FOR MENTAL HEALTH CLINICIANS/ COMMUNITY PROFESSIONALS

EVIDENCE SUMMARY

SSRI AND SNRI ANTIDEPRESSANTS IN THE TREATMENT OF DEPRESSION

Depression across the lifespan is prevalent in around a fifth of the population worldwide.(1) Three-quarters of those who experience depression have an illness onset before the age of 25.(1) Depression in young people has potential long-term adverse consequences, causing disruption to emotional well-being, interpersonal relationships and educational and occupational functioning.(2) Early identification of depression, combined with early, targeted intervention, can have beneficial effects for young people.(3-5) However, determining which treatment is the most appropriate, effective and safe is often not straight forward, especially when there is conflicting evidence on the efficacy of antidepressant medications.

This resource will provide a review of the latest evidence for antidepressant medication, primarily selective serotonin-reuptake inhibitors (SSRIs) and selective noradrenaline reuptake inhibitors (SNRIs), in the treatment of depressive disorders in young people. For the purpose of this document the term 'young people' refers to individuals aged 12-25, unless otherwise specified.

BACKGROUND

Controversy surrounding antidepressant use, particularly in children and adolescents, emerged in the early 2000s, with concerns around their effectiveness and safety.(6, 7) Early industry-sponsored (drug company-funded) trials were criticised for under-reporting negative outcomes, overstating positive findings and failing to adequately assess the risk of suicidality (that is, suicidal ideation and behaviour).

In 2004 the US Food and Drug Administration (USFDA) added cautionary 'black box warnings' to SSRI medications for children and adolescents,(8) and in 2006 raised the age of potential vulnerability to 24 years.(9) These warnings indicate that SSRIs are associated with risk of increased suicidality (although with no evidence of death by suicide).(8) It is critically important that treatment with antidepressants involve close monitoring of suicidality, self-harm and hostility.(10)

In Australia, no antidepressant is currently approved for the treatment of depressive disorders in young people under the age of 18, although such medications are used 'off-label' for this purpose.(11) If considering prescribing an antidepressant to a young person it is important to seek advice from a psychiatrist or specialist service, and follow clinical guidelines.

An initial assumption that children, adolescents and young adults might benefit from the same antidepressant treatments as older adults failed to take into account the effects of neurodevelopment. Antidepressants act on brain neurotransmitter systems (for example, serotonergic and noradrenergic systems), which show continued development until at least the age of 25.(12-14) While there appears to be reasonable evidence for the efficacy and tolerability of SSRIs and SNRIs in the treatment of adult depression,(15) these medicines may be less effective for young people, which we explore in this resource.

WHAT ARE THE CURRENT GUIDELINES?

AUSTRALIAN GUIDELINES

There are no current Australian guidelines specifically for the treatment of young people with depression.

CHILDREN AND ADOLESCENTS UNDER 18 YEARS OF AGE

The UK National Institute for Health and Care Excellence (NICE) guidelines state that antidepressants are not suitable as an initial treatment for mild depression in children and adolescents (ages 5–18).(10) NICE recommends that pharmacotherapy only be considered as an initial treatment for children and adolescents who present with the diagnosis of moderate to severe depression, and that this treatment be provided in conjunction with a psychological therapy (for example, cognitive behavioural therapy (CBT) or interpersonal psychotherapy (IPT)).

Combined therapy is suggested as an alternative to psychological therapy alone. Both psychological therapy and combined psychological-pharmacological therapy are considered initial treatment options for moderate to severe depression. It is further recommended that for young people with moderate to severe depression, combined antidepressant and psychological treatment be considered if there is no symptom improvement after an initial trial of 4–6 sessions of a psychological intervention, and after a multidisciplinary case review.(10) In these circumstances the SSRI fluoxetine is the suggested first-line pharmacotherapy. In instances where a young person shows no improvement with combined psychotherapy and fluoxetine treatment, other SSRIs can be considered. NICE guidelines suggest sertraline or citalopram as second-line pharmacological options.(10) SNRIs are not recommended for young people aged 5–18.(10)

The Royal Australian and New Zealand College of Psychiatrists treatment guidelines for mood disorders are similar to the NICE guidelines.(16) They recommend psychological interventions (in particular CBT or IPT) as first-line treatment of major depressive disorder (MDD) in children and adolescents, irrespective of illness severity. When psychological treatment has not been effective for those with moderate to severe MDD, they suggest trialing short-term use of fluoxetine, with consideration that this be combined with either the same or another psychological therapy.(16)

YOUNG ADULTS AGED 18–25 YEARS

There is currently inadequate evidence or guidance specifically for young people aged 18–25. This has unfortunately left practitioners having to determine best practice based on general adult needs and presentations. However, given that the USFDA cautions the use of antidepressants in young people under the age of 25,(9) combined with the evidence for continuing neurodevelopment in young people,(12) it can be argued that treatment of 18–25-year-olds is better informed by the child and adolescent guidelines than general adult guidelines.

