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Review

Depression and anxiety in children and adolescents with epilepsy: Prevalence, risk factors, and treatment

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ABSTRACT

Among the psychiatric comorbid conditions in children and adolescents with epilepsy, depression and anxiety disorders require further attention because they carry the risk of reduced quality of life and life-threatening complications (e.g., suicide). Research in recent years has shed light on both the prevalence of emotional problems in youth with epilepsy and the safety and efficacy of treatment options. A number of challenges exist in treating patients with epilepsy. This is particularly true when seizures are difficult to control and medication regimens are more complex. Some pharmaceutical options may provide assistance with both seizures and emotional distress, but care is needed when considering such treatment approaches. In addition, integration of mental health professionals into the care of patients is necessary when cases are complicated and risk factors are high. Thorough methods to accurately diagnose emotional conditions and regular monitoring of symptoms can help prevent serious problems that can negatively affect the success of children and adolescents in everyday life. Collaboration between disciplines offers the best hope for early identification and treatment of these conditions.

1. Introduction

Epilepsy is the most common neurological disorder in children, and its prevalence in childhood is estimated to be 0.05–1% [1–3]. Among these children, up to 28.6% may have coexisting psychiatric conditions. This increases to 58.3% in children with a known neurological disorder that may cause or be associated with epilepsy [4].

Various investigations focusing on the prevalance of psychopathology in pediatric epilepsy have documented that children with epilepsy have an estimated overall risk of 21–60% for childhood psychopathology [5,6]. This is at least three to six times higher than the risk for psychopathology in the general population (i.e., 6.6%) and among children with a chronic medical condition not involving the central nervous system (i.e., 11.6%) [4]. An epidemiological study by Davies et al. [7] revealed that the rate of psychiatric disorders was 37% in children with epilepsy, 11% in children with diabetes mellitus, and 9% in healthy controls. Moreover, children with complicated epilepsy have been found to have twice as much risk for psychopathology than children with uncomplicated epilepsy [4,7].

Historically, psychiatric disorders in epilepsy have been considered a consequence of psychosocial disturbance due to poor adaptation to a chronic disease, particularly one with significant stigma [8]. However, more recent investigations have suggested that epilepsy and psychiatric disorders are best conceptualized as epiphenomena rather than cause–consequence factors [9–11]. In a study completed by Austin et al. [9], approximately one-third of the children with new-onset seizures had psychiatric symptoms prior to the onset of seizures. Such a finding provides support for a bidirectional relationship between psychiatric disorders and epilepsy, suggesting that behavioral and psychosocial impairment in epilepsy may be the consequence of an unrecognized psychiatric disorder, rather than the cause of a psychiatric condition [8].

A number of psychiatric and neuropsychiatric disorders have been found to occur at a higher rate in children and adolescents with epilepsy. These include mental retardation [12,13], autism [14], attention problems and/or attention-deficit/hyperactivity disorder (ADHD) [15,16], depression [17,18], anxiety [19,20], and psychotic disorders [21,22].

Among these comorbid conditions, depression and anxiety seem to be highly common [17,19]. In fact, depression symptoms alone have an estimated prevalence of 23–26%, based on self-report instruments [20,23]. The prevalence of anxiety, in comparison, is estimated to be between 15 and 20% [24]. Unfortunately, however, these conditions are often unrecognized and left untreated in children with epilepsy [20,25], which can lead to negative outcomes on quality of life [17,26].

Although the general outcome and prognosis of children with epilepsy can be highly affected by psychiatric comorbid conditions

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such as depression and anxiety, clinicians often underestimate the importance of such conditions in these children. In a study of children with epilepsy and normal intelligence, 61% had a psychiatric diagnosis based on *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) criteria, but only 33% received mental health treatment [6]. A study completed by Caplan et al. [27] demonstrated that, among 171 children and adolescents with epilepsy, 33% had an affective or anxiety disorder, and 20% had suicidal ideation. However, among these children and adolescents, only 33% were receiving some form of mental health service [27].

In the epilepsy literature, especially in the past, there has been a tendency to group depression and anxiety disorders in one category under the label of "affective" or "mood" disorders. This approach seems advantageous because it provides an easier statistical analysis. Indeed, it is known that these two conditions have a high rate of comorbidity. However, depression and anxiety disorders, despite the similarities, have distinct symptoms, etiologies, and risk factors. In children with epilepsy, it is important to determine the prevalence, course, and risk factors of these conditions either when they are comorbid or when they occur alone. Thus, in this review, depression and anxiety disorders are summarized in distinct sections.

The purpose of this article was to provide a comprehensive review of the known information about depression and anxiety in children and adolescents with epilepsy with a detailed focus on prevalence, risk factors, and treatment options.

2. Depression

The clinical recognition of childhood depression has developed over the past decade. Multiple studies have demonstrated that depression in children and adolescents may present with different symptoms than adult depression. Juvenile-onset depression has been found to have a recurrent course and can include severe psychosocial morbidity and significant risk of suicide [28–30].

Some symptoms that differentiate childhood depression from the classic clinical picture of adult depression include irritable mood, anger, and decline in academic performance [17,28]. Depressed children may also exhibit psychomotor agitation, anxiety symptoms, phobias, and regressing behaviors, including separation anxiety [28]. Vegetative and somatic complaints can also be associated with depression in children [31,32].

During adolescence, psychomotor retardation, anhedonia, hypersomnia, hopelessness, weight changes, and drug abuse are more prominent [28,33]. Suicidal ideation occurs at about the same rate in children and adolescents, but there is a dramatic increase in suicide attempts and completion of suicide with the onset of puberty [28].

A further complicating factor in child and adolescent depression is the presence of comorbid psychiatric conditions. Commonly occurring comorbid psychiatric disorders include anxiety, attention-deficit/hyperactivity disorder, conduct disorder, and substance abuse, with an estimated prevelance rate of 40–70% [17,34,35]. It is important to keep in mind that, when compared with adult depression, pediatric depression has a higher risk of developing into bipolar disorder [36]. Psychotic symptoms, which are rarely seen in pediatric depression, are common features of manic episodes in children and adolescents.

