



Epilepsy Surgery and Postoperative Depression: Charting Difficult Territory

Profiling the Evolution of Depression After Epilepsy Surgery.

Wrench JM, Rayner G Wilson SJ. *Epilepsia* 2011;52:900–908.

PURPOSE: Both neurobiologic and psychosocial factors have been proposed to account for the high prevalence of depression surrounding epilepsy surgery. Using a prospective longitudinal approach, this study aimed to profile the evolution of depression after epilepsy surgery at multiple time points, including early and longer-term follow-up. We also sought to identify neurobiologic and psychosocial predictors of depression before and after surgery, including whether patients undergoing mesial temporal lobe resection (MTR) were at greater risk of depression than patients undergoing nonmesial temporal lobe resection (NMTR). **METHODS:** Sixty patients undergoing epilepsy surgery (38 MTR, 22 NMTR) for the treatment of medically intractable seizures were assessed preoperatively and at 1, 3, 6, and 12 months postoperatively in the Comprehensive Epilepsy Program of Austin Health. The diagnosis of depression was based on DSM-IV criteria for major depressive disorder, as assessed from a mental state examination. The Austin CEP Interview was used to obtain a detailed psychosocial assessment of each patient and family members. **KEY FINDINGS:** Before surgery, 43% of patients had a lifetime prevalence of depression, with no difference between the proportion of patients in the MTR (40%) and NMTR groups (50%). Predictive factors included a family history of psychiatric illness ($p = 0.015$) and financial dependence of either family members or government income benefits ($p = 0.024$). Discriminant function analysis indicated that these factors classified 69% of cases correctly ($p = 0.006$, partial $\eta^2 = 0.06$). In the 12 months following surgery, 37% of MTR and 27% of NMTR patients experienced major depression, with no significant difference between the two groups. The majority of depressed patients (70%) were diagnosed in the first 3 months and in 65% of diagnosed cases, the depression persisted for at least 6 months within the follow-up period. The pattern of recurrent and de novo depression differed significantly between the groups, with 13% of MTR patients developing de novo major depression in comparison to no NMTR patients ($p = 0.05$). A preoperative history of depression ($p = 0.003$) and poor postoperative family dynamics (1 month, $p < 0.001$; 3 months, $p = 0.007$; 6 months, $p = 0.021$; 12 months, $p = 0.097$) were predictive of depression after surgery. These factors correctly classified 78% of cases ($p = 0.000$, partial $\eta^2 = 0.19$). **Significance:** The findings of this study confirm high rates of major depression before and after epilepsy surgery, the etiology of which is multifactorial. They highlight the need for thorough assessment and diagnosis before surgery, as well as the provision of routine follow-up and psychological support, particularly early after surgery. When estimating level of risk for depression, patients should be counseled about the role of both neurobiologic and psychosocial factors. Before surgery, these include a family history of psychiatric illness and financial dependence, whereas poor family adjustment to life after surgery and a patient preoperative history of depression were risk factors for postoperative depression. Finally, disruption to mesial temporal structures known to play a role in mood via MTR may place patients at increased risk of new-onset depression after surgery.

Commentary

Depression and epilepsy are comorbid disorders with a bidirectional relationship (1, 2). The prevalence of depression in epilepsy is high and the incidence of epilepsy is certainly high in depression. Depression may even have a greater impact on quality of life than seizures (3). Nevertheless, the major focus in epilepsy remains achieving seizure freedom.

It seems logical that curing the epilepsy with surgery would also cure the depression.

Wrench and colleagues prospectively chart the course of postoperative depression for 1 year after epilepsy surgery. Not surprisingly they confirm, that the preoperative rate of depression is high. However, there is no real change in depression postoperatively. Depression occurs within 3 months of surgery and is usually longer lasting. Preoperative depression, poor family dynamics, and age were the only risk factors. Thirty percent of patients required postsurgical psychiatric or psychological assistance. Patients who were seizure free were as much depressed as patients who continued to have seizures.

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Another very recent similar study confirmed all of the above in additional 150 patients (4).

Depression leads to suicide, and fortunately no suicides occurred in the study. In another large sample of patients with epilepsy surgery, all patients who committed suicide postoperatively were seizure free (5). It seems apparent that rendering the patient seizure free does not necessarily eliminate depression. For us as medical professionals, it seems hard to understand that curing the patients' biggest problem does not make them happier.

