Chapter 12
Anhedonia and Epilepsy

Marco Mula

Abstract Mood and anxiety disorders represent the most frequent psychiatric comorbidity in patients with epilepsy and reasons for such a close link are both biological and psychosocial. On one hand, epilepsy is a chronic disorder that brings about a number of social limitations (e.g. driving license, job opportunities etc.) and social discriminations leading to demoralization, poor self-esteem and phobic avoidance. On the other hand, the biological contribution to this association is given by neuroanatomical and neurochemical principles such as the involvement of the mesiotemporal structures in temporal lobe epilepsy.

The issue of phenomenology of depression has been matter of debate for a long time. A number of authors pointed out that atypical features characterize depression in epilepsy and such atypical symptoms are poorly captured by conventional classificatory systems such as DSM. In general terms, the psychopathological spectrum of depression in epilepsy is likely to be large. On one hand, it is reasonable to hypothesize that patients with epilepsy can experience forms of mood disorders identical to those of patients without epilepsy. On the other hand, it is equally reasonable to assume that the underlying brain pathology can influence the final phenomenology of mood disorder symptoms making less evident some aspects or emphasizing others. A number of variables may account for such atypical features such as peri-ictal manifestations, the high comorbidity between mood and anxiety disorders (up to 73 %), the underlying neurologic condition and the psychotropic effect of AEDs.

In this chapter, the relationship between epilepsy and mood disorders is discussed with special attention to anhedonia, discussing phenomenology and pathophysiology in the context of epilepsy.

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Abbreviations

AEDs	Antiepileptic drugs
IDD	Interictal dysphoric disorder
DSM	Diagnostic and statistical manual of mental disorders
ICD	International classification of diseases

12.1 Introduction

Epilepsy is one of the most common neurological disorders, affecting about 50 million people around the world [1]. However, it is not a single entity, encompassing many different conditions with many different causes. Nevertheless, all these forms share the same degree of stigmatization and psychosocial burden [2]. In fact, a number of epidemiological studies have pointed out that any epilepsy syndrome, even those relatively uncomplicated, brings a multitude of complications that can be somatic, developmental, cognitive, behavioral and psychiatric [3, 4]. Such complications have a multifactorial origin, being related to the epilepsy itself, to specific characteristics of the individual patient and to the long-term treatment with antiepileptic drugs (AEDs).

Mood disorders represent an example of such a multifactorial and complex relationship [5]. In fact, epilepsy is a chronic disorder that brings about a number of social limitations (e.g. driving license, job opportunities etc.) and discriminations leading to demoralization, poor self-esteem and phobic avoidance. Nevertheless, the biological contribution to the association between epilepsy and depression is given by neuroanatomical and neurochemical principles such as the involvement of the mesiotemporal structures [6] and the psychotropic effect of AEDs [7].

12.2 Epidemiology of Depression in Epilepsy

Community-based studies report prevalence rates for depressive disorders in the region of 20–22 % [8, 9]. In selected samples, such as tertiary referral centers or surgery programs, the prevalence is even higher and raising up to 50 % [10, 11]. Such differences partially reflect the severity of the seizure disorder [12, 13]. However, epidemiological studies point out that the relationship between epilepsy and depression is not necessarily unidirectional, namely that some patients may present a mood disorder before the emergence of the seizure disorder [14].

The bidirectional relationship between epilepsy and depression may be related to a number of variables. Not least, a shared neurobiology that seems to be operant in both conditions [15].

12.3 Phenomenology of Depression in Epilepsy

During the last 20 years, the issue of phenomenology of depression in epilepsy has been matter of debate mainly because it has relevant implications in terms of treatment and prognosis. According to some authors, comorbid mood disorders are often characterized by atypical features, which are poorly reflected by conventional classificatory systems such as DSM and ICD [16–18]. In particular, classic endogenous-type depressive symptoms, such as feelings of guilt, "*Gefühl der Gefühllosigkeit*", and a circadian pattern of symptom severity are rarely reported [19]. However, other studies clearly show that it is possible to apply standardized criteria of DSM in a not negligible proportion of patients [20, 21].

