Early onset major depressive disorder

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The present paper provides an overview of the clinical diagnosis and presentation, epidemiology, coexisting problems, and treatment issues of child and adolescent depressive disorders, with a focus on major depressive disorder (MDD). Depression is a common and potentially debilitating disorder for youth; has significant comorbid, behavioural and systemic sequelae; and is associated with a significant suicidal risk. Although rigorous study of psychosocial and pharmacological treatment modalities is in its infancy, current treatment is also informed by judicious and patient-specific clinical judgment. In view of the duration of MDD, remission and recurrence rates, morbidity, and potential chronicity of impaired psychosocial functioning, both active treatment and research involving MDD are indicated.

Key Words: *Depression; Major depression; Psychopharmacology; Psychotherapy*

Les troubles dépressifs majeurs à apparition précoce

RÉSUMÉ : Le présent article donne un aperçu du diagnostic clinique et de la présentation, de l'épidémiologie, des problèmes coexistants et des enjeux en matière de traitements relatifs aux troubles dépressifs de l'enfant et de l'adolescent, et est axé sur les troubles dépressifs majeurs (TDM). La dépression est un trouble courant au potentiel débilitant chez l'adolescent. Elle s'accompagne de séquelles comorbides, comportementales et systémiques importantes et s'associe à un risque de suicide élevé. Bien que l'étude rigoureuse des modalités de traitement psychosocial et pharmacologique en soit encore à ses balbutiements, le traitement actuel dépend également d'un jugement clinique judicieux adapté à chaque patient. Étant donné la durée des TDM, les taux de rémission et de récurrence, la morbidité et la chronicité possible d'une altération psychosociale fonctionnelle, tant un traitement actif que des recherches sur les TDM sont à conseiller.

Early medical and psychiatric beliefs regarding depression in children and adolescents were that juveniles were psychologically unable to experience 'true' depression, and consequently, depression in this population was considered to be rare. As the theoretical and clinical understanding of depression has grown, it has become apparent that depression does occur in juveniles and that it is diagnostically predictive (1,2). It is now recognized that despressive disorders occur more frequently than previously believed, and, if left untreated, may seriously compromise a patient's sense of self-worth, impair school performance, damage familial bonds, and impair both interpersonal and peer functioning, as well as intrapersonal capacities (3). The present review examines the epidemiological features, clinical presentation, comorbid features and sequelae of early onset depressive disorders, and reviews treatment and management issues.

CLINICAL DIAGNOSIS AND PRESENTATION

Every child may occasionally experience event-appropriate sadness throughout his or her life. From a formal psychiatric perspective, children and adolescents must meet the same *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition: DSM-IV* (4) diagnostic criteria as applied to adults to qualify for the diagnosis of major depressive disorder (MDD). They must report at least a two-week duration of pervasive change in mood (dysphoria or irritability), and/or loss of interest and pleasure. As well, other diagnostic criteria, such as changes in appetite, weight, sleep, activity, concentration, energy level, self-esteem and motivation, are sought out by clinicians. The symptoms must be severe enough to impair relationships or activities, and not be attributable to substance or medication use, other psychiatric disturbances, bereavement or medical illness.

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As clear as the above criteria are, there is controversy regarding behavioural equivalents of depression for children and adolescents. Indeed, both clinical and research studies infer that oppositional behaviours, eating disturbances, social withdrawal and self-injurious behaviours may often be expressions of depression. These behavioural disturbances are not considered indicators of depression because there are significant comorbid relationships between depression, and other psychiatric and behavioural disturbances.

Symptomatic manifestations of depression also vary with age. Prepubertal children often display more somatic complaints (especially headaches and stomachaches), auditory hallucinations, agitation, separation anxiety and phobias (5,6). Adolescents tend to display more sleep disturbance (often hypersomnia), appetite disturbance and suicidal attempts than children (5-7).

The presence of auditory hallucinations is a specific concern in the juvenile population. Besides their presence within the depressive-spectrum disorders, hallucinations may also signify other disorders such as bipolar disorders, severe trauma-related disorders or early manifestations of psychotic disorders.

