

OVERLAPPING PHENOMENA OF BIPOLAR DISORDER AND EPILEPSY - A COMMON PHARMACOLOGICAL PATHWAY

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SUMMARY

Background: Studies and data on prevalence, recognition and clinical features of bipolar disorder (BD) in epilepsy remain limited. Still, there is a growing evidence of BD and epilepsy being frequent co-morbid conditions with some features suggesting shared pathophysiological mechanisms that include the episodic course of both conditions, the possible kindling mechanism and the efficacy of some antiepileptic drugs (AEDs) in BD.

Subjects and methods: The aim of this paper is to review concepts of overlapping phenomena of bipolar disorder and epilepsy. A literature review of the theoretical bases of the relationship between BD and epilepsy is presented.

Conclusions: The comorbidity of epilepsy and mood disorders was a subject of interest of many studies for decades. Bipolar disorder and epilepsy have a number of clinical, biochemical and pathophysiological features in common. Bipolar disorder in epilepsy, excluding the ictal or periictal symptoms, can be categorized using standardized measures. Standardized psychiatric interview procedures based on DSM criteria like SCID-I or MINI provide comprehensive way to diagnose mood disorders in patients with epilepsy.

Key words: bipolar disorder – mania – depression – epilepsy - antiepileptic drugs - DSM-IV-TR

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INTRODUCTION

Epilepsy is one of the most common and serious neurological disorders with lifetime prevalence of 2-5% (Hirtz 2007). A number of studies demonstrated that affective disorders represent a frequent psychiatric comorbidity in epilepsy (Lehrner 1999, Barry 2007). The majority of studies focused on depression as it is the most frequent psychiatric comorbidity in people with epilepsy (PWE) with the lifetime prevalence of 11-62% (Barry 2007, Hermann 2000). Data on prevalence, recognition and clinical features of bipolar disorder (BD) in epilepsy remain limited. Nevertheless, there is a growing evidence of bipolar and epilepsy disorders being frequent co-morbid conditions with some features suggesting shared pathophysiological mechanisms that include the episodic course of both conditions, the possible kindling mechanism and the efficacy of some antiepileptic drugs (AEDs) in BD. Moreover, the symptomatology of mood disorders in epilepsy is often atypical, intermittent and pleomorphic with prominent dysphoric but also euphoric mood and has similarities with clinical picture of BD. Due to such a diverse symptomatology it is often difficult to classify mood disorders in PWE according to Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.; DSM-IV-TR; American Psychiatric Association (APA) 2000) categories with symptoms overlapping in particular between unipolar and bipolar spectrum disorders.

Clinical presentation of Bipolar Disorder in Epilepsy

There are two main types of BD depending on the occurrence of manic (type I) or hypomanic (type II)

episodes in addition to major depressive episodes. DSM-IV-TR (APA 2000) featured also mixed episode defined as coexistence of Manic Episode and Major Depressive Episode (except for the duration) nearly every day during at least a week period. According to such strict definition several subthreshold mixed states could not have been properly recognized. The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5; APA 2013) replaced the diagnosis of “mixed episode” with a mixed-features specifier that can be applied to major depressive episodes (both in unipolar and bipolar disorder), hypomania or mania. Mania with a prominent dysphoric mood, marked anxiety, burst of anger was also described in patients with BD. Cyclothymic disorder represent more chronic and less severe clinical form of bipolar disorder with periods of hypomanic symptoms alternating with periods of mild or moderate depression. Lifetime prevalence of bipolar disorder type I is generally estimated at 2% (Soldani 2005). However, including bipolar II type cyclothymic disorder and sub-threshold diagnostic criteria for BD 6.4 % of general population is classified as having bipolar spectrum disorder (Judd 2003).

Limited studies on bipolar disorder in epilepsy exist to date and most of them were based on psychiatric clinical evaluation without using standardized diagnostic instruments for DSM or ICD specified criteria. This probably explains, at least partially, why bipolar disorder used to be reported as a rare diagnosis in epilepsy (Wolf 1982, Alliez 1978).

