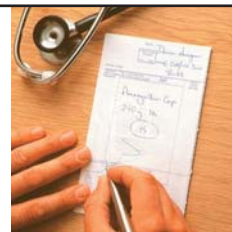


When should GPs prescribe SSRIs for adolescent depression?



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BACKGROUND

Depression is a common disorder, increasing in prevalence in all ages. Research on the effective treatment of adolescent depression is lacking. Concern is growing about the recent increase in general practitioner prescribing of antidepressants and reports that selective serotonin reuptake inhibitors (SSRIs) may precipitate suicidal behaviour in adolescents.

OBJECTIVE

This article discusses the importance of recognising and treating adolescent depression, methodological issues in research and recommendations for SSRI prescribing by Australian GPs.

DISCUSSION

The lack of access to the mental health services and harmful effects of untreated adolescent depression are a cause for concern. On the balance of current information, the only SSRI Australian GPs may prescribe for the treatment of depression in adolescents is fluoxetine, and then only where cognitive behavioural therapy has failed or the depression is life threatening. The key to successful antidepressant drug treatment in adolescents is frequent review to monitor response, compliance and side effects.

Depression is a common disorder, affecting approximately 3–5% of adolescents in the general population,¹ and it is increasing in prevalence in all ages.² General practitioners provide approximately 11 million consultations to young people each year and are often requested to detect and manage adolescent depression.^{3–5} Lack of access to public and private specialist mental health services is a major concern.

Depressive symptoms in adolescents correlate with serious and significant consequences.^{6,7} Morbidity from untreated depression is associated with poor school and work performance, breakdown of family relationships, substance abuse, delinquency, poor self esteem, increased dependency on others, stress, and suicide.^{1,6}

The findings of a number of studies indicate that having a psychological disorder that remains unrecognised and untreated is harmful and associated with more adverse outcomes and longer duration of episodes.^{8,9} There is evidence of critical adverse neurological and psychological consequences and societal impact of untreated depression.¹⁰ The economic costs of depression although difficult to measure, must be substantial and

include costs associated with disability, high health care utilisation, teenage child bearing, hospital admission, days of reduced school and work capacity, and financial adversity.^{2,11}

The rate of detection of depressed adult patients by GPs is generally reported to be lower than 50% in Australia,¹² with some international studies giving the value as low as 14%.¹³ These rates are likely to be even lower for young people due to factors that hinder their presentation to a GP such as concern about confidentiality, cost, and unfamiliarity with the health system and clinic environment.²

Undertreatment is also a particular problem in young people due to the increased stigma of mental illness among this group.² A crucial and limiting step in the capacity of GPs to respond is the relatively limited evidence about which treatments of adolescent depression are effective.^{14–17} Many studies on psychological and pharmacological therapies have been performed in mental health services rather than general practice and community settings.

The National Health and Medical Research Council (NHMRC) *Clinical guidelines for depression in young people*¹

recommend cognitive behavioural therapy as the treatment of first choice for adolescent depression and antidepressant therapy if:

- cognitive behaviour therapy (CBT) is unsuccessful
- the depression is so severe that it interferes with the young person's capacity to engage in counselling, or
- the depression is life threatening.

What are the risks of SSRIs in adolescents?

Despite the increasing prevalence of youth depression, the high levels of underdetection and undertreatment and the harmful effects of untreated depression, concern is growing about the recent increase in GP prescribing of antidepressants and reports that selective serotonin reuptake inhibitors (SSRIs) may precipitate suicidal behaviour in adolescents.¹⁸ In a recent literature review published in *The Lancet*, Whittington et al¹⁸ compared and contrasted published and unpublished data on the risks and benefits of SSRI treatment in the under 18 years age group. The study concluded that the risks could outweigh the benefits of these drugs (except for fluoxetine) to treat depression in young people.