Pre-modern psychiatrists, such as Kraepelin and Bleuler, observed that patients with epilepsy could develop a pleomorphic pattern of depressive symptoms intermixed with euphoric moods, irritability, fear and anxiety as well as anergia, pain and insomnia [22, 23]. This concept has been revitalized during the twentieth century by Blumer [24] who coined the term interictal dysphoric disorder (IDD) to refer to this type of somatoform-depressive disorder claimed as typical of patients with epilepsy. According to Blumer, IDD is characterized by eight key symptoms, grouped in three major categories, namely labile depressive symptoms (depressive mood, anergia, pain, and insomnia), labile affective symptoms (fear, anxiety), and supposedly "specific" symptoms (paroxysmal irritability, and euphoric moods). The latter group, in particular, identifies a peculiar symptom cluster of IDD that is reflected by the term "dysphoria" that mirrors the original definition of Kraepelin "*Verstimmungszustand*", emphasizing the periodicity of mood changes and the presence of outbursts of irritability and aggressive behavior. Such dysphoric episodes are described as occurring without external triggers and without clouding of consciousness, beginning and ending rapidly and recurring fairly regularly in a uniform manner (every few days to every few months and lasting a few hours up to 2 days). Since its introduction, the concept of IDD has been matter of debate. A cross-sectional study conducted in two epilepsy centers in Europe report prevalence rates of 17 % [25], raising up to 27 % [26] and 57 % [27] in selected samples, such as severe seizure disorders and surgery patients.

Notably, the concept of the IDD, theorized by Blumer, goes beyond the mood disorder per se, encompassing a spectrum of conditions which embraces a mood disorder with fleeting symptoms, a more severe syndrome with transient psychotic features till an even more debilitating disorder with prolonged psychotic states. In fact, according to Blumer's view, the schizophrenia-like psychoses of epilepsy [28] can be considered as a severe IDD with prominent psychotic features. Such a hypothesis is clearly influenced by the Kraepelinian view of the relationship between mood disorders and schizophrenia.

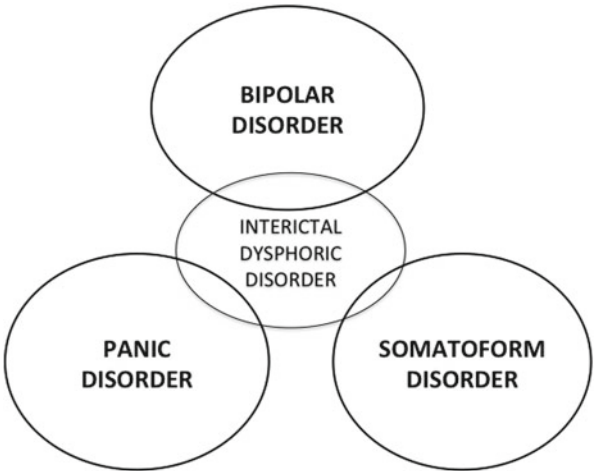

Fig. 12.1 The clinical spectrum of the interictal dysphoric disorder

In general terms, it is reasonable to hypothesize that the IDD observed today might have features different from those described by premodern psychiatry. For example, depressed mood and anergia may be much more evident than before because antiepileptic medications attenuate dysphoria and mood instability. Along these lines, different authors 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 [5, 29]. However, a detailed description of the clinical phenomenology of the IDD, using the operative definition of Blumer, has shown several commonalities with a specific subset of cyclothymic subjects, where depressive periods and labile-angry-irritable moods dominate the clinical picture [25]. This is in keeping with the original observation that patients with IDD benefit from a combined therapy of AEDs and antidepressant drugs [30], a combination extensively used in psychiatry in bipolar depression. Nevertheless, a validation of the concept of IDD against DSM criteria has shown that comorbid anxiety (especially generalized anxiety disorder) [25] and somatoform symptoms [31] represent important elements in the phenomenology of IDD. It is, therefore, evident, that the psychopathological characteristics of this syndrome overlap with a variety of clinical entities seen in clinical psychiatric practice (Fig. 12.1).

