3. Pharmacovigilance matters for advice

3.01 Antidepressants and youth suicide – multiple medicines - multiple sponsors

3.01.1 Medicine Details

The ACM considered the referral for advice from the Delegate of the Secretary of Health in relation to antidepressants (selective serotonin reuptake inhibitors (SSRI) and serotonin and noradrenaline reuptake inhibitors (SNRI)) and youth suicide.

Numerous SSRI and SNRI antidepressants are registered on the Australian Register of Therapeutic Goods (ARTG), listed below.

SSRIs **Active ingredient**	**Innovator tradename**	**Current sponsor**
Citalopram	Cipramil	Lundbeck Australia Pty Ltd
Dapoxetine	Priligy	A Menarini Australia Pty Ltd
Escitalopram	Lexapro	Lundbeck Australia Pty Ltd
Fluoxetine	Prozac	Eli Lilly Australia Pty Ltd
Fluvoxamine	Luvox	Mylan Health Pty Ltd
Paroxetine	Aropax	Aspen Pharmacare Australia Pty Ltd
Sertraline	Zoloft	Upjohn Australia Pty Ltd

SNRIs **Active ingredient**	**Innovator tradename**	**Current sponsor**
Desvenlafaxine	Pristiq	Pfizer Australia Pty Ltd
Duloxetine	Cymbalta	Eli Lilly Australia Pty Ltd
Milnacipran	Jonica	Pierre Fabre Australia Pty Ltd
Venlafaxine	Efexor	Upjohn Australia Pty Ltd

Other sponsors that supply these medicines are Accord Healthcare, Alembic Pharmaceuticals, Alphapharm, Amneal Pharma, Apotex, Arrow Pharma, Avallon Pharmaceuticals, Cipla Australia,

CNS Pharma, Dr Reddy's Laboratories, Eris Pharmaceuticals, Fair-Med Healthcare, Generic Health, Generic Partners, Ipca Pharma, Lupin, Medis Pharma, Micro Labs, Pharmacor, Sandoz and Sun Pharma.

Indications (abridged):

Approved indications differ across SSRIs and SNRIs.

Major depression in adults is an approved indication for all the above medicines, other than dapoxetine and milnacipran. Product Information (PI) documents state that use for in children and adolescents under the age of 18 is advised against or not recommended, as efficacy and safety in these patients has not been established.

The only approved indication in children and adolescents is Obsessive Compulsive Disorder (OCD), for fluvoxamine (in patients 8 years of age and older) and sertraline (in patients 6 years of age and older).

3.01.2 Background and request for advice

A recent article by Whitely, Raven and Jureidini on antidepressants and youth suicide[1] identified a signal from ecological evidence correlating a 66% increase in dispensing of antidepressants in young Australians aged less than 28 years and a 49% increase in suicidality or self-harm in young Australians aged less than 25 years. Although there are significant uncontrolled confounding factors that limit the interpretation of this conclusion, the article has prompted further TGA consideration of this issue.

SSRIs and SNRIs are prescribed off-label to children and adolescents for psychiatric indications. For example, fluoxetine is recommended by the Royal Australian and New Zealand College of Psychiatrists (RANZCP) as second line treatment for moderate to severe major depressive disorder in children and adolescents. However, the PI for fluoxetine states that use in patients under the age of 18 years is not recommended.

Clinical worsening of depression and suicidality is a recognised and well-known risk with the use of antidepressant medicines. The TGA approved PI documents for antidepressants include warnings about these risks and specifically mention children, adolescents and young adults. This information is also conveyed in the Consumer Medicines Information (CMI) for these products.

A highly cited systematic review concluded that the efficacy of antidepressants correlates with depression severity, and that the benefits over placebo are substantial for severe symptoms, but minimal or non-existent with mild-moderate depression.[2]

The Delegate requested advice on specific issues as below and comment on any other aspect of this safety issue that should be considered by the Delegate.

