Early intervention for depressive disorders in young people: the opportunity and the (lack of) evidence

Nicholas B Allen, Sarah E Hetrick, Julian G Simmons and Ian B Hickie

ABSTRACT

- Young people experiencing their first onset of depression are a group at risk of relapse and recurrence to whom early intervention and prevention efforts should be targeted.
- Despite the argument for a significant research effort addressing these issues, the evidence regarding optimal intervention strategies for first episodes is lacking.
- Cognitive behaviour therapy is an effective approach to treatment and relapse prevention among depressed adolescents, and is likely to be an important component of any evidenced-based approach to early intervention.
- Antidepressants are not recommended as first-line treatment for most first episodes of depression. The role that they may play in patients with severe depression, or those who do not respond to psychological therapies, requires further evaluation.
- Given the high prevalence of depressive disorders, and the significant burden of disease they represent within our community, early intervention in depressive disorders is a critical research agenda for the future.

MJA 2007; 187: S15–S17

Adolescence, in comparison with childhood, is associated with a marked rise in the incidence of depressive symptoms and disorders.[1,2] Epidemiological studies estimate the point prevalence of unipolar depressive disorders to be between 0.4% and 8%, with 20% of adolescents experiencing a diagnosable depressive episode by age 18 years.[1,3] In addition, longitudinal data indicate that an episode of depression is a substantial risk factor for subsequent episodes, both within adolescence and into adulthood.[3,4] This increased vulnerability is likely to reflect the adverse impact of depressive episodes on neurobiological and cognitive development,[5,6] as well as on emotional, social, and occupational functioning.[7,8] These data indicate the public health significance of adolescent depressive syndromes, and the need to intervene effectively and early in adolescents who suffer from these disorders.

Despite a great deal of research being directed to the *prevention* of depressive disorders in children and adolescents,[9,10] *early intervention* has received little attention. By early intervention, we are particularly referring to optimal treatment of the first episode or first presentation of depressive disorders. Such optimal treatment should not only effectively ameliorate the symptoms of the presenting episode, but should also aim to prevent the development or exacerbation of risk factors for relapse. Some authors have argued that early and effective intervention might greatly reduce the ongoing prevalence rates of depression,[11,12] and that the development of cognitive factors that increase the risk of depression could be halted early in life.[13-15]

Here, we outline the opportunities for early intervention in depressive disorders, highlighting the pressing need for intervention studies of treatment and relapse prevention targeted at the early phases of illness in younger age groups.

The imperative for early intervention in depressive disorders

It has been argued that early intervention in depressive disorders represents a potentially significant preventive strategy. Harrington and Clark[11] have suggested that, if all cases of depression in 13-year-olds were successfully treated, the risk of depressive disorders could be reduced by 10%. Indeed, achieving full remission from the acute phase is a significant factor in preventing relapse or recurrence.[12]

There is evidence from longitudinal studies suggesting that intervening in the first episode of depression may be crucial in halting the development of a vulnerable cognitive style linked with recurrent episodes. A substantial body of evidence from adult studies suggests that psychosocial stressors, often in the form of major stressful life events, play a greater role in the onset of the first episode of depression than in subsequent episodes.[16] This implies that subsequent episodes require decreasing external triggering. This may be related to increasingly negative information processing modes associated with dysphoric mood.[15]

In support of this hypothesis, Kendler et al[13] showed that the impact of stressful events on the onset of depressive episodes decreased with each successive episode. In one of the few studies to evaluate this model in a longitudinal cohort of community-based young people, major life events were a stronger predictor of the first episode of a major depressive disorder than recurrent episodes.[14] Recurrent episodes, on the other hand, were more strongly predicted by the interaction between depressed mood and negative thinking, suggesting that while characteristics of the environment were the critical predictors of first episodes, characteristics of the individual (potentially influenced by previous experiences of depression) are the major predictors of subsequent episodes.

The evidence

Early intervention in depressive disorders

There are no studies, either in adults or adolescents, of treatment or prevention of relapse or recurrence specifically focused on the first episode of depression. While studies of adolescents are likely to contain a greater proportion of those who are experiencing a first episode of depression, they are not exclusively first-episode cases. Furthermore, most intervention studies are undertaken within clinical services. Many young people experiencing an initial episode may not be in contact with these services. Recognition of depressive disorders within primary health care services and the school setting is therefore also an important focus.[11]

There are many studies on the use of psychosocial interventions with children and adolescents suffering from depressive disorders, especially cognitive behaviour therapy. A recent review by Comp-

ton and colleagues[17] concluded that, from an evidence-based perspective, cognitive behaviour therapy is currently the treatment of choice for anxiety and depressive disorders in children and adolescents. Clearly, as a benign and effective intervention for depressive disorders in children and adolescents, cognitive behaviour therapy represents one of the "best bests" for early intervention approaches to depression.