The authors measured depression as present or absent based on a psychiatric exam in addition to a detailed analysis of psychosocial factors. The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* criteria are applied. This certainly is a well-accepted and standardized approach. But, depression can be difficult to measure and always includes subjectivity on the side of the examiner or the patient. What role do self-assessment scales play such as the Beck Depression Inventory in comparison with a psychiatric structured or non-structured interview? *DSM-IV* criteria define depression as the presence of five key depressive symptoms present for 2 weeks. Do those criteria apply to the epilepsy population, in whom an underlying medical etiology, the epilepsy, certainly cannot be excluded as demanded by *DSM-IV*. Fatigue and psychomotor slowing are frequently a result of antiepileptic drugs (AEDs). Depression in epilepsy can be intermittent and of shorter duration or merely related to seizures in the preictal or postictal phase (6). Is it possible that depression in epilepsy is a different disease process altogether than major depression without epilepsy?

Wrench and colleagues certainly attempted to factor in psychosocial components that further cloud the problem. In addition, the influence of antiepileptic medications on depression cannot be ignored. AED differences on depression were not systematically examined in this study, most likely due the variety of AEDs and the fact that all patients were taking AEDs.

What is the true pathophysiological substrate of depression in epileptic patients? Is it the seizures, the psychosocial burden of the disease, the underlying pathology, or some other neurobiological factor? We like to think about depression as a "neurochemical or receptor disease," with a disturbance of serotonin or other neurotransmitters at the cause. The successful use of serotonin reuptake inhibitors supports that model. Focal epilepsy is conceptualized as structural disease, originating in a clearly identifiable part of the brain. Removal of the responsible tissue successfully treats the seizures. Imaging and postmortem studies of depressed patients found structural and perfusion changes in hippocampus, the amygdala, the prefrontal and cingulate cortex, as well as deeper brain regions such as the thalamus or nucleus accumbens (7). Those structural abnormalities are certainly not the missing link but confirm that structural and neurochemical changes may go hand in hand. Approaching the problem from the receptor side, 5-HT1A receptors and binding are diminished on PET imaging in epileptic temporal structures (8). This may be a possible link to explain depression in epilepsy. Further along this line, it is not inconceivable that removing those receptors altogether could worsen depression. This may explain why thirteen percent of patients developed de novo

depression after surgery, a rate comparable with other previous reports (4).

It is thought that medial temporal structures play a greater role in depression than lateral temporal cortex (7). Wrench and colleagues did not find that patients with resection of the medial temporal structures were more depressed than patients with resections in the lateral temporal cortex or other resection sides. De novo depression occurred more frequently after removal of the medial temporal structures. Right-sided resections were not more likely to be correlated with depression, in contrast to other reports (9). A clear neuro-anatomical correlation of postoperative depression remains elusive. Depression is certainly a disturbance of neuronal networks, and it may be difficult to correlate single anatomical structures to the entire spectrum of depression.

In most epilepsy surgery centers, it has been observed that postoperatively patients can be psychologically and psychiatrically quite labile, even if they are seizure free. It is thought that the "burden of normality" is a result of psychosocial maladjustment after elimination of a chronic illness (10). The authors show that patients with higher burden of normality are more depressed. It is conceivable that the burden of normality is not only caused by psychosocial factors, but is a result of disturbed brain physiology or emotional functioning.

The study raises more questions than it answers, not to the fault of the authors who conducted the study well. Do we need to counsel patients about de novo postoperative depression? Should we send all of our patients to psychiatrists after surgery? Should patients after surgery be treated with selective serotonin reuptake inhibitors? What is the best way to measure depression? Would a pure medial temporal resection such as a selective amygdalo-hippocampectomy lead to a better psychiatric outcome than a standard temporal resection, including the temporal neocortex or vice versa? How much of the burden of normality is neurobiologic and how much is psychosocial? Do patients with medial temporal lobe resections without epilepsy have a higher incidence of postoperative depression? Are the seizures or the underlying pathology the culprit for depression? The first step certainly remains to turn our attention to depression away from mere seizure freedom and carefully screen our patients. Above that, there is certainly lots of opportunity to chart out more of the unknown territory.

by Barbara C. Jobst, MD

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___ One of the coauthors (Rod Scott) has since then joined one of basic science research labs at Dartmouth on sabbatical, however he is not involved in clinical care. The study above had absolutely no relationship to research

performed at Dartmouth.

Thank you for your assistance.
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