EXPERT REVIEWS

Epilepsy and bipolar disorders

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Although mood disorders represent a frequent psychiatric comorbidity among patients with epilepsy, data regarding bipolar disorders are still limited. However, these two conditions apparently share a number of biochemical and pathophysiological underpinnings, such as the kindling phenomenon, changes in neurotransmitters and modifications in voltage-opened ion channels and second messenger systems. Moreover, epilepsy and bipolar disorders are both episodic conditions with a time course of illness that can become chronic. Recent data suggest that mood instability is actually frequent among patients with epilepsy but is phenomenologically different from that described in bipolar disorder. The present paper reviews available evidence regarding such an intriguing comorbidity in order to discuss valuable clinical issues and to suggest novel therapeutic strategies.

KEYWORDS: antidepressants • antiepllepticlcs • antipsychotics - bipolar disorder • depression • epilepsy • lithium • mania' seizure \

The relationship between epilepsy and mood disorders has a long story. Around 400 B.C., the Greek physician Hippocrates observed that "melancholies ordinarily become epileptics, and epileptics, melancholies: what determines the preference is the direction the malady takes; if it bears upon the body, epilepsy, if upon the intelligence, melancholy" [1,2]. Nowadays, it seems well established that reasons for such a close link are both biological and psychosocial [3]. Epilepsy is a chronic disorder and, as such, it brings about social discrimination leading to demoralization, poor self-esteem and a negative perspective towards life. However, a number of authors have pointed out the biological contribution to this association given by neuro- anatomical and neurochemical principles, such as the involvement of the temporal lobes [4] and the psychotropic effects of antiepileptic drugs (AEDs) [5].

In contrast to the associations with depression, bipolar disorders or overt mania in epilepsy were always considered to be much less common, and indeed, classic bipolar disorder was considered to be rare [6]. Such statements were usually made prior to the use of standardized diagnostic manuals, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) PI, and were also based upon clinical impression rather than a structured assessment of psychopathology. A US survey demonstrated bipolar symptoms to be present in 12.2% of epilepsy patients, which was twice as common as in people with asthma, and seven times as common as in the healthy comparison group [8], A European study reported very similar prevalence rates in a selected population of patients recruited in tertiary referral centers [9], These data have raised some doubts about the previous suggestions that bipolar disorder was rare in people with epilepsy, and have also raised doubts as to our knowledge of the association between these two disorders.

Theoretically, epilepsy and bipolar disorders have many similarities, including the episodic course of the illness, the possible pathogenetic mechanism of kindling and the efficacy of some AEDs in the treatment of both conditions [10]. All these observations suggest a common underlying pathophysiology or, better, a close link between the neurobiology of seizures and that of mood polarity. However, there is still a lack of convincing scientific evidence supporting such a relationship, with most of the evidence being largely based on historical works and theoretical considerations.

The present paper is aimed at reviewing and discussing the biological links and clinically relevant aspects of such an association, identifying the main variables complicating the management of patients with epilepsy and mood disorders.

Bipolar disorders

Bipolar disorders represent serious psychiatric conditions defined recurrent episodes of significant disturbance in mood. These ..sturbances can occur on a spectrum that ranges from debilitating depression to unbridled mania, resulting in damaged relationships, poor job or school performance, and even suicide, Bipolar disorder typically develops in late adolescence or early adulthood; however, it is often not recognized, and people may suffer for years before it is properly diagnosed and treated. It has been estimated that approximately 5.7 million adult Americans or approximately 2,6% of the population aged 18 years or older, in any given year, have bipolar disorder [11,12]. Individuals suffering from this condition typically experience fluid states of mania, hypomania or what is referred to as a mixed episode in conjunction with depressive episodes. These clinical periods typically alternate with a normal range of mood.

The contemporary psychiatric conceptualization of the manic-depressive illness can be traced back to the 1850s. In 1854, Baillarger described to the French Imperial Academy of Medicine a biphasic mental illness causing recurrent oscillations between mania and depression [13]. The same year, Falret presented a case description on what was essentially the same disorder. This illness was designated 'folie circulaire' (circular insanity) by Falret, and 'folie k double forme' (dual-form insanity) by Baillarger [14]. The German psychiatrist Kraepelin categorized and studied the natural course of untreated bipolar patients and coined the term 'manic-depressive psychosis'. He noted that intervals of acute illness, manic or depressive in nature, were generally punctuated by relatively symptom-free intervals in which the patient was able to function normally. In 1968, both the newly revised classification systems, International Statistical Classification of Diseases and Related Health Problems (ICD)-8 and DSM-II termed the condition 'manic-depressive illness'.