By contrast, there is increasing consensus that antidepressant medication should not be used as first-line treatment for children and adolescents with mild-to-moderate depression.[18,19] Tricyclic antidepressants in children and adolescents have long been shown to be ineffective at best, and harmful at worse,[20,21] in contrast to results in adults. The evidence for the clinical benefit of selective serotonin reuptake inhibitors (SSRIs) is not compelling. The small statistically significant benefits of fluoxetine in ameliorating depressive symptoms may not be of overwhelming clinical significance, with fewer than half the treated adolescents recovering completely.[22,23] The possibility that SSRIs might be associated with increased risk of suicidal ideation and attempts must also be taken into account,[24] although recent studies make it clear that this risk is small and easily managed by adequate clinical practice.[25,26] The clinical trials of therapy with SSRIs, including fluoxetine, do not include children and adolescents typically seen in clinical practice, and patients at risk of suicide, those with comorbidity, and "placebo-responders" are often excluded. While the risks of untreated depression are great, especially the risks of poor long-term outcomes noted above, it is not clear if treatment with an SSRI will modify this risk greatly.

Clinicians, as advised in recent clinical guidelines,[19] should consider the threshold of severity at which they use SSRIs (ie, use should be reserved for severe or treatment-resistant depression) and assess and monitor suicide-related behaviours closely. Guidelines also recommend that when SSRIs are used, they should be used in combination with psychological interventions.[19] The Treatment for Adolescents With Depression Study,[27] which did show fluoxetine to be more effective than placebo in treating adolescents with depression, also showed that the combination of fluoxetine and cognitive behaviour therapy was significantly more effective than either intervention alone. A recent meta-analysis also showed superior results for integrated psychological and medical care among adults.[28] Further studies are required to corroborate this emerging evidence — that combined psychological and pharmacological therapies represent best practice, especially for young people with more severe forms of depression. Another important matter is the cost-effectiveness of treatments, especially over the long term. A recent study found that, while there are a range of cost-effective treatments for depression, including cognitive behaviour therapy and SSRIs, long-term treatment with SSRIs was identified as the most expensive.[29]

The reduced effectiveness of antidepressant medication, especially tricyclic antidepressants, in young people may be due to the development of neurotransmitter systems. For example, the noradrenergic system is not fully developed until early adulthood.[30] Drug distribution characteristics differ in young people, and hormonal changes may also lead to differences in response to antidepressants.[21,23] On the other hand, and consistent with the finding that the experience of depression is associated with neurobiological changes (especially in terms of atrophy of the hippocampal regions),[31] it may be that the brains of those who have experienced less depression are less responsive to antidepressants. Indeed, some models of antidepressant action propose that neurotropic factors that reverse such brain atrophy are crucial to antidepressant effects,[32] and point to some of the mechanisms that may render antidepressants less effective for those suffering early episodes, where such atrophy may be less pronounced. This again points to the need to intervene early with more benign but effective interventions to prevent progression to a more chronic stage.

Relapse prevention in depressive disorders

Pharmacological treatment has been consistently shown to prevent relapse in adults who have responded to acute treatment, but only as long as the medication continues to be taken.[33-36] Cognitive behaviour therapy has been shown to have longer-lasting effects than tricyclic antidepressants, and is effective in preventing relapse in adult populations.[37] More recently, a modification of cognitive behaviour therapy specifically designed for relapse prevention — mindfulness-based cognitive therapy — has been shown to lower rates of relapse over 60 weeks; however, this effect was only shown to have occurred in patients who had had three or more previous episodes.[38] These positive results have recently been replicated in a second study.[15]

These studies on relapse prevention have been undertaken in adult populations, despite evidence that earlier onset appears to be associated with a higher risk of relapse or recurrence.[15,38] Of the few studies undertaken in young people, Emslie and colleagues[39] found that continuation of fluoxetine treatment in children and adolescents significantly delayed the return of symptoms. With respect to psychosocial treatments, the effect of booster cognitive behaviour therapy sessions has been compared, using a randomised controlled design, with frequent or annual assessment only.[40] The results showed that booster sessions did not reduce the rate of recurrence in the follow-up period, although they did accelerate recovery for adolescents who were still depressed at the end of the acute phase of treatment.[40] In another small study, adolescents who had responded to cognitive behaviour therapy had booster sessions or no continued therapy, with relapse rates at 3 months of 6% and 50%, respectively, providing some initial support for the effectiveness of cognitive behaviour therapy booster sessions.[41]

Competing interests

None identified.