Recent studies pointed out that manic or hypomanic symptoms are not rare in epilepsy. A large U.S. survey revealed that bipolar symptoms occurred in 12.2 % of community-based epilepsy patients, screened with

Mood Disorders Questionnaire (MDQ) (Ettinger et al. 2005). Symptoms suggesting BD were 1.6 to 2.2 times more common in subjects with epilepsy than with the ones suffering from migraine, asthma, or diabetes mellitus and 6.6 times more common than in the healthy controls. A total of 49.7% of PWE (n=142) compared to 21.2 % with diabetes (n=186) who screened positive for bipolar symptoms were diagnosed with bipolar disorder by a physician (Ettinger 2005). In another study (Mula et al. 2008a) a group consecutive PWE or migraine (M) have been evaluated using the MINI for DSM-IV Axis I disorders (Sheehan et al. 1997). All subjects were also screened with MDQ. Patients with epilepsy were more likely to screen positively at MDQ (PWE=17% vs. M=5.3% p=0.006) and to have a diagnosis of bipolar disorder (PWE=14.5% vs. M=4.5% p=0.013) as compared to migraine patients (Mula 2008a).

Similarities and differences between epilepsy specific mood disorders and BD

Mood disorders in epilepsy have often atypical symptomatology and fail to meet DSM-IV-TR criteria. They can be classified according to the temporal relationship between the onset of psychiatric symptoms and seizure occurrence into ictal, periictal and interictal.

Ictal psychiatric symptoms can occur as a part of the ictus itself. Ictal depression appears to be more common in patients with temporal lobe epilepsy with rates reaching 15% (Williams 1956, Blanchet 1986). The symptoms can range from mild feelings of sadness to profound helplessness and despair, guilty feelings, anhedonia. Ictal laughter has been also reported as a manifestation of gelastic seizures.

Preictal dysphoria could be described as prodromal depressive mood or irritability which may occur hours to days before seizure and is often relieved by the ictus (Williams 1956, Blanchet 1986, Kanner 2000). Preictal instable mood with euphoria and paroxysmal irritability was also observed (Mula 2010).

Postictal symptoms usually last up to 48 hours after ictus with median duration from 6 to 24 hours (Kanner 2001) lasting sometimes up to 2 weeks post ictus (Daly 1958, Mendez 1992, Kanner 2000). Most common symptoms include anhedonia, irritability, poor frustration tolerance, feelings of hopelessness and helplessness, suicidal ideation, feelings of guilt and crying bouts (Kanner 2000). Postictal manic/hypomanic symptoms were also reported (Kanner 2004). The above mentioned symptoms may represent a part of a mixed episode with psychotic features (Boylan 2002, Kanner 2004, Nishida 2006).

The interictal recurrent syndrome of periodic dysphoria is the most common form of mood disorder in epilepsy. Frequently, it does not fulfill any of the DSM-IV-TR criteria and has an atypical clinical presentation of depressive symptoms with paroxysmal irritability but also euphoric mood. It is commonly described as a chronic depression or dysthymic disorder but without fulfilling time criteria for those DSM based diagnoses.

It can also be a part of bipolar disorder spectrum. Blumer (2004) drew attention to these atypical forms of mood disorder in PWE and coined the term interictal dysphoric disorder (IDD). Long time before Blumer similar clinical observations were made by Kraepelin (1923) who provided the similar clinical description of such form of mood disturbances in epilepsy. IDD is characterized by a constellation of eight symptoms and requires the presence of three of the following: depressive mood, anergia, pain, paroxysmal irritability, euphoric moods, fear/anxiety and insomnia. IDD is typically of short duration and symptoms occur at various intervals and tend to last from hours to two or three days (Blumer 2004). Unfortunately, there is only limited comparative data evaluating this form of mood disorder in epilepsy using standardized DSM based diagnostic techniques with IDD criteria.

