

Psychiatric Comorbidity in Epilepsy and End Stage Renal Disease

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INTRODUCTION

Many chronic serious medical conditions are associated with increased psychiatric comorbidity. Two such conditions are epilepsy and chronic renal failure. While specialists are often involved in the care of these patients, well-established primary care remains an important part of their treatment. When psychiatric conditions arise, primary care providers will often be the first to see these disorders. These can be very complicated patients, and coordination of care between primary care physicians, specialists, and other health care providers is essential. Recognition, treatment initiation, and referral when needed are reviewed in this article.

EPILEPSY

Epilepsy is a complex disorder afflicting approximately 1% of the population. New treatment modalities have exploded in recent years, giving patients more options and a greater chance of becoming seizure free. These include newer anticonvulsants, vagus nerve stimulation, and epilepsy surgery. Comorbid psychiatric disorders of a wide variety occur in epilepsy to a greater degree than in the general population.¹ These include various forms of depression, anxiety, and psychosis. In general these comorbid disorders are classified based on their temporal relationship to the ictal event or seizure. Preictal symptoms occur hours to days before a seizure and represent a prodrome of a coming seizure. Ictal symptoms represent an actual simple partial seizure, usually of a temporal lobe origin. Postictal symptoms last hours to days—usually occurring after a volley of seizures—are time limited, and rarely require treat-

ment. Interictal depression, anxiety, and psychosis are more chronic and typical disorders, not occurring in relation to seizures. These are far more likely to be encountered in a primary care setting, and will be the main focus of this review.

Depression in Epilepsy

Depression is the most frequently occurring comorbid psychiatric condition in epilepsy. While patients with epilepsy face many well-documented psychosocial difficulties (work discrimination, driving restrictions, etc) it is a mistake to view depression in epilepsy as a purely reactive phenomenon.² The influence of anti-epileptic drugs (AED) and the neurobiology of epilepsy itself contribute to the etiology of depression in these patients. There is a substantially increased risk of suicide for epileptic patients experiencing depressive disorders (DD).³ Further, impaired quality of life (QOL) in epilepsy is strongly linked to mood disorders, making recognition and treatment of depression in these patients especially important.

The incidence of depression in epilepsy far exceeds the general population and also exceeds patients with chronic illness or other neurological conditions. Depression occurs more frequently in partial epilepsy with a temporal or frontal lobe focus.² Stigmas associated with mental illness often lead patients to underreport their symptoms. Interictal DD are by far the most common and most likely to require treatment. While interictal DD are common, they frequently do not meet DSM-IV criteria for major depression, often leading to lack of recognition. These disorders often present as a less severe chronic depression with some endogenous depressive features and an intermittent or waxing and waning course.³ If depressive symptoms are severe enough to disrupt normal activities, relationships, or impair QOL they should be treated.

AED selection may strongly influence the development of depression in epileptic patients. Barbiturates (i.e. phenobarbital) can cause depression and have been associated with suicidal ideation. Other AEDs known

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to be associated with depression include vigabatrin, topiramate, and tiagabine.⁴ Conversely, carbamazepine, valproic acid, and lamotrigine have mood stabilizing properties, and their decrease or discontinuation can be associated with depression.² A reasonable initial approach is to look at whether the development of depression is closely associated with a recent change in AEDs. Maintaining good seizure control is always clinically a first priority. If it is feasible to decrease or eliminate an offending agent (i.e. phenobarbital), or restore a favorable drug (i.e. lamotrigine), this by itself may alleviate depression. When these types of adjustments in AED therapy are not possible, proceeding with antidepressant treatment is indicated.

When antidepressants are needed, a number of factors guide selection, including proconvulsant properties and drug-drug interactions. Most antidepressants, even tricyclics, can be safely used to treat depression in epilepsy. With careful selection of medication, clinicians need not be dissuaded from adequately treating depression by fear of antidepressant-induced seizures.² Three antidepressants, clomipramine, bupropion, and maprotiline should be avoided because of their excessive seizure risk.⁵ Clinically relevant drug interactions relate primarily to metabolism of antidepressants and AEDs by cytochrome P-450 (CYP 450) isoenzymes. Several AEDs (phenobarbital, phenytoin, and carbamazepine) are strong inducers of these enzymes and can lead to accelerated metabolism of antidepressants.³ For example, serum concentrations of most tricyclic antidepressants can be lowered by concurrent treatment with barbiturates or carbamazepine.⁶ Conversely, several selective serotonin reuptake inhibitors (SSRIs), including paroxetine, fluoxetine, and fluvoxamine are inhibitors of one or more CYP 450 enzymes and can lead to elevated or toxic AED levels.³ For example, carbamazepine levels may be elevated or toxic when concurrently administered with fluvoxamine. More frequent monitoring of AED levels may be needed with the addition of some antidepressants. Many authors recommend SSRIs with low metabolic interaction (sertraline or citalopram) as first line treatment for DD in epilepsy.²

