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Integrative Assessment and Management of Pediatric Depression


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This issue of Pediatric Review is intended for pediatricians, family physicians, pediatric psychopharmacologists, and all other interested medical professionals. For CME purposes the authors have no relevant financial relationships to disclose.

Objectives

At the conclusion of this activity, participants should be able to:

1. Describe contemporary methods of differential diagnosis, markers and protective factors of unipolar depression in pediatric cases
2. Discuss the advantages of psychosocial modalities and when they are most appropriate
3. Describe core behavioral interventions in the primary care setting for managing depressive disorders and make appropriate referrals to mental health professionals
4. Identify best practices of antidepressant (AD) therapy, encompassing issues of comorbidity, nonadherence and acuity

Introduction

The term pediatric depression denotes a unipolar, noncyclical and nonpsychotic group of heterogeneous syndromes entailing a range of lowered mood states and physiological symptoms in children (4-12 years old) and adolescents (13-17 years). Symptoms vary from subthreshold (e.g., Adjustment Disorder) to acute major depression (Major Depressive Disorder, or MDD), to a prolonged course of negative mood (e.g., Dysthymic Disorder; DD). The present article focuses on MDD and DD, the most common subtypes, as defined by the American Psychiatric Association's Diagnostic and Statistical Manual, 5th Edition (DSM-5).

MDD refers to a clinically significant depressed or irritable mood often accompanied by neurovegetative disturbance (e.g., suppressed or elevated appetite, insomnia/hypersomnia), anhedonia, anergia, inattention, excessive guilt or rumination, psychomotor agitation or retardation and/or parasuicidal behaviors. At least five of the characteristic symptoms should be observed for a minimum of two weeks duration and engender clinically significant distress or impairment in the child's ability to function at home, school or other settings. They are also not attributable to the physiological effects of a substance (e.g., illicit agents, beta blockers, corticosteroids, benzodiazapines) or a medical condition, such as hypothyroidism, B12 deficiency, hyponatremia or Cushing's Syndrome. Pediatric depression likely stems from a complex interplay of heredity, biology and environment.

Developmental Variations in the Clinical Picture

Preschoolers and young children with depression tend to display more somatic, anxious-behavioral, affective lability, and psychomotor disturbances than older youth or adults, coupled with a greater preponderance of irritability in mood. Depressed adolescents are more likely than children to complain of negative affect (e.g., feelings of worthlessness, hopelessness), anhedonia, hypersomnia and weight change. The clinician may also expect the depressed teenager, as compared to depressed adults, to display a more variable course, greater interpersonal upheaval, denial of diffuse anhedonia, fewer delusions, and more frequent parasuicidal behaviors (e.g., ideation, attempts/gestures).

Prevalence, Comorbidity, and Differential Diagnosis: Let's Sleep On It

MDD and DD are comparatively common disorders in the pediatric population. In MDD, prevalence estimates for children range from 2-4% and double that in adolescents (4-8%), with an additional 5-10% displaying subclinical symptoms in both groups. Risk of unipolar depression at least doubles post puberty, particularly among females and cumulative incidence in community samples by age 18 hovers around 20%. The few studies examining DD produce widely varying prevalence estimates of 0.6%-1.7% in children and 1.6%-8.0% in teenagers.

Unfortunately, national survey data indicate that children and youth in Louisiana rank among the worst of five states with the highest prevalence of mental illness and lowest rate of access to care. This greatly complicates the work of pediatric providers in managing their clients' mood disorder.

Studies indicate an increased risk over the last half of the 20th century for depressive symptomatology in the pediatric population, with an even earlier age of onset across successive generations of children. Perhaps not surprisingly, meta-analytic data evaluating prevalence of pediatric disorders, particularly neurodevelopmental, find parallel generational trends in patterns of sleep. Thus, it is distinctly possible that youth in successive cohorts who report greater depression on average are concurrently experiencing delayed sleep onset, reduction in sleep duration or its combination. This is an area in which pediatricians are well positioned to assess and intervene. Primary care providers are often families' first entrance to care and pediatricians are able to provide valuable education regarding the relationship between mood disorders and sleep disturbances. Moreover, sleep difficulties are so prevalent and impact such a wide range of functioning that the American Academy of Pediatrics (AAP) felt compelled to publish a policy statement last year indirectly addressing this issue. AAP specifically promoted later start times (e.g., 8:30 a.m. or later) for the adolescents' school day, primarily to increase sleep to an optimal 8.5 hours. Prescribers should therefore routinely assess sleep in their initial evaluation of depression and consider its role in maintenance of symptomatology and relapse.