3.01.3 International regulators

SSRI and SNRI approved in New Zealand, Canada, Europe and the USA have similar indications and safety information to Australian PI documents with some exceptions:

[1] Whitely M, Raven M & Jureidini J. Antidepressant Prescribing and Suicide/Self-Harm by Young Australians: Regulatory Warnings, Contradictory Advice, and Long-Term Trends. Frontiers in Psychiatry. 2020;11:478.

[2] Fournier JC, DeRubeis RJ, Hollon SD et al. Antidepressant drug effects and depression severity: A patient-level meta-analysis. Journal of the American Medical Association, 2010; 303:47-53

- there is a paediatric indication in Europe: fluoxetine is indicated for the treatment of severe major depression (that is unresponsive to psychological therapy after 4-6 sessions) in children and adolescents aged 8 years and above
- in Canada, stronger wording is used: '*Not indicated for use in patients below the age of 18*'
- since 2004, the US FDA has required a boxed warning that outlines the risk of increased suicidality in children, adolescents and young adults with major depressive disorder and other psychiatric disorders.

3.01.4 ACM Discussion

Whitely paper

The committee's comments on the Whitely paper included:

- absence of statistical analysis of the correlation of antidepressant use and suicide rates for young Australians from 2012 to 2018
- the ecological study by Hall was cited misleadingly[3]
- selective use of data from Cairns[4] . The substances most commonly taken in self-poisonings were over-the-counter paracetamol and ibuprofen, followed by prescription fluoxetine. It was not confirmed that the SSRI taken for self-poisoning had been prescribed for the young person.

Correlation does not prove causation and many factors impact suicide rates.

The committee did not support the conclusion drawn by Whitely. The paper does not properly demonstrate a correlation or causation between increase in antidepressant prescribing and increase in rate of suicide. The committee commented that suicide is a complex outcome, the author's conclusions are simplistic and do not speak to the multitude of factors over a long period of time that can contribute to suicide as an outcome.

Treating depression in young people

Child and adolescent patients are very complex. Mental health is affected by parents, family, social group, school, drugs and alcohol, social media and gaming use. Some children may begin to talk openly about suicidal ideation only after their condition begins to improve with treatment, even though they have had these thoughts all along.

The committee noted that the use of SSRIs and SNRIs in young patients with major depression is off-label use. Determining safe use for an unapproved indication is generally the role of the clinical colleges, rather than the TGA. Given the number of generic versions of these medicines, it is unlikely an innovator sponsor would seek approval for an extension of indication for paediatric use.

Paediatric emergency departments have seen children with serotonin syndrome due to drug interactions of antidepressants with other medications with serotonergic effects.

The ACM suggested that recently-announced mental health funding offered an opportunity to improve access to information and care. In particular, improved access to Cognitive Behavioural Therapy (CBT) and Interpersonal Psychotherapy (IPT) will assist young people.

[3] Hall WD, Mant A, Mitchell PB, et al. Association between antidepressant prescribing and suicide in Australia, 1991-2000: trend analysis. BMJ (2003) 326:1008. doi: 10.1136/bmj.326.7397.1008

[4] Cairns R, Karanges EA, Wong A, et al. Trends in self-poisoning and psychotropic drug use in people aged 5-19 years: a population-based retrospective cohort study in Australia. BMJ Open (2019) 9:e026001. doi: 10.1136/bmjopen-2018-026001

3.01.5 Advice

The ACM advised the following in response to the questions from the Delegate.

1. ***Can the committee comment 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 committee advised that there is a valid and important role for SSRIs and SNRIs in current clinical practice, supported by professional guidelines rather than TGA-approved indications.

The increasing use of antidepressants in children is of concern. The committee noted that current clinical guidelines have 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, in practice, access to publicly funded psychological therapies such as cognitive behavioural therapy (CBT) and interpersonal therapy (IPT) is often extremely limited, GPs face great difficulty in having their patients seen by a child/adolescent psychiatrist in a timely manner, referral pathways are complex and there are significant equity issues in accessing private psychiatric services.