Psychosis in Epilepsy

Psychosis in epileptic patients occurs more frequently than in the general population.¹ Interictal psychosis, often referred to as schizophrenia-like psychosis of epilepsy (SLPE), is a more common and chronic psychotic illness, not temporally related to the occurrence of seizures.¹ Risk factors include temporal lobe focus (left > right), complex partial seizures, early age of

onset of epilepsy, duration of epilepsy greater than 10 years, and family history of psychosis.⁷ Clinically these patients often have prominent delusional features, and visual hallucinations occur more frequently than auditory. These patients often show an absence of the affective blunting, thought disorder, and deterioration that often accompanies schizophrenia.¹ Unlike ictal or postictal psychoses, interictal psychosis generally requires treatment with antipsychotic medication. With the exception of clozapine, which carries a significantly elevated seizure risk, the atypical antipsychotics can be safely used in these patients.⁸ In general, patients with a psychotic illness should have a psychiatric referral.

Anxiety and Pseudoseizures in Epilepsy

Anxiety disorders occur far more frequently in epileptic patients than in the general population. Interictal anxiety often presents as typical anxiety disorders such as panic disorder (PD), generalized anxiety disorder (GAD), obsessive compulsive disorder (OCD), and post-traumatic stress disorder (PTSD). Panic disorder is particularly common and presents some difficulties in differential diagnosis. Specifically, panic disorder and temporal lobe epilepsy share many overlapping symptoms, can be difficult to distinguish, and can co-exist in the same patient.⁹ If patients with panic disorder fail standard management (SSRI, alprazolam) psychiatric referral should be considered. Further, if what appears to be panic disorder is accompanied by odd or atypical features (impaired consciousness after attacks, stereotyped behavior, absence of anticipatory anxiety, or agoraphobia), neurological referral may be helpful. In general, the SSRIs as a class are effective for these anxiety disorders, though they have not been studied systematically in patients with epilepsy. Potential interactions between SSRIs and AEDs are outlined in the earlier section on depression. Venlafaxine is approved for use in GAD. Benzodiazepines offer further alternatives (clonazepam approved for PD, alprazolam approved for PD and GAD) and offer the advantage of not lowering seizure threshold.⁹ Pseudoseizures, more correctly termed non-epileptic seizures (NES), are especially challenging, even for specialists.¹⁰ Among patients with epilepsy, up to 10% may also have NES. The diagnosis of NES can be very difficult, and usually relies on video EEG monitoring coupled with other observations.¹¹ If NES is suspected clinically, referral to a neurologist with appropriate monitoring capability can be essential to confirm the diagnosis. Once a diagnosis of NES is

confirmed, it is best to refer to a psychiatrist or psychologist familiar with the disorder.¹⁰

END STAGE RENAL DISEASE

Rates of end stage renal disease (ESRD) have substantially increased in recent years. The number of patients starting dialysis has doubled since the early 1990s.¹² Rates of hospitalization for psychiatric illness are much higher in dialysis patients than in the general public.¹³ Comorbid psychiatric illness is significant in the ESRD population, and successful identification and treatment can lead to improved clinical outcomes and QOL for these patients. Psychiatric problems include depression, organic mental disturbances, substance abuse, and anxiety. Special considerations exist for transplant recipients.

Depression in ESRD

Depression is the most common comorbid psychiatric disorder in ESRD patients.¹² The impact of depression can be significant in these patients and is associated with increased rates of peritonitis, hypoalbuminemia, non-compliance, missed dialysis, and overall higher mortality.^{12,14} There can be significant overlap between symptoms of depression and renal failure, making the diagnosis more difficult. For example fatigue, anorexia, weight loss, and insomnia are common in both conditions. Attention to the cognitive aspects of depression (hopelessness, guilt, low self esteem, suicidal thoughts) can help confirm the diagnosis of depression.¹⁵ Some authors have found the Beck Depression Inventory (BDI) to be a useful tool to screen for depression in ESRD patients. Scores of 11 or greater on the BDI are associated with high rates of clinical depression and warrant further evaluation and possible treatment.¹⁶ The BDI is a 21-item self-rating scale used for measuring depression.¹⁷

Despite the additional burden of illness associated with ESRD, all evidence suggests that these patients respond well to treatment for depression. Social support can be extremely important, and correlates with improved levels of depression. Measures that improve social support (i.e. social service consult, home care services, increased family involvement) can help reduce depression. Antidepressant medications are safe and effective in these patients as long as a few guidelines are followed. The SSRIs can be used in doses similar to the general population. An exception is paroxetine, in which dose reductions of 50%-75% are recommended due to elevated plasma concentrations that occur in ESRD.¹⁸ A number of the newer non-SSRI antidepressants require caution in ESRD pa-

tients. Venlafaxine is primarily eliminated in the urine leading to reduced clearance in renal disease. Careful dose adjustments and regular blood pressure monitoring are also recommended. Bupropion has active metabolites that are primarily eliminated through renal excretion. Nefazodone kinetics in renal disease is not well understood.¹⁹ Tricyclic antidepressants (TCA) are effective in ESRD, but should be considered second line agents due to their cardiac, sedative, and anticholinergic properties. Depression that is severe, associated with suicidal ideation or psychosis, or fails to respond to reasonable treatment should have psychiatric referral.