Bipolar disorder is commonly categorized as either bipolar type I, where an individual experiences full-blown mania, or bipolar type II, in which the hypomanic 'heights' do not go to the extremes of mania (TABLE L). The latter form is much more difficult to diagnose, since the hypomanic episodes may simply appear as a period of successful high productivity and is reported less frequently than distressing depression. Psychotic symptoms may occur, particularly in manic periods. There is no consensus as to how many 'types' of bipolar disorder exist. Many people with bipolar disorder experience severe anxiety and are very irritable (to the point of rage) when in a manic state, while others are euphoric and grandiose [15]. Due to the great variability in the severity and nature of bipolar symptoms, the concept of a bipolar spectrum is often employed, which includes cyclothymia. According to Diagnostic and Statistical Manual, Fourth Edition (Text Revision), there are currently four types of bipolar illness: bipolar I, bipolar II, cyclothymia, and bipolar disorder not otherwise specified (NOS). For a diagnosis of bipolar I disorder there requires one or more manic or mixed episodes. A depressive episode is not required for the diagnosis of bipolar I disorder but it usually occurs. Bipolar II, which can be seen more frequently, is usually characterized by at least one episode of hypomania and at least one episode of depression. A diagnosis of cyclothymic disorder requires the presence of numerous hypomanic episodes, intermingled with depressive episodes that do not meet the full criteria for major depressive episodes. The main idea here is that there is a low-grade cycling of mood that appears to the observer as a personality trait, but interferes with functioning. If an individual clearly seems to be suffering from some type of bipolar disorder but does not meet the criteria for one of the subtypes above, the patient receives a diagnosis of bipolar disorder NOS [7).

Common links between epilepsy & bipolar disorders

Epilepsy and bipolar disorders are both episodic conditions with a time course of illness that can become chronic. Approximately 30% of patients with epilepsy are drug refractory [16) and 40% of bipolar patients do not respond adequately to lithium or alternative treatments [17]. Moreover, without treatment, the rate of episodes in bipolar disorders increases and the symptom-free intervals become shorter [is], a progression of the disease very similar to that discussed for epilepsy [16], Both disorders respond to AEDs and seem to share a number of biochemical and pathophysiological underpinnings such as the kindling phenomenon,

Table 1. Classification of mood disorders according to the Diagnostic and Statistical Manual of Mental Disorders and the International Statistical Classification of Diseases and Related Health Problems.

ICD-10	DSM-IV-TR
Unipolar depressive disorders	
Depressive episode	Major depressive episode
Other depressive episodes	
Recurrent depressive disorders	Major recurrent depressive disorder
Permanent mood disorders Cyclothymia Dysthymia	Dysthymic disorder
Other mood disorders	Depressive disorders not otherwise specified
Bipolar disorders	
Manic episode Hypomania Mania Mania with psychosis	Hypomanic episode Manic episode
Bipolar affective disorder	Bipolar type I and bipolar type II disorders Bipolar disorder not otherwise specified Cyclothymia

DSM: Diagnostic and Statistical Manual of Mental Disorders; ICD: International Statistical Classification of Diseases and Related Health Problems.

changes in neurotransmitters (i.e., GABA, excitatory aminoacids, dopamine and serotonin), modifications in voltage-opened ion channels (i.e., sodium, calcium and potassium) and changes in second messenger systems (i.e., G-proteins, phosphatidylinositol, protein kinase C, myristoylated alanine-rich C kinase substrate and [MARCKS]) [19,20].

