Depression in children and adolescents with epilepsy

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Received 28 August 2003; accepted 28 August 2003

Abstract

Depression in children and adolescents with epilepsy is a common but often unrecognized disorder. Both epilepsy and depression are characterized by a chronic course and poor long-term psychosocial outcome. The risk of suicide is even greater in depressed youth with epilepsy than in the general youth population. Educating parents about mood disorders may allow them to be more receptive to psychiatric treatment for their child or themselves. Epidemiological and clinical data on depression in children/adolescents with epilepsy are presented. Seizure-related and general risk factors for the development of depression in youth with epilepsy are reviewed. General guidelines for diagnosis and treatment of depression in children and adolescents are discussed. The early identification and treatment of childhood-onset depression is an important clinical task for all pediatric specialists. Safe and effective multimodal treatment approaches are available.

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Keywords: Depression; Epilepsy; Childhood; Adolescence; Psychopathology; Treatment

1. Introduction

During the past decade considerable research evidence has demonstrated that juvenile-onset depression is a chronic illness characterized by a recurrent course, severe psychosocial morbidity, and the risk of suicide [1]. Studies of the general population have reported 2–6% prevalence rates of depression in children and adolescents [2–4]. Suicide is the third leading cause of death among adolescents in the United States, with a mortality rate of about 8 per 100,000 among 15- to 19-year-olds [5]. Practice parameters are available from the American Academy of Child and Adolescent Psychiatry to guide in diagnosis and management of youths with depression (available at www.aacap.org). Consensus guidelines for medication treatment algorithms for childhood depression and comorbid psychiatric disorders were proposed in 1999 through the Texas Children's Medication Algorithm Project [6].

Unfortunately, psychiatric illnesses, including major depressive disorder, are underdiagnosed and under-treated in patients with epilepsy [7]. Ott et al. [8] reported a disconcerting discrepancy between the high rate of psychiatric diagnoses (60%) and the low rate of mental health services (33%) in youth with epilepsy. The rate of depression in youths with chronic epilepsy as measured by self-reporting instruments varies between 23 and 26% [9,10]. These findings may explain the reported increased suicidality in youths with epilepsy [11,12]. There are only a few published longitudinal studies exploring the development and course of emotional and behavioral problems, including depression, in youths with epilepsy [13–15].

This article summarizes the current data on the evaluation and treatment of depression in the general population of youths, with specific focus on issues related to comorbid epilepsy.

2. Etiological factors

Children and adolescents with epilepsy are vulnerable to the same multietiological risk factors for psychiatric disorders as the general population. Moreover, living with epilepsy creates an additional burden on the child
and the entire family. The understanding of childhood depression requires the evaluation of the relationships between biological, social, and iatrogenic risk factors and negative life events. In patients with epilepsy, a fundamental question remains unanswered: do seizures independently cause depression? The type and laterality of seizures, the age at seizure onset, and electroencephalographic findings have not been associated with depression [11,16], but seizure recurrence, high frequency, and longer duration of epilepsy have been [11,13]. In adults, forced normalization has been associated with the development of depression, particularly in patients with preexisting mood disorders [17,18]; however, this phenomenon has not been well recognized in pediatric samples. In adults, complex partial seizures originating in the left temporal lobe and associated with frontal lobe dysregulation, as demonstrated with positron emission tomography (PET) and single-photon emission computed tomography (SPECT) data, are highly correlated with depression [19–21]. However, this hypothesis has not been comprehensively explored in youths with epilepsy. Other epilepsy-related risk factors, such as depressogenic effects of antiepileptic drugs (AEDs), cannot single-handedly explain the development of depression, as this depends on the specific effects of each particular medication. In the adult literature, depression and increased suicidality have been reported with the use of phenobarbital, topiramate, vigabatrin, and tiagabine [22–24]. Brent et al. [22] reported an association between phenobarbital and depression in children with epilepsy; however, it was reported in children with a positive family history of depression.

Depression is a familial illness [25,26]. Twin and adoption studies have demonstrated that genetic factors account for at least 50% of the variance in the transmission of mood disorders [27,28]. Children of parents with depression are up to eight times more likely to develop depression than children whose parents do not have major depression [29]. A family history of depression was also reported in about 50% of patients with epilepsy and depression [30]. Rutter et al. [31] found a high rate of psychiatric disorders in mothers of epileptic children, but Hoare [32] did not. Interestingly, anxiety and depression in mothers were associated with behavior problems in epileptic children [33–35]. As reported by Dunn et al. [16], a youth’s negative attitude toward having epilepsy, unsatisfactory and highly stressful family relationships, and an individual perception of loss of control over seizures were significantly associated with the development of depression [36].

