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Review

Should adult neurologists play a role in the management of the most common psychiatric comorbidities? Practical considerations

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ABSTRACT

Despite the high prevalence and negative impact of psychiatric comorbidities on the life of adults with epilepsy, significant unmet mental health care need exists because of a variety of factors, including poor access to mental health care providers. A potential solution to address access barriers is neurologist-driven diagnosis and management of common psychiatric conditions in epilepsy, of which mood and anxiety disorders are the most common. In this manuscript, patient selection criteria and practical treatment strategies are outlined for common mood and anxiety disorders that can be safely managed by neurologists.

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1. Introduction: barriers to psychiatry/mental health access

Despite increased recognition that psychiatric comorbidities in adults with epilepsy are highly prevalent and important, unmet mental health care need is substantial, outnumbering physical health need 2:1 in a recent systematic review [1]. Although 84% of individuals with psychological distress and epilepsy in the California Health Interview Survey perceived a need for mental health care, only 57% had seen a mental health provider, and 30% reported delays in mental health treatment [2]. A needs assessment conducted in South Carolina demonstrated that more than 50% of individuals experienced difficulty finding behavioral or mental health services [3]. Not only do patients perceive unmet need for treatment of psychiatric symptoms, but epileptologists do as well. Epileptologists who responded to the American Epilepsy Society Quantitative Practical Use-Driven Learning Survey in Epilepsy (Q-PULSE) survey on screening for anxiety and depression in epilepsy indicated the two top barriers to screening were inadequate availability of local psychiatrists and inadequate availability of counseling/psychotherapy services (55.4% and 53.5% of respondents) [4].

Why do these gaps and barriers to mental health care exist? Multiple factors contribute, including insurance-related factors, an overall shortage of mental health providers, reluctance of patients to seek psychiatric care because of stigma of mental illness, limited communication between psychiatrists and neurologists, limited education of psychiatrists on neurological illness, and limited education of neurologists on psychiatric illness [2–7]. Ultimately, the result of this conundrum is that even when mental illness is recognized, it is undertreated in persons with epilepsy. An intuitive solution may be to have neurologists provide mental health care concomitant with epilepsy care.

1.1. Nonpsychiatrists can provide safe treatment

Studies done in primary care populations have demonstrated that nonpsychiatrists can manage anxiety and depression safely and effectively, particularly with the use of validated screening instruments [8,9]. For example, in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, individuals with depression were treated with citalopram aided by symptom measurement every two weeks in multiple primary care and psychiatry practices. Outcomes did not differ among individuals treated in primary care settings compared with those from psychiatry settings. Specifically, remission measured with the Hamilton Depression Rating Scale was 26.6% in primary care and 28% in psychiatry settings; response rates were 46% in primary care and 48% in psychiatry settings, measured by the Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR) [8]. Zupancic et al. demonstrated in a primary care clinic that using the Generalized Anxiety Disorder-7 and Quick Inventory of Depressive Symptomatology, Self-Report instruments for anxiety and depression more than doubled treatment rates for these conditions [9]. Treatment of common

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psychiatric comorbidities by neurologists thus is likely feasible and could address some of the barriers to accessing mental health care.

2. Common psychiatric comorbidities that neurologists can identify and treat in the clinic: diagnostic criteria

2.1. Major depressive episodes/disorder

A major depressive episode is defined as at least two weeks of impairing symptoms most of the day, nearly every day, including 5 of the 9 symptoms outlined below [10]. These include the following: 1) depressed mood, 2) markedly diminished interest or pleasure in activities, 3) decreased or increased appetite, or significant weight loss or gain when not dieting, 4) insomnia or hypersomnia, 5) psychomotor agitation or retardation, 6) fatigue or loss of energy, 7) feelings of worthlessness or excessive inappropriate guilt, 8) diminished concentration/thinking or indecisiveness, and 9) recurrent thoughts of death or suicidal ideation [10]. At least one of the symptoms must be depressed mood or loss of interest or pleasure in activities [10].

2.2. Dysthymia

Dysthymia is the presence of depressed mood most of the day for most days lasting at least two years, along with two of the following 6 additional features: 1) poor appetite or overeating, 2) insomnia or hypersomnia, 3) low energy or fatigue, 4) low self-esteem, 5) poor concentration or difficulty making decisions, and 6) hopelessness [10]. The symptoms must cause distress or impairment and must not have resolved for more than 2 months consecutively during the 2-year period [10].

2.3. Generalized anxiety disorder

Generalized anxiety disorder is characterized by at least 6 months of excessive, difficult to control anxiety and worry on most days, causing impairment or distress, along with 3 of 6 additional features [10]. These include the following: 1) restlessness or feeling keyed up/on edge, 2) easy fatigue, 3) difficulty concentrating or mind going blank, 4) irritability, 5) muscle tension, and 6) sleep disturbance [10].