The kindling model

The kindling paradigm, especially of the amygdala, has been invoked as a model for understanding epileptogenesis and has also been applied to the episodic nature of bipolar disorders. Such a model was first described by Goddard and colleagues [21], Repetitive stimulation with subthreshold stimuli induces seizures until seizures occur spontaneously [22]. The kindling phenomenon is accompanied by long-lasting, and possibly permanent, functional and structural changes in the brain and can be modified by pharmacological intervention. Many widely used anticonvulsants, such as phenytoin, carbamazepine, lamotrigine and oxcar- bazepine, have shown to be highly effective in blocking complete kindled seizures [23,24] and, interestingly, they also showed potent mood-stabilizing properties. Starting from the kindling paradigm, Post and Weiss have theorized a process of sensitization that may possess temporal similarities to the episodic behavioral disturbances of bipolar disorders [25]. According to their view, in a genetically predisposed individual, ccrtain types of stressors, repetitively experienced in a vulnerable period and environment, may lead to mood symptoms of increasing intensity and duration until a full-blown depressive or manic episode occurs. In addition, it is postulated that every new episode leaves a trace and thus contributes to the vulnerability of the individual, a mechanism that has been referred to as 'episodic sensitization' [26],

Neuro transmitters

Information about shared changes in neurotransmitters in both epilepsy and bipolar disorders are still limited. However, it is interesting to note that in both conditions dopamine and serotonin follow a bimodal regulatory model. Good evidence exists that mania could be related to a hyperdopaminergic function [13,19] but it is becoming evident that a serotonergic hypofunction is also involved [27], On the other hand, serotonin and dopamine seem to be important for epilepsy in which D2 receptor blockade and high serotonin concentrations, due to 5-HT1A receptor blockade, exhibit proconvulsive properties and may aggravate seizures [28], Another neurochemical imbalance typically described as a relevant pathogenetic mechanism in epilepsy is that between GABA and glutamate. A GABAergic mechanism for bipolar disorders has been suggested for many years [2[1];]. Neurochemical autopsy studies have reported decreases in reelin in patients with schizophrenia and bipolar disorders in both the prefrontal cortex and hippocampus [30]. Reelin is an important compound in brain development and is secreted from one type of GABAergic interneurons onto the postsynaptic density of cortical and hip- pocampal pyramidal cells [31]. Decreased inhibition of pyramidal cell firing by GABAergic interneurons could lead to excitotoxic- ity or apoptosis, which could be a mechanism of the cell loss found in schizophrenia and bipolar disorder [20]. Glutamate is the main excitatory transmitter and has been shown to important in epileptogenesis but it is probably also involved in stress-related neurotoxicity [20]. It is thus possible to speculate that the imbalance between GABA-mediated inhibition and glutamate-related excitation plays a similar role in epilepsy and bipolar disorders.

Ion *channels*

As for ion channels, an excess of the inward sodium current correlates with neuronal hyperexcitability and may make patients more prone to seizures. Besides, calcium influx appears to be the underlying etiology of giant epileptic potentials [32]. Interestingly, such an increased intracellular calcium concentration has been noted in both acute mania and bipolar disorders [33]. All major AEDs that are also mood stabilizers, such as carbamazepine, lamotrigine, valproate and phenytoin, are known to inhibit sodium and calcium currents. Moreover, clinical research has indicated that patients with bipolar disorders receiving regular treatment with mood stabilizers have not only fewer episodes but also a lesser degree of lasting disabilities, such as cognitive impairment [20].

In this section of the paper we have briefly pointed out the potential presence of neurochemical underpinnings between epilepsy and bipolar disorders. Such a hypothesis is intriguing but further research is required for a better understanding of the similarities between these two conditions and more studies are clearly warranted to find out which mechanisms are really decisive for the treatment of both illnesses.

The interictal dysphoric disorder & bipolar depression

Kraepelin [34], followed by Bleuler [35], were the first to describe the 'periodic dysphoria' of patients with epilepsy. Such a condition was characterized by a pleomorphic pattern of symptoms, including affective symptoms with prominent irritability intermixed with euphoric moods, outbursts of aggressive behavior and anxiety. Gastaut [36] confirmed such observations and, subsequently, Blumer coined the term interictal dysphoric disorder (IDD) [37] to identify a condition characterized by eight key symptoms grouped in three major categories: labile depressive symptoms (anergia, depressive mood, insomnia and pain), labile affective symptoms (anxiety and fear), and supposedly specific symptoms (euphoric moods and paroxysmal irritability) (TABLE2), Blumer used the term 'dysphoria' to more accurately translate the original definition by Kraepelin 'Verstimmungszustand', to stress the periodicity of mood changes and to emphasize the presence of irritability, outbursts of aggressive behavior and euphoric moods as specific symptoms, The dysphoric episodes are described as occurring without external triggers, without clouding of consciousness, as very short lasting (from a few hours up to two days) and as characterized by a sudden onset and an equally sudden ending.

