

STUDYING EPILEPSY TO UNDERSTAND BIPOLAR DISORDER?

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The modern conceptualization of bipolar disorder goes back to 1854, when Jules Baillarger described to the French Imperial Academy of Medicine, a biphasic mental illness causing mood oscillations between mania and depression that he called "*folie à double forme*" (dual-form insanity) (1). The same year, Jean-Pierre Falret presented a case of what was essentially the same disorder but named "*folie circulaire*" (circular insanity) (2). After that, Emil Kraepelin described the natural course of bipolar patients and coined the term "manic depressive psychosis" (3). The Kraepelinian hierarchical and categorical approach to mental illnesses remained influential for many years and definitely contributed to the theoretical conceptualisation of DSM. Over time, the need for a dimensional approach to psychopathology became evident and clinicians became aware that not only threshold-level manifestations, but also atypical symptoms, behavioural traits and temperamental features had to be taken into account (4). The novelty of the dimensional approach is that psychiatric symptoms may occur throughout the lifetime, sometimes in isolation rather than as part of a temporally circumscribed clinical syndrome. These symptoms are not pathological per se and they don't encompass a categorical diagnosis but rather represent the biological or constitutional core of personality features that refer to reactivity, variability, and intensity of emotional dispositions. However, they obviously impact on the natural course of a specific disease in terms of response to treatment and prognosis. This concept is particularly evident for bipolar symptoms (5). Current categorical systems define a manic episode as characterized by a period of at least one week where an elevated, expansive or unusually irritable mood, as well as notably persistent goal-directed activity is present. However, it is now recognised that DSM criteria do not adequately capture the phenomenological nuances of mania (6) and unrecognized bipolar symptoms represent a common source of treatment resistant depression (7) and suicidality during antidepressant drug treatment (8).

An important point raised by this Targeted Review (9) is that the previous assumption that mood instability was uncommon in epilepsy was wrong. It is now evident that bipolar symptoms are not rare in patients with epilepsy and can be exacerbated in some circumstances. A cross sectional study showed that the irritable temperament is more frequent in epilepsy as compared to healthy controls (10). Although less defined than other temperaments, the irritable one is much closer to the mixed aspects of bipolarity. Mixed symptoms, especially mixed irritability, are often difficult to recognise by non-expert clinicians and one of the key elements is represented by rapid mood changes, hostility and irritability while taking medications other than those prescribed for mood problems or during medical illnesses. Interestingly enough, increased irritability/aggressive behaviour with medications other than those prescribed for mood problems is a well-known phenomenon in epilepsy (11). Thus, there is no doubt that subthreshold bipolar symptoms, in particular mixed-irritability, are present in patients with epilepsy and probably explain most of the psychiatric adverse effects of antiepileptic drugs. In addition, emerging data suggests that mixed irritability is associated with increased hospitalization (12) and high suicide risk in patients with mood disorders (13). It is thus possible that bipolar symptoms may also account for the increased suicidality risk in patients with epilepsy. Further studies on this topic are clearly needed.

What is the natural consequence of this observation? Should we screen patients with epilepsy for bipolar symptoms? As discussed in this Targeted Review current screening instruments are not satisfactory with a clear tendency to overdiagnose but from a clinical perspective, psychiatric reactions to antiepileptic drugs, especially counterpolar ones (i.e. irritability, agitation or psychotic

symptoms with sedative/GABAergic antiepileptic drugs) should represent a red flag for an underlying bipolarity.

The relationship between epilepsy and bipolar disorder raises also the question whether the two disorders are neurobiologically connected and whether neurobiological findings in the epilepsy field can help our understanding of the neurobiology of bipolar disorder and vice versa. In 1976, Robert Post published his seminal paper on kindling on the American Journal of Psychiatry (14) where he eloquently discussed how the repetitive subthreshold stimulation of the limbic system could be eventually associated with spontaneous seizures and behavioural manifestations. After 40 years, his observations are still contemporary and fascinating but there are a number of limitations when the kindling model is translated into practice. Apart from the number of species-specific issues related to the kindling phenomenon per se, it is now clear that animal models of kindling used in the epilepsy field are not satisfactory to predict potential mood stabilizing properties of a specific compound. For example, the amygdala-kindled rat was initially considered a good animal model to test potential anti-manic drugs (15) but it became apparent over time that this is not the case. In fact, compounds like GBP, which shows good results in that animal model (16), failed dramatically in clinical trials of acute mania (17). In this regard, it has to be acknowledged that it is only superficially understood how antiepileptic drugs mediate a mood-stabilizing activity (18). Furthermore, antiepileptic drugs present a clear class effect in terms of preventing seizures but this does not seem to be the case for mood stabilisation. The neurobiology of bipolar disorder is still unknown and most importantly there are no universally accepted animal models (19), limiting the possibility of screening for new therapeutic agents. This Targeted Review discusses possible genetic mechanisms shared by bipolar disorder and epilepsy but much remains unknown regarding the contribution of genetic versus environmental variables in the development of both conditions. Epidemiological studies show that patients with bipolar disorders are at increased risk of unprovoked seizures and epilepsy. In some cases this seems to be due to alcohol abuse or illicit drug use (20), but other studies confirmed an increased risk in bipolar patients even after adjusting for potential confounders (21-22).

Current data clearly suggest a connexion between epilepsy and bipolarity. The nature of such a relationship is still obscure. New insights into the neurobiology of psychiatric manifestations of epilepsy will probably shed light into the neurobiology of mood control and polarity.

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