In the case of children and adolescents with epilepsy, unfortunately, depressive disorders are often underdiagnosed and undertreated [17,25,27]. Devinsky [37] pointed out that this may be due to the somewhat atypical presentation of depression in this population. He suggested that, besides the typical sleep and appetite disturbances of depression, these youngsters often present with an irritable mood and negative ruminations about themselves, their lives, and friends and family. Attentional problems and academic failure are also frequently reported in children with epilepsy who are experiencing depression [38,39]. When conceptualizing depressed children with epilepsy, coexisting behavioral problems must be taken into account. It has been found that depression tends to be comorbid with other psychiatric conditions like disruptive behavior disorders and anxiety disorders [27].

A number of studies have clearly highlighted that suicidal ideation and attempts are more likely to be seen in children and adolescents with epilepsy than in the general pediatric population [25,27,40,41]. In studying suicidal ideation, Caplan et al. [27] reported a prevalence rate of 20% in their sample of 171 children (aged 5–16) with complex partial seizures and childhood absence epilepsy. This was significantly higher than both the control group rate (9%) and estimates from the general population of 9- to 17-year-olds (5.2%) [42]. Caplan et al. also found that duration of epilepsy was related to suicidal ideation. The authors concluded that the combination of depression with anxiety and disruptive behavior disorders with impulsivity seems to be more related to suicide than either a solo depression or anxiety disorder diagnosis [27]. These findings about suicidality may mean that children and adolescents with epilepsy, as a group, are at higher risk for more severe and complicated depression, resulting in a higher mortality rate when compared with children without epilepsy. Future studies with larger sample sizes are needed to clarify the specific phenomenology and features of depression in children with epilepsy.

2.1. Prevalence and risk factors

Research over the past 20 years indicates that depression is one of the most common psychiatric comorbid conditions in patients with epilepsy of all ages. In pediatric epilepsy, the rate of depression appears to be significantly higher than rates in the general population of children and adolescents, which are estimated to be 1–3 and 4–8%, respectively [43–45]. Ettinger et al. [20] reported the prevalance of depression in patients with pediatric epilepsy (aged 7–18) as being about 26%. Alwash et al. [46] found depression in 33% of children and adolescents with seizures in contrast to 16% in controls. Examining only adolescents with epilepsy, Dunn et al. [23] reported a rate of 23%, whereas a Nigerian study [47] reported a prevalence rate of 28.4% for depression.

Although rates of depression can vary due to the use of different rating and diagnostic instruments, a number of predictive factors have been recognized that may affect the prevalence of depression. Oguz et al. [40] found that age was an important predictive factor, noting more symptoms of depression in adolescents 12–18 years of age with epilepsy as compared with children 9–11 years of age with or without seizures. Thome-Souza et al. [8] also found a predominance of depression in adolescents.

Although it has been suggested that adolescent girls experience more depressive symptoms than adolescent boys or younger children in the general population [45,48], this association has been inconsistent in the epilepsy population [49]. Hoare et al. [50] found no correlation between gender and depression in children and adolescents with epilepsy. In contrast, Austin et al. [51] found more emotional problems in girls, whereas an older study by Stores [52] suggested a higher rate of depressive complaints in boys. A more recent Turkish study also found adolescent boys to have more emotional problems and suggested that, in epilepsy, male gender may be a risk factor for emotional symptoms [53].

The etiology or the risk factors for depression in children and adolescents with epilepsy are likely multifactorial, involving neurobiological, psychosocial, and iatrogenic risk factors (i.e., the drugs used). Investigations on the association between seizure type and psychiatric disorders and depression have yielded mixed

results, with the majority of studies not supporting a significant relationship [5,23,40]. In a study examining emotional functioning in children with complex partial seizures (CPS) and childhood absence epilepsy (CAE), Ott et al. [5] found no difference in rates of depression between the two groups on the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS). Caplan et al. [27], however, using the same measure, reported significantly higher rates of depression and comorbid depression and anxiety in children with CPS as compared with children with CAE. When explaining this difference between the two groups, Caplan et al. speculated about the potential effect of having older patients with CPS in the sample and the possible role of seizure involvement in differing cerebral regions.

Thome-Souza et al. [8] demonstrated that, in comparison to generalized seizures, focal seizures are associated with a higher risk of psychopathology in children, which is also consistent with the majority of adult studies [54,55]. Among focal seizure disorders, the relationship of psychopathology to temporal lobe epilepsy (TLE) has been extensively examined in the adult literature [56–62]. However, there has been less examination of this issue in children and adolescents with epilepsy. A 1988 study of 26 adolescents found similar rates of depression in patients with TLE and patients with chronic asthma, suggesting that elevated psychopathology in adolescents with epilepsy may be associated with chronic illness rather than epilepsy-specific factors [63]. However, a more recent study suggested a distinction among subgroups in children and adolescents with epilepsy based on seizure localization. Titus et al. reported significantly higher rates of depressive symptoms in children and adolescents with TLE when compared with children and adolescents with frontal lobe epilepsy. A similar distinction was not found between children with TLE and children with generalized seizures [15]. Recent research also suggests a possible relationship between juvenile myoclonic epilepsy (JME) and depression [64–66]. Nevertheless, more research is needed to determine if seizure location and syndrome are valid risk factors for depression in children and adolescents with epilepsy.

Most studies in children and adolescents do not support a relationship between laterality of seizures and depression [5,8,23,27,40]. Moreover, studies using EEG findings have failed to demonstrate an association between electrographic findings and depressive symptoms in children with epilepsy [5,8,23,27,40].

Frequency and/or recurrence of seizures is another proposed risk factor for depression in children with epilepsy. Austin et al. [67] found a significant relationship between recurrent seizures and internalizing problems and depression in children. A more recent study also showed that seizure severity appears significantly associated with emotional problems and depression [68]. However, a prospective study with adolescents with epilepsy demonstrated no difference in emotional problems between teenagers with ongoing seizures and those in full remission [69]. Thome-Souza et al. [8] and Caplan et al. [27] also found no association between seizure frequency and the risk for general psychopathology and affective disorders, respectively [8,27]. These findings are supported by a recent review of the literature that suggested psychopathology and emotional problems cannot be independently predicted by seizure frequency [70].