The theoretical framework suggested by Blumer goes beyond IDD as a mood disorder *per se.* According to his view, affective symptoms in epilepsy exist along a continuum, from a dysphoric disorder with fleeting symptoms, to a more severe disorder with transient psychotic features, to an even more debilitating disorder with prolonged psychotic states. This scenario is deeply

influenced by classic German psychiatry, especially Kraepelin's view of the relationship between manic-depressive illness and schizophrenia [34].

Himmeloch [38], and subsequently Kanner [39], highlighted the chronic course of this state of moderate neurotic depression with symptom-free intervals typical of epilepsy, referring to a dimension very close to dysthymia. In our opinion, some features of IDD, especially the co-occurrence of mood instability and irritability, belong to the bipolar spectrum rather than to unipolar depression [40-41], Recently, we investigated the psychopathological features of IDD using standardized clinical instruments for manic and depressive symptoms and we observed that the Mood Disorder Questionnaire was morespedfic for the diagnosis of IDD (86.0%) when compared with Beck Depression Inventory (65.9%), further confirming the close relationship between IDD and the bipolar spectrum. In fact, the Mood Disorder Questionnaire is highly sensitive and specific for manic symptoms [42]. Furthermore, from a clinical point of view, IDD patients have several features in common with a specific subset of cyclothymic subjects in whom depressive periods and labile-angry-irritable moods dominate the clinical picture, representing the more unstable form of bipolar II disorder [43]. In this regard, it is interesting to note that Blumer himself reported that patients with IDD benefitted from a combined therapy of AEDs and antidepressant drugs [44], a combination extensively used to treat bipolar depression.

In another study from our group, we looked at the prevalence and clinical features of manic symptoms and bipolar disorder diagnoses in patients with epilepsy, observing that, although they are highly present (from 12 to 14%), in a large proportion of cases these symptoms are related to phenotype copies of bipolar disorder, such as IDD [45]. In fact, the prevalence of a true manic depressive illness in epilepsy patients was shown to be in line with that reported in the general population (~2%) [46].

The features of IDD overlap with a variety of affective disorders seen in clinical psychiatric practice and the condition needs to be further elucidated in terms of semeiology and clinical description. However, all these evidences taken together suggest that IDD relevantly contributes to the observation of mood instability in patients with epilepsy.

Do peri-ictal symptoms account for bipolar symptoms in epilepsy?

Psychiatric symptoms that are intimately related to the occurrence of seizures are referred to as peri-ictal symptoms and are obviously unique to patients with epilepsy [47]. These include symptoms preceding (pre-ictal) or following (post-ictal) the seizure or occurring as an expression of the seizure activity (ictal). The practicality of classifying behavioral symptoms according to their temporal relation to seizure occurrence has been recognized for a long time.

Peri-ictal psychiatric symptoms usually consist of a cluster of symptoms of short duration ranging from a few minutes up to 3 days, although post-ictal psychotic episodes can at times last up to 4 weeks, and they are usually the expression of the underlying epileptic activity both directly, as simple partial seizures (auras), and indirectly. It is reasonable to assume that peri-ictal *symptoms* may account for the clinical differences of psychiatric disorders between patients with and without epilepsy [48].

Blanchet and Frommer [49], investigated the presence of pre- ictal psychiatric symptoms in 27 consecutive patients who were asked to rate their mood on a daily basis for a period of 1 month. Rating scales identified the presence of dysphoric symptoms, consisting of irritability and mood changes, starting approximately 3 days before the seizures. These symptoms worsened in severity closer to the time of the seizure and remitted approximately 1 day after the seizure, although in some cases the symptoms persisted for up to 3 days after the seizure. A recently published study pointed out that behavioral changes are the most frequently reported pre-ictal symptoms, being characterized by irritability, decreased tolerance and lasting several hours [so],