Consistent with the findings of Whittington,¹⁸ the Expert Working Group of the Committee on Safety of Medicines (CSM) analysis of available data led to the Medicines and Health Care Products Regulatory Agency (MHRA) in the United Kingdom recommending cessation of all antidepressants except for fluoxetine in the treatment of depression in young people under 18 years of age.¹⁹

Two randomised controlled trials have demonstrated the efficacy of fluoxetine compared to placebo in paediatric samples.^{20,21} In addition, a recent study demonstrated that the combination of fluoxetine and CBT offered the most favourable trade-off between benefit and risk for adolescents with major depressive disorder when compared with placebo and CBT or fluoxetine alone.²² In this study, clinically significant suicidal thinking, which was present in 29% of

the sample at baseline, improved significantly and showed the greatest reduction in the group treated with fluoxetine and CBT.

In the United States, the Food and Drug Administration (FDA) has taken a more conservative approach in comparison with authorities in the UK. The FDA has required manufacturers to change labels on antidepressant drugs to include a 'black box' warning about the increased risk of suicidality in children and adolescents treated with these agents.²³ This action has resulted because of the finding that in a pooled sample of 4400 children and adolescents with major depressive disorder, obsessive compulsive disorder and other psychiatric disorders, there was a 4% risk of suicidality in those treated with an antidepressant compared with 2% in those who received a placebo.²³ No completed suicides occurred in the sample. The FDA recommends regular observation of paediatric patients treated with antidepressants by the physician and family for clinical worsening, especially during the first few months and at times of dose change.

What are the methodological issues related to studies on antidepressant treatment of youth depression?

The preliminary report of the Taskforce on SSRIs and Suicidal Behaviour in Youth by the American College of Neuropsychopharmacology²⁴ questioned *The Lancet* study¹⁸ as the rate of suicidal behaviour in treatment groups was usually no more than 2% and not statistically significant for any SSRI. Furthermore, despite the fact that citalopram (Cipramil) improved suicide ratings compared with placebo in two clinical trials, *The Lancet* study¹⁸ concluded that citalopram may increase self harm on the basis of reports of suicidal acts or self injury. The American College of Neuropsychopharmacology Taskforce²⁴ also noted that patients considered at high risk of suicide were excluded from most of the trials and therefore reports of adverse drug effects did not systematically assess potential benefits of medication in relation to

suicidal thoughts. There were no completed suicides in any trials.

There are a number of issues related to response and compliance to treatment of children and adolescents that may have added to the methodological issues in the studies. The response rate to SSRIs in depressed teenagers is approximately 50%, which is somewhat less than the 70% response seen in adult depression.²⁵ A number of factors may play a role in the reduced response rate in adolescents compared with adults. Side effects may be less tolerable to adolescents and adolescents may be less likely to comply with treatment. The drug half life is lower in adolescents due to more rapid absorption, rapid uptake by growing tissue and breakdown by proportionally larger livers.²⁶ Brent and Birmaher²⁷ argue that methodological limitations of some antidepressant trials might have influenced conclusions about the risk and benefits of antidepressants such as varying definitions of response and suicidality, a lack of monitoring of compliance, a need to stratify by age and high rates of attrition. Further, Brent and Birmaher²⁷ demonstrated that in the studies examined by the MHRA, slightly higher rates of suicidality in SSRI samples compared with placebo may suggest increased suicidality; but no statistically significant difference was found between these groups even with large samples.

The findings of *The Lancet* study¹⁸ are at odds with epidemiological studies from several countries suggesting the increased use of SSRIs lowers the risk of suicide.^{28,29} A review of World Health Organisation data on the rate of youth suicide showed a significant decline in rates in 15 countries including Australia in recent years; coinciding with increases of prescribing of SSRIs.²⁴ Autopsy studies suggest that suicide is more likely when depressed people do not take their medication; suggesting that the underlying depression is responsible not the SSRI.²⁴

Further research and monitoring of safety and prescribing variability, systematic reporting of adverse events, and adjunctive psychological and educational interventions

for the management of adolescent depression are required. A number of other authors have called for additional research to provide scientific evidence on the effectiveness of SSRIs in adolescent depression and recurrent and unresponsive depression.^{27,30,31} Clearly these studies must also be done in the general practice setting.