Finally, another relevant issue relates to the specificity of IDD with epilepsy. According to Blumer, IDD represents the most frequently seen comorbidity among patients with seizure disorders, being unique for this neurological condition [30]. A cross-sectional study in patients with epilepsy and migraine shows similar prevalence rates in both conditions, disfavoring the hypothesis that IDD is typical only of patients with epilepsy. However, it has to be acknowledged that Blumer points out that IDD can be occasionally seen in the absence of clinical seizures, in patients with brain lesions (with or without an abnormal EEG) [32]. Epilepsy and migraine

share a number of elements in terms of pathophysiology [33]. Therefore, further studies are needed to clarify whether IDD is an organic affective syndrome of neurological patients or is generally associated to chronically ill populations.

12.4 The Issue of Peri-ictal Mood Symptoms

A number of atypical and pleomorphic features of mood disorders in epilepsy are related to peri-ictal symptoms [34], namely a number of behavioral manifestations that occur around the ictus, either preceding or following. This point has relevant implications in terms of diagnosis, prognosis and treatment, emphasizing the need to dissect out peri-ictal manifestations from interictal ones. In fact, such symptoms are almost indistinguishable from interictal ones, apart from duration and the close relation with seizure occurrence and cannot be detected by rating scales or questionnaires [35].

Peri-ictal symptoms are usually classified according to their temporal relationship with seizures (Fig. 12.2). Pre-ictal symptoms are very rarely reported by patients, if not specifically questioned, and poorly investigated by clinicians. However, around one-third of patients with partial seizures report premonitory symptoms, usually preceding secondary generalized tonic-clonic seizures [4]. Among pre-ictal symptoms, behavioral changes are those most frequently experienced [36]. Prodromal moods of depression or irritability may occur hours to days before a seizure and are often relieved by the convulsion [37]. In a cross-sectional study in tertiary referral centers in Europe, around 13 % of patients experience irritability, dysphoria or depressed mood preceding seizures [34].

As for pre-ictal symptoms, post-ictal mood changes are rarely recognized in clinical practice. A case series of presurgical patients reports a 18 % prevalence of patients having post-ictally at least five symptoms of depression lasting more than 24 h [38]. Anhedonia, in particular, is the most frequently reported post-ictal

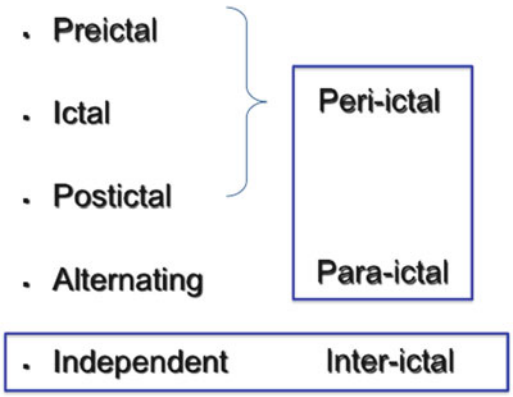

Fig. 12.2 Classification of peri-ictal symptoms in epilepsy

mood symptoms, about 33 % [38]. This quite interesting since that, as discussed before, anhedonia is rarely reported interictally.

Manic and hypomanic symptoms are also reported during the post-ictal phase. It has been reported that around 22 % of patients may present manic symptoms often with associated hallucinations or delusions [38]. Post-ictal mania seems to have a distinct position among psychiatric manifestations observed in the post-ictal period. Compared to post-ictal psychoses, post-ictal mania has a longer duration, a high frequency of recurrence, an old age at onset and is associated with EEG frontal discharges involving the non-dominant hemisphere [39]. Post-ictal anxiety is reported by 45 % of patients [38]. The median duration of symptoms ranges from 6 to 24 h but in one third of cases, post-ictal anxiety may last 24 h or longer.

12.5 Conclusions

Mood disorders in epilepsy present a number of atypical manifestations probably related to the neurobiology of the underlying neurological condition. However, anhedonia present a typical spectrum of presentation, being more frequently reported post-ictally than interictally. Further investigations in this subset of patients may shed light into the neurobiology of anhedonia, confirming the role of epilepsy as a privileged neurobiological model for the understanding of behavior and emotions.