Overall, children and adolescent guidelines strongly recommend antidepressant medication not be offered as an initial treatment for mild depression, and only be offered in combination with a psychological therapy for the treatment of moderate to severe depression.(10)

If considering prescribing an antidepressant to a young person it is important to seek advice from a psychiatrist or specialist service, and follow clinical guidelines.

WHAT IS THE CURRENT EVIDENCE FOR ANTIDEPRESSANT MEDICATIONS IN THE TREATMENT OF DEPRESSION IN YOUNG PEOPLE?

The most recent Cochrane meta-analysis compared antidepressants (primarily SSRIs) to a placebo in over 3000 young people aged 6–18 with a depressive disorder in the acute phase of illness.(17) This meta-analysis found antidepressant treatment for 6–12 weeks was modestly beneficial for reducing symptom severity and increasing remission rates. These statistically significant effects were of small magnitude, where depression symptoms reduced by an average of 3.51 points on a scale that ranged from 17 to 113, and where an additional 6.8 per cent of participants remitted with antidepressants compared to placebo. The review further found a greater improvement in global functioning for young people treated with antidepressants.(17) There was no evidence that a particular type of antidepressant was more effective than other types.

A more recent meta-analysis in over 5000 young people (aged 9–18) with MDD found fluoxetine to be superior over other antidepressant types (including other SSRIs, SNRIs and tricyclic/tetracyclic agents), both in terms of efficacy for reducing symptoms and tolerability.(18) However, given the variability in studies' results within this meta-analysis, the authors concluded that antidepressant medications did not show a clear advantage over placebo in children and adolescents.

There is a lack of systematic research into the efficacy of antidepressant treatment in young people aged 18–25. From a clinical and scientific perspective, it is inappropriate to draw conclusions from the general adult literature, given that the average age of participants included in those studies is around 44 years old.(15)

A handful of randomised controlled trials (RCTs) in young people aged 7–18 have been published since these meta-analyses were conducted, some of which examined the newer SNRIs duloxetine and desvenlafaxine.(19-24) However, none of these trials found antidepressant medication to significantly reduce depression symptom severity when compared to placebo treatment. Another research trial examined whether adding fluoxetine to CBT for 15- to 25-year-olds with depression was beneficial. (25) It failed to find overall evidence of benefit, although it did show greater evidence of effectiveness in patients who were aged 18 years and older, because of their poorer response to CBT and placebo. A recently completed unpublished trial of the SSRI vilazodone found no difference compared to placebo,(26) and an unpublished trial of the SNRI levomilnacipran is ongoing.(27)

In summary, there is a lack of evidence to inform clinical decision-making related to antidepressants for the treatment of depression in young people. The more recent RCTs confirm earlier findings that the outcomes for fluoxetine in young people have been highly variable.(18) To date, research into the efficacy of other SSRIs and SNRIs in treating depressive symptoms in young people has found these antidepressants to have no benefit over placebo, though only a limited number of trials have been conducted with the newer antidepressants. In offering antidepressant treatments to young people, both benefit and risk need to be considered. Despite the limited and variable evidence, current guidelines recommend the SSRI fluoxetine as first-line pharmacotherapy when antidepressant medication is indicated.(10)

WHAT IS THE EVIDENCE THAT ANTIDEPRESSANTS CAUSE INCREASED SUICIDALITY IN YOUNG PEOPLE?

There is comparatively more consistent evidence of an increased risk of suicidality in young people prescribed antidepressants, compared to evidence relating to the efficacy of these medications.

One meta-analysis found a 58 per cent increased risk of suicidality for participants on antidepressants compared to placebo,(17) equivalent to an increase from 25 to 40 young people in 1000 experiencing suicidal ideation or engaging in suicidal behaviour. A more recent meta-analysis similarly found young people aged under 19 years who were taking antidepressant medication were at least two times more likely to experience suicidality than those taking a placebo medication.(28) The risk of suicidality following antidepressant use was twice as high in children and adolescents than in adults. (28) For the trials included in these two meta-analyses, no deaths by suicide occurred in children or adolescents.

