Australian Prescriber
VOLUME 45 : NUMBER 2 : APRIL 2022

ARTICLE

# Antidepressants in adolescence

## SUMMARY

In adolescence, antidepressants are second-line treatment options after psychological therapy for anxiety and obsessive compulsive disorder. They may be first- or second-line options for severe cases of major depressive disorder.

The response to antidepressant treatment is generally good for anxiety and obsessive compulsive disorder, but is less convincing for major depressive disorder. Adolescents who do not respond to an adequate trial of one antidepressant should be referred for a psychiatric opinion.

Patients must be monitored for rare but serious adverse effects. These include suicide-related behaviours, switching to mania, and serotonin syndrome.

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**Keywords**
adolescent, antidepressive drugs, anxiety disorders, depressive disorder, obsessive compulsive disorder

*Aust Prescr 2022;45:49–52*
https://doi.org/10.18773/austprescr.2022.011

## Introduction

The antidepressants approved for use in Australia are the selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), and a miscellaneous group that includes drugs such as agomelatine and mirtazapine. Other drugs such as quetiapine and lurasidone, may be used to manage depressive symptoms under special circumstances. For adolescents (aged 12–17 years) the approval of the Therapeutic Goods Administration is limited to the SSRIs fluvoxamine and sertraline for obsessive compulsive disorder, and the tricyclic antidepressants amitriptyline and imipramine for enuresis.[1] All other prescribing is 'off label'.

The rate of antidepressant prescribing to Australian adolescents rose steadily between 2013 and 2019, with SSRIs being by far the most commonly prescribed class.[1] General practitioners accounted for 55% of the antidepressant prescribing to 12–14 year olds, increasing to 78% for 15–17 year olds.[1]

Potential indications in adolescence for antidepressant drugs include enuresis, attention deficit hyperactivity disorder, anxiety, obsessive compulsive disorder, selective mutism, anxiety or obsessionality associated with autism and intellectual disability, aggression, bulimia and major depressive disorder. General practitioners are most likely to consider starting an antidepressant for major depressive disorder or an anxiety disorder,[2] but they may be asked to provide maintenance prescriptions for treatment started by a paediatrician or psychiatrist.

## Evidence of efficacy

For adolescents, more antidepressant drugs are effective for anxiety disorders and obsessive compulsive disorder than they are for major depressive disorder. Reviews of efficacy and safety have increased in sophistication with time, but the overall conclusions have not altered much in the past two decades. Key findings of a meta-review[3] are summarised in the Table.

There are limitations in the current evidence. Relative to studies in adults, there are fewer trials in children and adolescents, the sample sizes are small, and study quality is low. The evidence is almost exclusively about first-line treatment in the acute phase of illness. There is little evidence to guide maintenance treatment, or the strategies to use if first-line treatment is ineffective. Unfortunately, most treatment trials combine data from children and adolescents, which is then reflected in the scope of systematic reviews. It is plausible that, as adolescents approach adulthood, their pattern of response to drugs also begins to approximate that of adults. As such, GPs must use judgement in interpreting and communicating efficacy data derived from paediatric populations when applied to older adolescents.

## Adverse effects

Common, generally mild adverse effects include sleep disturbance, tremor, sweating, gastrointestinal discomfort and sexual dysfunction. Abruptly stopping SSRIs may lead to a discontinuation syndrome, characterised by malaise and other flu-like symptoms. Antidepressants can also cause behavioural activation, characterised by irritability, agitation and anxiety. Important but rare adverse reactions are the induction of manic symptoms (known as 'switching'), and serotonin syndrome.

### *Suicidal behaviour*

A concern is the small potential for antidepressants to trigger suicide-related behaviours in some adolescent patients. No positive association has been found between antidepressant prescriptions

and suicide deaths. Suicide-related behaviours refer to self-harm and suicidal thoughts, which are sometimes associated with stimulation or agitation (known as 'activation syndrome'). These behaviours occur in the weeks after starting antidepressant drugs in about 4% of adolescents, which is double the rate seen in those given a placebo.[4] Suicide-related behaviours are most likely to occur with the SNRI venlafaxine, and less likely to occur with SSRIs such as fluoxetine and escitalopram.[5] An analysis of safety data from paediatric antidepressant trials found the risk for developing suicide-related behaviours was significantly elevated in patients with major depressive disorder, but not in other mental disorders.[4] SSRIs and SNRIs are safer in overdose than the older tricyclic antidepressants and MAOIs.

## Anxiety and obsessive compulsive disorder

Neither anxiety nor obsessive compulsive disorder interferes with the capacity to engage with treatment. Provided that it is accessible, psychological therapy is the treatment of first choice for both disorders because it avoids exposure to adverse effects. Pharmacotherapy is reserved for patients who do not respond to psychological therapy, or for some reason are unable to engage with therapy.

For anxiety, there is stronger evidence supporting the use of fluvoxamine than the other drugs listed in the Table. Fluvoxamine is relatively sedating which can be useful for a patient who is experiencing disturbed sleep.

In obsessive compulsive disorder, fluoxetine is the first-choice drug because of its favourable safety profile relative to other drugs (Table). Clomipramine (a tricyclic antidepressant with a strong serotonergic action) is reserved for treatment-refractory cases.

Initial and maximum doses are summarised in the Table. Try the initial dose for two weeks. If the drug is tolerated, titrate the dose upward in increments of half the initial dose every two weeks. When there is an inadequate response to six weeks of treatment at the highest tolerated dose, seek the opinion of a psychiatrist. If treatment is effective, it may need to be indefinite, as anxiety and obsessive compulsive disorder are chronic relapsing conditions.