3. The clinical issues

The concept of childhood depression is relatively new. As recently as 20–30 years ago, it was generally accepted that prepubertal children were unable to suffer from depression because of insufficient ego and superego development for the understanding of self and for feelings of guilt, which is a central part of depression [37]. Adolescents and children as young as 6 years old exhibit the typical phenomenology of depression, comparable to that in adulthood [38,39]. The DSM-IV-R adult diagnostic criteria for depressive disorders are now being used to diagnose childhood depression, but clinical assessment should be adjusted to the age-specific symptom manifestation [40] and to the information obtained from parents and teachers. To date, there are no research data demonstrating that depression in youths with epilepsy is characterized by a different phenomenology, clinical course, or response to treatment compared with depression in youths without epilepsy.

The major categories of the symptoms of depression are described in Table 1. Screening instruments such as the Mood and Feelings Questionnaire [41] and the Center for Epidemiologic Studies Depression Scale [42] may be used to screen for symptoms of depression. Irritability, anger, and a decline in academic performance are the red flags of depression in youths. Vegetative and somatic complaints also are frequently associated with depression [43]. Children may exhibit new regressed behaviors, such as separation anxiety, because their coping skills are maladaptive and immature. Depression with psychotic features characterized by auditory hallucinations is rare in school-aged children, but its incidence increases with age [38]. Depression is associated with the deterioration of social relationships, increased isolation, and poor self-esteem [1,44].

Forty to seventy percent of depressed children and adolescents have comorbid psychiatric disorders, such as anxiety, disruptive disorders, and substance abuse [45–47]. Psychiatric comorbidities are common in youths with epilepsy [48]. They furthermore complicate the treatment of a major depressive episode and increase the risk of suicide attempts [47,49]. The natural course of depression occasionally leads to the development of mania and a switch to a bipolar episode. Follow-up studies have demonstrated that approximately 20% of children and adolescents with depression develop mania or hypomania within 5 years of the onset of depression.

<p>| Table 1 |</p>
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<th>Depressive symptoms in children and adolescents</th>
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<td><strong>Emotional</strong></td>
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<td><strong>Cognitive</strong></td>
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<td><strong>Physical</strong></td>
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4. Treatment strategies

The explosive increase in new classes of antidepressants and the recognition that children and adolescents with depression grow up to be adults with depression have prompted the development of new standards for safe and effective treatment [50,53,54]. However, the treatment of youths with epilepsy and depression presents considerable challenges.

The mean length of a depressive episode in children and adolescents is approximately 7 to 9 months [2,45] and there is a 40% relapse rate by 2 years [2,45,55]. Because of high relapse rates and persistence into adulthood, the treatment of depression requires a long-term commitment from patients and their families. The specific clinical aspects of depression and epilepsy must be taken into consideration in planning a comprehensive treatment protocol, whether executed by a pediatric psychiatrist, a neurologist, or a pediatrician. The child’s individual developmental needs, ongoing psychosocial stressors, the school environment, and family functioning, including parental mental health, must be evaluated before determining the specific treatment modality. Youths with the first episode of depression in the absence of other psychiatric comorbid conditions, and in a stable family environment, can be successfully managed by a primary care physician [56] or pediatric neurologist. However, referral to a child psychiatrist is recommended if a patient has recurrent or treatment-resistant depression, recent suicide attempts or ideations, coexisting substance abuse or other psychiatric disorders, or an unsafe family environment or parents with mental illness. Children with prior suicide attempts or gestures should be identified early, because past suicide attempts significantly increase the risk for future attempts [57]. Moreover, a careful examination of AEDs in light of potential overdose is important. Cases of overdose are reported with the majority of AEDs, but barbiturates and benzodiazepines should be avoided in this patient group because of risk for fatal respiratory and cardiovascular suppression. A careful evaluation of the current AEDs should occur before the decision regarding psychiatric treatment modality is made.

Two main psychiatric treatment concepts have been developed: somatic treatment and psychotherapy. A discussion of the various psychotherapy modalities is beyond the scope of this article [58].

Somatic treatment consists of pharmacotherapy, electroconvulsive therapy (ECT), vagus nerve stimulation (VNS), repetitive transcranial magnetic stimulation (TMS), and alternative therapies. (VNS and TMS are investigational treatments for depression not approved for this use in the United States, although VNS was recently approved for treatment-resistant major depression in the European Union and Canada.) Except for pharmacotherapy, little is known about the use of these treatment modalities in children and adolescents [59–61]. Data on the safety and effectiveness of TMS in youths with epilepsy and depression are lacking. Electroconvulsive treatment and VNS are not contraindicated in patients with seizures; however, the invasive nature of such procedures, the need for general anesthesia, and the lack of validated research data on their efficacy in the treatment of depression in youths with epilepsy prevent their use in everyday practice [62]. Research is needed to explore whether VNS is an effective treatment for depression in children and adolescents, as promising results have been demonstrated in depressed adults with epilepsy [63–65].