Recently Mula et al. (2008b) examined a group of 143 adult outpatients with epilepsy and revealed that 11.8% had the DSM-IV-TR based diagnosis of bipolar disorder but only 1.4% of whom could be considered as having “pure” Bipolar Disorder. He concluded that in all other cases BD symptoms were more likely related to epilepsy related mood disorders (IDD, postictal manic or hypomanic states, and preictal dysphoria). It was suggested that IDD with its specific features and labile-angry-irritable states may represent more unstable form of bipolar spectrum disorders (Mula 2008b, Mula 2010). IDD could be a form of cyclothimic disorder that sometimes exacerbate and meets criteria of Major Depression episode. Mula speculated that there is enough evidence further suggesting that IDD may be closer to bipolar rather than unipolar mood disorders (Mula 2008b).

Similarities in mode of action of AEDs in BD and epilepsy

There is a considerable overlap in the pharmacological agents used in epilepsy and BD. A number of AEDs are effective in acute treatment of manic episode as well as bipolar depression. They are also used in long-term prophylaxis treatment in BD (APA 2002, Goodwin 2003). The mechanism of action of AEDs both in BD and epilepsy is still not fully understood. The delayed clinical response of AEDs in BD in comparison to epilepsy suggests that the underlying mechanisms may be distinct from those that are relevant to epilepsy (Rogawski 2004). AEDs exhibit more than one mechanism of action each of which may be responsible for efficacy in different types of epilepsy as well as in a different phases of BD treatment (Perucca 2005). Nevertheless, due to limited and obscure knowledge on pharmacology and pathophysiology of both conditions choosing the right treatment is often based on clinical observations of efficacy rather than based on the mechanisms of action of AEDs. Most important AEDs that are approved in treatment of both epilepsy and BD are: valproic acid (VPA), carbamazepine (CBZ) and

lamotrigine (LTG). The main targets for AEDs in the synapses include enhancement of GABAergic inhibitory neurotransmission, decrease in glutamatergic excitatory neurotransmission directly or via inhibition of voltage-dependent sodium and calcium channels, and interference with intracellular signaling pathways (Landmark 2007).

Some of AEDs share pharmacological modes of action with lithium which is the golden standard in the treatment of different phases of BD (Williams 2002). Probably the most important mechanism underlying the mood-stabilizing action of lithium is depletion of inositol by inhibition of the enzymatic breakdown of inositol phosphates to free inositol (Berridge 1989). The resulting reduction of free intracellular inositol slows the recycling of inositol-containing metabolites required for signal transduction leading to stabilization of the structural integrity of neurons and enhancement of synaptic plasticity (Lenox 2003, Rogawski 2004). The mood-stabilizing action of valproate and carbamazepine was also linked to inositol depletion (Berridge 1989, Vaden 2001, Rogawski 2004)

Valproic acid (VLA) is a broad-spectrum AED and is effective in all seizure types as well as in BD. The drug enhances GABAergic neurotransmission and decreases neuronal excitability increasing GABA synthesis and inhibition of GABA metabolism (Löscher 2002). This mechanism could be of importance in acute treatment of status epilepticus and mania (Landmark 2007). In addition, valproate is involved in the modulation of intracellular signaling pathways. The effects on intracellular proteins are regarded as important for the understanding of the pathophysiology of BD as well as the efficacy of valproate in BD. Intracellular targets include modulation of inositol metabolism, kinases such as ERK and MARCK, glycogen synthase-3, protein kinase C, and early inducible genes (Brunello 2003).