2.4. Panic disorder

Recurrent, unexpected panic attacks followed by at least one month of significant worry about attacks, and/or resulting maladaptive behavior define panic disorder [10]. A panic attack is a surge of intense fear or discomfort peaking within minutes, and involving at least 4 of the following symptoms: 1) palpitations or increased heart rate, 2) sweating, 3) trembling or shaking, 4) shortness of breath or smothering sensation, 5) choking sensation, 6) chest discomfort/pain, 7) nausea or abdominal distress, 8) dizziness, unsteadiness, lightheadedness, 9) chills or heat sensation, 10) paresthesias, 11) feeling of unreality or being detached from self, 12) fear of losing control, and 13) fear of dying [10]. Distinguishing between panic attacks and focal seizures with ictal fear/panic is important for patient management, and this can be complex because of occasional coexistence of panic attacks and focal seizures with ictal fear [11]. Features most consistent with panic attack include longer duration than seizures (5–10 min for panic attack vs. less than 2 min for seizure), initiation from wakefulness and not out of sleep (in contrast to focal seizures which may directly arise from sleep), and lack of features commonly seen in focal seizures such as automatisms, déjà vu, or hallucinations [12,13].

3. Management of common psychiatric comorbidities: practical suggestions

3.1. Type of anxiety and depression symptoms: temporal relation to seizures and iatrogenic symptoms

To appropriately manage anxiety and depression in persons with epilepsy, it is important to first identify the type of psychiatric symptoms at hand: are the symptoms temporally related to seizure occurrence (periictal), seizure treatment (iatrogenic, following pharmacologic with antiepileptic drugs (AEDs) and/or surgical treatment), or unrelated to seizures or seizure treatment (interictal). Each of these types of symptoms has a distinct treatment approach.

Periictal psychiatric symptoms can be either preictal (occurring one to three days before a seizure), ictal (a psychiatric symptom that is part of the seizure semiology, such as ictal fear), or postictal (occurring after a seizure or cluster of seizures, typically starting within three days after the seizure or seizure cluster). The management of periictal psychiatric symptoms focuses on prevention by achievement of seizure control. Postictal anxiety and depression typically do not respond well to treatment with antidepressant/anxiolytic drugs, but postictal psychosis may be effectively treated with antipsychotic medications such as risperidone [14–16].

The development of *iatrogenic adverse events of pharmacologic and surgical treatment of epilepsy* has been identified in patients with a current, past, and/or family history of psychiatric disorders [17,18]. Iatrogenic symptoms/episodes of anxiety and depression related to pharmacologic treatment may include a) the addition of an AED with potential negative psychotropic properties (barbiturates, felbamate, levetiracetam, topiramate, zonisamide, vigabatrin, clobazam, brivaracetam, and perampanel); b) withdrawal of an AED with mood stabilizing (carbamazepine, oxcarbazepine, valproic acid, and lamotrigine) or anxiolytic properties (benzodiazepines, gabapentin, pregabalin, valproic acid); or c) reduced levels of ongoing psychotropic drugs caused by the addition of an enzyme-inducing AED (e.g., addition of phenytoin, carbamazepine, phenobarbital, primidone, rufinamide to ongoing fluoxetine treatment). To prevent iatrogenic psychiatric symptoms, it is essential to identify individuals at risk: those with prior, current, or family history of psychiatric disorders.

Interictal psychiatric symptoms/episodes occur independently of seizure occurrence. Nonetheless, periictal symptoms may occur in patients with interictal symptoms (e.g., patients with ictal fear have an increased risk of having interictal panic disorder), and iatrogenic symptoms may at times occur in patients with interictal and periictal symptoms. A careful history can properly identify the nature of the different types of symptoms in the same patient. Diagnostic and treatment approaches, as outlined in the sections below, are similar to approaches used for people without epilepsy.

3.2. Interictal mood and anxiety disorders

Fortunately for neurologists, some simple screening strategies and treatment principles can be employed to tackle psychiatric comorbidities with a practical approach, thus enabling competent neurologists to manage interictal depression and/or anxiety in epilepsy in addition to periictal and iatrogenic symptoms as described above. An approach is composed of two freely available, validated screening instruments and simple dosing guidelines for medication therapies advantageous for use in epilepsy and efficacious for interictal major depression, dysthymia, panic disorder, and generalized anxiety.

3.2.1. Identification

In the setting of a busy outpatient clinic, self-rating screening instruments can be used to identify the presence of symptoms of depression and anxiety [17–21]. Of note, these instruments were developed and validated in patients with a minimum reading level of fourth grade.