It is worth mentioning a specific form of auditory hallucinations called 'command hallucinations' when reviewing the risk of suicide. It is generally considered appropriate to question the patient actively about any current suicide wishes, past attempts or wishes, any pervasive current plans, and any passive wishes or wants not to have to live anymore. Experiencing command hallucinations that often 'tell' patients to harm or kill themselves constitutes a serious risk, which should alert the practitioner to provide a patient with safety and treatment.

EPIDEMIOLOGY

The epidemiology of early onset depressive disorders is complicated by the apparent increase in prevalence rates with increasing age, as well as the use of highly variable diagnostic methodologies to verify cases when reporting findings in the research literature. Other complicating factors include an apparent cohort effect given that each successive generation since 1940 appears to be at greater risk for the development of MDD and that these disorders appear to manifest at progressively younger ages (8,9).

MDD is estimated to have a point prevalence of slightly less than 3% in children (10), and between 4% to 8% in adolescents (10-12). In retrospective studies, about 50% of adult depressed patients claimed that their first depressive episode occurred before the age of 20 years (8). Estimated lifetime prevalence rates for MDD of 15% to 20% (13,14) highlight the magnitude of the MDD problem. Many studies suggest an equal prepubertal incidence between males and females, and note a sudden increase in female cases during adolescence (14). Such studies support the need for a more aggressive agenda regarding both the detection of and intervention for early onset depressive disorders, as well as further study regarding the mediating variables influencing sex ratios.

COMORBID AND DIFFERENTIAL ISSUES

It is quite common for children and adolescents with MDD to meet criteria for other concomitant psychiatric disorders and problems (15). Forty per cent to 90% of youth with MDD have at least one other disorder, and from 20% to 50% of such depressed youth have two or more comorbid diagnoses. Common comorbid diagnoses in youth include anxiety disorders (30% to 80%), disruptive disorders (10% to 80%) and substance use disorders (20% to 30%). The more common anxiety-related comorbidities include obsessive-compulsive disorder and social anxiety disorder. The above comorbidities are more common in adolescents, whereas separation anxiety disorder is more common in children. Although some adolescents display comorbid personality disturbances, many physicians recommend withholding a diagnosis of personality disturbance until the depressive elements are treated. A subset of children has experienced sexual abuse; for these children, depressive symptoms are part of the post-traumatic response (16). Mood-related differential considerations should include bipolar disorder, premenstrual dysphoric disorder, adjustment disorder with depressed mood, bereavement and general medical conditions that may mimic MDD, as well as psychotic depression with either mood-congruent or mood-incongruent psychotic features.

SEQUELAE OF MDD

Children with MDD are at high risk for developing suicidal behaviour, substance abuse, physical disorders, early unwanted pregnancy, exposure to subsequent adverse life events, and compromised work, academic and psychosocial functioning (15,17). Of concern is the devastating sequelae of both suicide attempts and completions. The suicide rate for adolescents has almost quadrupled since 1950 and represents a significant percentage of mortality for adolescents (18). Many factors exacerbate the risk for suicide, with socioenvironmental circumstances such as poor parent-child communications, school problems and negative life events associated with increased suicide risks (19).

Approximately 60% of youth sustain a relapse after initial success in acute treatment (20-22). At least a part of this somewhat high relapse rate may be due to the natural course of the illness, early discontinuation of treatment, inadequate initial treatment or treatment adherence problems. Specific treatment adherence problems that may be encountered include parental and physician mistrust in the use of medications in youth, family power struggles that compromise treatment plans, the stigma of being psychiatrically labelled, tolerating one's own emotional and behavioural deficits in the face of the adolescent need of omnipotence and the belief that symptoms of depression indicate character flaws instead of a treatable disorder.

The rate of recurrence in depressed youth is approximately 50% within two years and approximately 70% five

years after diagnosis (10,20-24). Known factors associated with higher recurrence rates include earlier age of initial depressive episode, severity of the first episode, presence of psychotic features, the number of previous episodes, presence of comorbid problems, biological relatives with MDD and a past history of treatment adherence problems.