According to the American Academy of Child and Adolescent Psychiatry (AACAP), the majority of children diagnosed with a depressive disorder (40-90%) are believed to have a co-occurring psychiatric disorder. Nearly half (20-50%) have two or more comorbid diagnoses. The most common entail anxiety, disruptive behavior, ADHD, and substance use disorders.

A discussion of comorbidity and differential diagnosis would not be complete without addressing the thorny issue of bipolar disorder (BPD), a condition which tends to be overdiagnosed and probably overtreated in North America. Unipolar depression is likely present in a pediatric case in the absence of a strong genetic history for BPD, exclusion of psychosis, no history of psychotropically induced mania/hypomania and if evidence fails to indicate any previously subtle or short-lived episodes of hypomania. Moreover, AACAP notes that not all children taking AD therapy who subsequently display activation or hypomania have BPD. This may reassure pediatricians contemplating management of pediatric depression.

Risk and Protective Factors

Those variables which increase risk of depression and that might protect against its development, relapse following treatment or recurrence are equally worthy of consideration and have a direct bearing on prognosis. Factors placing the child at significant risk include: (a) earlier age of onset; (b) severity of initial episode; (c) number and duration of index episodes; (d) family history of mood disorder or substance abuse (including loss of appetite or weight in first-order relatives); (e) degree of comorbid psychiatric or medical disorders; (f) presence of psychosocial stressors (e.g., abuse, neglect, losses); (g) the child's attributional style or coping mechanisms (e.g., perfectionism/overachievement), (h) nonadherence to care; and (i) lack of social support.

Conversely, risk of depression or relapse is attenuated in those cases with (a) a good level of insight; (b) high resilience; (c) higher parental education and/or socioeconomic status; (d) absence of genetic markers; (e) good network of social support; (f) intact family system; (g) adequate therapeutic rapport with the health professional; and (h) sustained investment by the child and family in treatment compliance.

Contemporary Heteromethod Assessment: Let's Rate It

It is widely acknowledged that an array of investigative tools, both qualitative and quantitative, should be at the clinician's disposal in order to competently assess pediatric depression and differentiate it from other comorbid conditions. Overreliance on any single method (e.g., brief psychiatric interview) is increasingly discouraged given the complex realities of (a) the current practice environment; and (b) comorbidity trends. The former includes increasing demand for specialized behavioral health services (e.g., from the ACA), transitioning to electronic records, accountability, and movement toward establishment of a medical home model placing the primary care provider squarely at the gate of access. The latter domain encompasses aforementioned changes in the epidemiology of childhood depression and co-occurring conditions, coupled with advances in pharmacotherapy. The need for greater diagnostic precision is therefore evident.

Clinicians remain a long way off from the potentially rapid and personalized medicine recently envisioned via genotyping for interindividual variability in diagnostic formulation, biotransformation and drug action. However, comprehensive, individualized, and highly efficient screening for the busy physician may still be achieved. This can be done with the combined use of brief rating scales, clinical interview, history and medical evaluation as deemed appropriate by the provider. Integration of these diverse sources of data may facilitate accurate diagnosis and further reduce risk of relapse or recurrence. In this process efficient determination of acuity level, not unlike triaging, is a key component.

Hence the need to consider use of focused parent-, teacher- or patient-based rating scales of depression: They can augment traditional methods of evaluation by providing a quick picture of severity-targeted treatment that best fits the individual's symptoms. Several inexpensive measures, many of which require minimal specialized training and may be administered and scored

Table 1

SELECTED DIAGNOSTIC AND RATING SCALES ENUMERATING SEVERITY LEVEL

SCALE	AGE RANGE	TIME REQUIRED (IN MINUTES)	REPORTER	SEVERITY
Beck Depression Inventory 2 (BDI 2)	13-86	5-10	S	**Normal:** Raw Score 0-13 **Mild:** Raw 14-19 **Moderate:** Raw 20-28 **Severe:** Raw29-63
Child Depression Inventory 2 (CDI 2)	7-17	5-20	S, P, T	**Normal:** Total T Score <or =59 **Mild:** Total T Score 60-64 **Moderate:** Total T Score 65-69 **Severe:** Total T Score > or =70

Key:
Reporter: S=self-report; P=parent; T=teacher
Commercial Publishers: The Psychological Corporation (BDI 2), Multihealth Systems, Inc. (CDI 2)

by office staff, are available from commercial publishers for this purpose. Two of the measures most commonly used by pediatric psychopharmacologists possess good sensitivity and specificity and are listed in Table 1, with acuity criteria included.

