Review Paper

Major Depressive Disorder in Adolescence: A Brief Review of the Recent Treatment Literature

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Objective: Treating adolescents with depression remains a major clinical and public health challenge. Because of the serious morbidity and mortality associated with adolescent major depressive disorder (MDD), there is a need to review the published literature on treatment efficacy to establish effective treatment choices for these adolescents.

Method: We reviewed the recent literature on the treatment of MDD in adolescents using the Medline and PsycINFO computerized databases.

Results: Results of open studies of MDD treatment in adolescents suggested therapeutic efficacy; however, later, better-controlled studies are more difficult to interpret, owing to the high rate of improvement with placebo. Currently, there is limited evidence of robust, effective therapeutic interventions in children and in adolescent depressive disorders.

Conclusions: Despite limitations, current findings from studies investigating selective serotonin reuptake inhibitors (SSRIs), cognitive-behavioural therapy, and interpersonal therapy generally support these treatments as safe and effective for adolescent MDD. Still, further investigations into these treatments for adolescent depression are warranted.

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Clinical Implications

- Major depressive disorder (MDD) in adolescence is an important public health concern.
- The sequelae of MDD are serious and may include adolescent suicide.
- Effective treatments for MDD in adolescents may include selective serotonin reuptake inhibitors (SSRIs), cognitive-behavioural therapy, and interpersonal therapy.

Limitations

- There is limited evidence of robust, effective therapeutic interventions for MDD in adolescents.
- Studies published to date suffer from methodological flaws that limit their conclusions.
- Strong placebo effects that were found in studies investigating effective treatment for adolescent MDD confound results.

Key Words*: major depressive disorder, pharmacotherapy, psychosocial treatment, adolescence, review*

It is widely accepted that children and adolescents suffer from depressive disorders. Community surveys indicate an estimated prevalence rate of between 1.8% and 7.8% for depression in adolescents (1,2). Lifetime prevalence rates of major depressive disorder (MDD) in adolescents are estimated to range from 15% to 20%, compared with the adult lifetime rates (2,3). In adolescents, twice as many girls as boys present with MDD (4).

In family studies of children and adolescents, first-degree relatives who present with MDD have higher lifetime rates for depression than those expected in the general population (5) or compared with relatives of healthy control subjects (6–15).

Depression in adolescents remains underrecognized and misdiagnosed in clinical practice. DSM criteria for adult MDD apply to children and adolescents, with some minor age

differences (16–19). There is prospective longitudinal evidence from a birth-cohort study (age, birth to 26 years) to suggest that childhood and adolescent onset of MDD may be distinguished from adult onset of MDD on the basis of early childhood risk factors. These include developmental deficits, family instability, psychopathology and criminality in the biological family, and either inhibited or undercontrolled temperaments in childhood (20). Early onset of depression has been shown to predict future depressive episodes during adolescence and adulthood (21,22).

Major depressive episodes in adolescence are long in duration, with a high risk of relapse, and are usually associated with school, family, and social difficulties (23). Community, high risk, and clinical studies have shown that the mean length of an episode of early-onset MDD is 6 to 9 months. The longer the duration, the greater the severity, and the number of maternal depressive episodes has been shown to increase the likelihood of MDD persisting (22,24,25). In a large community study of adolescents, most depressive episodes were brief, with a median of 8 weeks, although a substantial risk of reoccurrence exists (3,4,21,22,26). In adolescent high-risk and clinical samples, the median duration for MDD ranged from 12 to 16 weeks (25). The median duration may represent a more accurate figure, compared with the mean duration, because it is unaffected by methodological variables and extreme scores (25).

Clinical and epidemiologic studies indicate that 40% to 93% of children and adolescents with depression have comorbid psychiatric disorders (3,24). Comorbidity with substance use disorders may have a negative effect on severity of MDD symptoms (24,27,28). The impact of comorbidity on MDD duration is less clear (25).

The strongest risk factor for adolescent suicide is MDD (29). The longer the duration of MDD, the greater the risk of suicidality (3). Because of the serious morbidity and mortality associated with adolescent MDD, there is a need to investigate the efficacy of interventions. Currently, there is limited evidence that indicates effective therapeutic interventions in child and adolescent depressive disorders. Clinical research is complicated by methodological difficulties, by lack of consensus for testable hypotheses, and by inadequate financial support for research. Placebo-controlled trials of antidepressants and other treatments in child and adolescent populations have been difficult to implement for various reasons, including reluctance to take placebo, concerns with safety and compliance, and high rates of study attrition.

