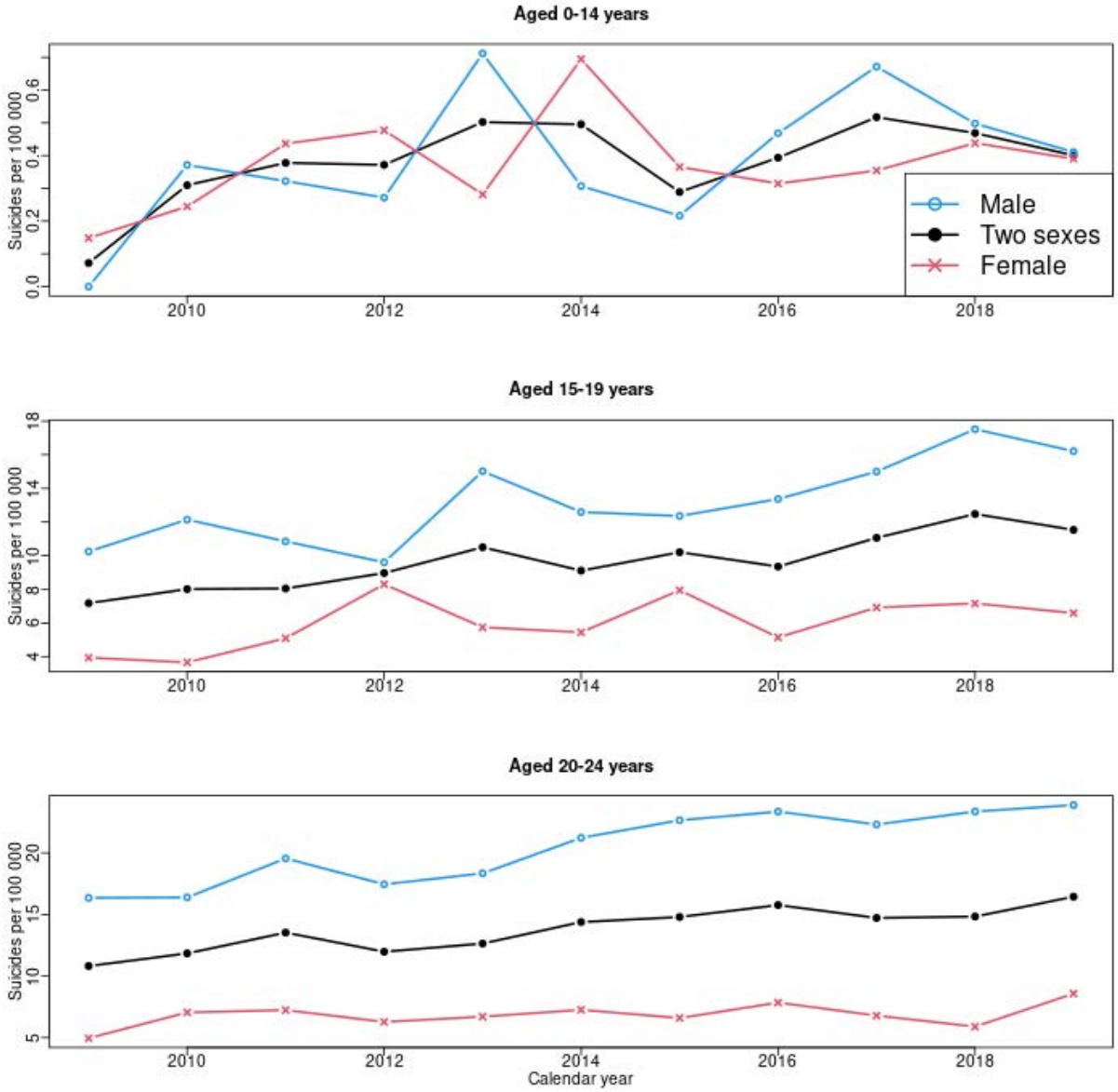
Suicide rates in Table 3 were grouped across calendar years to reduce fluctuations. However, the annual rates (Figures 9 and 10) were consistent with a broad trend of mortality increases that continued at a smaller pace for males and halted for females from around 2013 onwards, except for an uptick in 2019.