4.1. Family education

It is essential that children and parents receive objective information about depression before referral to a psychiatrist. Families who have a trusting relationship with their treating neurologist are more open to accepting such a referral. Education about mood disorders as biological occurrence decreases parental self-blame [66]. It is also very important to educate parents that children and adolescents with depression are at risk for suicidal behaviors. Specific recommendations about securing access to medications and locking up firearms or removing them from the home should be given to families [57]. Unfortunately, most parents do not comply with this recommendation [67].

4.2. Parental mental health

High levels of stress in the family environment were found to be associated with poorer psychosocial competence in children. It has been reported that 30–50% of depressed adolescents have a parent with a mood disorder; however, such data are not available for children with epilepsy and depression. It is possible that the burden of parenting a child with chronic illness further affects the parental mental state and parenting abilities. It is very important to identify these parents and to recommend that they obtain psychiatric treatment for themselves as part of the management of their child’s illness.

4.3. Pharmacotherapy

The goal of treatment is to achieve a complete remission of depressive symptoms, because partial or
incomplete remission increases the likelihood of a relapse. The new nontricyclic antidepressants include selective serotonin reuptake inhibitors (SSRIs) and mixed receptor agents. A few available randomized placebo-controlled studies of the SSRIs fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, and escitalopram oxalate in children and adolescents with depression have demonstrated significant efficacy and a response rate of approximately 60% [68–71], but children with comorbid epilepsy tend to be excluded from the majority of drug studies. Therefore, treatment practices in this clinical population tend to be based on a clinician’s experience rather than on validated research data. Favorable side effect profile, once-a-day administration, minimal risk of fatal overdose, and safe drug–drug interactions with AEDs make SSRIs the first-line treatment option for depressed youth with epilepsy. In contrast, trials of tricyclic antidepressants (TCAs) have failed to demonstrate effectiveness in treatment of depression in the general population of children and adolescents compared with placebo [72]. Tricyclic antidepressants are not recommended as first-line treatment for depression in youths, because of the lack of effectiveness, significant anticholinergic side effects, and the potential for a lethal overdose. Although monoamine oxidase inhibitors (MAOIs) are effective in the treatment of atypical and treatment-resistant depression in adults, these agents are rarely used in children, because of the risk of hypertensive crisis and difficulties in getting children and adolescents to follow the restrictive dietary requirements [60].

Mixed receptor agents (venlafaxine, mirtazapine, bupropion, nefazodone, and trazodone) modulate several neurotransmitter systems (noradrenergic, serotonergic, and dopaminergic) and act less selectively compared with SSRIs. They are used for treatment-resistant depression or for specific targeted symptoms (e.g., insomnia, loss of appetite) in adults with depression [61]. Bupropion should be carefully considered for use in patients with epilepsy, because of its 0.4 to 0.8% rate of association with seizures when taken at high total daily doses [73]. Venlafaxine has demonstrated effectiveness in open trials in adults with epilepsy and was not associated with worsening of seizures [74]. Nefazodone is a potent antidepressant, but it has received a black box warning about the occurrence of hepatic failure in adults. It is not currently recommended for use in the pediatric population, particularly in patients taking AEDs.

### 4.4. General pharmacokinetic issues of SSRIs and mixed-mechanism agents

Very few pharmacokinetic and dose-ranging studies have been done in children; thus, the current knowledge is obtained mostly from adult literature. Most of these agents inhibit cytochrome P450 (CYP450) isoenzymes, but to various degrees. The least CYP450 inhibition, and thus the least potential for drug–drug interactions, has been reported with citalopram, escitalopram, paroxetine, sertraline, and venlafaxine [75–79].

### 4.5. Adverse effects of SSRIs and mixed-mechanism agents

The most common side effects in children are nausea, drowsiness, constipation, nervousness, and tiredness [68,69]. There are also other, less frequent, but very important side effects that are pertinent in a clinical population of children with epilepsy.

#### 4.5.1. Neuropsychiatric side effects

The important question of whether SSRIs are pro- or anticonvulsive in a clinical pediatric sample remains unanswered. This clinical topic in adults with depression and epilepsy has been extensively reviewed elsewhere [80,81]. In the adult literature, fluoxetine has been reported to demonstrate anticonvulsant effects in animal and human studies [82,83]. In clinical studies of paroxetine and sertraline, the seizure risk in adult patients was minimal [84,85]. Citalopram has not demonstrated an association with an increase in seizure frequency in adults with epilepsy [86].