Post-ictal symptoms may begin either immediately after the seizure (in the immediate post-ictal period) or, more characteristically, from 12 to 120 h after a seizure. Itwas accepted that in the context of the post-ictal state, patients could develop a psychosis, the features ofwhich were often manic or hypomanic, although more generally the presentation was one of a mixed mood episode with psychotic features. Original descriptions date back to Esquirol, Jackson and Gowers [51,52], A case series in a monitoring unit, specifically investigating post-ictal symptoms, described manic/hypomanic symptoms in 22% of patients, often with associated psychotic phenomenology [53]. It seems that post-ictal mania has a distinct position among the psychiatric manifestations observed in the postictal period. In fact, such manic episodes last for a longer period, have a higher frequency of recurrence than post-ictal psychoses, are associated with an older age at onset, EEG frontal discharges and nondominant hemisphere involvement [54], Literature about psychoses of epilepsy point out that post-ictal psychosis may represent a risk factor for the development of an inter-ictal schizophrenia-like chronic psychotic disorder [55]. Therefore, it is possible to speculate that post-ictal mania may represent a negative prognostic factor for the development of a chronic condition and, because of this, it should be promptly recognized and treated. However, data regarding the prognostic value of post-ictal mania are scant, and further studies are needed to elucidate the relationships between mood disorders and peri-ictal mood symptoms.

Finally, the forced normalization phenomenon is another important issue that needs to be taken into account when considering peri-ictal psychiatric symptoms. As Landolt himself pointed out, there is no specific clinical presentation of this phenomenon [56]. Of ***44*** clinical episodes of forced normalization described by Wolf, the commonest syndrome was psychosis but in nine cases prepsychotic dysphoria was described, characterized by insomnia, restlessness, anxiety and social withdrawal; in other two cases a dysphoric episode occurred and a true manic episode was also described in two patients [57], Wolf made the point that the symptomatology was often determined by the personality structure, previous psychiatric history or familial predisposition.

In conclusion, peri-ictal manic symptoms may occur among patients with epilepsy and such cases need to be recognized in order to operate a correct differential diagnosis with true

psychopathology. The failure in identifying such conditions has several practical implications because seizure control represents the best therapeutic strategy for peri-ictal psychiatric symptoms and psychotropic drugs (e.g., neuroleptics or benzodiazepines) should be prescribed temporarily to avoid self injuries or damages.

Role of AEDs

Since their introduction into the clinical management of epilepsy, all AEDs have been tried as psychotropic agents in a number of psychiatric disorders [58]. Nowadays, AEDs are extensively used in psychiatric practice for a broad spectrum of conditions, especially bipolar disorders.

The favorable psychotropic effect of carbamazepine on mood is well known [59]. Over time, several controlled studies have been carried out comparing the effects of carbamazepine in acute mania with placebo, lithium or neuroleptics [60], These studies have shown that carbamazepine seems to be equivalent to lithium in many cases, and that the time course of the antimanic effect is a little slower than with neuroleptics but equivalent to lithium [61]. This is relevant for those patients who are refractory to lithium and require an alternative. Carbamazepine has also shown to be an effective treatment for the prophylaxis of bipolar disorders, controlled studies suggesting that patients with an unstable bipolar disorder with rapid fluctuations (rapid cyclers) do better on carbamazepine or a combination of carbamazepine and lithium [62,63],

Valproate has been used in manic episodes, depressive episodes and for the maintenance treatment of bipolar disorder; the strongest supporting evidence is for acute mania [61-63]. There is possibly an effect in behavioral problems associated with affective liability, aggression, and impulsivity across a range of different clinical contexts, but controlled studies are at present available mainly for bipolar depression [64].

During clinical trials in the development of lamotrigine as an AED, it was observed that the drug had antidepressant properties. The cumulative results of the studies so far provide evidence that lamotrigine is effective in the management of the depressed phase of bipolar disorder type II and in the long-term stabilization of mood in patients with rapid cycling bipolar disorder [62,63].

Among new AEDs, some of them have failed to show any efficacy in primary psychiatric disorders (i.e. tiagabine, felbamate and vigabatrin) while others (topiramate) might have adjunctive uses, such as weight loss in the management of weight gain as a side effect of atypical antipsychotics or in comorbid eating disorders [65], Data about oxcarbazepine are limited and definitely less conclusive than those regarding carbamazepine. However, oxcarbazepine seems to be less effective than lithium but as effective as carbamazepine in acute mania, with probably a better tolerability profile than carbamazepine. The lack of efficacy of gabapentin in bipolar disorders has emerged from controlled studies that failed to show any effect on the acute or maintenance phase [61], Pregabalin is one of the newly introduced AEDs and evidence from controlled studies has indicated it may possess interesting antianxiety properties [66].

Table 2. Major symptom categories of the interictal dysphoric disorder of epilepsy as defined by Blumer.