Figure 9: Rates of suicide under age 25 years, Australia 2009-2019



Source: ABS

Figure 10: Age-specific rates of suicide, Australia 2009-2019



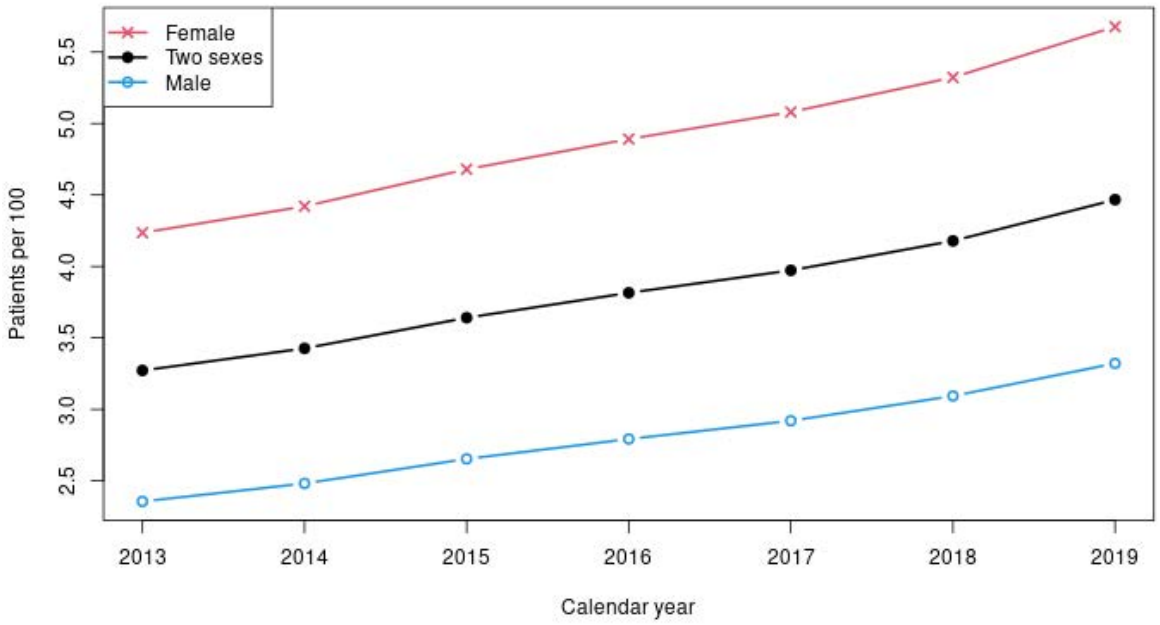
Source: ABS

Prevalent users of antidepressants

Rates of antidepressant dispensing in the PBS increased steadily from 3.3 per 100 in 2013 to 4.5 per 100 in 2019, with an average annual increase of 0.17 percentage points (Figure 11). Dispensing was higher for females than males, but increased over time for both sexes: from 2.4 to 3.3 per 100 for males and from 4.2 to 5.7 per 100 for females. The increase was smooth over time, with an annual change of 0.14 and 0.21 percentage points for males and females respectively. Age-specific dispensing rates also increased similarly for males and females (Figure 12).

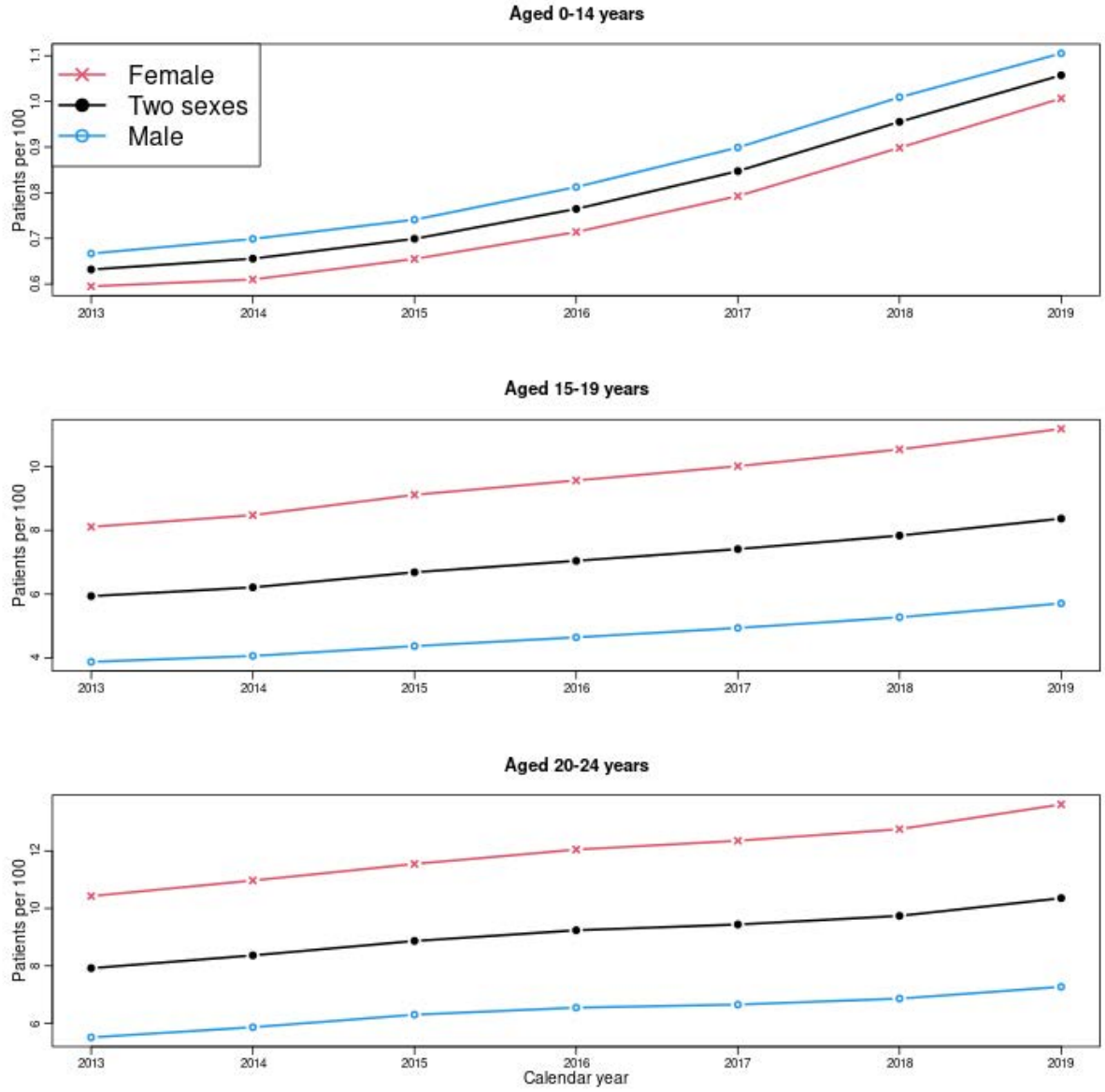
SSRIs took up the majority of antidepressant use, increasing from about two-thirds in 2013 to three-fourths of all antidepressant dispensing in 2019 (see Appendix 4). The share of the SSRIs was largest in the youngest ages, decreasing from 88% at ages 0-14 to 68% of all antidepressants at ages 20-24 in 2019 (see Appendix 5). There were no notable sex differences in the distribution of antidepressant medication classes.