Author details

Nicholas B Allen, PhD, Associate Professor, Principal Research Fellow[1,3]
Sarah E Hetrick, MA, DPsych, Research Fellow[1,2]
Julian G Simmons, BSc, PostGradDipPsych, PhD Candidate[1,3]
Ian B Hickie, MD, FRANZCP, Professor of Psychiatry, Executive Director[4]
1 ORYGEN Research Centre, University of Melbourne, Melbourne, VIC.
2 Centre of Excellence, *headspace*: The National Youth Mental Health Foundation, Melbourne, VIC.
3 Department of Psychology, University of Melbourne, Melbourne, VIC.
4 Brain and Mind Research Institute, University of Sydney, Sydney, NSW.
Correspondence: nba@unimelb.edu.au

References

1 Lewinsohn PM, Hops H, Roberts RE, et al. Adolescent psychopathology: I. Prevalence and incidence of depression and other DSM-III-R disorders in high school students. *J Abnorm Psychol* 1993; 102: 133-144.
2 Lewinsohn PM, Rohde P, Seeley JR. Major depressive disorder in older adolescents: prevalence, risk factors, and clinical implications. *Clin Psychol Rev* 1998; 18: 765-794.
3 Birmaher B, Ryan ND, Wiliamson DE, et al. Childhood and adolescent depression: a review of the past 10 years. Part 1. *J Am Acad Child Adolesc Psychiatry* 1996; 35: 1427-1439.
4 Harrington R, Vostanis P. Longitudinal perspectives and affective disorder in children and adolescents. In: Goodyer IM, editor. The depressed child and adolescent. Cambridge: Cambridge University Press, 1995: 311-341.
5 Harrison PJ. The neuropathology of primary mood disorder. *Brain* 2002; 125: 1428-1449.
6 Vythilingam M, Heim C, Newport J, et al. Childhood trauma associated with smaller hippocampal volume in women with major depression. *Am J Psychiatry* 2002; 159: 2072-2080.
7 Bardone AM, Moffitt T, Caspi A, Dickson N. Adult mental health and social outcomes of adolescent girls with depression and conduct disorder. *Dev Psychopathol* 1996; 8: 811-829.
8 Rohde P, Lewinsohn PM, Seeley JR. Are adolescents changed by an episode of major depression? *J Am Acad Child Adolesc Psychiatry* 1994; 33: 1289-1298.
9 Horowitz JL, Garber J. The prevention of depressive symptoms in children and adolescents: a meta-analytic review. *J Consult Clin Psychol* 2006; 74: 401-415.
10 Merry SN. Prevention and early intervention for depression in young people — a practical possibility? *Curr Opin Psychiatry* 2007; 20: 325-329.
11 Harrington R, Clark A. Prevention and early intervention for depression in adolescence and early adult life. *Eur Arch Psychiatry Clin Neurosci* 1998; 248: 32-45.
12 Lam RW, Kennedy SH. Evidence-based strategies for achieving and sustaining full remission in depression: focus on metaanalyses. *Can J Psychiatry* 2004; 49 (3 Suppl 1): 17S-26S.
13 Kendler KS, Thornton LM, Gardner CO. Stressful life events and previous episodes in the etiology of major depression in women: an evaluation of the "kindling" hypothesis. *Am J Psychiatry* 2000; 157: 1243-1251.
14 Lewinsohn PM, Allen NB, Seeley JR, Gotlib IH. First onset versus recurrence of depression: differential processes of psychosocial risk. *J Abnorm Psychol* 1999; 108: 483-489.
15 Ma SH, Teasdale JD. Mindfulness-based cognitive therapy for depression: replication and exploration of differential relapse prevention effects. *J Consult Clin Psychol* 2004; 72: 31-40.
16 Post RM. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *Am J Psychiatry* 1992; 149: 999-1010.
17 Compton SN, March JS, Brent D, et al. Cognitive-behavioral psychotherapy for anxiety and depressive disorders in children and adolescents: an evidence-based medicine review. *J Am Acad Child Adolesc Psychiatry* 2004; 43: 930-959.
18 Lyndon B, Rowe L, Fraser A, et al. Clinical guidance on the use of antidepressant medications in children and adolescents. *Aust Fam Physician* 2005; 34: 777-778.