The Royal Australian and New Zealand College of Psychiatrists (RANZCP) guidelines for mood disorders[5] recommends fluoxetine as second line treatment for moderate to severe major depressive disorder in children and adolescents.

The National Institute for Health and Care Excellence (NICE) guidelines[6] from the UK emphasise firstly psychosocial interventions and therapy, then pharmacotherapy as second line treatment (with fluoxetine as the first choice), and third line treatment using a number of modalities. The guidelines are clear that the emphasis in young people is on psychosocial interventions, not prescribing an antidepressant.

Of the SSRIs, fluoxetine has the most consistent evidence of efficacy over placebo. Sertraline would be the next choice.

SNRIs are used in patients aged about 16 years and older, if SSRIs have been ineffective.

Australian research has found that the amount of psychotropic medications prescribed by paediatricians appears to be increasing.[7] In a sample of patient consults in 2013, about 4% of consultations involved the prescription of an SSRI. Rather than for depression, paediatricians tend to prescribe SSRIs for anxiety disorders, autism spectrum disorder and OCD, and mixed presentations with ADHD.

2. ***Can the committee comment on the strength of the current evidence for an association between use of antidepressants and rates of youth suicide in Australia?***

The committee advised that the current evidence for an association between the use of antidepressants and rates of youth suicide in Australia has not been materially affected by the

[5] Malhi G, Bassett D, Boyce P, et al. A. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Australian and New Zealand Journal of Psychiatry, 2015;49(12): 1-185 https://www.ranzcp.org/files/resources/college_statements/clinician/cpg/mood-disorders-cpg.aspx

[6] National Institute for Health and Care Excellence (NICE). Depression in Children and Young People: Identification and Management in Primary, Community and Secondary Care, 2005.

[7] Efron D, Danchin M, Cranswick N, et al. Medication Prescribed by Paediatricians: Psychotropics predominate. J Paediatr Child Health 2017. 53(10):957-962. DOI: 10.1111/jpc.13615

Whitely paper. Confounding by indication remains an unresolved issue when interpreting data of this type and the conclusion in Whitely is tenuous at best.

Activation syndrome[8] is recognised and includes the possible emergence of suicidal thoughts during the initial few months of antidepressant treatment or at times of dose adjustments. The risk is minimised by starting with a low dose and increasing slowly. Healthcare professionals need to provide education on the risk of suicidal ideation, and the benefit-risk of pharmacotherapy, to patients and family members.

3. Can the committee comment on 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 committee supported prescriber education.

- The RACGP website does not include a guideline for the management of depression in children.[9] The RACGP and its paediatrics special interest group could be approached to address this omission. Advice on starting doses, dose escalation and dose tapering should be provided.
- NPS MedicineWise could be approached regarding educational material.
- Guidance on appropriate dosing for off-label use.

The committee supported consumer education. The RANZCP and RACGP are best placed to develop material for GPs, as GPs as the first point of contact will generally need to manage the patient and family prior to specialist advice. Consumer support organisations could be approached to expand information regarding the management options for treating depression in young people.

The committee advised there would be no advantage from a narrowing of indications to specify an age range (i.e., to exclude young adults).

Current warnings and precautions in PI documents were adequate.

Any restriction on the types of medical practitioners who can prescribe these medicines (e.g. only paediatricians and psychiatrists, via changes to the Poisons Standard) is not justified on the strength of the current evidence and would further disadvantage children and adolescents, especially in regional, rural and remote areas where access to specialists is limited. Similarly, any restriction on access via PBS prescribing conditions would further disadvantage children and adolescents with limited access to other treatment modalities.

[8] 'Clinical worsening' in the Prozac PI

[9] A joint RANZCP, RACGP and RACP Clinical guidance on the use of antidepressant medications in children and adolescents (March 2005) is under review.
https://www.racgp.org.au/afpbackissues/2005/200509/200509lyndon.pdf