Behavioral activation, such as restlessness, anxiety, jitteriness, disinhibition, and frank agitation, has been reported with most SSRIs [61]. Approximately 3–6% of children treated with antidepressants convert to mania. This has been reported in studies of fluoxetine and paroxetine treatment for depression in children and adolescents, even when patients with a family history of bipolar disorder, depression with psychosis, or bipolar symptoms were excluded [68,69]. The new information from British drug regulators about the increased suicide rates in children with depression treated with antidepressants convert to mania. This is important if this medication is prescribed for the first time.

Movement disorders, myoclonus, and extrapyramidal signs, particularly on the abrupt discontinuation of treatment, were reported with the use of fluoxetine, paroxetine, fluvoxamine, and sertraline [87–90]. Frontal lobe-like "amotivational" syndrome, characterized by apathy, indifference, and disinhibition, has been reported in youths [91]. This effect was dose related and reversible. The SSRIs can alter sleep architecture and affect the quality of sleep. Fluoxetine can increase rapid eye movement (REM) latency and suppress REM sleep [92]. This is an important clinical aspect, because sleep plays a considerable role in children’s normal growth as well as occurrence of seizures.

#### 4.5.2. Bleeding complications

Five cases of bruising or epistaxis were reported in children aged 8–15 years at 1 week to 3 months after
starting treatment with sertraline [93]. Symptoms remitted when the medication was discontinued or the dose was reduced. Selective serotonin reuptake inhibitors should be used cautiously in patients with platelet disorders or thrombocytopenia and in those taking AEDs that affect the hematopoietic system.

4.5.3. Serotonin syndrome
The serotonin syndrome may be caused by any serotonergic agent, but most commonly it occurs because of an interaction between an MAOI and SSRI leading to excessive release of serotonin in the brain and spinal cord. It shares common symptoms with the neuroleptic malignant syndrome and is a medical emergency in psychiatry. It is characterized by acute changes in mental status, agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremors, diarrhea, and fever with no specific laboratory findings. Clinically it is diagnosed if any three symptoms are present and the use of a serotonergic agent is confirmed [94]. After discontinuation of the serotonergic agent, supportive measures, propranolol, and, if needed, cyproheptadine may be used [95].

4.6. Course of pharmacotherapy

4.6.1. Initiation of treatment
The treatment of children and adolescents who are already taking AEDs should be guided by the old and wise principle of pharmacological management: “start low, go slow.” This helps to prevent potential side effects and improve compliance with the treatment. Most important, it decreases parental anxiety about giving yet another medication in addition to the current regimen of AEDs. Children often are sensitive to new psychotropic agents because of their immature nervous system; thus, it is recommended to start with a low dose for 1 week and then increase to the full dose over the next 3 weeks, if medication is well tolerated [56]. If a patient fails to demonstrate even minimal improvement in the symptoms of depression, further increases of the dose should take place every 3–4 weeks, to have enough time to re-evaluate the effectiveness of the current dose. Mixed receptor agents (i.e., bupropion, nefazodone, venlafaxine, and mirtazapine) are not recommended for the initiation of treatment of depression at present, because of the lack of supporting randomized controlled studies in children and adolescents [6]. Currently, there are no indications for baseline laboratory tests before and during the administration of SSRIs.

4.6.2. Continuation of treatment
If the patient does not respond to an initial SSRI and continues to exhibit sadness, irritability, changes in sleep or appetite, anhedonia, or school difficulties, or exhibits significant side effects, then another SSRI can be tried [6], followed by an agent from the mixed receptor agent group. Augmentation strategies with lithium are supported [6].

4.6.3. Termination of treatment
It is a general consensus that treatment with antidepressants should be continued for at least 6 to 12 months after a complete remission of depressive symptoms, because early termination of treatment increases the relapse rate [57]. It is recommended to maintain treatment for 1 to 3 years in youths with two or more episodes of major depressive disorder [57]. Abrupt discontinuation of SSRIs or mixed receptor agents with shorter half-lives, such as paroxetine and fluvoxamine, may be associated with a withdrawal syndrome characterized by dizziness, paresthesias, tiredness, nausea, visual disturbances, movement disorders, and headaches [57]. Gradual titration and discontinuation over a 6-week period is generally recommended [57].

5. Conclusion
Depression in youth with epilepsy is a common but often unrecognized disorder. Patients may experience impairment of successful development because both epilepsy and depression are characterized by a chronic course and a poor long-term psychosocial outcome. Safe and effective multimodal treatment approaches are available. More research is necessary to develop effective prevention and intervention strategies and to improve the long-term outcome.

References