Remember that such quantitative ratings can confirm diagnoses or treatment outcome only in combination with other evaluative methods, including direct behavioral observations, labs and/or clinical interview.

Practice Parameters of Psychosocial Treatment and Available Resources

Evidence-based practice parameters of various professional groups, including AACAP, support the superior efficacy of psychoeducation, supportive measures and particularly psychotherapy in the treatment of pediatric depression for those cases of minor through moderate severity. This is particularly true for techniques utilizing a cognitive-behavioral model of care (CBT).

CBT is a model of psychotherapy conceptualization, assessment and intervention. Briefly, this model is based upon the interplay between contextual factors (i.e. environment) and individual characteristics (i.e. thoughts, feelings, behavior). A bidirectional relationship is assumed in that context impacts individuals and individuals influence their environment. A developmentally appropriate, systemic approach involving families is often recommended for the pediatric population given their dependence upon adults and accompanying lack of autonomy. CBT is designed to assist children in modifying their perceptions and interpretations of events in order to change their resulting feelings and behaviors. It is a common therapeutic model but requires specialized training.

Regarding medication intervention, the UK National Institute for Clinical Health and Excellence (NICE) has even advised that antidepressant (AD) agents should not be prescribed in moderate to severe cases unless combined with ongoing psychotherapy. This recommendation is based in part on findings of the Treatment for Adolescents with Depression study of 2004 (TADS). Of importance, psychotherapy alone is particularly helpful in milder forms of MDD and DD, in which AD therapy is demonstrably less effective. Some researchers even contend that CBT should be considered first-line treatment in adolescent depression. Depending on severity, this information can be useful for families who are hesitant to utilize a pharmacological approach and may prefer psychotherapy.

Within a medical context, pediatricians can also contribute to basic mental health intervention. Primary care practices are often a family's first introduction to the mental health care system and the manner in which this intervention is presented can set the stage for successful treatment by a mental health provider. Specifically, simple psychoeducation for families can help children and their caregivers by normalizing symptoms that may have been previously conceptualized medically (e.g., erroneously searching for a medical cause for significant fatigue). Explaining the link between mental and physical health can reduce potential stigma in association with a mental health referral.

Taking seriously concerns presented by families about changes in mood and behavior represents an often underutilized intervention of simply providing support. When concerns are minimized (e.g., "You're in high school! What could you possibly be depressed about?"), families are less likely to share serious mental health symptomtatology and mood disorders are more likely to go untreated and become more severe. Thus, the importance of this behaviorally-based intervention cannot be overestimated. While primary care practices are often stretched for time and resources, actively listening to families' worries about their child can contribute greatly to treatment adherence and outcome.

Use of Antidepressant Therapy: Best Practices

Although the scientific literature supports the combined use of psychotherapy and AD therapy for cases of moderate to severe acuity levels, there is one exception: AD care may be the most appropriate option if the child, teen or family are simply not receptive or amenable to psychotherapy. This may be due to the presence of other risk factors (e.g., severe denial, poor insight), extensive comorbidity, or family preferences.

Selection of AD treatment should be rational, evidence based, and individualized. According to AACAP, it should include acute, continuation, and in some cases, maintenance phases. Achieving a response and eventually full remission of symptoms constitutes the primary aim of acute care, a process requiring a minimum of 4-8 weeks of AD therapy with adequate dosing. In continuation the prescriber ensures reinforcement of the previous response and avoidance of relapse, preferably by continuing AD care for 6-12 months. In more severe cases, the clinician may need to focus on maintenance and further consolidation of gains to prevent recurrence, with the hope that full recovery (no more than 1-2

residual symptoms) is sustained beyond the first year of therapy. Agents designed to normalize serotonergic dysregulation are clearly favored in this regard.

Black Box Warning: Controversy, Paradox, and Fear Not

The FDA's warning over 10 years ago regarding risk of suicidality with AD treatment initially sparked alarm among both the lay public and practitioners about the safety of these compounds. Since then the pendulum has swung in the opposite direction, with a majority of leading psychiatrists suggesting the dire warning should be removed. This is due to (a) an absence of completed suicides in the pooled trials data analyzed by the FDA; (b) meta analyses indicating the ratio of number needed to treat (NNT) pediatric depression (e.g., 10) over number needed to harm (NNH) (e.g., 112) greatly favors appropriateness of pharmacotherapy; and (c) emerging evidence of negative outcomes tied to troubling prescription trends since the warning was issued.