Labile depressive symptoms	Labile affective symptoms	Specific symptoms
Anergia	Anxiety	Euphoric moods
Depressed mood	Fear	Paroxysmal irritability
Insomnia		
Pain		

Data from [37].

It is difficult to extrapolate data from studies in psychiatric patients directly to patients with epilepsy. It would clearly be very useful to know whether AEDs have a positive influence on the mental state of patients with epilepsy beyond their influence on seizure activity. However, there is little scientific evidence for this; most of the studies are uncontrolled and are based on quality of life parameters rather than on a formal psychiatric evaluation. On the contrary, data from the epilepsy literature has shown that, in some cases, AEDs may even have detrimental effects on mood, with the occurrence of depression as a side effect [5]. While information about AEDs induced depression is becoming available, drug-related mania still remains a poorly understood and poorly investigated phenomenon. Organic mania, or better secondary mania, is a clinical syndrome that resembles a manic state but is due to specific factors such as physical illnesses (e.g., hyperthyroidism) or drugs (e.g., L-dopa, decongestants, sympathomimetics and steroids, among others). This concept received little attention in the neuropsychiatric literature because it was thought to be relatively uncommon before the seminal paper by Krauthammer and Klerman [67].

The occurrence of manic/hypomanic symptoms has been described with almost all the AEDs [68], Among the first-generation drugs, barbiturates [69], phenytoin [70] and carbamazepine [71-73], have been associated with the precipitation of manic symptoms. More recently, similar observations have been reported with second-generation drugs such as vigabatrin [74], gabapentin [75], felbamate [76], topiramate [77,78] andzonisamide [79.80]. In this regard, a case of hypomania driven by vagus nerve stimulation is of particular interest [si], because it may suggest that the mechanism underlying the control of seizures could be strictly interlinked with that of the regulation of mood and the control of its polarity.

In patients with epilepsy, AED-related manic symptoms can be classified into three main groups: the first, due to a toxic effect of the drug; the second, in the context of post-ictal psychopathology; and the third, due to the forced normalization phenomenon. The first group resembles the concept of secondary mania, while the other two are completely di fferent entities whose pathophysiology resides in that of the epilepsy itself and are, therefore, unique to patients with epilepsy. In fact, directly AED-induced mania (the first group) represents just the toxic effect of the AED in susceptible patients and may also occur in subjects who take the drug for reasons other than the epilepsy (e.g., pain syndromes, migraine or movement disorders). In this case, drug withdrawal is indicated and a second

Box 1. Arguments for and against a link between epilepsy and bipolar disorder.

For
- Episodic conditions
- Response to some antiepileptic drugs
- Kindling phenomenon
- Changes in voltage-opened channels
- Changes in neurotransmitters (i.e., GABA, excitatory aminoacids, dopamine and serotonine)

Against
- Lack of animal models
- Lack of epidemiological evidence
- Lack of genetic evidence
- Lack of response to some antiepileptic drugs
- Effect of lithium in epilepsy

trial with the same molecule is highly discouraged. On the contrary, post-ictal mania and forced normalization are only indirectly related to the drug and do not depend on the specific mechanism of action of the compound. These episodes may be misleadingly interpreted by epileptologists as a side effect of the anticonvulsant while they are strictly connected to the seizure precipitation or control and must be carefully noted because this differentiation has important implications regarding prognosis and treatment.

In conclusion, AEDs have positive and negative psychotropic properties and the choice of the single drug or combination of drugs should be always tailored on the basis of the mental state of the patient. Manic symptoms represent a rare treatment-emergent adverse effect of AED therapy but may seriously complicate the management of psychiatric disorders in epilepsy.

Treatment of bipolar disorders in epilepsy

Internationally accepted guidelines for the treatment of bipolar disorders in patients with epilepsy based on controlled data are not available. Thus, our knowledge about treatment issues has to rely on information coming from the psychiatric literature. The only published paper specifically addressing this point is a Consensus Statement from the American Epilepsy Society [82].

Acute depressive episode

The depressive phase of a bipolar disorder is treated differently compared to how unipolar depression is treated. The use of an antidepressant drug without a mood-stabilizing agent runs the risk of pushing the patient into the manic phase or changing the appearance of the disorder with the development of a rapid-cycling bipolar disorder (i.e. four or more depressive or manic/hypomanic episodes within a 12-month period). Rapid-cycling disease affects approximately 15% of patients with bipolar disorder and is characterized by a poor response to treatment [83]. For these reasons, guidelines for the treatment of acute depression in bipolar disorder advise against the initial use of antidepressant drugs in favor of the use of a mood stabilizer [84], First-line therapies include FDA-approved agents such as quetiapine, lithium and valproate.