Figure 11: Rates of antidepressant dispensing, under age 25 years, Australia 2013-2019



Source: ABS; PBS

Figure 12: Age-specific rates of antidepressant dispensing, Australia 2013-2019



Source: ABS; PBS

Incident users and type of prescribers

Over the five years between 2015 and 2019, a total of 211,534 children and adolescents aged 5-17 years received their first-ever prescriptions of PBS-subsidised antidepressants, increasing from 37,711 to 47,531 incident uses annually (see Appendix 6). One third of the first antidepressant dispensings were prescribed by a paediatrician or psychiatrist (15% and 18%, respectively). The proportion of paediatrician/psychiatrist prescribers increased from 30% in 2015 to 33% in 2019, but decreased from 70% in those aged 5-11 years to 40% in those aged 12-14 and 17% in those aged 15-17. Paediatrician/psychiatrist prescribing was higher for boys than girls (43% vs. 25%), for patients residing in major cities than in very remote areas (35% vs. 19%), and for patients in areas that are more socioeconomically advantageous (43% in the top decile vs. 28% in the bottom decile of the Index for Relative Socioeconomic Advantage and Disadvantage or IRSAD, a area-level measure of socioeconomic status).

Two linear probability models of prescribing by paediatricians/psychiatrists vs. others were estimated (see Appendix 7). Under Model 1, specialist prescribing was inversely associated with geographic remoteness and age, but increased over time and was higher for boys. Compared with those living in major cities, the percentage of paediatrician/psychiatrist prescribing was lower by 7 percentage points in inner regional areas,10 points in outer regional areas, 8 points in remote areas and 14 points in very remote areas, all else being equal. All estimates were statistically significant.

Under Model 2, statistical adjustment for the IRSAD deciles had no notable impact on age, sex or time differences in specialist prescribing. However, socioeconomic conditions explained part of the association between remoteness and specialist prescribing. After adjusting for deciles of the socio-economic index, variations across remoteness areas in the proportion of specialist prescribing were reduced but remained statistically significant. Relative to patients in major cities, the IRSAD-adjusted percentage of paediatrician/psychiatrist prescribing was lower by 3 percentage points in inner regional areas, 6 points in outer regional areas, 5 points in remote areas and 10 points in very remote areas, all else being equal. The proportionate reduction in percentage differences was larger for the comparison of major cities with the two regional areas and smallest for the comparison with the very remote areas. These results suggest that in addition to material and social resources, physical distance itself could be a significant barrier to accessing specialist care for paediatric mental health conditions; this is particularly the case in Australia's very remote areas.

In 2019, for girls aged 5-11 years living in areas that were in the top decile of the IRSAD index, the proportion of having the first antidepressant prescription written by a paediatrician/psychiatrist was 75% in major cities, 72% in inner regional areas, 69% in outer regional areas, 70% in outer regional areas and 65% in very remote areas. These proportions specific to each of the five remoteness areas would increase by 10 percentage points for boys, and decrease by 27 percentage points for patients aged 12-14 years and by 49 points for patients aged 15-17 years and by 13 points if the IRSAD index was in the bottom decile. The annual increase in specialist initiation of antidepressant treatment was 0.4 percentage points.

Summary

Antidepressant use in young Australians has increased steadily over time, and the increase and patterning of antidepressant classes were similar between the sexes. There are higher rates of antidepressant prescribing to girls/women aged 15-24, but higher rates of prescribing to boys aged 0-14. It is possible that the gender differences in antidepressant prescribing in this younger age group are related to treatment of neurodevelopmental disorders such as attention-deficit/hyperactivity disorder, which are more prevalent in boys.[16] In contrast, suicide mortality increased for males but not as noticeably for females in recent years. Overall, the differences in mortality and PBS dispensing statistics between males and females, and between different age groups, demonstrate that the trends are not completely aligned, and therefore do not support a consistent association between rising antidepressant use and rising suicide risk. The majority of antidepressant treatment in children and adolescents was initiated by GPs. The prescriber type (GP vs. non-GP specialist) for the first PBS script identified varied across population subgroups and geographic areas. There are also gender differences in the prescriber type for the first antidepressant script with boys more likely to be first prescribed antidepressants by a specialist. Higher rates of initiation by GPs are consistent with the key role that they play in the assessment and management of paediatric mental health problems, in particular, in areas with access to fewer social and economic resources.

3.2.5 ACM advice on strength of the current evidence

The TGA sought advice from the ACM on 7 August 2020 on the current role of SSRIs and SNRIs in clinical practice in Australia for treating psychiatric disorders and developmental disorders in children, adolescents and young adults, the strength of the current evidence for an association between use of antidepressants and rates of youth suicide in Australia, and whether additional risk minimisation measures are warranted and would be effective to address any potential risk of suicide amongst children, adolescents and young adults prescribed SSRIs or SNRIs.

The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines. Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.[40] In addition to a psychiatrist who is a permanent member of the ACM, two additional experts nominated by the ACM Chair were invited to respond to the TGA's questions. The two invited experts were a Paediatrician/Associate Professor in Paediatrics and a Child and Adolescent Psychiatrist/Public Health Physician.

The ACM acknowledged that clinical worsening of depression and suicidal thoughts is a recognised and well-known risk observed in clinical trials of antidepressant medicines and can occur in a small number of patients during the early phases of treatment.

The ACM discussed the information presented in the paper by Whitely, et al.,[1] and highlighted that:

- Confounding by the condition being treated (known as confounding by indication) remains an unresolved issue when interpreting data of this type.
- Correlation does not prove causation.
- Suicide is a complex outcome with many factors affecting the mental health of children and adolescents, including family dynamics, school and social dynamics, drug and alcohol use, social media and gaming use.

The ACM did not support the authors' interpretation of a possible causal relationship between the dispensing of antidepressants on the PBS and rates of youth suicide in Australia.

The ACM advised that there is a valid and important role for SSRIs and SNRIs in current clinical practice in treating moderate-to-severe depression in children and adolescents, supported by professional guidelines.

3.3 Are current risk minimisation measures adequate?

3.3.1 Efficacy of risk minimisation in Australia to date

The TGA has published a number of communications since 2004 with the aim of educating prescribers and the general public about the increased risk of suicidality observed in clinical trials, the need to ensure treatment of mood disorders in children is consistent with clinical guidelines, and to underscore the importance of monitoring patients when they commence treatment with an antidepressant for worsening of the condition and emerging suicidality. Other organisations such as NPS MedicineWise, with which the TGA works closely to amplify and align risk communications, have published editorials in the Australian Prescriber publication to further promulgate messaging about appropriate treatment of depression in children and adolescents, and the need to monitor closely for clinical worsening or emergent suicidality.