Pharmacotherapy

Multiple open-label pharmacologic trials in adolescents with MDD have shown clinical improvements using tricyclic antidepressants (TCAs)—amitriptyline, nortriptyline, desipramine, and imipramine (30–32)—and selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, paroxetine, and sertraline (33–41). Retrospective chart reviews have also provided preliminary evidence on the effectiveness of SSRIs (specifically, fluoxetine, sertraline, and citalopram) in the treatment of adolescent MDD (42–44). Ambrosini and colleagues found that, in a sertraline treatment study of adolescent MDD, maximal clinical response, based on clinician and self-reported depressive symptoms, occurred after week 10, leading them to conclude that, to fully evaluate efficacy, acute-phase antidepressant therapy should extend to at least 10 weeks (37). An open-label study of sertraline in adolescents with MDD who had a minimum 3-month illness duration indicated that maintenance therapy of 6 months was effective in reducing depressive symptoms and in improving functioning (36). An open-label naturalistic study of sertraline in children and adolescent patients with MDD or obsessive–compulsive disorder showed evidence to suggest that the pharmacokinetic profile, tolerability, and recommended titration regime are similar to those in adults (40).

A 6-week clinical trial compared open-label fluoxetine treatment in 52 adolescent inpatients with 28 historical control subjects who were treated with imipramine (39). Greater improvements were found with fluoxetine than with imipramine, based on reductions in the Hamilton Depression Rating Scale scores and final scores on the Clinical Global Impression (CGI) scale. The authors concluded that adolescent MDD may respond better to SSRIs than to TCA treatment.

Consistently, double-blind randomized controlled trials (RCTs) in adolescent MDD outpatients, comparing TCAs (that is, amitriptyline, nortriptyline, imipramine, and desipramine) with placebo have reported no significant treatment differences (45–51). Response rates to TCAs and to placebo ranged from 40% to 60%. These studies suggest that TCAs are no more effective than are placebos for treating MDD in adolescents. An RCT of intravenous pulse infusion of the TCA clomipramine, however, demonstrated a significant improvement in depressive symptoms and clinical functioning in a small sample of adolescent outpatients with MDD after 6 days, compared with the saline control group (52). After 2 weeks, however, most responders had experienced significant relapse of depressive symptoms that required subsequent SSRI treatment.

A review of antidepressant treatment of MDD in children and in adolescents concluded that TCAs were ineffective (53). Previous metaanalysis of TCA treatment of children and adolescent MDD supported the lack of clinical efficacy (54). A recent further metaanalysis by the same authors (55) supported the lack of efficacy of TCAs in the treatment of childhood (that is, prepubertal) MDD. A trend, however, toward a

positive treatment response for adolescents was determined with effect-size estimates, suggesting a moderate yet significant treatment benefit for adolescents. The authors concluded that the evidence to support using TCAs in treating adolescent MDD was marginal. Concern has been raised about TCA use; various reports have indicated side effects, particularly cardiovascular adverse events (49,51) and "sudden death" in children taking therapeutic doses (56).

Conflicting findings of SSRI efficacy have been reported in RCT studies. An 8-week RCT in 40 adolescents with MDD did not find significant statistical differences between placebo and fluoxetine in response rates (66%), although a trend favoured fluoxetine for response (57). A larger 8-week RCT of fluoxetine treatment in 96 children and adolescent outpatients who presented with MDD reported a significant improvement in MDD on CGI scores, with response rates of 56% for fluoxetine, compared with 33% for placebo control subjects (58). Response rates for children aged 12 years and under (n = 48) did not differ from adolescents aged 13 and over (n = 48). In a subsequent 1-year naturalistic follow-up of 87 patients from this sample, Emslie and colleagues (59) reported that 74 (47 with fluoxetine, 22 without medication, and 5 with other antidepressants or lithium), or 85%, had recovered from the depression during the 1-year period. Unfortunately, 39% experienced a reoccurrence of depression during follow-up. Poor outcome was associated with increased age, severity of depressive symptoms and comorbidity, and decreased family functioning. Recently, in a multicentre study, Emslie and colleagues reported significant improvement in depressive symptoms, remission rates (41% vs 20%), and clinical global functioning in a second RCT of fluoxetine for 9 weeks in 122 children and 97 adolescents with MDD (60). No significant differences were seen based on age category. In January 2003, the US Food and Drug Administration (FDA) approved the use of fluoxetine to treat MDD in children and adolescents (61).