Electroconvulsive therapy (ECT) is not contraindicated in patients with epilepsy; and it is well-tolerated and worth considering in patients with a very severe and treatment-resistant depressive episode [85]. If patients are taking lithium, some authors suggest that it has to be discontinued at least 5 days before ECT because of the risk of prolonged seizures, memory loss and confusion. On the contrary, it has been also recommended to lower lithium plasma levels to below or around 0.4 mmol/1 and AED morning doses should be omitted just before an individual ECT session.

Acute manic episode

Lithium has a significant wealth of literature supporting its utility as an antimanic agent, although it seems to be less effective for symptoms of dysphoria, mixed states or rapid cycling [86], Valproate, carbamazepine and, to a lesser extent, oxcarbazepine all have proven efficacy for the treatment of manic symptoms. Atypical antipsychotics (olanzapine, quetiapine, risperidone, aripiprazole and ziprasidone) are also considered effective anti- manic agents and have less potential, compared with previous generation neuroleptics, to cause tardive dyskinesia and extrapyramidal symptoms [87]. Olanzapine, quetiapine and risperidone have been associated with weight gain and metabolic syndrome, therefore, they are not preferred in combination with valproate. Aripiprazole and ziprasidone seem to have a favorable metabolic profile but akathisia remains an unfavorable side effect [88]. All these agents, being as they are dopamine blockers, may lower the seizure threshold and need to be carefully used in patients with epilepsy.

Use of lithium in patients with epilepsy

The concomitant prescription of lithium carbonate and carbamazepine, although possibly associated with a favorable pharmacodynamic interaction on mood stabilization, may increase lithium toxicity, with a significant modification in many hematological parameters and in thyroid function [89). The opposing effects of carbamazepine and lithium on electrolyte regulation are well known, with the potential occurrence of severe hyponatraemia when lithium alone is stopped [90]. Conversely, the combination of lithium and valproate has a higher tolerability than the coadministration of lithium with carbamazepine [91], This combination may, however, induce additive side effects, such as weight gain, sedation and tremor [92], The combination with lamotrigine seems to be very well tolerated [93], with no significant differences in lithium pharmacokinetic parameters, while there is a single case report of lithium toxicity during cotherapy with topiramate [94] that may be due to the carbonic anhydrase inhibitor activity of the anticonvulsant, leading to a reduced clearance of lithium and, therefore, to toxic lithium plasma levels,

It is well known that lithium may have proconvulsant properties. This is, however, reported for plasma concentrations exceeding 3.0 mEq/1. At therapeutic levels, the effect of lithium on seizure threshold seems to be inconsistent [95,96], Thus, despite the limited available data, it seems reasonable to suggest that lithium can be prescribed in patients with epilepsy when mood-stabilizing

therapy is necessary and alternative agents either fail or are not tolerated. In these situations, vigilant monitoring of lithium blood levels and careful clinical follow-up are warranted. In addition, since it is common practice and guideline advice to augment anti- depressive drugs with lithium (not only in bipolar depression), the potential risk of a lower seizure threshold and/or serotonin syndrome need to be considered.

Maintenance phase

The maintenance treatment phase is based on the administration of a combination of mood-stabilizing agents (i.e. lithium or anticonvulsants) and antipsychotic drugs [97], In the case of lithium-resistant patients, valproate or carbamazepine should be used. Gabapentin and topiramate failed to show superior efficacy to placebo in the maintenance treatment of bipolar disorder [si]. Oxcarbazepine is extensively used in psychiatric practice but controlled data are based on studies with only small sample sizes [97]. Lamotrigine is approved for bipolar disorder maintenance, particularly for preventing depressive episodes. Aside from the risk of serious rash, it is generally well tolerated and appears to be adequate as the only therapy in subjects without a recent history of severe mania; otherwise, combination of lamotrigine with an antimanic agent (i.e., valproate or quetiapine) is indicated [98],

Psychotropic agents & seizure risk

Adverse effects on seizure thresholds should also be considered, but the seizure-inducing properties of antipsychotics and antidepressants at standard doses should not be overestimated. When precautions are taken, the risk of significant seizure aggravation is modest and should not be a reason for withholding therapy in patients who need it. Care should be taken, however, at high dose levels and with rapid dose increments, as well as with drug combinations, particularly of compounds that have the tendency to lower the seizure threshold [99-ioi],