As outlined above in section 2.3, the RANZCP clinical practice guidelines for mood disorders offer medical practitioners practical advice on risk mitigation in relation to prescribing for children and adolescents with psychiatric disorders.[18] These guidelines outline that while some therapies may be effective for the treatment of mood disorders they are yet to receive approval for such use in Australia and as such are used 'off-label'. The RANZCP recommends that practitioners carefully document any clinical decision to use therapeutic agents outside of their registered indications, and specifically outline that this issue should be explained to patients. In addition to this warning, the RANZCP advises clinicians that, "*children and adolescents prescribed antidepressants must be closely monitored for emergent suicidality, hostility, agitation, mania, and unusual changes in behaviour*".[18]

Formal evaluation of the impact of antidepressant PI updates about clinical worsening and suicidality has not been undertaken. Issues with the way PBS data was collected prior to 2012 made it difficult to obtain accurate information about the extent of antidepressant prescribing.

Evaluation of regulatory changes made in other countries has resulted in inconsistent findings. There is disagreement in the published literature about the impact of the FDA black box warning on patients. Some researchers have attributed a rise in suicide rates in the US following the black box warning to decreased use of antidepressants secondary to widespread media concern generated by the FDA's actions.[41] This hypothesis has been criticised for relying on ecological data, from which causal inference cannot be made.[42]

3.3.2 ACM advice on adequacy of current risk minimisation measures

In addition to considering the strength of current evidence for an association between antidepressants and youth suicide, the ACM considered the adequacy of existing risk minimisation measures. The ACM highlighted that the TGA approved PI documents for antidepressants include warnings about the risks of clinical worsening of depression and suicidal thoughts and specifically mention children, adolescents and young adults and that this information is also conveyed in the CMI for these products.

The ACM advised that current warnings and precautions in PI documents were adequate and noted that the possible emergence of suicidal thoughts during the initial few months of antidepressant treatment or at times of dose adjustment is addressed in PI documents. They advised that this risk is minimised by starting with a low dose and increasing slowly, coupled with close monitoring particularly following initiation or during dose titration.

The ACM acknowledged that antidepressants can be prescribed off-label to children and adolescents for psychiatric indications in Australia.

Advice from the ACM indicated that clinicians, particularly paediatricians and child psychiatrists, are well aware of issues around treatment-emergent clinical worsening or suicidality, and take warnings about monitoring patients seriously. In the general practice setting, anecdotal feedback has been that prescription of antidepressants to children and adolescents is seen as a stop-gap measure, particularly for moderate-to-severe depression, while waiting for access to psychological therapy.

The ACM supported prescriber and consumer education on what to expect when they start treatment with an antidepressant. The ACM also highlighted the need for additional clinical guidance for GPs around the management of depression and prescribing of antidepressants to young people, in particular, the need for supplementary information about appropriate dosing in younger age groups.

The ACM did not support additional restriction on the availability of antidepressants as it would further disadvantage young people, especially in regional, rural and remote areas. However, they did express concern around the increasing use of antidepressants in young people.

3.3.3 ACM advice on access to psychological therapies

As noted in section 2.3.2, current clinical guidelines place a strong emphasis on psychosocial therapies as the preferred mode of treatment for depressive disorders in children and adolescents, with the use of SSRIs reserved for moderate-to-severe depression when other treatments have failed. However, the ACM noted that, in practice, access to publicly funded psychological therapies is often extremely limited, GPs face great difficulty in having their patients seen by a child and adolescent psychiatrist in a timely manner, referral pathways are complex and there are significant equity issues in accessing private psychiatric services.

The ACM suggested that improving access to information and care, in particular improved access to psychological therapies, will assist young people and represents an opportunity to minimise risk in this population.

4. Conclusions and recommendations

4.1 Conclusions

Whilst the increasing use of antidepressants in young people is a concern, the strength of the current evidence available is insufficient to conclude that a causal relationship exists between prescribing of antidepressants and rates of youth suicide.

PBS dispensing data shows a steady increase in the rate of antidepressant prescribing to young people in Australia, both male and female, between 2013 and 2019. Rates of suicide of young people in Australia have also increased but with more a more complex trajectory. Male and female suicide rates show differing trends. The TGA found that male suicide rates increased over the ten-year period by 33%, but with a smaller increase of 10% from 2013-2015 to 2016-2018, compared with an increase of 20% from 2009-2012 to 2013-2015. In comparison, female suicide rates increased by nine per cent over the 10 years, but the trend reversed in the latter half of the 10 year period, with a decrease of four per cent from 2013-2015 to 2016-2018, compared with an increase of 14% in the earlier years. These complexities are important to consider when studying the relationship between antidepressants and suicide deaths. Aggregated trends are useful to generate hypotheses, but are not a sufficient base for making causal statements. Analysis of linked PBS data and suicide data is required to further explore any potential causal relationship between antidepressants and increased rates of youth suicide in the Australian context.

Review of peer-reviewed literature published in the last five years did not add substantially to the body of evidence in support of either the efficacy or safety of antidepressants in children and adolescents.

Clinical worsening of depression and suicidality is a recognised potential risk with the use of antidepressant medicines, based on clinical trial data that showed an increased risk of suicidality in children, adolescents, and young adults (ages 18-24) with MDD and other psychiatric disorders. However, no suicides occurred in these trials and it is unknown whether the suicidality risk in children and adolescents extends to use beyond several months. Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidality, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs.

The regulatory status of SSRIs and SNRIs in overseas jurisdictions is similar to Australia except that certain SSRIs are approved for use in children in the United Kingdom and the United States and all SSRI and SNRI products approved in the United States contain a boxed warning that outlines the risk of increased suicidality in children, adolescents and young adults. The TGA approved PIs for antidepressants include warnings about this risk and specifically mention children, adolescents and young adults. This information is also conveyed in the CMI for these products.