The research on an association between age at seizure onset and depression is mixed. Although many earlier studies did not support age at onset as being a risk factor for depression [8–10,23,40], Sabbagh et al. in 2006 suggested that there may be a relationship [71]. Longer duration of epilepsy has also been linked to a risk of depression in some studies [40,67].

Just as psychiatric disorders and epilepsy are believed to have a bidirectional relationship, depression and epilepsy also tend to influence one another. Although it has long been recognized that epilepsy increases the risk for depression [38], several population-based, controlled studies performed over the last decade have demonstrated that adult patients with newly diagnosed epilepsy were more likely to have a history of depression than matched control subjects [72–74]. Another interesting result of these studies is that the depressive episodes of patients who later developed epilepsy appear to have occurred much closer in time to the onset of epilepsy than the depressive episodes in the matched controls [39]. There is also evidence for common pathological mechanisms for depression and epilepsy from animal and neuroimaging studies. In kindling animal models of epilepsy, high rates of depressive behaviors have been reported [75]. PET and SPECT studies in human samples have shown decreased binding of serotonin-1A receptors both in depression and in epilepsy [76–78]. Kanner [79] presented the latest data on the issue in his recent review and indicated that a history of depression has a negative impact on pharmacological and surgical treatment outcomes in patients with epilepsy. As mentioned before, poorly controlled seizures and seizure severity are also among the shown predictors of depression in patients with epilepsy. These intriguing findings strongly suggest that the bidirectional relationship between depression and epilepsy also affects the prognoses of both conditions.

Hesdorffer et al. [72] examined the bidirectional relationship between depression and epilepsy in pediatric epilepsy and found that a history of depression preceding the onset of epilepsy was four times more common among children with epilepsy than among age- and gender-matched controls. Based on this finding, the authors suggested that depression may be a risk factor for the development of epilepsy in children. Although the specific cause–consequence relationship between depression and epilepsy in children and adolescents deserves further investigation, additional studies confirm that up to one-third of children with epilepsy have psychiatric symptoms prior to the onset of seizures [9]. Such reports support the results of adult studies that suggest an interactional relationship between epilepsy and depression.

Familial factors have also been found to be an important predictive factor for depression. It has been well documented that depression is a familial illness [80], and children of parents with depression are up to eight times more likely to develop depression than children of parents without depression [81]. This relationship appears to hold true for patients with epilepsy as well. A family history of depression has been reported in up to 50% of patients with epilepsy and depression [17]. Specifically in children, Thome-Souza et al. [8] found that a family history of psychopathology increases the risk of depression.

Rodenburg et al. [82,83] used a classification system to order family factors according to the level of proximity to the child's everyday life. These include: proximal family factors (quality of the parent–child relationship and parenting), distal family factors (parental characteristics and psychopathology), and contextual family factors (quality of other family relationships).

In children with epilepsy, a number of studies examining distal family factors have reported both increased risk of depression in mothers [84,85] and an association of mother's anxiety and depression with behavior problems in children [85–88]. Conversely, Baki et al. [89] found no correlation between depressive symptoms in mothers and depressive complaints in their children with epilepsy.

In addition to simply the presence of psychiatric conditions in the family or distal family factors, proximal family factors seem to be of equal or greater importance. Rodenburg et al. [84] indicated that the influence of the most proximal family factors on child psychopathology is stronger than the effects of other familial factors. In their study, parental rejection appeared to be a risk factor that significantly contributed to internalizing behavior problems, withdrawal, and depression. Previous studies also found

poorer parent–child interactions and higher family stress to be associated with behavior problems, even when controlling for seizure variables [23,90,91]. Carlton-Ford et al. [92] examined the relationship between children's perceptions of their parents' behaviors and children's adjustment to epilepsy and behavioral problems. They found that perceived parental overcontrol was associated with more behavior problems and more depressive symptoms in children. In a study of adolescents with epilepsy, unsatisfactory and highly stressful family environments were found to be associated with symptoms of depression [23]. In addition, Austin et al. indicated that factors such as deficient family mastery and low parent confidence about managing their child's discipline were also associated with psychopathology in children and adolescents with epilepsy [93].

The experience of stigma and its effects on health-related quality of life are additional burdens to children with seizures. High rates of stigma are estimated in about half of patients with epilepsy and seem to be highest in younger age groups [94,95]. Among youth with epilepsy, adolescents, especially older adolescents, may be more prone to experience higher stigma and, in association, reduced health-related quality of life [96,97]. Studies have clearly shown that perceived stigma and/or fear of stigma greatly contributes to poor self-esteem, rejection by peers, avoidance of age-appropriate activities, and social isolation [96–99]. Stigma and fear of stigma may also lead to lower expectations by caregivers [58]. Given these findings, it is not surprising that emotional symptoms and depression are highly related to stigma [23,96]. Similarly, a negative attitude about having epilepsy and an individual perception of loss of control have also been associated with the development of depression [17,23].

Among proposed risk factors, sociocultural variables seem to be minimally predictive of psychiatric or behavioral problems in children with epilepsy. The rates of depression do not appear to differ significantly between cultures or countries [20,23,27,46,47]. Although the findings on socioeconomic status (SES) are similar, results have been more mixed. The majority of studies do not support an association between SES and psychopathology [9,27,47,100,101]. However, Devinksy et al. [97] reported a link between living in households of lower SES and higher levels of stigma, negative health perceptions, and overall poor health-related quality of life. As previously discussed, these features are often associated with a risk of depression. Stores [52] reported a higher rate of behavior problems in children with epilepsy who were also from low-SES homes. In contrast, an Indian study demonstrated a higher risk of behavior problems in children from higher-SES homes [102]. The effects of SES in different countries on psychopathology in children with epilepsy must be considered with various regional and cultural factors, such as awareness of epilepsy and psychiatric comorbidity, social support, and traditional beliefs.

Antiepileptic drugs (AEDs), with their potential behavioral and cognitive side effects, have always been a questionable risk factor for depression. Depression and increased suicidality have been associated with the use of phenobarbital in children with epilepsy [41,103], and newer AEDs, such as levetiracetam, zonisamide, topiramate, and tiagabine, have been found to increase the risk of depressive symptoms in patients with epilepsy [104–107]. However, in most of the studies with adolescents with epilepsy, AEDs have not been found to be consistent predictors of mood problems and depression [19,23,27,40,44,46].