In a 12-week, multicentre, international RCT of paroxetine treatment in 286 adolescents with unipolar MDD, statistically significant differences in efficacy were not found between paroxetine and placebo, although there was a trend for adolescents aged 16 years and over to have a higher proportion of paroxetine responders (82.6%), compared with placebo responders (66.7%) (62).

A 6-week RCT of low-dose venlafaxine, a selective serotonin norepinephrine reuptake inhibitor (SNRI), in 33 children and adolescents with MDD found significant improvement in depressive symptoms over the study duration, with no difference between venlafaxine and placebo (63).

An 8-week, multicentre RCT of paroxetine and imipramine showed efficacy of paroxetine in treating unipolar major depression in 275 adolescents (51). Paroxetine (response rate 63.3%) was superior to placebo (response rate 46%) on clinician ratings of affect, clinical global functioning, and reduction in depressive symptoms. Imipramine (response rate 50%) was not superior to placebo on any outcome measure.

In an 8-week, multicentre, double-blind, randomized comparison trial of the efficacy of the SSRI paroxetine and the TCA clomipramine with SRI activity treatments in 122 adolescents with MDD, the response rates were similar (64). Based on a 50% reduction in depression scores, 48.3% responded to clomipramine and 65.1% responded to paroxetine. Similarly, based on CGI scores, 58.2% responded to clomipramine and 59.3% responded to paroxetine. Clomipramine, however, induced significantly more adverse effects than did paroxetine. No placebo control arm was present in the study to confirm efficacy of clomipramine and paroxetine.

There have been few small-scale studies that have investigated the effectiveness of SSRI in a specific population of adolescents with MDD and comorbid substance use disorders (SUDs), despite the negative impact that comorbidity with substance use and other disorders has on severity of symptoms and persistence of adolescent MDD (65). An open-label study of the potential safety and efficacy of fluoxetine in 8 adolescent boys with MDD comorbid with conduct and SUD (abstinent for at least 1 month) suggested that fluoxetine may reduce depressive symptoms and increase global functioning (66). In a 12-week RCT of sertraline in 10 adolescents with MDD and alcohol dependence, depressive symptoms and drinking were reduced over the study duration; however, no significant group (that is, sertraline vs placebo) differences were found. These results may have been owing, in part, to concurrent cognitive-behavioural therapy (CBT), which was offered to all study participants regardless of group membership, suggesting CBT efficacy in treating MDD and alcohol dependence (67).

Psychosocial Therapies

In a review of psychosocial therapies for treating depression in children and adolescents, Harrington and coworkers investigated the efficacy of 3 psychotherapies: CBT, interpersonal therapy (IPT), and family therapy (68). CBT involved role playing, problem solving, and monitoring thoughts and behaviours, using behavioural techniques and cognitive strategies. A quantitative metaanalysis that included 6 RCTs with a follow-up component of CBT for predominately nonclinical samples of adolescents with depressive disorders found significant improvement in depressive symptoms in the CBT group (n = 109) over comparison groups (n = 108), including waiting list, supportive therapy, and relaxation techniques (69). Improvements were maintained over the course of the follow-up period (range 1 month to 24 months).

A large controlled study of MDD in adolescents (n = 107, completers n = 78), comparing 12 weeks to 16 weeks of individual CBT, nondirective supportive psychotherapy, and systemic behavioural family therapy (70), showed a significant improvement over the study duration for each of the 3 treatments. All 3 treatment groups received family psychoeducation sessions about mental illness and its treatment. Significant differences among treatments began to emerge at 12 to 16 weeks, with the CBT group scoring significantly lower than the supportive therapy group on the Beck Depression Inventory and the CBT group having significantly higher remission rates (60%), compared with the family therapy (29%) and the supportive therapy (36.4%) groups. Adolescents with comorbid anxiety responded better to CBT than to the other 2 psychosocial treatments (71). However, adolescents whose mothers had depressive symptoms negatively impacted the efficacy of CBT (71). In a subsequent follow-up study (72), 45 study participants received additional treatment during the 24-month follow-up phase (62% for depression). The percentage of adolescents from each treatment group who subsequently received additional treatment services did not differ (CBT 48.6%, family therapy 37.1%, and supportive therapy 40%). Predictors of additional treatment included greater ratings of severity for depression at intake, higher frequency of comorbid disruptive disorder, and self-ratings of greater family dysfunction. At 2 years posttreatment, the 3 treatment groups did not differ significantly on depressive symptomatology, clinical global functioning, cognitive variables, or family functioning (73). Increased risk for chronicity and relapse of depression were associated with family conflict and increased severity of MDD (73).