19 Middleton H, Shaw I, Hull S, Feder G. NICE guidelines for the management of depression. *BMJ* 2005; 330: 267-268.
20 Hazell P, O'Connell D, Heathcote D, Henry D. Tricyclic drugs for depression in children and adolescents. *Cochrane Database Syst Rev* 2002; (2): CD002317.
21 Weller EB, Weller RA. Treatment options in the management of adolescent depression. *J Affect Disord* 2000; 61 (Suppl 1): 23-28.
22 Emslie GJ, Heiligenstein JH, Wagner KD, et al. Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. *J Am Acad Child Adolesc Psychiatry* 2002; 41: 1205-1215.
23 Emslie GJ, Rush AJ, Weinberg WA, et al. A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Arch Gen Psychiatry* 1997; 54: 1031-1037.
24 Hammad TA, Laughren TP, Racoosin JA. Suicide rates in short-term randomized controlled trials of newer antidepressants. *J Clin Psychopharmacol* 2006; 26: 203-207.
25 Friedman RA, Leon AC. Expanding the black box — depression, antidepressants, and the risk of suicide. *N Engl J Med* 2007; 356: 2343-2346.
26 Simon GE, Savarino J, Operskalski B, Wang PS. Suicide risk during antidepressant treatment. *Am J Psychiatry* 2006; 163: 41-47.
27 March J, Silva S, Petrycki S, et al. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA* 2004; 292: 807-820.
28 Gilbody S, Bower P, Fletcher J, et al. Collaborative care for depression: a cumulative meta-analysis and review of longer-term outcomes. *Arch Intern Med* 2006; 166: 2314-2321.
29 Vos T, Corry J, Haby MM, et al. Cost-effectiveness of cognitive-behavioural therapy and drug interventions for major depression. *Aust N Z J Psychiatry* 2005; 39: 683-692.
30 Andersen SL. Trajectories of brain development: point of vulnerability or window of opportunity? *Neurosci Biobehav Rev* 2003; 27: 3-18.
31 Hickie I, Naismith S, Ward PB, et al. Reduced hippocampal volumes and memory loss in patients with early- and late-onset depression. *Br J Psychiatry* 2005; 186: 197-202.
32 Shirayama Y, Chen AC, Nakagawa S, et al. Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression. *J Neurosci* 2002; 22: 3251-3261.
33 Geddes JR, Carney SM, Davies C, et al. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. *Lancet* 2003; 361: 653-661.
34 Keller MB, Ruwe FJ, Janssens CJ, et al. Relapse prevention with gepirone ER in outpatients with major depression. *J Clin Psychopharmacol* 2005; 25: 79-84.
35 Rapaport MH, Bose A, Zheng H. Escitalopram continuation treatment prevents relapse of depressive episodes. *J Clin Psychiatry* 2004; 65: 44-49.
36 Simon JS, Aguiar LM, Kunz NR, Lei D. Extended-release venlafaxine in relapse prevention for patients with major depressive disorder. *J Psychiatr Res* 2004; 38: 249-257.
37 Hensley PL, Nadiga D, Uhlenhuth EH. Long-term effectiveness of cognitive therapy in major depressive disorder. *Depress Anxiety* 2004; 20: 1-7.
38 Teasdale JD, Segal ZV, Williams JM, et al. Prevention of relapse/recurrence in major depression by mindfulness-based cognitive therapy. *J Consult Clin Psychol* 2000; 68: 615-623.
39 Emslie GJ, Heiligenstein JH, Hoog SL, et al. Fluoxetine treatment for prevention of relapse of depression in children and adolescents: a double-blind, placebo-controlled study. *J Am Acad Child Adolesc Psychiatry* 2004; 43: 1397-1405.
40 Clarke GN, Rohde P, Lewinsohn PM, et al. Cognitive-behavioral treatment of adolescent depression: efficacy of acute group treatment and booster sessions. *J Am Acad Child Adolesc Psychiatry* 1999; 38: 272-279.
41 Kroll L, Harrington R, Jayson D, et al. Pilot study of continuation cognitive-behavioral therapy for major depression in adolescent psychiatric patients. *J Am Acad Child Adolesc Psychiatry* 1996; 35: 1156-1161.

(Received 15 Mar 2007, accepted 24 Jun 2007) ❑