Some concern has also been raised about the potential risk of emotional side effects in treatment regimens that combine multiple antiepileptic medications. For instance, Sabbagh et al. [71] found a significant relationship between polytherapy and behavior problems in school-aged children with epilepsy. Polytherapy was also noted to be related to the type of school placement. Hermann et al. [44] also described behavior problems in patients on polytherapy, and in a Turkish study, polytherapy was found to significantly predict the presence of depression in both children and adolescents with epilepsy [40]. However, in contrast, other studies have offered more equivocal results, suggesting no significant difference in rates of depression between children on monotherapy and those on polytherapy [8,9,27]. It is important to keep in mind that depression, as mentioned before, is commonly comorbid with other psychiatric conditions, including anxiety disorders, and there seems to be a stronger link between AED polytherapy and anxiety disorders in children with epilepsy. The relationship between polytherapy and anxiety disorders is discussed in more detail later. Nevertheless, given the potential for psychiatric side effects from AEDs, it is always up to the clinician to consider the cost–benefit balance when choosing polytherapy for children and adolescents with epilepsy.

When considering the use of AEDs in children, it should be noted that it is unlikely that AEDs singlehandedly explain the highly increased risk of depression in this population [17]. AEDs are quite variable in their mechanisms of action, and the manner in which patients respond to certain AEDs can significantly influence the probability of complicating emotional side effects. In fact, lamotrigine has been found to have antidepressant effects and, in adult studies, has been proven to be effective in the management of bipolar depression [108]. Recent studies also suggest its efficacy in combination with other drugs in treatment-resistant unipolar depression of adults [109,110]. Moreover, an adult study examined the efficacy of lamotrigine in patients with epilepsy and depressive symptoms and demonstrated that lamotrigine may have antidepressant effects for patients with epilepsy and comorbid low to moderate depressive symptoms [111]. In pediatric populations, lamotrigine is currently used primarily as an AED, and there are only a few studies advocating its efficacy in adolescent bipolar depression [112]. Its effect on depression in children with epilepsy has yet to be studied. Nevertheless, the increasing acceptance of lamotrigine as an antidepressant agent in adults suggests that it may be the drug of choice for children with epilepsy who have recurrent depressive episodes or are considered to be at high risk for depression.

2.2. Treatment

Depression in children with epilepsy poses considerable challenges, such as higher suicide risk and a more severe course. Adverse effects of AED monotherapy or polytherapy in addition to antidepressant medications can complicate the clinical picture and should be taken into account. As such, it is often prudent to refer children with epilepsy to a child psychiatrist with experience in epilepsy when depressive symptoms are apparent. The greater severity of the depressive symptoms increases the need for psychiatric evaluation and treatment. Such symptoms include recurrent or treatment-resistant depression, recent suicide attempts or ideation, and coexisting conditions. Conditions comorbid with depression (e.g., substance abuse or other psychiatic disorders) warrant more immediate psychiatric consultation, particularly if the patient is experiencing significant anxiety, has disruptive behavior (e.g., impulsivity), or lives in an unsafe family environment (e.g., parents with mental illness) [17]. Children and adolescents with epilepsy who have multiple risk factors for depression should also be evaluated by child psychiatrists at regular intervals. This can be critical to the prevention, early diagnosis, and treatment of depression and other psychiatric conditions.

For the treatment of depression in children with epilepsy, as in the treatment of depression in children without epilepsy, pharmacotherapy accompanied by cognitive-behavioral approaches in selected children seems to be the most efficacious means of management. When considering and applying cognitive behavioral

strategies and techniques, it is important to evaluate a child's individual needs, social situation, family and school enviromental dynamics, and psychological development [17]. This will help in developing a therapeutic relationship between the child and the therapist, as well as help foster educational and supportive efforts with other family members. Both individual and group sessions aimed at educating children and parents about the course of the illness and aspects of the medical management have been found to be effective [113]. Group sessions of varying size have been investigated and demonstrate significant improvements in behavior, knowledge, and social competence of children and parents [114–116]. Research using psychotherapatic interventions, such as teaching relaxation techniques and coping skills, have been found to improve self-concept as well as reduce seizure frequency [113]. Such techniques can help children and adolescents adjust to the condition and manage everyday stressors, which can ultimately serve to reduce the risk of depression.

A number of open-label and randomized placebo-controlled studies have been performed to date that demonstrate the efficacy and safety of the selective serotonin reuptake inhibitor (SSRI) group of antidepressants (i.e., fluoxetine, paroxetine, citalopram, and sertraline) in children and adolescents with depression. Response rates as high as 60% have been reported [117–120]. However, in almost all of these studies, children with depression who also had epilepsy were excluded from the sample groups. A recent study in children and adolescents with epilepsy and depression showed promise for the use of SSRIs in this population, finding that sertraline and fluoxetine were good therapeutic options in terms of remission of depression symptoms and number of side effects. This included having satisfactory maintenance of seizure control. Of the 36 patients with epilepsy in the study, only 2 children experienced a worsening of seizures and one of those children regained seizure control by modifying the AED [25].

Various studies in adults examining the efficacy and safety of SSRIs in epilepsy and depression have shown similar and positive results. Two studies of the use of citalopram in depressed patients with epilepsy found that citalopram was effective in reducing depression symptoms without affecting seizure control [121,122]. In fact, one study suggested a reduction in seizure frequency with citalopram use [122]. Sertraline is associated with only a 6% risk of worsening seizures [123], and paroxetine is associated with only a minimal seizure risk in adults [124].

Fluoxetine has been found to have varying effects on seizure threshold in animal studies. Ferrero et al. [125] discovered that, in an animal model of depression, chronic treatment with fluoxetine decreases the seizure threshold in rats. However, conversely, two earlier animal studies demonstrated that fluoxetine may have anticonvulsant effects [126,127].