Organic Mental Disorders in ESRD

Renal failure patients are at increased risk for delirium and dementia, and these conditions are frequently responsible for hospitalization.¹⁹ Higher rates of dementia are due mainly to vascular disease in this population. Optimizing treatment for concurrent conditions associated with cerebrovascular disease (hypertension, diabetes, arrhythmia, and coagulopathies) can improve prospects for preserving cognition. Specific medications for treatment of primary degenerative dementia (cholinesterase inhibitors, NDMA antagonists) are available, but their use and pharmacokinetics have not been systematically evaluated in ESRD. Features that distinguish delirium from dementia include a fluctuating course, impaired sensorium, and reversibility when the offending cause is treated. Common causes of delirium in renal failure include uremia, electrolyte disorders (especially hypercalcemia), and drug effects due to impaired renal clearance (morphine, metoclopramide, illicit drugs). For management of acute agitation in these patients, oral or parenteral haloperidol remains a common drug of choice.¹⁹

Alcohol and Drug Abuse in ESRD

The substance abuse rate among some dialysis populations is extremely high. Alcoholism in urban hemodialysis groups exceeds 25% in some reports.²⁰ Heroin and cocaine use can lead to renal failure through specific drug-induced nephropathies.²¹ Illicit drug use in these patients frequently continues once formal dialysis has begun. Many clinicians struggle to provide care for what is clearly a difficult population. The impact of serious substance abuse in these patients, and its appropriate treatment, is not well studied. Even basic questions such as the effect this has on compliance need much further study. Efforts should be made to get patients into traditional drug and alcohol treatment programs.

Anxiety and Insomnia in ESRD

Anxiety is common in patients with renal disease and can range in severity from mild situational anxiety to frank panic disorder. Mild anxiety is best handled with reassurance and by addressing any underlying causes. More severe anxiety may be seen in relation to dialysis treatments. Rapid shifts in fluids and electrolytes can lead to nausea, vomiting, hypotension, and muscle cramps, and may be associated with significant anxiety.²² Standard doses of benzodiazepines given before or during dialysis are often effective. Because they are metabolized in the liver, dose reduction of benzodiazepines is usually not necessary. Busparone, commonly used for more chronic anxiety, must be carefully used in ESRD due to prolonged half-life in these patients.¹⁹ For more sustained or severe anxiety (panic disorder, generalized anxiety, social phobia) SSRIs may be used in doses similar to those used to treat depression (see depression section). Insomnia is common in patients with renal failure, and may be related to such problems as muscle cramps, restless leg syndrome, and pain associated with peripheral neuropathy.¹⁹ Successful treatment of these conditions may alleviate insomnia. Attention to sleep hygiene, regular exercise, and eliminating daytime napping can improve sleep without sedative hypnotics. If necessary, sleep medications (zolpidem, temazepam) can be used on a short-term basis without dose reduction. With more chronic insomnia, or when substance abuse is a concern, sedating antidepressants (trazadone, mirtazepine) can be very effective sleep aids.

Renal Transplantation

While renal transplant improves life expectancy and overall QOL, comorbid psychiatric disorders, especially depression and anxiety, remain high. Depression in renal transplant recipients is associated with increased risk of rejection, return to dialysis, and death by suicide.²³ Psychotherapy has been shown to improve overall emotional states and to decrease levels of depression in transplant patients.²⁴ Selection of psychotropic medications is mainly limited by drug interactions with cyclosporine and tacrolimus. Antidepressants nefazodone and fluvoxamine can lead to toxic levels of these drugs and should be avoided.²⁵ Most other antidepressants and anxiolytics can be used safely following renal transplant. Finally, neuropsychiatric effects of commonly used transplant medications need to be considered. Corti-costeroids, such as prednisone, are associated with a wide variety of symptoms ranging from simple anxiety and depression to delirium and

mania. Tacrolimus and cyclosporine are associated with anxiety, insomnia, disorientation, and psychosis.

CONCLUSION

Comorbid psychiatric disorders of a wide variety occur in epilepsy and renal disease to a much greater degree than healthy populations. Each of these disorders has special conditions (drug-drug interactions, effect of concurrent medications, etc.) that need to be taken into account before initiating treatment. Primary care physicians can play an important role by recognizing these co-morbid disorders, initiating treatment, and referring when necessary.

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