Concerning specific antidepressants,(18) the SNRI venlafaxine in particular has been associated with increased risk of suicidal behaviour in young people, relative not only to placebo but also five other types of antidepressants. It is currently unknown whether increased suicidality subsides with longer-term (for example, longer than 16 weeks) antidepressant use, as trials to date have predominantly focused on short-term treatment.

Most of the clinical trials that were published after these meta-analyses stated there were no statistically significant differences in suicidality rates between antidepressant treatment and placebo.(19-23) One study however, stated that paroxetine was associated with a significantly increased risk of suicidal ideation and behaviour,(24) while another found a non-statistically significant increase in non-specific active suicidal thoughts with vilazodone 15mg/

day.(21) Across these studies, the incidence of suicidal ideation during placebo treatment ranged between 8–33 per cent, while incidence during antidepressant treatment ranged between 15–31 per cent. One trial showed twice the rate of self harm in the group treated with fluoxetine compared with placebo, and self harm was more prevalent in younger individuals. (25) While the difference was not statistically significant, it suggests that the possible effects of medication on suicidal ideation and behaviours extends to self harm.

WHAT ABOUT OTHER SIDE EFFECTS OF ANTIDEPRESSANTS?

Several adverse effects have been reported in research trials of antidepressant medications in young people. These include but are not restricted to abdominal pain, headache, nausea, vomiting, diarrhoea, dizziness, fatigue, weight gain, somnolence, insomnia, respiratory problems (for example, pharyngitis) and emotional lability.(17) There is evidence for young people prescribed antidepressant treatment to have a 5–17 per cent chance of experiencing more adverse events than young people prescribed a placebo medication.(17) Evidence also suggests that adverse events associated with certain antidepressants are related to increased risk of treatment discontinuation.(18)

One cluster of side effects that have received particular attention recently relate to 'activation'. Activation side effects are symptoms characteristic of a hyper-aroused state (for example, restlessness, agitation, insomnia, impulsivity). The growing interest in these side effects is due to the theory that antidepressant-induced activation is a precursor for increased suicidal behaviour and aggression in young people.(29) At present, there is insufficient evidence to corroborate this theory.(29) Further, a meta-analysis (28) failed to find a significant increase in akathisia (extreme restlessness) for antidepressant-treated versus placebo-treated young people. It did however find that those taking antidepressants were twice as likely to display aggressive behaviour than those on placebo, which equated to about one in every 28 young people.(28)

Overall, there appears to be some small risk of young people experiencing other adverse events, besides suicidality, following antidepressant use. It is important to note that good quality research into the side effects of SSRIs and SNRIs in young people is lacking, including sexual dysfunction, which is a common side-effect in adults who are taking antidepressants.(30, 31) There is also insufficient research on the effects of withdrawal or discontinuation of antidepressants in young people. In addition, risk for specific side effects will differ by medication type and this should be carefully considered by clinicians and discussed with the young person, and their family and friends (if appropriate), prior to commencing treatment.

WHAT IS THE EVIDENCE FOR ANTIDEPRESSANT MEDICATIONS IN THE TREATMENT OF ANXIETY AND OTHER DISORDERS IN YOUNG PEOPLE?

There is some evidence to suggest that antidepressant medications may be more effective in treating anxiety symptoms than depression symptoms.

One possible explanation for this is the relatively weaker placebo effect in young people with anxiety disorders.(25, 32) Recent meta-analyses showed that SSRIs and SNRIs, when compared to placebo, were associated with statistically significant reductions in anxiety symptoms of children and adolescents (aged 18 years or under) with an anxiety disorder diagnosis.(32, 33) The effect was of medium magnitude and considered clinically relevant. Similar results were found by a Cochrane meta-analysis of 22 anxiety trials in young people aged 18 years or under (which additionally included individuals with obsessive-compulsive disorder (OCD) or post-traumatic/acute stress disorder).(34) The limited evidence in this area suggests that SSRIs may be somewhat more effective in treating anxiety than SNRIs.(32, 33) In one depression trial, which included a large proportion of participants (63 per cent) with depression and a comorbid anxiety disorder, combined fluoxetine and CBT treatment was more effective than placebo and CBT for treating anxiety symptoms.(25)

Systematic reporting of adverse events is lacking in clinical trials involving young people with anxiety and other disorders. While there is some suggestion that children and adolescents treated for anxiety experience a minimal number of adverse events with SSRI or SNRI medication,(32, 34) research also shows that those treated with an SSRI are at least three times more likely to discontinue treatment due to adverse effects. (32) Preliminary evidence suggests there is potentially less risk for increased suicidality in these populations than in young people with depression,(34) but more research is needed before firm conclusions can be drawn.