The beneficial effect of antidepressant treatment on seizure threshold has been theorized by Jobe and Browning [128] as being related to their effect on noradrenergic and serotonergic systems. They suggest that noradrenergic and serotonergic deficiencies contribute to seizure predisposition, and treatment with antidepressants can potentially minimize seizure predisposition in epilepsy by increasing serotonergic and noradrenergic activity. This theory is supported by a handful of clinical studies with SSRIs [122,129].

Jobe and Browning go on to suggest that larger doses of SSRIs can activate other biological processes that may actually lead to seizure induction [128]. Cuenca et al. [130] provided a case report that highlighted the risk of seizures in assocation with citalopram overdose. One Swedish study demonstrated that the median SSRI dosages were above average in patients experiencing seizures as a side effect [131].

When using SSRIs with other medications, it is also important to consider the cytochrome P450 (CYP450) isoenzyme-inhibiting features of these agents. As most of the AEDs are also substrates or inducers/inhibitors of the CYP450 isoenzymes, prescribing SSRIs in conjunction with AEDs may result in low or toxic levels of the medications. The SSRIs that seem less likely to inhibit CYP450, and therefore have the least potential for interaction with other drugs, including AEDs, are citalopram, escitalopram, and sertraline [132–134].

For the rare cases in which adequate trials of different SSRIs fail to achieve clinical efficacy, other classes of antidepressants are taken into consideration. Tricylic antidepressants (TCAs) are not recomended for treatment of depression in youth because of limited effectiveness and the risk of adverse events, such as anticholinergic side effects, cardiac arrhythmia, and potential for lethal overdose [17]. Indeed, the risk of seizures is significantly higher with TCAs in comparison with SSRIs (approximate risks of 0.3–0.5% for imipramine, 1% for clomipramine, and 0.1% for SSRIs) [135–138]. For these reasons, TCAs are not in the treatment algorithm for SSRI-resistant depression in children and adolescents with epilepsy.

Newer antidepressants—venlafaxine, mirtazapine, and bupropion—act on multiple receptors and have been shown to be effective in adults with depression [139]. Opinion on the seizure risk with the use of these agents is reported to be mixed. Although mirtazapine seems to have a minimal risk of seizures (approximate risk of 0.05%), the risk is slightly more with venlafaxine (approximate risk of 0.3%) [26]. Bupropion, however, has been shown to lower seizure threshold in a dose-dependent manner (approximate risk of 0.4–0.8%), and is not the drug of choice in patients with epilepsy [140]. When compared with SSRIs, research data for these agents are generally lacking in children and adolescents with depression. Thus, they are not considered first-line medications for depression in pediatric populations with epilepsy.

The importance of treating depression in children and adolescents with epilepsy is supported by the clear negative impact of depression on quality of life and the potential risk for suicide. By treating depression, patients may sleep better and their compliance with treatment regimens may increase, resulting in an indirect improvement in seizure control and quality of life [25]. The research literature strongly argues for the use of SSRIs as the first line of pharmaceutical treatment for depression in youth with epilepsy because of high effectiveness, minimal side effects, ease of administration, little risk of fatal overdose, minimal drug–drug interactions with AEDs, and minor and/or favorable effects on seizure threshold [17,25,70,113,132,136]. Medication management of more severe depression should be most appropriately done with the input of a psychiatrist; however, safe treatment in most cases can be achieved by attending to the need for slow titration when beginning treatment, maintenance of therapatic doses, and close monitoring for side effects or complications.

3. Anxiety

The DSM-IV-TR classifies anxiety disorders into several groups, including panic disorder (PD), obsessive–compulsive disorder (OCD), generalized anxiety disorder (GAD), social phobia (SB), and, in the childhood psychiatric disorders subgroup, separation anxiety disorder (SAD). The core symptoms of GAD are disabling, uncontrolled, and persistent worries about various themes for a duration of at least 6 months [141]. Panic attacks are defined by sudden and severe paroxysmal episodes of anxiety that last minutes or longer, accompanied by multiple physiological symptoms, such as palpitation, sweating, difficulty in breathing, and a prominent fear of death or losing control. OCD is typified by recurrent, intrusive, and unpleasant thoughts, impulses, or fantasies that are often allied with behavioral or mental compulsive actions. All of these disorders are also identified in children and adolescents with some specific variations in diagnostic criteria [141].

The prevalence rates of anxiety disorders in the general population are estimated to be 9.1 and 18.1% in men and women, respectively [142]. In children and adolescents, anxiety disorders are considered to be one of the most common psychiatric diagnoses [143], and have been shown to affect 5–18% of children, 0.3–12.9% of preadolescents, and 0.6–7% of adolescents [144].

Although depression has received more attention as being a common comorbid condition in epilepsy, many recent studies in adults have shown that anxiety disorders are also highly frequent. They have an estimated prevalance rate of 11% in community samples and up to 50% in secondary care and specialist settings [26]. Indeed, in a study from Korea, anxiety was the most significant predictor of reduced health-related quality of life in patients with epilepsy, when compared with the impact of depression and seizure frequency [145]. Several studies have reported elevated rates of panic attacks, panic disorder, OCD, and GAD in adult patients with epilepsy as compared with the general population [18,24,136,146]. In adolescents, Baker et al. [147] reported high rates of OCD and social anxiety symptoms. Although any anxiety syndrome can occur interictally, GAD seems to be more common in epilepsy. This may be due to the unpredictability of seizures and the helplessness many patients experience over not being able to control their seizures [26]. In epilepsy, a chronic disease with a high risk of morbidity and mortality, GAD is often associated with excessive fears of future seizures, negative progression of the disease, and the potential for death [26,145]. Because of the complexity of epilepsy, the phenomenology of anxiety disorders may be different than in the general population, which can make it difficult to isolate symptoms to a single DSM-IV-TR diagnosis. For example, the fear of seizures or seizure-related accidents may lead to a variant of agoraphobia; or, from a pediatric perspective, the fear of having a seizure can be associated with anxiety about separation from the parents or home. The fear of embarrassment about having a seizure in public may also lead to a variant of social phobia and result in isolation of the patient from social activites [26].