The ACM advised that there is a valid and important role for SSRIs and SNRIs in current clinical practice in treating moderate-to-severe depression in children and adolescents, supported by professional guidelines. Guidelines produced by the RANZCP recommend psychological therapies as the first line treatment for MDD of all levels of severity in young people with fluoxetine as second line treatment for moderate to severe MDD in children and adolescents.16 However, in practice, access to publicly funded psychological therapies is often extremely limited. The Committee advised that current warnings and precautions in Australian PI documents were adequate and that the possible emergence of suicidal thoughts during the initial few months of antidepressant treatment or at times of dose adjustment is addressed in PI documents.

4.2 Recommendations

Based on the findings of this safety investigation, the TGA will:

1. Liaise with the relevant professional colleges regarding the outcomes of our review and ACM advice, and, in particular, the need for additional clinical guidelines for general practitioners around the management of depression and prescribing of antidepressants to children, adolescents and young people. Letters have already been sent from the TGA to the Royal Australian College of General Practitioners, the Royal College of Physicians and the Royal Australian and New Zealand College of Psychiatrists, to advise them of the ACM advice and request that these bodies work collaboratively towards providing additional guidance for pharmacological management of depression in young people.
2. Explore potential analysis of linked PBS, Medicare Benefits Schedule (MBS), hospital and death data to further investigate the clinical journeys of young people prescribed antidepressants in Australia and the relationship between antidepressants and rates of youth suicide. In addition there will be consideration of the utility of established datasets held by the Australian Bureau of Statistics and the Australian Institute of Health and Welfare. This work will commence in early 2021 subject to access to data.

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6. Appendices

Appendix 1 – List of antidepressants registered for the treatment of depression in Australia (ATC code N06A) – registered indications and PBS availability

Selective serotonin reuptake inhibitors (SSRIs)			
Generic name (innovator trade name)	**Innovator Sponsor**	**Registered indication(s)**	**PBS availability**
Citalopram (Cipramil)	Lundbeck Australia Pty Ltd	• Major depression	• Restricted Benefit* – Major depressive disorders
Escitalopram (Lexapro)	Lundbeck Australia Pty Ltd	• Major depression • Social anxiety disorder (social phobia) • Generalised anxiety disorder • Obsessive compulsive disorder	• Restricted Benefit – Major depressive disorders – Moderate to severe generalised anxiety disorder – Moderate to severe social anxiety disorder (social phobia, SAD)
Fluoxetine (Prozac)	Eli Lilly Australia Pty Ltd	• Major depression • Obsessive compulsive disorder • Pre-menstrual dysphoric disorder	• Restricted Benefit – Major depressive disorders – Obsessive-compulsive disorder
Fluvoxamine (Luvox)	Mylan Health Pty Ltd	Children and Adolescents (8 years and over) • Obsessive compulsive disorder Adults • Major depression • Obsessive compulsive disorder	• Restricted Benefit – Major depressive disorders – Obsessive-compulsive disorder

Paroxetine (Aropax)	Aspen Pharmacare Australia Pty Ltd	• Major depression and prevention of relapse of depressive symptoms • Obsessive compulsive disorder and prevention of its relapse • Panic disorder and prevention of its relapse • Social anxiety disorder • Generalised anxiety disorder • Post-traumatic stress disorder	• Restricted Benefit – Major depressive disorders – Obsessive-compulsive disorder – Panic disorder
Sertraline (Zoloft)	Upjohn Australia Pty Ltd	Children and Adolescents (6 years and over) • Obsessive compulsive disorder Adults • Major depression • Obsessive compulsive disorder • Panic disorder • Social phobia and prevention of its relapse • Pre-menstrual dysphoric disorder	• Restricted Benefit – Major depressive disorders
Serotonin and noradrenaline reuptake inhibitors (SSRIs)			
Generic name (trade name)	**Innovator Sponsor**	**Indication(s)**	
Desvenlafaxine (Pristiq)	Pfizer Australia Pty Ltd	• Major depressive disorder, including the prevention of relapse • "Not indicated for paediatric use"	• Restricted Benefit – Major depressive disorders

Duloxetine (Cymbalta)	Eli Lilly Australia Pty Ltd	• Major depressive disorder • Diabetic peripheral neuropathic pain • Generalised anxiety disorder	• Restricted Benefit – Major depressive disorders
Venlafaxine (Efexor)	Upjohn Australia Pty Ltd	• Major depression, including prevention of relapse and recurrence • Generalised anxiety disorder • Social anxiety disorder • Panic disorder, including prevention of relapse	• Restricted Benefit – Major depressive disorders
Tricyclic antidepressants (TCAs)			
Amitriptyline (Endep)	Alphapharm Pty Ltd	• Major depression • Nocturnal enuresis where organic pathology has been excluded	• General Schedule
Clomipramine (Anafranil)	Novartis Pharmaceuticals Australia Pty Ltd	• Major depression • Obsessive-compulsive disorders and phobias in adults • Cataplexy associated with narcolepsy	• Restricted Benefit – Cataplexy associated with narcolepsy – Obsessive-compulsive disorder – Phobic disorders in adults
Dosulepin/Dothiepin (Dothep)	Alphapharm Pty Ltd	• Major depression	• General Schedule
Doxepin (Sinequan)	Pfizer Australia Pty Ltd	• Major depression	• General Schedule

Imipramine (Tofranil)	Amdipharm Mercury Australia Pty Ltd	• Major depression • Nocturnal enuresis (from the age of 5 years onwards and provided the possibility of • organic causes has first been excluded)	• General Schedule
Nortriptyline (Allegron)	Arrow Pharma Pty Ltd	• Major depression	• General Schedule
Monoamine oxidase inhibitors (MAOIs)			
Phenelzine (Nardil)	Link Medical Products Pty Ltd T/A Link Pharmaceuticals	• Major depression	• Restricted Benefit – Depression The treatment must be for when all other anti-depressant therapy has failed; OR The treatment must be for when all other anti-depressant therapy is inappropriate.
Tranylcypromine (Parnate)	Amdipharm Mercury Australia Pty Ltd	• The treatment of symptoms of depressive illness especially where treatment with other types of antidepressants has failed.	• General Schedule
Other			
Agomelatine (Valdoxan)	Servier Laboratories Australia Pty Ltd	• Major depression in adults including prevention of relapse	• Not applicable
Mianserin (Lumin)	Alphapharm Pty Ltd	• Major depression	• Restricted Benefit – Severe depression

