The observation that mood disorders and epilepsy often go hand in hand is certainly not new. Indeed, the reported prevalence of depression in patients with epilepsy has been reported to range between 12 and 40 percent in various patient populations and settings. One recent meta-analysis suggested an overall prevalence of active depression of about 24% (1). Left inadequately treated, depression may not only contribute to decreased quality of life but may also contribute to increased healthcare costs and decreased economic productivity (2). In patients with temporal lobe epilepsy (TLE) who have pharmacologically refractory seizures, depression may be even more common and severe. Despite common misperceptions, this apparent relationship is likely bidirectional. Not only are patients with epilepsy at increased risk of developing depression, but patients with psychiatric comorbidities are at substantially greater risk of developing epilepsy (3). Given this relationship, is it truly appropriate to consider mood and seizure disorders as simply comorbidities? The answer to that question will require an understanding of the neurobiological associations between the two disorders.

While much progress has been made in both highlighting the importance and clinical identification of this common, debilitating comorbidity in our patients, our understanding of its neurobiological underpinnings is still rather unclear. While the biochemical causes of depression in patients with epilepsy are most certainly multifactorial (4, 5), the role of serotonin dysregulation and epilepsy has become an increasingly interesting story. Serotonin neurotransmission is important in modulating cortical excitatory and inhibitory balance in the brain. Both animal models and limited clinical experience suggest that reduced serotonergic tone is associated with seizure genesis and exacerbation (6) and that enhanced serotonergic activity may have anticonvulsant effects (7, 8).

Previous work using PET has demonstrated reductions in binding of serotonin (5-HT1A) in mesial temporal structures in patients with TLE (9), and that patients with TLE who are not depressed (10, 11). Taken together, experimental data and studies in patients clearly demonstrate impaired 5-HT binding in patients with epilepsy. Alterations in 5-HT1A receptor density is only one part of the story. The serotonin transporter (5-HTT) is the key regulator in serotonergic transmission and is primarily responsible for 5-HT inactivation via selective reuptake. Studies have suggested a possible role for genetic polymorphisms of this transporter in patients with TLE (12), with some data hinting that greater 5-HTT activity, leading to reduced synaptic 5-HT, might be associated with poorer response to antiepileptic drugs in patients with TLE (13).

Now, in a report by Martinez and colleagues, 13 patients with TLE were compared with 29 healthy volunteers who...
had never met criteria for a major psychiatric disorder. Of the patients, four had a history of major depression, with two of these individuals reporting symptoms of depression at the time of study. Using PET, 5-HTT and 5-HT\textsubscript{1A} binding was assessed in the insula, hippocampus, amygdala, parahippocampal gyrus, fusiform gyrus, and cingulate cortex. In agreement with previous studies, the investigators found that 5-HT\textsubscript{1A} binding was reduced in the limbic areas on the ipsilateral side in patients with TLE, and that 5-HT\textsubscript{1A} asymmetry binding was greater for patients as compared with healthy controls. Overall, 5-HTT-binding differences in patients with TLE, however, were not apparent. Neither sex, nor AED use, nor side of epilepsy focus appeared to affect 5-HTT binding. Of interest, differences in 5-HTT binding were noted in patients with TLE and a history of major depression. In these patients, greater asymmetry in transporter activity was seen in the insular cortex (likely an important neural structure in major depression) (14) and in the fusiform gyrus on the ipsilateral side. Correlations between 5-HT\textsubscript{1A} and 5-HTT asymmetry in the insular cortex were also seen in TLE patients but not healthy controls. These observations suggest several things. First, patients with TLE appear to have subtle alterations in 5-HT neurotransmission as compared with healthy individuals. Those patients with clinical expressions of depression may have a somewhat different neurochemical marker. In the patient with TLE and depression, a compensatory mechanism may exist. Perhaps, in response to markedly reduced 5-HT\textsubscript{1A}-receptor density, uptake, the primary mechanism terminating serotonin activity, is also reduced, allowing for increased synaptic serotonin concentrations.

Clearly, one must be cautious not to overinterpret these findings. Subtle differences in clinical expression of TLE and depressive symptoms may have been obscured by the relatively small sample size. These findings do raise interesting questions. Could it be that in patients with TLE and depression, there is an endogenous mechanism in place to try and increase synaptic serotonin concentrations? If so, clearly this compensatory mechanism is not entirely sufficient in all patients. Of note, in this report, there was a trend (albeit not statistically significant) toward a correlation between higher Beck Depression scores and increased insular 5-HT\textsubscript{1A} asymmetry. Perhaps these neurochemical markers are indicative of either severity of the mood disorder or of differing clinical syndromes in patients with TLE. It is possible therefore that neuroimaging might lend insight as to potential patient subtypes that might benefit from treatment with selective serotonin reuptake inhibitors (SSRIs).

Finally, the observations of Martinez and colleagues also prompts one to ask whether it is entirely appropriate to consider depression simply a comorbid finding in patients with epilepsy. As it is commonly defined, comorbidity refers to the presence of more than one diagnosis occurring at the same time in a given patient. This implies a distinct clinical disorder occurring during the course of the “index” disease. This might be imprecise, if not frankly inaccurate, in this patient population. Given the observed bidirectionality of epilepsy and depression, common neurochemical markers, and perhaps compensatory neurotransmitter adaptations, it is perhaps more correct to view epilepsy and depression as different expressions of a single disorder. Clearly, TLE is a heterogeneous disorder. Perhaps patients with TLE and significant mood disturbance represent a subgroup of patients with a unique neurochemical signature. These observations take us one step closer to understanding the mechanistic underpinnings of this common debilitating “comorbidity” and, perhaps, to designing personalized screening and treatment approaches.

by Barry E. Gidal, PharmD

References


Disclosure of Potential Conflicts of Interest

Instructions
The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.
   Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

2. The work under consideration for publication.
   This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.
   This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. For example, if your article is about testing an epidermal growth factor receptor (DGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

   Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work’s sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

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2. First Name  Barry    Last Name Gidal  Degree PharmD

3. Are you the Main Assigned Author?  ☒ Yes   ☐ No

   If no, enter your name as co-author:

4. Manuscript/Article Title:

5. Journal Issue you are submitting for:  13.6

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Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

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*  This means money that your institution received for your efforts on this study.
** Use this section to provide any needed explanation.
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