It is important to highlight that DSM-IV-TR criteria require the absence of a physiological condition when considering symptoms associated with various anxiety disorders [141]. However, experimental studies suggest that kindling mechanisms and the recurrent epileptic stimulation of the amygdala may predispose patients with epilepsy to interictal anxiety [148]. Because of this, it would be reasonable to consider an alternative classification system for epilepsy-related anxiety that accounts for the different manifestations of anxiety in individuals with epilepsy. For instance, some individuals experience anxiety because of the fear of having a seizure in public settings, whereas others experience anxiety in response to the stress of the condition (i.e., reactive) or because of a preexisting propensity for anxiety (i.e., endogenous). Beyenburg et al. [26] offer several phenomenologic suggestions about the types of anxiety disorders in epilepsy and the reader is referred to their review for further discussion of this topic.

In examining the psychiatric comorbidity of anxiety disorders in children with epilepsy, Caplan et al. [27] found anxiety disorders to be highly comorbid with disruptive behavior disorders but, interestingly, not with depression [27]. This finding is consistent with results from some adult studies [149]. However, research with children and adolescents without epilepsy has revealed anxiety disorders occurring more commonly in conjunction with depression, rather than disruptive behavior disorders [144]. Brady and Kendall [150] indicated that 15.9–61.9% of children identified as anxious or depressed have the other disorder as well, whereas the rate of comorbidity between disruptive behavior disorders and anxiety disorders is estimated to be around 20% [151]. More studies are needed to clarify the psychiatric comorbidity of anxiety disorders in children with epilepsy.

3.1. Prevalence and risk factors

Although anxiety disorders are highly common and have a negative impact on quality of life in patients with epilepsy of all ages [26,38], the number of studies that have examined this condition in children and adolescents is relatively small [19]. In a sample of 44 children and adolescents with epilepsy, Ettinger et al. [20] found a 16% prevalance rate of anxiety using the Revised Children's Manifest Anxiety Scale (RCMAS). Also using the RCMAS, Williams et al. [19] found that, among 101 children with epilepsy between the ages of 6 and 16 years, 18% had mild to moderate symptoms of anxiety and 5% had moderate to severe symptoms of anxiety. Another study found that children and adolescents with epilepsy had a significantly higher tendency to develop symptoms of anxiety (48.5%) when compared with healthy controls (16.8%) [46]. Moreover, Caplan et al. [27] concluded that anxiety disorders are more common than depression in children with epilepsy. Based on K-SADS ratings, Caplan et al. reported a 33% prevalence rate of affective disorders in children with epilepsy. Among these, 63% had anxiety disorders.

In a study using the State–Trait Anxiety Inventory for Children (STAIc), Baki et al. [91] found that 49% of their pediatric patients with epilepsy had mild to moderate symptoms of anxiety; however, they also found that mean STAIc scores of patients with epilepsy did not differ significantly from those of normal control children. This suggests a higher degree of variability in the pediatric epilepsy sample.

Although differences in methodology have affected the consistency of prevalence rates in the literature, studies examining risk factors have provided better insight into how and why anxiety is more common in children and adolescents with epilepsy. As has been demonstrated in adult studies, psychological factors, such as the unpredictability of seizures, the fear of death, feeling of poor control over seizures, and perceived stigma, likely predispose some children and adolescents to anxiety [38]. Misinformation or insufficient information about the disorder also seems to be related to increased anxiety. In a study completed by Baker et al. [147], lower levels of epilepsy knowledge were found to be significantly related to higher levels of social anxiety, higher levels of depression, and lower levels of self-esteem in adolescents. Parental reactions of fear, anxiety, and distress also contribute to symptoms of anxiety, highlighting the importance of parental effects and the need for education and support not only for the children but also for the parents [19,26,38].

Age has also been found to be a significant risk factor for anxiety. For instance, adolescents with epilepsy are considered to be at higher risk for anxiety than younger children [113]. Oguz et al. [40] used the STAIc to compare children and adolescents with epilepsy and healthy controls and found increased anxiety for patients with epilepsy, especially after puberty. According to this study, younger children (9–11 years) had elevated levels of trait anxiety whereas older children (12–18 years) had elevated levels of both trait and state anxiety, when compared with healthy controls. Oguz et al. also discovered that increased seizure frequency and polytherapy were the main risk factors for heightened anxiety in both age groups. Epilepsy duration was associated with increased anxiety only for the older age group [40].

These reported differences between children and adolescents may reflect the greater cognitive capacity of older children to understand and question the unpredictable and poorly controlled nature of the seizure disorder. This can, in turn, potentiate anxiety and contribute to negative affective responses. Because of the significant social demands and challenges at this age, adolescence is unique among the other phases of development. Peer relationships are central to the teenage experience and the risk of having a seizure at school or in a social activity with friends is a severe threat

to an adolescent's ability to successfully achieve the developmental milestones for this age. This can result in significant problems with self-esteem and potential social isolation, thus increasing the likelihood of anxiety in various forms. This may be further complicated by the realization of poor seizure control in adolescence, which can be associated with more tenuous prognostic indications for independent living as an adult.

Some other studies have not supported a difference in anxiety prevalence by age [19,20,91]. In fact, one study suggested that younger age is a risk factor for anxiety [27]. One possible explanation to reconcile the discordant findings of the influence of age on anxiety is to consider that a higher rate of anxiety may be present at all ages. The differences between age groups in various studies may reflect the fact that anxiety presents itself differently in children and adolescents. That is, anxiety in younger children may comprise primarily more autonomic and agitation symptoms, whereas adolescents are more likely to exhibit more cognitive and socially avoidant symptoms.

Although age may affect the risk of anxiety disorders in children and adolescents, the same does not appear to be true for gender. Despite the well-known female predominance for anxiety disorders in the general population, the majority of studies have found no relationship between gender and anxiety in children with epilepsy [19,20,40,91].

In addition, most studies do not support a relationship between age at seizure onset and increased risk of anxiety [19,20,40,91]. However, a recent study by Bromfield et al. [55] on school placement suggests that depression and anxiety problems may be more common in children with a later age of onset.