It is important to note that clinical practice guidelines recommend psychological therapy as first-line treatment of anxiety in children and adolescents (age 18 years and under).(35) General practitioners/medical practitioners considering prescribing an antidepressant to treat anxiety in young people should first consult with a psychiatrist or specialist service.(35)

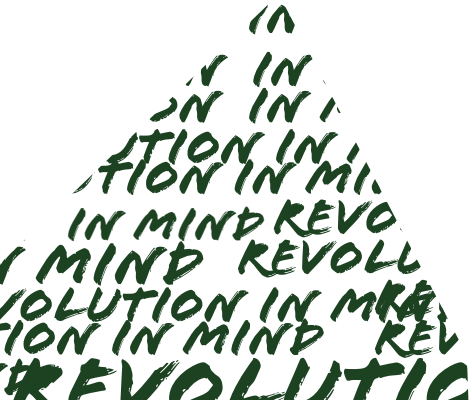
Guidelines strongly recommend antidepressant medication not be offered as an initial treatment for mild depression.

ARE THERE LIMITATIONS WITHIN THE EVIDENCE BASE?

Randomised clinical trials attempt to create conditions in which the primary difference between two treatment groups is the medication administered (that is, placebo versus active drug). However there are several methodological factors that influence outcomes and may contribute to inconsistent results across studies, including:

- selection of participants, determined by inclusion and exclusion criteria – for example, many studies exclude young people with comorbid mental illnesses, as well as those with suicidal ideation or behaviour, making findings less able to be generalised to real-world clinical settings;
- variations in the type(s) of antidepressant and dosage;
- variations in the types of outcome measures – for example symptom reduction, remission of depression, and/or functional recovery;
- self-report versus clinician-rated measures or a combination of both; and
- length of treatment (ranging between six and 16 weeks in clinical trials, which may not represent the typical course of an episode of care in the real world).

If a young person commences antidepressant medication, they must be closely monitored, particularly for suicidality and self-harm – if they miss appointments, assertive follow-up is recommended.



WHAT DOES ALL THIS MEAN FOR CLINICIANS TREATING YOUNG PEOPLE WITH DEPRESSION?

There is a clear imperative to engage young people who are experiencing a depressive disorder in good clinical care.

The following clinical practice considerations are not exhaustive and should be read in conjunction with the NICE guidelines.(10) Here we focus on points that have particular relevance to antidepressant treatment, and are useful for both therapists and general practitioners (GPs).

1. Establishing a diagnosis of depression is based on clinical judgement and assessment in line with the current *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) (36) and/or *International Classification of Diseases 11th Revision* (ICD-11)(37) guidelines. This process should take into consideration the impact of symptoms and distress on functioning, and developmental implications. In addition to conducting a clinical interview, it is recommended that a standardised measure also be administered to aid in evaluation of symptom severity and symptom change over time. Examples of such measures include the Mood and Feelings Questionnaire,(38) Children's Depression Rating Scale – Revised,(39) Depression Anxiety Stress Scale,(40) Revised Child Anxiety and Depression Scale,(41) and Outcome Rating Scale.(42)
2. The clinician should encourage the young person to involve family and friends to support them in decision-making and during their assessment and treatment. It is also critical to make efforts to build rapport and engage the young person in the help-seeking and treatment process.
3. Comprehensive assessment of physical observations, sexual health and suicidality should be taken at the initial assessment phase. This assessment should also involve screening for any history of hypomania or mania (as there is a possible risk of triggering a mixed or manic episode with antidepressant treatment in these circumstances).(43) Collecting information about alcohol and other drug use is particularly relevant when considering antidepressant medication, as drug interactions can have potentially serious consequences (for example serotonin syndrome).
4. Age appropriate written and verbal psychoeducation about the nature of depression, its course and treatment should be given to young people and their family/friends at an appropriate time and with consideration for the context of the young person's family history and mental state.