*Table* **Drugs with established short-term efficacy for selected mental disorders in adolescents[3] and suggested doses**

| Indication | Effective drug |
|---|---|
| Anxiety disorder (including generalised anxiety, mixed anxiety, social anxiety, separation anxiety, school phobia and elective mutism) | Fluvoxamine<br>initial dose 25 mg/day<br>maximum dose 300 mg/day (doses over 50 mg should be divided)<br>Sertraline<br>initial dose 50 mg/day<br>maximum dose 200 mg/day<br>Paroxetine<br>initial dose 20 mg/day<br>maximum dose 60 mg/day<br>Fluoxetine<br>initial dose 20 mg/day<br>maximum dose 80 mg/day |
| Obsessive compulsive disorder | Fluoxetine<br>initial dose 20 mg/day<br>maximum dose 80 mg/day<br>Sertraline<br>initial dose 50 mg/day<br>maximum dose 200 mg/day<br>Paroxetine<br>initial dose 20 mg/day<br>maximum dose 60 mg/day<br>Clomipramine<br>initial dose 25 mg/day<br>maximum dose 250 mg/day |
| Major depressive disorder | Fluoxetine<br>initial dose 20 mg/day<br>maximum dose 80 mg/day |

## Depression

Adolescents with a major depressive disorder do not have a particularly good response to either psychological therapy or pharmacotherapy. The characteristics of the illness compromise engagement with psychological therapy ('I'm too tired, I'm not worthy of treatment, I can't concentrate, what's the point, I'm soon going to be dead anyway'). Adherence to pharmacotherapy may also be poor. Adolescents who present with depressive symptoms may not have a primary mood disorder. The depressed (or more often dysphoric) mood may be a feature of borderline personality disorder, eating disorder, gender identity disturbance, conduct disorder, or a reaction to traumatic experiences. With the exception of bulimia, none of these conditions is likely to respond to antidepressant therapy. Depressed adolescents with complex or ambiguous presentations should be referred for a psychiatric opinion.

For adolescents with a mild case of major depressive disorder (symptomatic but with no or minimal functional impairment), supportive care and psycho-education is the first-line management. Attention to their sleep routine, diet and exercise may be sufficient to resolve symptoms. If not, these patients should be referred for psychological therapy.

The approach to moderate to severe cases of major depressive disorder (significant functional impairment or suicidality) in adolescence is less clear-cut. UK

guidelines recommend psychological therapy first.[6] US guidelines recommend starting with either psychological therapy or pharmacotherapy, then switching to or adding the other modality if there has been an inadequate response.[7] Evidence shows that the response to psychological therapy and fluoxetine is similar. The time to response is shorter with fluoxetine than with psychological therapy, but suicide-related behaviours are more common.[8] Fluoxetine is the treatment of first choice when a rapid remission is a high priority. This is important because the longer the episode of major depressive disorder, the greater the impact on academic and social functioning. If safety is the top priority, psychological therapy is the treatment of choice. This is relevant when a young person with major depressive disorder has prominent suicide ideation, or has engaged in self-harm. In contrast to studies in adults, combined therapy is not superior to psychological or pharmacological monotherapy for first-line treatment of adolescents with major depressive disorder.[8]

While most responders to fluoxetine will start to improve within a few weeks of starting treatment, some may take several months. In the initial phase, the adolescent should be reviewed at least every two weeks. Emphasis in the early weeks will be on the detection of serious adverse effects such as behavioural activation, and emergent or increasing suicidality. The adolescent is typically the last person to notice improvement, so corroborative information from family or teachers can be very helpful. Clinicians should focus on functional improvement (objective data) over subjective reports of mood. Greater engagement in school and social activities and an improvement in total sleep time are useful markers of improvement.

If after 12 weeks there has been an inadequate response to any first-line treatment, seek the opinion of a psychiatrist. The recommended interval for review is longer than for anxiety disorders, because major depressive disorder is typically slower to respond to treatment. If there are severe adverse effects, refer to an emergency service.

For an adolescent who has responded to fluoxetine, the drug should be continued for a further 12 months to prevent relapse. Discuss this with the adolescent at the consenting phase, so there are no later misunderstandings about the need to continue therapy. Adolescents are likely to stop treatment if there are adverse effects,[9] so be pro-active in surveying symptoms at each review.

### Stopping treatment

When withdrawing antidepressant treatment, taper the dose in two or more steps over one to two weeks. If a discontinuation syndrome emerges, raise the dose to stop the symptoms and then resume withdrawal at a much slower rate.

## Conclusion

Antidepressants are an effective second-line treatment for adolescents with anxiety or obsessive compulsive disorder who have not responded to, or not engaged with, psychological therapy. Antidepressants also have a first- or second-line role in the treatment of adolescents with moderate to severe major depressive disorder.

Adolescents treated with antidepressants must be monitored for the emergence of rare but serious adverse effects, such as suicide-related behaviours, switching to mania and serotonin syndrome. If effective and well tolerated, the antidepressant drug should be continued for 12 months for major depressive disorder and indefinitely for anxiety and obsessive compulsive disorder. <

*Conflicts of interest: Philip Hazell or his employer has received payment from Eli Lilly and Janssen for consultancies with Eli Lilly, Janssen, Novartis and Shire, and for participation in advisory boards with Eli Lilly, Janssen, Pfizer and Shire, and for speaker's bureau with Eli Lilly and Celltech, and for the conduct of clinical trials. All work has been in the field of attention deficit hyperactivity disorder.*

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## FURTHER READING

NPS MedicineWise. Mental health and young people: opportunities to empower and engage. https://www.nps.org.au/professionals/mental-health-and-young-people [cited 2022 Mar 20]