Mirtazapine (Avanza)	Merck Sharp & Dohme (Australia) Pty Ltd	• Major depression including relapse prevention	• Restricted Benefit – Major depressive disorders
Moclobemide (Aurorix)	Mylan Health Pty Ltd	• Major depression	• Restricted Benefit – Major depressive disorders
Reboxetine (Edronax)	Pfizer Australia Pty Ltd	• Major depression	• Restricted Benefit – Major depressive disorders
Vortioxetine (Brintellix)	Lundbeck Australia Pty Ltd	• Major depressive disorder in adults including prevention of relapse.	• Not applicable

*Restricted medicines listed in the schedule are only prescribed if the condition meets the stated restrictions.

Appendix 2 – TGA DAEN search strategy for youth suicide reported with the use of antidepressants – 19 November 2020

Medicine:

SSRIs: Citalopram, dapoxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline.

SNRIs: Desvenlafaxine, duloxetine, milnacipram, venlafaxine.

TCAs: Amitriptyline, clomipramine, dosulepin, doxepin, imipramine, nortriptyline.

MAOIs: Phenelzine, tranylcypromine.

Other: Agomelatine, mianserin, mirtazapine, moclobemide, reboxetine, vortioxetine.

MedDRA system organ class: Psychiatric disorders

MedDRA Reaction Terms: Completed suicide, suicidal attempt, suicidal ideation, suicidal behaviour.

Sort by: 'Age – lowest first'

Appendix 3 – Case line listing of completed suicides reported with use of antidepressants – 19 November 2020

Case No.	Report Date	Sex	Age	Medicine (Onset Time)	Reaction	Sole Suspect
208539	7/06/2005	Female	21	- Aropax (**paroxetine hydrochloride**) - Suspect; - Lamictal (**Lamotrigine**) - Suspect; - Trade Name Not Specified (**Carbamazepine**) - Suspect; - Trade Name Not Specified (**Thioridazine hydrochloride**) - Suspect	Completed suicide ; Overdose ; Toxicity to various agents	No
209759	12/07/2005	Male	21	- Efexor-XR (**Venlafaxine hydrochloride**) - Suspect	Completed suicide	Yes
215419	31/01/2006	Female	14	- Diane-35 ED (**cyproterone acetate ; ethinylestradiol**) - Concomitant; - Efexor-XR (**Venlafaxine hydrochloride**) - Suspect (60 days); - Endep (**amitriptyline hydrochloride**) - Concomitant; - Ritalin (**methylphenidate hydrochloride**) - Concomitant; - Stilnox (**zolpidem tartrate**) - Concomitant; - Trade Name Not Specified (**Fluoxetine hydrochloride**) - Concomitant (149 days); - Zyprexa (**Olanzapine**) - Concomitant (21 days)	Akathisia ; Completed suicide ; Drug ineffective	Yes
235955	5/12/2007	Female	20	- Zoloft (**Sertraline hydrochloride**) - Suspect	Completed suicide ; Suicidal behaviour	Yes
246877	8/12/2008	Male	19	- Luvox (**Fluvoxamine maleate**) - Suspect (0 days)	Abdominal pain ; Completed suicide ; Headache ; Nightmare ; Poor quality sleep ; Rash ; Weight decreased	Yes
248391	9/02/2009	Male	24	- Efexor (**Venlafaxine hydrochloride**) - Suspect (27 days)	Completed suicide	Yes
252667	24/06/2009	Male	20	- Dothep (**dosulepin (dothiepin) hydrochloride)** - Suspect	Completed suicide ; Overdose	Yes
260274	24/11/2009	Male	24	- Amphetamine (**amfetamine**) - Suspect; - Luvox (**Fluvoxamine maleate**) - Suspect; - Zyprexa (**Olanzapine**) - Suspect	Completed suicide ; Drug interaction	No

Case No.	Report Date	Sex	Age	Medicine (Onset Time)	Reaction	Sole Suspect
287948	25/08/2011	Female	16	- Zoloft (**Sertraline hydrochloride**) - Suspect	Completed suicide ; Intentional overdose	Yes
287951	25/08/2011	Female	18	- Efexor-XR (Venlafaxine hydrochloride) - Suspect	Completed suicide	Yes
295619	8/02/2012	Male	19	- Zoloft (**Sertraline hydrochloride**) - Suspect	Completed suicide ; Gambling disorder	Yes
332300	10/12/2013	Female	22	- Zoloft (**Sertraline hydrochloride**) - Suspect	Completed suicide ; Feeling abnormal ; Psychotic disorder	Yes
343236	4/07/2014	Male	22	- Zoloft (**Sertraline hydrochloride**) - Suspect	Completed suicide ; Drug ineffective ; Mania	Yes
347609	16/09/2014	Male	21	- Valdoxan **(Agomelatine)** - Suspect	Completed suicide ; Drug ineffective	Yes
350180	12/11/2014	Male	20	- Cymbalta (**Duloxetine hydrochloride**) - Suspect (7 days); - Temtabs (**Temazepam**) - Concomitant	Abdominal pain ; Completed suicide ; Influenza ; Insomnia	Yes
360182	26/05/2015	Male	16	- Trade Name Not Specified (**Escitalopram**) - Suspect (121 days)	Completed suicide	Yes
366628	31/08/2015	Female	17	- Trade Name Not Specified (**Fluvoxamine maleate**) - Suspect	Completed suicide	Yes
387403	4/05/2016	Male	15	- Sertraline (**Sertraline hydrochloride**) - Suspect (45 days); - Symbicort (**Budesonide ; formoterol (eformoterol) fumarate dihydrate**) - Concomitant; - Trade Name Not Specified (**Melatonin**) - Concomitant; - Ventolin (**Salbutamol**) - Concomitant	Completed suicide	Yes
390527	22/06/2016	Male	21	- Pristiq (**Desvenlafaxine**) - Suspect	Completed suicide	Yes