The possible association between seizure type and the presence of anxiety symptoms has also been studied. In adults, there is evidence that the risk of anxiety disorders is higher in focal epilepsy, particularly if there is temporal lobe involvement [26]. As is the case in depression, the contribution of seizure type to anxiety appears to be much less clear in children and adolescents. Although a number of investigations have failed to demonstrate a relationship between seizure type and risk of anxiety [19,20,40,91], Caplan et al. [27] discovered that children with CAE had higher rates of anxiety disorders than children with CPS. As previously discussed, the authors attributed this finding to involvement of differing cerebral regions and the relatively younger age of CAE patients in the sample.

Learning problems also appear to increase the risk of anxiety disorders [19]. Certainly, it is reasonable to expect that academic underachivement is likely to increase the probability of emotional distress in children and adolescents who suffer from cognitive difficulties. This is illustrated well in a study completed by Caplan et al. [27] who found higher rates of affective and anxiety disorders in children with epilepsy who also had lower verbal abilities. Such cognitive inefficiencies can interfere with a child's ability to perform up to their potential, thus increasing the chances of severe frustration and anxiety. This effect, however, is only sporadically recognized by educators who may assume a child's potential is best reflected in their deficiencies rather than their unapparent strengths. As a result, expectations become lowered. Although the lowered expectations may eventually help manage the anxiety, children in this situation often become accustomed to the reality of failure. This can lead to further lowering of self-esteem and more complicated emotional issues.

Such scenarios are not uncommon in school systems where there is limited understanding about the effects of epilepsy on learning. When a child's cognitive functioning fluctuates in concert with better or worse seizure management, the effects on emotional functioning can be even more severe. Indeed, much of the literature supports a direct relationship between anxiety and increased seizure frequency and intractable seizures in children and adolescents [19,40,44,46,47].

A number of studies have demonstrated that polytherapy with AEDs can increase the risk of anxiety disorders [19,20,40,47]. This increased risk can occur as a side effect of the AEDs or as a function of complications related to AED withdrawal [24,152]. The risk appears to be higher for polytherapy versus monotherapy. It is unclear, however, whether there is a causal relationship between polytherapy and anxiety, as it is possible that the intractability of the seizures may be increasing the anxiety symptoms. Further research is needed to delineate this relationship.

The development of anxiety has also been found to be mediated by cross-cultural differences. Although similar effects have not been found in the depressed population with epilepsy, Williams et al. [19] discovered higher anxiety scores in Caucasian children with epilepsy than in African-American children. Moreover, additional research suggests differences in prevalence between Western and non-Western countries. Nigerian and Jordanian studies reported prevalence rates of 31.7 and 48.5%, respectively [46,47]; however, Western-based studies by Ettinger et al. [20] and Williams et al. [19] reported somewhat lower prevalance rates; 16 and 23%, respectively. These results may reflect the different sociocultural structure and different emotional responses of adolescents in various cultures. The opinion of the general population about epilepsy and the perception of stigma in the various cultures may also play a role. In fact, a study completed by Baker et al. [95] demonstrated that social stigma among European countries is strongly affected by cross-cultural variables.

It is important to point out that patients with epilepsy can experience fluctuations in anxiety at different stages of the seizure event, such as preictally, ictally, or postictally. This type of anxiety is different from the intercital anxiety symptoms previously discussed. Ictal fear is known to be associated with CPS of temporal origin, particularly when there is amygdalar involvement. Fear and anxiety symptoms similar to those in panic attacks can also be observed prodromally and postictally in TLE and less frequently in extratemporal lobe epilepsies [26]. The differential diagnosis of seizure-related events is sometimes problematic, as clinicians can sometimes be misled by panic attacks that present like CPS [153]. Differentiating symptoms that are more suggestive of CPS include motor automatisms, alterations in consciousness, and the possible presence of an aura [24,135]. In addition, panic attacks are typically longer (lasting several minutes), whereas CPS are usually more brief (lasting less than a minute). The exception to this, of course, is seizures that secondarily generalize or progress to status epilepticus. Also, although confusion sometimes follows a seizure, it is not traditionally associated with panic attacks [135]. Complicated cases that are more difficult to distinguish may warrant further investigation with EEG, video/EEG monitoring, and/or brain imaging studies [154].

3.2. Treatment

The literature on the treatment of anxiety in patients with epilepsy is based mostly on adult studies. A variety of strategies can be used to manage anxiety in patients with epilepsy, but one cornerstone of effective management is an attempt to gain optimal seizure control. Without total seizure control, complete treatment of anxiety is considered unlikely [26].

For optimal management of anxiety in children and adolescents with epilepsy, regular psychiatric and/or psychological consultation that involves developmentally appropriate methods of treatment is essential. As is the case in children with depression, this holds especially true in more complex cases. Children who are demonstrating anxiety symptoms should be seen at regular intervals by a child psychiatrist, at which time they can be routinely screened for commonly occurring comorbid conditions, such as disruptive behavior disorders and depression. In addition, as is

the case in depression, one of the most essential components of the treatment plan should be a thorough explanation of the condition to the child and the caregivers. Group and individual sessions may help to provide the adequate education and support needed by the family [113–115]. This multimodal approach can improve effective outcomes in children with epilepsy and reduce the potential for life-threatening risks (e.g., suicide).

The effectiveness of psychological treatments, such as cognitive-behavioral therapy (CBT), has been well established in the adult literature. For example, studies have revealed that CBT and other psychological approaches can lead to improvements in quality of life and even reductions in seizure frequency [155,156]. Unfortunately, despite the recognized clinical need for psychosocial interventions in pediatric epilepsy [157], similar studies with children and adolescents have been minimal. Among the available studies, there are multiple methodological limitations that affect their applicability to clinical practice, such as small sample sizes, poor treatment specificity, and questionable differential diagnosis within the samples. One of the larger studies completed by Lewis and colleagues [114] investigated the efficacy of an intervention to improve competency through educational techniques in children aged 7–14. They found that children benefited significantly from educational approaches that focused on decision-making and communication skills and used a perspective that emphasized the child and the family. This led to children feeling more socially competent up to 5 months after the study. A more recent study with adolescents using cognitive-behavioral techniques to provide a psychoeducational intervention found some positive gains in the adolescents' understanding of epilepsy and their own specific condition [158]. Although objective measures of depressive and anxiety symptoms revealed no changes from the pretreatment condition, adolescents reported benefiting from the group process with other adolescents, and there were trends toward improvements in quality of life.