Although data are lacking for children, studies demonstrate marked absolute reductions in AD use and concurrent increases in psychotropic drug poisonings and other attempts among adolescents and young adults. This was especially true in the second year following the FDA warning. The need to avoid undertreatment of mood disorders among our youth is evident. It is nonetheless appropriate for the clinician to periodically monitor parasuicidal status, as well as other side effects, after initiation of AD care and following upward titration. This may be particularly true for those agents with a relatively short elimination half-life (e.g., paroxetine/Paxil), which increases risk of discontinuation syndrome if abruptly stopped.

Choice of Medication, Initiation, and Follow-Up: SSRIs Strongly Encouraged

Despite the FDA's warning of suicidality, the first-line pharmacologic treatment of MDD and DD in pediatric cases continues to be the selective serotonergic reuptake inhibitors (SSRIs). As with all medications, they should be used with caution in this population. The most common side effects include headache, gastrointestinal symptoms, impaired concentration and sleep disturbances. Less commonly seen are activation, amotivation, withdrawal symptoms and parasuicidal behaviors. Although quite rare, serotonin syndrome can be life threatening and usually occurs in combination with other serotonin enhancing agents. For those cases at risk of QTc prolongation or taking drugs known to affect this parameter, citalopram/Celexa and its more potent sister (escitalopram/Lexapro) may not be the drugs of choice. Overall, SSRIs are quite safe, with minimal symptoms noted in cases of overdose.

How do prescribers avoid bothersome side effects of SSRIs? Start at very low doses, titrate slowly, and during the first several weeks monitor the patient closely. In cases with potential adherence problems, consider compounds with longer half-lives (e.g., fluoxetine/Prozac, sertraline/Zoloft) when possible. Monotherapy should always be preferred over polypharmacy. However, trimonoamine modulators like L-methylfolate 15 mg q d (e.g., Deplin) are FDA approved as an adjunct to AD treatment in adults. They may reduce vulnerability to AD side effects and boost the initial AD response. Its off label use in middle to older adolescents with SSRIs may therefore be useful. Testing of serum folate is not required. Augmentation with this nutritional supplement may also yield higher adherence rates than second generation antipsychotics (SGAs), which have a notable cardiometabolic burden.

If there is no response in the initial 2-4 weeks of SSRI therapy, slowly increase the AD dose into the medium to high dose range for that agent for a minimum of 4-6 weeks. An adequate SSRI trial is defined as 8-12 weeks of pharmacotherapy at optimally tolerated prescribed dosages. A regimen at less than this duration or maximum tolerated dose is unlikely to result in full recovery from the depressive episode, the ultimate goal of care. Once remission is achieved, some patients may require at least one year of maintenance treatment or longer, depending on severity or frequency of recurrences.

Future Directions

A major drawback of AD treatment is its slow onset of action. However, the search for faster acting AD agents has recently yielded promising results. Discoveries that IV injections of glutamatergic NMDA antagonists (e.g., Ketamine) and anticholinergics (e.g., scopolamine) produce rapid and robust elevations in mood comprise some noteworthy examples. Efforts are underway to circumvent serious side effects of these medications by modifying delivery systems (e.g., Ketamine in nasal spray form) or exploring safer alternatives. Nitrous oxide has even emerged as a compound thought to have the same mechanism of action as Ketamine but with a much lower side effect burden. Stay tuned to these and other exciting developments in the chemical pipeline.

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   a. Promptly send the patient to the nearest emergency department for psych consult
   b. Refer the case for individual psychotherapy, preferably CBT-based, and family therapy as appropriate
   c. Order an SSRI
   d. B and C

2. A prudent early behavioral intervention primary care physicians can implement when managing a child's depressive symptomatology is:
   a. Psychoeducation with the family in order to reduce stigma associated with mental health diagnoses and recommendation of appropriate referral sources for treatment
   b. A full course of cognitive-behavioral therapy, designed by the physician and implemented through weekly sessions
   c. Telling the child to cheer up and reminding her that childhood is a carefree time
   d. Immediate referral to a mental health professional with no further discussion

3. Contributing factors to depressive symptomatology sometimes include:
   a. Sleep disruption
   b. Grief and loss
   c. Being grounded for a weekend
   d. A and B

4. The best methods primary care providers can use to avoid SSRI side effects include:
   a. Avoid frequent follow up appointments with the family in order to minimize conversation about side-effects
   b. Concurrently initiate psychotherapy, which is known to alleviate medication side effects
   c. Initiate any new medication at very low doses, titrate slowly, and monitor the patient closely
   d. Never prescribe an SSRI for children or adolescents to avoid the problem entirely

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