Case No.	Report Date	Sex	Age	Medicine (Onset Time)	Reaction	Sole Suspect
403490	10/02/2017	Female	22	- Fluoxetine (**Fluoxetine hydrochloride**) - Suspect; - Paracetamol-Codeine Phosphate (**codeine phosphate hemihydrate ; Paracetamol**) - Concomitant; - Trade Name Not Specified (**Diazepam**) - Concomitant; - Trade Name Not Specified **(Quetiapine**) - Concomitant	Completed suicide	Yes
403506	10/02/2017	Female	17	- Trade Name Not Specified (**Venlafaxine hydrochloride**) - Suspect	Completed suicide ; Neurotoxicity	Yes
414707	24/07/2017	Female	14	- Endep **(amitriptyline hydrochloride)** - Suspect	Completed suicide ; Overdose	Yes
421896	14/11/2017	Male	16	- Fish Oil (**natural fish oil**) - Concomitant; - Lovan (**Fluoxetine hydrochloride**) - Suspect	Completed suicide	Yes
432995	10/05/2018	Male	24	- Trade Name Not Specified **(Amitriptyline)** – Suspect - Trade Name Not Specified **(Diazepam)** - Suspect	Completed suicide ; Toxicity to various agents	No

Appendix 4 – Number of antidepressant patients and distribution for drug classes, under age 25 years, Australia 2013-2019

		Proportions for drug classes (4th-level ATC codes)				
Calendar year	Total patients (N)	N06AA	N06AB	N06AF N06AG	N06AX	Total
Two sexes						
2013	245 068	0.091	0.665	0.002	0.242	1.000
2014	259 465	0.085	0.676	0.002	0.237	1.000
2015	278 375	0.079	0.690	0.002	0.229	1.000
2016	295 372	0.077	0.707	0.002	0.215	1.000
2017	311 470	0.072	0.726	0.002	0.200	1.000
2018	331 075	0.071	0.740	0.002	0.188	1.000
2019	357 037	0.068	0.753	0.001	0.177	1.000
Male						
2013	90 435	0.099	0.651	0.002	0.248	1.000
2014	96 330	0.087	0.667	0.002	0.244	1.000
2015	103 986	0.078	0.681	0.002	0.239	1.000
2016	110 802	0.074	0.698	0.002	0.226	1.000
2017	117 416	0.069	0.718	0.002	0.211	1.000
2018	125 784	0.066	0.733	0.002	0.199	1.000
2019	136 386	0.062	0.746	0.002	0.190	1.000
Female						
2013	154 633	0.086	0.674	0.002	0.239	1.000
2014	163 135	0.084	0.681	0.002	0.233	1.000
2015	174 389	0.080	0.696	0.002	0.223	1.000
2016	184 570	0.079	0.712	0.002	0.208	1.000
2017	194 054	0.074	0.731	0.002	0.193	1.000
2018	205 291	0.073	0.745	0.002	0.180	1.000
2019	220 651	0.071	0.758	0.001	0.170	1.000

Source: PBS

Note: N06AA for monoamine reuptake inhibitors, N06AB selective serotonin reuptake inhibitors, N06AF non-selective monoamine oxidase inhibitors, N06AG monamine oxidase A inhibitors, N06AX other antidepressants

Appendix 5 – Age-specific number of antidepressant patients and distribution for drug classes, Australia 2013-2019

	Two sexes				Male				Female			
		Proportions for drug classes (4th-level ATC codes)				Proportions for drug classes (4th-level ATC codes)				Proportions for drug classes (4th-level ATC codes)		
Calendar year	Total patients (N)	N06AA	N06AB	N06AF N06AG N06AX	Total patients (N)	N06AA	N06AB	N06AF N06AG N06AX	Total patients (N)	N06AA	N06AB	N06AF N06AG N06AX
Aged 0-14												
2013	27 664	0.193	0.749	0.058	14 986	0.206	0.742	0.051	12 678	0.178	0.757	0.065
2014	29 110	0.166	0.776	0.058	15 929	0.168	0.779	0.053	13 181	0.164	0.773	0.063
2015	31 461	0.136	0.810	0.054	17 120	0.140	0.811	0.050	14 341	0.132	0.810	0.058
2016	34 958	0.126	0.825	0.050	19 072	0.123	0.831	0.047	15 886	0.129	0.818	0.053
2017	39 309	0.107	0.849	0.044	21 420	0.105	0.852	0.043	17 889	0.109	0.846	0.045
2018	44 832	0.094	0.867	0.039	24 328	0.095	0.869	0.036	20 504	0.092	0.866	0.042
2019	50 134	0.085	0.879	0.036	26 917	0.086	0.879	0.034	23 217	0.085	0.879	0.037
Aged 15-19												
2013	87 062	0.073	0.722	0.205	29 158	0.076	0.704	0.220	57 904	0.072	0.731	0.197
2014	91 360	0.070	0.733	0.197	30 637	0.068	0.723	0.209	60 723	0.071	0.738	0.191
2015	98 275	0.066	0.749	0.185	32 883	0.061	0.740	0.199	65 392	0.069	0.753	0.178
2016	103 918	0.066	0.762	0.172	35 092	0.059	0.755	0.185	68 826	0.069	0.766	0.165
2017	109 889	0.061	0.783	0.157	37 536	0.054	0.773	0.173	72 353	0.064	0.788	0.148
2018	116 828	0.058	0.795	0.146	40 350	0.051	0.787	0.162	76 478	0.062	0.800	0.138
2019	125 515	0.056	0.805	0.139	44 020	0.047	0.797	0.156	81 495	0.060	0.810	0.130
Aged 20-24												
2013	130 342	0.081	0.609	0.310	46 291	0.079	0.587	0.334	84 051	0.082	0.621	0.297
2014	138 995	0.078	0.617	0.304	49 764	0.073	0.596	0.331	89 231	0.081	0.629	0.289
2015	148 639	0.076	0.626	0.298	53 983	0.070	0.603	0.327	94 656	0.080	0.639	0.281