The main mode of action of carbamazepine (CBZ) and lamotrigine (LTG) is blockade of voltage-dependent sodium channels resulting in increased inhibition of action-potential firing activity and excitatory glutamatergic neurotransmission (Landmark 2007). In addition, carbamazepine, as in the case of valproate, modulates intracellular signaling pathways (Rogawski 2004). Lamotrigine also dose-dependently decreases extracellular serotonin and dopamine in rats, which could explain its effectiveness in preventing depression relapse in bipolar disorder (Ketter 2003, Landmark 2007).

Electroconvulsive therapy, antidepressants and seizures

The increased interest in the interconnection between mental disorders and epileptic seizures contributed also to the discovery of electroconvulsive therapy (ECT). Pioneers of ECT, Meduna and Cerletti, assumed the mechanism of action of shock therapy based on observations of the time relationship between mental illness and epilepsy (Zyss 2009). The concept of thera-

peutic effect of ECT in the treatment of mental disorders was based on opinion prevailing at that time that there is some kind of antagonism between epilepsy and psychiatric disorders. This was due to the results of epidemiological studies available at that time which indicated that depression rarely coexists with epilepsy. Current research led to different observations. Patients with epilepsy often suffer from depression and in patients with depression epileptic seizures are also not uncommon as it was once thought (Zyss 2009). Nevertheless, ECT has proven to be very efficacious treatment in drug resistant schizophrenia, unipolar depression and also in both depressive and maniac episodes in BD (Fink 2000, Jobe 2003).

PWE experience more frequent psychiatric symptoms when there is an increase in seizure frequency (Jobe 2003). Therefore first step in treating mood disorders in PWE is to optimize AEDs treatment in order to decrease seizure frequency which could improve psychiatric symptoms as well.

These facts seem to suggest that there is some kind of linkage between affective disorders and seizures. It is also known that some of antidepressant drugs (ADDs) can provoke seizure. The proconvulsive risk is dose dependent and the risk of inducing seizures is relatively low in newer antidepressants. On the other hand the antidepressants monoamine oxidase inhibitors and norepinephrine (NE) and serotonin (5-HT) reuptake inhibitors can produce anticonvulsant effects in some humans with epilepsy (Dailey 1996, Jobe 2003).

Episodic nature of BD and Epilepsy. Kindling model

Bipolar disorder and epilepsy both have chronic, episodic course, often with mounting disability and drug resistance if untreated. Unipolar depression may evolve to bipolar disorder (Fiedorowicz 2011) and more mood episodes may lead to more chronic course of illness whilst in epilepsy each epileptic event may increase the risk of future seizures. Those observations led to proposed kindling model as a common mechanism of pathogenesis of both disorders. The kindling phenomenon was discovered in epilepsy by Graham Goddard in 1967 and is commonly used as a model for the development of seizures in epilepsy (Goddard 1969, Bertram 2007). Repetitive subthreshold stimulation induces seizures until seizures occur spontaneously without any stimuli. This could also apply to pathophysiology of bipolar disorder. It was postulated that in BD life events trigger affective episodes but finally relapse occurs in the absence of any obvious stress factor. Also, each new mood episode contributes to the progression of the mood disorder in similar manner as in epilepsy (Post 1996). Those hypotheses were stated partly on the observation that some of antiepileptic drugs (AEDs) having anti-kindling properties (Post 1982, Löscher 1989, O'Donnell 1991) and are broadly used in BD due to their mood-stabilizing properties (APA 2002, Goodwin 2003).

CONCLUSION

The comorbidity of epilepsy and mood disorders was a subject of interest of many studies for decades. Although the data on prevalence of bipolar disorder in epilepsy is still limited there is a growing evidence of bipolar and epilepsy disorders being frequent co-morbid conditions. Bipolar disorder and epilepsy have a number of clinical, biochemical and pathophysiological features in common. Bipolar disorder in epilepsy, excluding the ictal or periictal symptoms can be categorized using standardized measures. Standardized psychiatric interview procedures based on DSM criteria like SCID-I or MINI provide comprehensive way to diagnose mood disorders in patients with epilepsy.

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