In what circumstances should Australian GPs prescribe SSRIs to adolescents?

In Australia, it should be noted that despite the NHMRC guidelines¹ in relation to antidepressant therapy in young people, none of the SSRIs is approved in the Pharmaceutical Benefits Schedule for the treatment of depression in adolescents.³² Selective serotonin reuptake inhibitors are only approved for the treatment of obsessive compulsive disorder in adolescents by the Therapeutic Goods Administration.³²

Following a consideration of the evaluation by the UK Committee on Safety and Medicines, the Australian Adverse Drug Reactions Advisory Committee (ADRAC)^{19,32} released three recommendations for the treatment of depression with SSRIs:

- any SSRI use in adolescents with major depressive disorder (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*.¹ Such management should include careful monitoring for the emergence of suicidal ideation and behaviour
- the choice of SSRI for adolescents should be made taking into account the recent evaluations of clinical trial data and product information. Note that the current Australian product information for paroxetine and venlafaxine recommends against their use in children and adolescents, and
- adolescents who are currently being treated for MDD with an SSRI should not have their medication ceased abruptly.

More recently pharmaceutical companies have written to Australian GPs clarifying the indication for SSRIs. For example, Pfizer

recommends that sertraline (Zoloft) should not be used in children and adolescents below the age of 18 years for the treatment of MDD.³³

Although the case against SSRIs in the management of adolescent depression is as yet unproved, on the balance of current information and according the recommendations of the NHMRC,¹ ADRAC³² and pharmaceutical companies, in cases where CBT has failed or the depression is life threatening, Australian GPs may currently prescribe fluoxetine.

The Better Outcomes in Mental Health Care Initiative is assisting many Australian GPs with CBT training and is currently being evaluated. A recent Australian study³⁴ provided evidence that, with appropriate training, GPs can incorporate CBT skills into their practice. Many of the perceived barriers experienced by GPs in providing services to adolescents with depression were effectively addressed with education and skills training in the study.³⁴ Changing the service environment of general practice facilitates GP implementation of new knowledge and skills into practice.³⁴

When prescribing antidepressants for adolescent depression, GPs must:

- first establish diagnosis, which may be assisted by the use of diagnostic interviews and/or self report questionnaires
- consider the differential diagnosis of depressive disorders and comorbidity
- discuss the medication with the young person or parent to ensure they are comfortable with the treatment
- explain potential side effects including suicidality, and
- discuss the importance of taking the medication as prescribed and the impact that other substances may have.³⁵

The key to successful antidepressant drug treatment in adolescents is frequent review by the GP to monitor response, compliance and side effects, preferably with the use of a depression symptom checklist in the context of providing psychological support. The role of parents, school teachers and peers in providing support must not be underestimated. General practitioners may also share care or

refer to a psychologist, psychiatrist and other mental health professionals in the management of adolescent depression.

Conclusion

The increasing prevalence, high levels of underdetection and undertreatment, lack of access to the mental health system and harmful effects of untreated adolescent depression are a cause for concern. On the balance of current information and according the recommendations of the NHMRC,¹ ADRAC³² and pharmaceutical companies, the only SSRI Australian GPs may currently prescribe for the treatment of depression in adolescents where CBT has failed or the depression is life threatening, is fluoxetine. However, there is an urgent need for further research to clarify what constitutes effective management of adolescent depression in the general practice setting.

The Better Outcomes in Mental Health Care Initiative provides education and training and incentives to assist GPs recognise and treat depression. The program also improves GP access to allied health professionals and psychiatrists. For more information visit www.racgp.org.au/mental-health or email gpmhsc@racgp.org.au.

Conflict of interest: none declared.

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