Interest in the relationship between child and adolescent MDD and bipolar disorder (BD) is fueled by evolving evidence indicating that 20% to 40% of youth are likely to develop BD within five years of onset of MDD (10,21-26). Factors associated with an increased risk of development of BD include a family history of BD or psychotic depression, heavy genetic loading for mood disorders, early childhood onset MDD with psychotic features and pharmacologically induced hypomania. Bipolar disorder is explored in greater depth in Katz and Fleisher (pages 439 to 443 in the present issue).

TREATMENT

The desire and need to provide effective and safe treatments to children and adolescents with MDD is understandable. Notwithstanding, the application of various psychosocial and pharmacological intervention strategies has clinically progressed beyond the outcome studies currently available in the literature and beyond a more comprehensive understanding of MDD. MDD is most likely a multi-determinant problem that may often respond to a variety of interventions. In the present paper, some of the literature regarding such interventions is briefly reviewed, with some potential recommendations presented. Although the use of electroconvulsive therapy in early onset MDD is not discussed in this review, its role should not be discounted prematurely (27) for cases that are severe and resistant to other interventions.

Treatment strategies for adolescents and children benefit from systemic interventions for youth and their families. The promotion of multilevel treatments should be encouraged.

Psychoeducation

One of the primary treatment goals for youth with MDD is to educate their families and other significant systems (28-30) because MDD invariably affects the family and friends of the patient, and the patient's behaviours may be individualized (31). Irrespective of the role that interpersonal issues may play in MDD development or whether they are subsequent to the MDD, attention to these areas of tension will often facilitate any potential rehabilitation.

Such systemic and familial intervention also serves as an opportunity to address certain stigmata and attitudinal fallacies about early onset depression. These fallacies include beliefs such as the following: the MDD is just 'normal adolescent turmoil'; he or she is just lazy; he or she just needs more rest or better nutrition; the patient is depressed by nature (a character flaw); he or she has a defect of a spiritual nature; and other esoteric or alternative health beliefs. It is imperative to begin to understand such beliefs and present a cogent biopsychosocial understanding to the patient's caregivers. If done early, this proactive intervention enhances the subsequent treatment alliance, and its importance cannot be emphasized enough.

Systemic interventions are often of great importance, regardless of the degree of biological weighting in the disorder. It is worth highlighting the continuum between systemic psychoeducation and formal systemic therapy interventions, and to recognize the central roles that they play in the treatment of MDD.

Psychosocial

Notwithstanding significant advances in biologically driven treatments, psychosocial therapeutic interventions remain the usual and standard initial treatment choice for mild and moderate early onset depression (32). Current clinical practice suggests that youth are more likely to succeed with psychotherapy interventions if they have identified stressors initiating dysphoric changes; are experiencing difficulty in relationships with family, friends or school; or display persistently dysfunctional or self-destructive intrapsychic or interpersonal patterns. Retrospective reviews have described the benefits of using cognitive behaviour therapy (CBT) (33), intensive dynamic psychotherapy (34) and interpersonal therapy (35) for depressed children and adolescents.

A recent review of research about psychological treatments has been undertaken (36). CBT, interpersonal therapy and a specific family therapy approach were all compared using prospective methodology. The three therapies were shown to be effective; however, CBT showed the most promise. In another study (37) that compared CBT, systemic behaviour family therapy and nondirective supportive therapy, all three treatments showed significant reductions in suicidality and functional impairment. CBT was superior in attaining a lower rate of MDD at the end of treatment.

The provision and successful outcome of such psychosocial interventions are complex and challenging in their clinical application, and are usually out of the therapeutic range of primary physicians without previous training and supervision for such treatments. Details of some of these therapeutic techniques are available elsewhere (38,39) and are beyond the scope of this brief review.