Studies on the pharmacotherapy of anxiety disorders have revealed that SSRIs, including fluoxetine, fluvoxamine, sertraline, and citalopram are effective in treating anxiety disorders in children and adolescents [159–162]. At this time, there are no known controlled studies of the medication therapy of anxiety disorders in adults or children with epilepsy. However, investigations supporting the safety of SSRIs in the treatment of depression in patients with epilepsy are likely applicable to the treatment of anxiety disorders in this population. Given the known efficacy of SSRIs in the treatment of general childhood anxiety disorders, together with the demonstrated safety of using these agents in patients with epilepsy, it is reasonable to consider SSRIs a first choice for pharmacotherapy of anxiety disorders in children with epilepsy [26,70,113]. Altough not extensively studied in pediatric populations, buspiron, which acts as a partial agonist in serotonin-1A receptors, has been found to be effective in reducing anxiety symptoms and is considered relatively safe in adult patients with epilepsy [135].

As previously discussed, some AEDs can exacarbate anxiety in certain types of patients, especially in the context of polytherapy. However, it has been further shown that some AEDs have anxiolytic effects. Valproate, gabapentin, tiagabine, and vigabatrin have been used with varying success in the treatment of anxiety disorders in adult studies [163–168]. In a review of the literature, Mula et al. [169] indicated that the strongest evidence for the antianxiety effects of AEDs has been demonstrated for pregabalin in social phobia and generalized anxiety disorder, lamotrigine in posttraumatic stress disorder, and gabapentin in social anxiety.

Several hypotheses and suggestions have been made for why some AEDs increase anxiety in patients with epilepsy whereas others have anti-anxiety effects. There is some evidence that a past history of psychiatric disorders increases the risk for psychiatric side effects with AEDs [136]. Ketter et al. [152] suggested that AEDs that attenuate glutamate excitatory neurotransmission (e.g., lamotrigine and felbamate) may cause neurotransmitter activation that leads to an increase in anxiety. In contrast, GABAergic AEDs, which are associated with side effects such as sedation and cognitive slowing, can also serve to decrease anxiety symptoms (e.g., barbiturates, benzodiazepines, valporate, tiagabine, gabapentin and vigabatrin) [153,170]. Certainly, because of this, a patient's baseline psychiatric profile is important to consider when choosing an appropriate AED. This can help maximize potential psychiatric benefits and minimize adverse side effects from these agents. Unfortunately, there are no placebo-controlled studies on the anxiolytic effects of AEDs in adults or pediatric patients with epilepsy. Nevertheless, based on the extant literature thus far, it is reasonable to consider choosing an AED with anxiolytic potential in a patient with epilepsy who also has a comorbid anxiety disorder.

In addition to the potential of AEDs to be helpful in the management of psychiatric conditions, it is important to note that some psychotropic medications have been found to have the benefit of being anticonvulsant. Besides their traditional indication for anxiety disorders, some benzodiazepines, such as diazepam and lorazepam, have indications as anticonvulsants in children with epilepsy. They are particularly effective as abortive treatments for prolonged seizures [171]. In addition, clonazepam has been found to be effective in the treatment of absence, myoclonic, and atonic seizures [172].

In their general psychiatric use, benzodiazepines are routinely used in conjunction with SSRIs in the management of anxiety disorders in adults. Their use with children is typically reserved for symptomatic treatment of severe anxiety on a short-term basis [136,173]. However, it should be highlighted that benzodiazepines carry with them a high risk of dependency when used in long term treatment [24,132,136]. Moreover, despite their antiepileptic efficacy in some children, they are not generally considered to be a first-line treatment option for anxiety in children with epilepsy.

4. Conclusion

In the past 20 years, advances in psychiatry and research methods have increased our awareness and knowledge of emotional problems such as depression and anxiety in children and adolescents with epilepsy. We now know that depression and anxiety disorders are frequent and are not simply reactive emotional responses to epilepsy or just a feature of the seizures themselves. Rather, they represent true comorbid conditions that can significantly complicate treatment. Although various seizure-related and parental factors have been found to be, either directly or indirectly, associated with depression and anxiety in children with epilepsy, the relative mediating effects of these factors are not well understood. Future research can help address this question by using more standardized methods of psychiatric evaluation.

Because of the potentially severe impact of these conditions on the quality of life of children and adolescents with epilepsy, depression and anxiety in this population should be screened and treated early. More robust research studies are needed to better examine the specific phenomenology of depression and anxiety symptoms in children and adolescents with epilepsy to help guide clinicians about when psychiatric referrals are needed. Certainly, more in-depth and comprehensive management of depression and anxiety in children and adolescents with epilepsy can be accomplished by a child psychiatrist and/or psychologist, particularly when a child's condition is more severe and/or refractory.

For the management and prevention of these comorbid conditions, education of the patients and families is the first step. Multidimensional treatment plans that include medications and psychotherapeutic interventions, accompanied by careful safety

and efficacy monitoring, must be developed. A healthy family environment and positive parent–child relationship seem to be important predictors of successful treatment in some children. Children with subthreshold emotional symptoms also must be evaluated regularly by a child psychiatrist and/or child psychologist to help with coping and symptom management. Parent and self-report instruments, such as the Child and Adolescent Symptom Inventory, the Child Behavior Checklist (CBCL), Youth Self-Report (YSR), the Behavioral Assessment System for Children, Second Edition (BASC-2), and the Child Depression Inventory (CDI), may be helpful to screen and monitor emotional and behavioral symptoms.

Increasing evidence is building for the safety and efficacy of psychiatric medication in children and adolescents with epilepsy. Previous concerns about the safety of SSRIs in children who are being treated for epilepsy have not been supported in the research. It is important for clinicians to be aware of more recent research about psychiatric treatment in children with epilepsy and approach treatment in an informed and considerate manner. To this end, collaborative work among child psychiatry, child psychology, pediatric neurology, and other related disciplines is crucial for the recognition and treatment of depression and anxiety in children with epilepsy.

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