☐ NDDI-E score: _____

☐ GAD-7 score: _____

IF NDDI-E item 4 score 3 or 4:

☐ assess for active suicidality

IF high NDDI-E or GAD-7 overall:

Assess risk of bipolar disorder

☐ manic symptoms in response to antidepressant in past?

☐ family history of bipolar disorder?

☐ onset of depression before age 15?

Assess for psychosis

☐ auditory hallucinations of voices?

IF high GAD-7:

☐ panic attacks?

Fig. 1. Checklist for assessing mood and anxiety.

Therefore, they should not be used in patients with cognitive impairment. One instrument, the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) was developed to identify a possible major depressive episode (MDE) in patients with epilepsy, with scores >15 demonstrating good sensitivity and specificity for major depression [19,20]. Scores of 15 or lower on the NDDI-E are of uncertain significance, though there is some data suggesting that scores in the 14-15 range may detect clinically relevant symptoms [19]. An alternative rating scale to identify symptoms of depression is the Beck Depression Inventory II (BDI-II) [21]. Patients who do not meet diagnostic criteria for MDE but endorse symptoms on the BDI-II may be considered to suffer from a form of subsyndromic depression. It is important to remember that these instruments do not establish a definitive diagnosis. Therefore, specific symptom items should be addressed in the clinical visit and expanded upon as appropriate.

The Generalized Anxiety Disorders-7 (GAD-7) is a reliable self-rating instrument used to identify symptoms of anxiety. Scores of 10 or higher have acceptable sensitivity and specificity for detecting a broad range of anxiety disorders in primary care, including 89% sensitivity and 82% specificity for generalized anxiety disorder and 74% sensitivity and 81% specificity for panic disorder [22]. Alternatively, some authors have suggested using a cutpoint of >10 for significant anxiety symptoms in epilepsy [23].

To identify clinically significant mood and/or anxiety symptoms, we recommend the use of the NDDI-E and GAD-7, which take less than 5 min to complete. If symptoms of depression are identified based on the NDDI-E cutpoints outlined above, we suggest asking follow-up questions for all items scored as "sometimes" or "always or often," especially item 4 ("I'd be better off dead"), which is a validated suicide screen for those responses [24]. Among individuals with high NDDI-E scores, we also recommend asking additional questions to assess for past manic episode, which would suggest bipolar disorder, and to assess for psychotic symptoms or suicidality any of which would necessitate prompt psychiatry referral (see Fig. 1 for suggested items/checklist). If anxiety symptoms are identified based on the GAD-7, we suggest a follow-up question to assess whether the patient has panic attacks. The use of self-rating instruments is reviewed in great detail in the article by Bermeo-Ovalle in this issue.

Of note, MDE can be the expression as well of a bipolar disorder, a more severe form of mood disorder, which should not be managed by a neurologist. A bipolar disorder should be suspected under the following conditions: a) a positive family history of bipolar illness established by the identification of manic and/or hypomanic episodes; b) a first MDE at the time of adolescence, as these patients have a 50% risk of having a bipolar disorder; c) the development of manic and/or hypomanic symptoms associated with the use of antidepressant drugs.

4. Pharmacologic treatment

Fortunately, the treatment of depression and anxiety disorders described in Section 2 can follow the same strategies used for the treatment of primary mood and anxiety disorders, based on the use of selective serotonin-reuptake inhibitors (SSRI) and serotonin-norepinephrine-reuptake inhibitors (SNRI) [17]. The following principles should be considered: a) An SSRI should be considered in patients with an MDE and/or anxiety disorder and/or symptoms of depression and/or anxiety as suggested in Table 1. b) An SNRI should be considered

Table 1
Dosing of advantageous medications to treat anxiety and depression in epilepsy.

Drug	Starting dose (mg daily)	Maximal dose (mg daily)	Potential schedule for dose increase
Escitalopram	5–10	20	5–10 mg biweekly
Citalopram	10	60	10–20 mg biweekly
Sertraline	25–50	200	25–50 mg biweekly

Table 2
FDA-approved indications of selected SSRI/SNRIs, potential for inhibition of antiseizure drugs.