Among the antidepressant drugs, maprotiline and clomipramine at high doses are the only compounds significantly associated with seizure occurrence [loo]. Bupropion in the slow-release formulation was demonstrated to be as safe as other new antidepressants [101]. Clozapine is the most proconvulsant antipsychotic. In fact, the tendency to provoke seizures is less pronounced with agents that have prominent extrapyramidal side effects; however, the seizure-aggravating effect of atypical antipsychotics is usually modest [100,101].

The causes of acute seizure exacerbations during treatment with psychotropic medications are often complex: drugs may only represent one of several subthreshold factors among a cascade of other events, including emotional factors, lack of sleep, and stress. Concomitant rapid withdrawal from benzodiazepines may enhance the risk of seizures.

The concept that psychotropic drugs may be likely to produce convulsions began with tricyclics and the most obvious explanation resides in their effect on serotonin and noradrena- lin neurotransmission [102,103], However, available data on the prevalence and incidence of seizures in humans come *From* psychiatric samples [101], and conclusions from these data do not apply to patients with epilepsy. Moreover, it is not clear whether the risk of seizure expression arises from the seizure liability itself or from a more complex predisposition inherent in the mechanisms of comorbidity between affective disorders and the epilepsies [103].

Expert commentary

The relationships between mood disorders and epilepsy have attracted the attention of scientists and clinicians for decades. Epilepsy and bipolar disorders represent fascinating comorbidities because both conditions respond to AEDs and seem to share a number of biochemical and pathophysiological underpinnings such as the kindling phenomenon, changes in neurotransmitters, modifications in voltage-opened ion channels and changes in second messenger systems. Furthermore, epilepsy and bipolar disorders are both episodic conditions with a time course of the illness that can become chronic and, in some cases, drug refractory. However, there is still a lack of convincing scientific evidence supporting such a relationship, being as it is largely based on historical works and theoretical considerations (Box 1).

Recent data suggest that manic/hypomanic symptoms are frequently observed among patients with epilepsy but, in the majority *of cases,* are related to phenotype copies of bipolar disorders such as the so-called interictal dysphoric disorder, pre- ictal dysphoria, post-ictal mania or hypomania and the forced normalization phenomenon. This point has relevant implications in terms of therapeutic strategies and prognosis. In fact, seizure control represents the best option for seizure-related manic/ hypomanic symptoms, while widely accepted guidelines for the treatment of acute mood episodes in bipolar disorder need to be followed in the case of a true psychiatric comorbidity. Finally, patients and their relatives need to be informed about the possible occurrence of these symptoms in order to limit the possible negative consequences.

Five-year view

It is evident that future research on therapeutic strategies in one condition will influence also the other and *vice versa.* In the next 5 years, a number of AEDs will become widely available and will also obviously be tried in drug-refractory bipolar disorder patients. Studies on neurobiology and genetics of mood instability will also influence research on the neurobiology of epilepsy and *vice versa.* A better understanding of the similarities between these two conditions will clearly influence future knowledge on their pathophysiology, which will be very decisive for the treatment of both illnesses.

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Key issues

- Bipolar symptoms are frequently observed in patients with epilepsy, with prevalence rates of up to 12%.
- In the majority of cases, bipolar symptoms are related to phenotype copies of bipolar disorders such as the so-called interictal dysphoric disorder, peri-ictal psychiatric symptoms (i.e. pre-ictal dysphoria, post-ictal mania or hypomania) and the forced normalization phenomenon.
- Antiepileptic drugs with well-known mood-stabilizing properties (i.e., carbamazepine, oxcarbazepine, valproate and lamotrigine) should be considered for patients with a comorbid bipolar disorder or a diagnosis of interictal dysphoric disorder.
- Electroconvulsive therapy is not contraindicated in patients with epilepsy, and it is well tolerated and worth considering in patients with very severe and treatment-resistant depressive or manic episodes.
- Adverse effects of antidepressant and antipsychotic drugs on seizure thresholds should be considered, but the seizure-inducing properties of such compounds at standard doses should not be overestimated. When precautions are taken, the risk of significant seizure aggravation is modest and should not be a reason for withholding therapy in patients who need it.

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