Antidepressant agents

The use of antidepressants in youth is a complicated and, at times, controversial process. The area of psychopharmacological research is plagued by the reticence of ethical review boards to approve studies; high placebo response rates in children and adolescents; a reluctance to precipitate potentially a manic response; and somewhat variable clinical success, especially with tricyclic antidepressants (TCAs). Although some case reports examine

TABLE 1: Psychopharmacological agents for early onset major depressive disorder*

Agents	Dosage level of initial treatment	Dosage level target range (mg/kg/24 h)
Selective serotonin reuptake inhibitors		
Fluoxetine	10 to 20 mg q am	0.25 to 0.7
Paroxetine	5 to 10 mg q od	0.25 to 0.7
Sertraline	25 to 50 mg q am	1.5 to 3.0
Fluvoxamine	25 to 50 mg q od	1.5 to 4.5
Other agents		
Venlafaxine	37.5 mg od	1 to 3
Nefazadone	25 to 50 mg bid	3 to 6
Bupropion	100 mg od	3 to 6
Citalopram	10 to 20 mg od	0.3 to 0.6

**These pharmacological agents have not been specifically approved in Canada for use in children and adolescents*

other agents, this review is restricted to the more common antidepressant agents. In the present review of such therapeutic agents, one must keep in mind that regulatory bodies in Canada and the United States have yet to approve any psychopharmacological agents for use in juvenile MDD. Other sources provide more detailed reviews (40-42).

TCAs were the only antidepressants that were available until the introduction of fluoxetine over 10 years ago. Most of the controlled trials that have been completed to date involved TCAs, and in contrast to open TCA trials, the controlled TCA trials have not shown an overall robust indication for TCA use in children and adolescents (43). The relatively high overdose lethality of TCAs, as well as the risk of sudden cardiovascular death with the use of desipramine, preclude their use as primary pharmacological agents for MDD. However, the use of TCAs may be considered to be appropriate in selective cases.

The introduction of the selective serotonin reuptake inhibitors (SSRIs) over the past 10 years has broadened the range of potential pharmacological treatments for many disorders, especially MDD. There are currently two controlled published SSRI studies (44,45) involving fluoxetine and paroxetine that suggest a significant improvement in MDD with these agents. Other studies involving fluoxetine (46) and venlafaxine (47), or most recently paroxetine (48), have not shown such significant results. Currently, there are ongoing multicentre and multinational studies, with further reports on other putatively effective agents pending. It remains to be seen whether the SSRIs will be seen to be truly more effective than TCAs after further comparison studies are completed.

Many open studies and retrospective chart reviews are well described elsewhere (40-42), and are more favourable toward the use of pharmacological agents in early onset MDD. Antidepressant agents with potential benefit, as outlined in open trials, include sertraline, fluvoxamine, venlafaxine, nefazadone, bupropion and citalopram. A further potential advantage of SSRIs and other newer agents is their relatively safer profile in suicide attempts (49). A sensitivity to developmental pharmacodynamics (50) is encouraged if their use is considered in patients. Table 1 summarizes possible dosage ranges of some antidepressants that may show promise in the treatment of MDD in children.

Consequently, the ongoing dilemma is whether the physician feels that it is appropriate to initiate pharmacological intervention in the face of mixed research evidence. In the face of a more severe MDD with neurovegetative symptoms or acute suicidality, a positive family history for MDD, previous MDD or a lack of adequate response to other treatments, a physician might be more willing to initiate a clinical pharmacological intervention.

Physicians needs to be proactive in communication with the parents, schools, etc, to facilitate and educate others with regard to the use of medication. Assuming a positive response, one still has to be cautious about treatment issues. The above potential psychopharmacological treatments for MDD must be further cautioned in patients with MDD and a history of bipolar disorders, where the use of mood stabilisers (either alone or with antidepressants) must be considered.

SUMMARY

The increased recognition of MDD and other depressive disorders in children and adolescents represents a significant conceptual, as well as a clinical shift. Progress in the development of useful treatment paradigms and the explosion in active clinical treatments has not been paralleled by research, where few randomized control studies exist, let alone can be replicated.

In general, psychotherapeutic intervention remains the appropriate initial response to juvenile MDD, whereas the application of pharmacological interventions may be indicated for more severe and persistent depression, a strong family history for MDD, recurrence of MDD, or the failure or exacerbation of MDD with psy-

chotherapy. Because only two psychotherapeutic and two phamacological agent controlled studies have shown short term efficacy, treatment and intervention for youth benefit from individualized risk-benefit applications that are informed by clinical reports. Although in its early years, the study of MDD may offer hope in changing the natural morbid course of this debilitating and often chronic disorder.

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