Kroll and colleagues investigated weekly maintenance CBT therapy for 6 months in 17 adolescents (74). Results of the study suggested that the relapse risk was lower in adolescents who received continuing CBT (6%) than in those who had not (50%). Community studies of adolescents have shown that group CBT in conjunction with relaxation and group problem-solving therapy may prevent relapses in depression for 9 to 24 months posttreatment (4,75). Children and adolescents with severe depressive disorders did not appear to respond as well to CBT, compared with those who had mild and moderate depression (71,76).

IPT is brief, time-limited therapy that identifies and treats the depressive symptoms and the problems associated with depression onset. In a 12-week open trial of IPT in adolescents with depression (77), a decrease in depressive symptoms and an overall improvement in social adjustment were found over the study duration. In a posttreatment study of this sample (78), results strongly suggested that the improvements were maintained over the 1-year follow-up period.

A 12-week RCT of the efficacy of IPT in 21 adolescents and in 11 adolescent control subjects who were clinically monitored (79) found that adolescents who received IPT had greater response rates (75%) to treatment than those who were clinically monitored (46%). Further, adolescents who received IPT reported a greater decrease in depressive symptoms, based on clinician and self-rated depression scores, and a greater improvement in overall social functioning, compared with those who received clinical monitoring. At study termination, only 9.1% of the IPT treatment group met criteria for MDD, while 30.3% of individuals in the control subject group showed clinical depression.

In a 12-week RCT of 71 Puerto Rican adolescents with depressive disorders (specifically, MDD, dysthymia, or both) comparing CBT and IPT with a wait-list control group (80), both IPT and CBT significantly reduced depressive symptoms on the Children's Depression Inventory. The IPT enhanced self-esteem and social adaptation. Measures of clinical significance showed that 82% of the adolescents who received IPT and 59% of those who received CBT were in the functional ranges.

Family therapy involves more than 1 member of a family and focuses on altering family interactions; therapists work to improve the presenting problem and the relationship patterns associated with the problem. There is strong evidence of an association between depression in children and adolescents and problems in family members, such as mental illness and dysfunctional family relationships (81). A recent 12-week RCT of attachement-based family therapy (ABFT) compared 32 adolescents with MDD to a wait-list control group. ABFT was shown to significantly reduce family conflict, suicidal ideation, and feelings of hopelessness, and to significantly enhance attachment to mothers (82). In addition, at study end, 81% of the adolescents who received ABFT had remitted, compared with 47% from the wait-list control group. For the ABFT group, follow-up at 6 months found that 87% did not meet criteria for MDD. Conversely, RCTs of family therapy in childhood depression have yielded negative results, compared with results of cognitive therapy and supportive counselling (71).

Electroconvulsive Therapy

Electroconvulsive therapy (ECT) for adolescents presenting with MDD is controversial. Evidence from the adult literature supports ECT as an effective therapy for MDD and other serious mental disorders. In a systematic review of the literature of ECT treatment in those aged 18 years and under, authors suggested that, despite numerous methodological problems, ECT may benefit adolescents who present with depression, mania, schizophrenia, or catatonia (83). Controlled studies of ECT effects in adolescents have not been published to date.

Discussion

Many published studies suffer from methodological flaws that limit the study's conclusions. Conflicting findings in the pharmacologic treatment of adolescent MDD result from methodological factors including limited sample size, variable inclusion criteria, rating issues, dosage ranges, concurrent psychotherapies, and short study duration. Similar methodological problems are found in the research that investigates the effectiveness of various psychosocial therapies for treating adolescent depression. High placebo or comparison therapy response rates rendered the results of many treatment trials difficult to interpret. Despite limitations, current findings from studies investigating SSRIs, CBT, and IPT generally support these therapies as safe and effective first-line treatment in the acute treatment of adolescent MDD. Follow-up of acute-treatment studies of SSRIs and psychosocial therapies has shown that a poorer treatment outcome is associated with increased severity of family dysfunction (59,73). Further efficacy studies are required for specific family therapies in the treatment of adolescents with MDD.