	Two sexes				Male				Female			
		Proportions for drug classes (4th-level ATC codes)				Proportions for drug classes (4th-level ATC codes)				Proportions for drug classes (4th-level ATC codes)		
Calendar year	Total patients (N)	N06AA	N06AB	N06AF N06AG N06AX	Total patients (N)	N06AA	N06AB	N06AF N06AG N06AX	Total patients (N)	N06AA	N06AB	N06AF N06AG N06AX
2016	156 496	0.074	0.643	0.283	56 638	0.067	0.617	0.316	99 858	0.077	0.658	0.265
2017	162 272	0.071	0.658	0.271	58 460	0.065	0.634	0.302	103 812	0.075	0.672	0.253
2018	169 415	0.073	0.669	0.258	61 106	0.065	0.643	0.292	108 309	0.077	0.683	0.240
2019	181 388	0.071	0.682	0.246	65 449	0.063	0.657	0.280	115 939	0.076	0.697	0.227

Source: PBS

Note: N06AA for monoamine reuptake inhibitors, N06AB selective serotonin reuptake inhibitors, N06AF non-selective monoamine oxidase inhibitors, N06AG monoamine oxidase A inhibitors, N06AX other antidepressants; N06AF, N06AG, N06AX medications were grouped for small cell suppression.

Appendix 6 – Prescriber specialty, incident antidepressant use by paediatric patients, Australia

Patient characteristics	N	Prescribing clinician (proportion)				
		Paedia-trician	Psy-chiatrist	General practitioner	Other	Missing
Total	211 534	0.147	0.178	0.630	0.029	0.016
Calendar year						
2015	37 711	0.156	0.145	0.664	0.031	0.004
2016	38 859	0.153	0.161	0.653	0.030	0.004
2017	42 398	0.149	0.179	0.635	0.028	0.008
2018	45 035	0.149	0.195	0.620	0.028	0.009
2019	47 531	0.132	0.201	0.591	0.028	0.049
Age in years						
5-11	39 948	0.142	0.555	0.262	0.029	0.012
12-14	49 993	0.198	0.200	0.552	0.028	0.023
15-17	121 593	0.128	0.045	0.784	0.029	0.015
Sex						
Female	125 273	0.141	0.111	0.699	0.032	0.017
Male	86 261	0.156	0.274	0.530	0.025	0.014
Socioeconomic status (IRSAD)						
Bottom decile	18 288	0.105	0.170	0.682	0.025	0.017
2	18 546	0.109	0.157	0.693	0.025	0.016
3	15 938	0.109	0.183	0.670	0.021	0.016
4	22 746	0.113	0.169	0.678	0.023	0.017
5	21 883	0.116	0.166	0.679	0.024	0.016
6	22 587	0.137	0.188	0.633	0.026	0.016
7	17 931	0.154	0.189	0.613	0.029	0.015
8	21 350	0.164	0.189	0.601	0.030	0.015
9	24 387	0.174	0.187	0.587	0.036	0.016
Top decile	25 533	0.249	0.179	0.517	0.042	0.014
Missing	2 345	0.162	0.171	0.606	0.035	0.026
Geographic remoteness						
Major cities	136 934	0.169	0.187	0.596	0.031	0.017
Inner regional	51 096	0.104	0.175	0.682	0.025	0.014
Outer regional	18 642	0.106	0.125	0.730	0.024	0.016
Remote	1 867	0.144	0.095	0.724	0.020	0.017
Very remote	698	0.095	0.095	0.751	0.043	0.017
Missing	2 297	0.162	0.173	0.606	0.034	0.025

Source: PBS

Appendix 7 – Results from linear probability models of paediatrician/psychiatrist prescribers vs. others, first antidepressant use by children and adolescents, Australia 2015-2019

	Model 1		Model 2	
Parameter	Estimate	95% confidence interval	Estimate	95% confidence interval
Intercept	0.666	(0.66, 0.671)	0.749	(0.742, 0.757)
Remoteness area (major cities as ref.)				
Inner regional	-0.065	(-0.069, -0.061)	-0.027	(-0.032, -0.022)
Outer regional	-0.096	(-0.102, -0.089)	-0.057	(-0.063, -0.05)
Remote	-0.083	(-0.102, -0.064)	-0.051	(-0.07, -0.032)
Very remote	-0.144	(-0.176, -0.113)	-0.104	(-0.135, -0.073)
Missing	-0.011	(-0.028, 0.007)	0.007	(-0.079, 0.094)
Age (5-11 years as ref.)				
12-14 years	-0.271	(-0.277, -0.266)	-0.274	(-0.28, -0.268)
15-17 years	-0.492	(-0.496, -0.487)	-0.494	(-0.499, -0.49)
Male (female as ref.)	0.097	(0.093, 0.101)	0.096	(0.093, 0.1)
Calendar year (centred at 2019)	0.004	(0.003, 0.005)	0.004	(0.002, 0.005)
Socioeconomic status (top decile as ref.)				
9			-0.067	(-0.074, -0.06)
8			-0.081	(-0.088, -0.073)
7			-0.094	(-0.102, -0.086)
6			-0.099	(-0.107, -0.092)
5			-0.134	(-0.142, -0.126)
4			-0.132	(-0.14, -0.124)
3			-0.12	(-0.129, -0.112)
2			-0.134	(-0.142, -0.125)
Bottom decile			-0.133	(-0.141, -0.124)
Missing			-0.101	(-0.186, -0.015)

Source: PBS

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Signal Investigation Unit, Pharmacovigilance and Special Access Branch	December 2020
V2.0	Updates to text to correct attribution, updated Figures 9 and 10.	Medicines Surveillance Section (formerly known as the Signal Investigation Unit); Pharmacovigilance and Special Access Branch	April 2021

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