5. The young person should be encouraged to actively engage in treatment decisions. Shared decision-making means that the clinician's recommended treatment choice is transparent and relayed in an accessible and defensible manner.(44)
6. In instances where the young person presents with mild symptoms of depression, a psychological intervention should be offered. If the young person chooses not to take part in a psychological intervention, or clinical judgment suggests that symptoms may spontaneously remit, 'watchful waiting' is recommended (that is, reassessment within two weeks and follow-up if they do not attend). If after 2–3 months of psychological therapy the young person continues to experience mild depression, and following a specialised care team review, consider treatment in accordance with that recommended for moderate to severe depression.(10)
7. For young people with mild depression where access to psychological therapy is an issue, or if it's the young person's preferred choice, consider youth-friendly digital CBT programs (for more information see **https://www.orygen.org.au/Training/Resources/E-Health/Clinical-practice-points/The-digital-age-Does-digital-technology-work-in-y**).
8. The age of the young person should be taken into consideration, with extra caution taken when considering antidepressant treatment for those under 18 years of age.
9. Consider antidepressants as initial treatment only in young people (12–18 years) presenting with moderate to severe depression as a combined therapy. If antidepressants are considered, the prefered treatment options are either a) trialling CBT with the plan to review and add on fluoxetine if there is no benefit after 4–6 sessions; or b) commencing with combined treatment from the start. GPs should consult with a psychiatrist and other mental health professionals prior to prescribing antidepressant medication. When indicated, the SSRI fluoxetine is suggested first-line pharmacotherapy.(10)
10. Both the benefits and risks of prescribing an antidepressant should be considered on an individual basis. In circumstances where the young person has moderate to severe depression, and psychological therapy is not possible (for example, due to poor engagement) or has been refused, an antidepressant medication may be considered. Note that, 'watchful waiting' (or doing nothing) is not recommended for young people with moderate to severe depression.(10)
11. Where the young person with moderate-severe recurrent depression has not benefited from a previous psychological therapy, either combined treatment or a psychological therapy alone is still recommended. Careful assessment is warranted to consider the young person's previous treatment history (including type and dose of psychological treatment received, engagement with therapist, and readiness for therapy at the time). It may be worth trialling CBT again if the young person was not well engaged, did not have an adequate dose of treatment (at least three months) or reports they were not ready to engage in treatment at the time. Referring on to other professionals for a different therapy (for example IPT for adolescents) or a more intensive psychological therapy (for exmaple CBT plus enhanced care/case management support) may be indicated. The choice of psychological treatment options should be discussed with the young person, considering their preferences.(10)
12. Explaining to the young person (and support person if appropriate) the risks, benefits and limitations of each potential treatment is paramount. For antidepressants this includes the risk of suicidal thoughts and behaviours, self-harm and hostility(10) alongside potential risk of other physical and psychological adverse events. A young person who has experienced medication-related adverse events in the past may struggle with compliancy. It is important to consider this when prescribing a new medication and to discuss the implications of non-compliancy with the young person.
13. A treatment plan should be collaboratively developed, and should include how the young person will notice any changes in their mood, thinking and behaviour, along with possible side effects.
14. If a young person commences antidepressant medication, they must be closely monitored (at least weekly) for the first four to six weeks, by the prescriber or a clinician who is involved in the young person's care. Assertive follow-up is recommended in the event of missed appointments. It is particularly important to monitor suicidality and self-harm. A collaborative safety plan should be devised which outlines what behaviours to look for and how to respond to these. Whenever possible, family members and friends should be enlisted to help monitor change, and advised to urgently seek care if they have concerns about suicidality, self-harm or hostility.

SUMMARY

Guidelines recommend psychological therapies as first-line treatments for depression in young people. Antidepressants as an initial treatment should be considered as an add-on/adjunct to psychological therapy only for moderate to severe depression. When indicated, the SSRI fluoxetine is the suggested first-line pharmacotherapy.

In instances where combination psychotherapy-fluoxetine treatment has not been effective, the SSRIs sertraline or citalopram can be considered as second-line pharmacotherapy. The decision to start an antidepressant and the plan for monitoring needs to be made in collaboration with the young person and, if possible, their support person/s, who have been clearly informed of potential risks and benefits of the treatment. In the absence of current youth-specific guidelines on managing depression, clinicians should follow the NICE child and adolescent guidelines (10) for all young people (aged 12–25 years) rather than using adult guidelines when treating 18–25 year olds.

It can be argued that treatment of 18–25-year-olds is better informed by the child and adolescent guidelines than general adult guidelines.

USEFUL RESOURCES

- 2019 NICE guidelines; Depression in children and young people: identification and management
- Antidepressants: frequently asked questions
- https://orygen.org.au/Training/Resources/Depression/Research-bulletins
- Shared decision making (SDM) for mental health - what is the evidence?
- Shared decision-making clinical practice point

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