In July 2003, Health Canada (84) issued an alert informing health care professionals about the possibility of increased risk of suicide-related and adverse events associated with paroxetine treatment in children and adolescents with MDD. Health Canada notes that the alert is based upon 3 pediatric, placebo-controlled trials. These trials demonstrated that the risk of suicidal thinking, suicidal attempts, and self-harm were 5.3% for the paroxetine group and 2.8% for the placebo group, some of which occurred during discontinuation of paroxetine treatment. There were no completed suicides for any study participant. Further, the trials indicated that paroxetine was no more effective than placebo in the treatment of MDD. It is important to note that the alert did not distinguish any differences in frequency of adverse events or in efficacy between children and adolescents, nor were the cited studies identified. Further analysis is required; however, in the interim, it is recommended that paroxetine treatment not be initiated for children and adolescents with MDD.

A preponderance of studies on the efficacy and tolerability of TCAs do not support the use of TCAs in treating adolescent MDD. Some evidence supports a graduated age response to TCA with adolescence; however, TCAs have not been found effective in adolescents with treatment-resistant MDD (45,55). Further study of the efficacy and tolerability of clomipramine, a TCA with serotonin activity (64), is required.

There are few follow-up studies of RCT trials. In fact, there is a paucity of studies investigating maintenance therapy and prophylaxis of recurrence. Studies investigating acute and maintenance treatment are required to determine the long-term effects of treatment on outcome in adolescents. Some studies—especially those in which the MDD duration was short—may have been biased toward subjects with mild-to-moderate MDD that resolved naturally and may further account for strong placebo effects. In studies where supportive therapy was not controlled, placebo effects may have resulted. Negative findings are rarely published, yet they add to the understanding of research methods and treatment and may suggest further directions for research, especially within early investigative stages of treatment trials. There is a paucity of studies investigating treatments that combine pharmacotherapy and psychosocial therapies.

Conclusion

Treating adolescents with depression remains a major clinical and public health challenge with clinically significant recent treatment advances in the areas of pharmacotherapy and psychotherapies. Future investigations into the efficacy and safety of treatments for adolescent depression would benefit greatly from replication, larger sample sizes, and RCT of specific medications, including within classes such as SSRIs, and from psychosocial therapy that extends to acute and long-term treatment phases. Comparison studies of pharmacotherapy, psychotherapies, and combined therapies are necessary to identify the adolescents who will benefit the most from specific or combined therapies. Further studies into the factors that influence treatment outcome—including genetics, age, illness course, duration, and severity—may help identify appropriate treatments and robust effects for adolescents with MDD.

Note added in proof

Wagner and colleagues published the results of a pooled sample from 2 multicentre, 10-week RCT studies of the efficacy and safety of sertraline in 376 children and adolescents with MDD (85). These authors found a response rate of 69% for sertraline, compared with 59% for placebo. There was a significant improvement in depressive symptoms in those treated with sertraline. Evidence of a possible preferential response for adolescents (n = 199) was noted, with a slightly greater improvement in depressive symptoms than was noted for children. No differences in suicidality (in either attempts or ideations) were noted between treatment and placebo groups. The authors concluded that sertraline was a well-tolerated and effective acute treatment for children and adolescents with MDD. This further supports the overall recommendations of the review.

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Résumé : Le trouble dépressif majeur à l'adolescence : une brève revue de la documentation récente sur les traitements

Objectif : Traiter les adolescents souffrant de dépression demeure un grand défi clinique et de santé publique. En raison de la morbidité et de la mortalité sérieuses associées au trouble dépressif majeur (TDM) à l'adolescence, il faut examiner la documentation publiée sur l'efficacité des traitements afin de faire des choix de traitement efficaces pour ces adolescents.

Méthode : Nous avons passé en revue la documentation récente sur le traitement du TDM chez les adolescents à l'aide des bases de données électroniques Medline et PsycINFO.

Résultats : Les résultats des études ouvertes sur le traitement du TDM chez les adolescents indiquaient une efficacité thérapeutique; cependant, ultérieurement, des études mieux contrôlées sont plus difficiles à interpréter, en raison du taux élevé d'amélioration avec placebo. Présentement, il n'y a que des preuves limitées d'interventions thérapeutiques robustes et efficaces auprès d'enfants et d'adolescents souffrant de troubles dépressifs.

Conclusions : Malgré les limites, les résultats actuels des études qui traitent des inhibiteurs spécifiques du recaptage de la sérotonine (ISRS), de la thérapie cognitive du comportement et de la thérapie interpersonnelle soutiennent généralement que ces traitements sont sûrs et efficaces pour le TDM adolescent. Il faut tout de même d'autres études sur ces traitements de la dépression adolescente.