Drug	Depression	Generalized anxiety disorder	Panic disorder	Inhibition of CYP enzymes with potential to affect antiseizure drugs?
SSRIs				
Citalopram	+			Lowest potential
Escitalopram	+	+		Lowest potential
Fluoxetine	+		+	Moderate inhibitor
Fluvoxamine				Maximal inhibitor
Paroxetine	+	+	+	Moderate inhibitor
Sertraline	+		+	Mild inhibitor
SNRIs				
Desvenlafaxine	+			Likely low potential
Duloxetine	+	+		Likely low potential
Milnacipran				Likely low potential
Venlafaxine	+	+	+	Likely low potential
Vortioxetine	+			Likely low potential

first in MDE associated with symptoms of fatigue and excessive sleepiness and/or if a previous trial with an SSRI was ineffective at optimal doses. c) The trial with an SSRI or SNRI should aim to achieve complete symptom remission. If symptoms persist at maximal doses and/or adverse events develop, a trial with an antidepressant of the alternate family should be considered. d) To ensure that optimal doses have been achieved, dose increments of up to 30% in certain SSRIs (citalopram, escitalopram) and SNRIs (duloxetine) may be necessary in the presence of enzyme-inducing AEDs. e) Patients need to be monitored for potential pharmacodynamic interactions between SSRIs, SNRIs, and some AEDs (e.g., hyponatremia, bruising, osteopenia, and osteoporosis).

Escitalopram and citalopram have low pharmacokinetic interaction with AEDs and are useful for depression, generalized anxiety, and panic [17]. Sertraline has a similar efficacy/common use in anxiety and depressive disorders, though with slight potential for inhibition of the metabolism of some AEDs via the CYP2D6 enzymes [17]. Dosing of these three advantageous drugs for use in epilepsy is outlined in Table 1. A more comprehensive list of SSRI and SNRI medications with Food and Drug Administration (FDA)-approved indications is outlined in Table 2, along with potential for inhibition of antiseizure drugs [13,17]. Response to treatment can be monitored by repeated assessment with the GAD-7 and NDDI-E and/or BDI-II on follow-up visits [17].

4.1. When to refer to psychiatry

Management by a psychiatrist rather than a neurologist is appropriate if psychotic symptoms such as delusional thinking, auditory hallucinations, risk factors for bipolar disorder, current history of alcohol and drug abuse, or suicidality are identified at the time of initial screening as outlined in Fig. 1 [24,25]. In addition, patients with personality disorders should be referred to the care of a psychiatrist.

If symptoms fail to remit after two trials, one with an SSRI and one with an SNRI, then referral to psychiatry should be considered [7].

5. Clinical strategies

The following are pitfalls to avoid:

a. Nonpsychiatrists often make two main mistakes when treating depression. The first is underappreciating the role that therapeutic efforts or support from family or social contacts can offer. In many ways, outcomes are related to engagement with others. Persons who are isolated may have little opportunity to socialize and that leads to independent problems in the depressive or anxiety realms. Furthermore, identification of depressive symptoms may be difficult even with validated rating scales. If an opportunity exists to collect corroborating information from family members or other supports, it can be invaluable to verify clinical impressions and also assess improvement. Engagement with family or supportive individuals is essential to accurately assess treatment approaches, even for seasoned psychiatrists.
b. The second mistake is in being overly aggressive with medication usage. Many clinicians are tempted to take a formulaic approach to antidepressants. An algorithmic, deliberate approach is consistent with the heuristic methods of treatment in primary care and in neurology. However, it may not be useful in psychiatry. Psychiatry is fraught with ambiguity and uncertainty regarding symptom definition and progression. Treatment approaches vary and little evidence exists for selecting one medication over another. Individual variability is the rule and thus rigid approaches may not be effective for most patients. Very gradual adjustments and frequent follow-up is the most reasonable approach. Frequent reassessment of the dosing schedule is important. Starting at a low dosage is usually the best initial step. A possible algorithm for treatment is listed in Table 3.

Table 3
Potential algorithm for treatment of depression or anxiety in the context of epilepsy.

1. Establish symptoms with in depth clinical interview and use of rating scales.
2. Consider whether mood or anxiety symptoms are exacerbated by current antiepileptic drugs, e.g., levetiracetam, phenobarbital.
3. Establish neurovegetative symptoms that may represent tangible targets of treatment. Examples include insomnia, appetite disturbance, decreased energy, blunted affect.
4. Initiate low dose of antidepressant and inform regarding common potential side effects.
5. Facilitate a return visit within 1–3 weeks in order to assess tolerability and to assure that activation related mood disruption is not occurring.
6. Consider dose adjustment in the first 2–5 weeks of treatment depending upon tolerability and symptom relief.
7. Expect that patients will return to the office every 1–3 weeks in the initial months of treatment as this is the riskiest time for adverse reactions.
8. Consider using follow-up rating scales to assess progress and to assist in making determinations about referral to psychiatry.

6. Conclusions

Simple strategies involving brief self-report instruments and prescribing SSRIs can empower neurologists to treat anxiety and depression in adults with epilepsy. Adoption of these management strategies may have a significant positive impact on patients, resulting in fewer delays to treatment among those likely to respond to a simple pharmacotherapy approach.

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Conflicts of interest

None.

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