References

1. Ngugi AK, Kariuki SM, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Incidence of epilepsy: a systematic review and meta-analysis. Neurology. 2011;77:1005–12.
2. de Boer HM, Mula M, Sander JW. The global burden and stigma of epilepsy. Epilepsy Behav. 2008;12:540–6.
3. Gaitatzis A, Sisodiya SM, Sander JW. The somatic comorbidity of epilepsy: a weighty but often unrecognized burden. Epilepsia. 2012;53:1282–93.
4. Gaitatzis A, Trimble MR, Sander JW. The psychiatric comorbidity of epilepsy. Acta Neurol Scand. 2004;110:207–20.
5. Kanner AM, Balabanov A. Depression and epilepsy: how closely related are they? Neurology. 2002;58:S27–39.
6. Quiske A, Helmstaedter C, Lux S, Elger CE. Depression in patients with temporal lobe epilepsy is related to mesial temporal sclerosis. Epilepsy Res. 2000;39:121–5.
7. Mula M, Sander JW. Negative effects of antiepileptic drugs on mood in patients with epilepsy. Drug Saf. 2007;30:555–67.
8. Edeh J, Toone BK. Antiepileptic therapy, folate deficiency, and psychiatric morbidity: a general practice survey. Epilepsia. 1985;26:434–40.
9. Tellez-Zenteno JF, Patten SB, Jette N, Williams J, Wiebe S. Psychiatric comorbidity in epilepsy: a population-based analysis. Epilepsia. 2007;48:2336–44.
10. Victoroff JI, Benson F, Grafton ST, Engel Jr J, Mazziotta JC. Depression in complex partial seizures. Electroencephalography and cerebral metabolic correlates. Arch Neurol. 1994;51:155–63.

11. Ring HA, Moriarty J, Trimble MR. A prospective study of the early postsurgical psychiatric associations of epilepsy surgery. J Neurol Neurosurg Psychiatry. 1998;64:601–4.
12. Jacoby A. Psychosocial functioning in people with epilepsy in remission and the outcomes of antiepileptic drug withdrawal [electronic resource]. Tyne: University of Newcastle upon Tyne; 1995.
13. O'Donoghue MF, Goodridge DM, Redhead K, Sander JW, Duncan JS. Assessing the psychosocial consequences of epilepsy: a community-based study. Br J Gen Pract. 1999;49:211–4.
14. Hesdorffer DC, Hauser WA, Annegers JF, Cascino G. Major depression is a risk factor for seizures in older adults. Ann Neurol. 2000;47:246–9.
15. Kanner AM. Depression and epilepsy: a bidirectional relation? Epilepsia. 2011;52 Suppl 1:21–7.
16. Kanner AM, Kozak AM, Frey M. The use of sertraline in patients with epilepsy: is it safe? Epilepsy Behav. 2000;1:100–5.
17. Mendez MF, Cummings JL, Benson DF. Depression in epilepsy. Significance and phenomenology. Arch Neurol. 1986;43:766–70.
18. Krishnamoorthy ES, Trimble MR, Blumer D. The classification of neuropsychiatric disorders in epilepsy: a proposal by the ILAE commission on psychobiology of epilepsy. Epilepsy Behav. 2007;10:349–53.
19. Mula M, Schmitz B. Depression in epilepsy: mechanisms and therapeutic approach. Ther Adv Neurol Disord. 2009;2:337–44.
20. Jones JE, Bell B, Fine J, Rutecki P, Seidenberg M, Hermann B. A controlled prospective investigation of psychiatric comorbidity in temporal lobe epilepsy. Epilepsia. 2007;48:2357–60.
21. Jones JE, Hermann BP, Barry JJ, Gilliam F, Kanner AM, Meador KJ. Clinical assessment of Axis I psychiatric morbidity in chronic epilepsy: a multicenter investigation. J Neuropsychiatry Clin Neurosci. 2005;17:172–9.
22. Kraepelin E, Diefendorf AR. Clinical psychiatry (1907). Delmar: Scholars' Facsimiles and Reprints; 1981.
23. Bleuler E. Textbook of psychiatry. New York: The Macmillan Co; 1924.
24. Blumer D. Dysphoric disorders and paroxysmal affects: recognition and treatment of epilepsy-related psychiatric disorders. Harv Rev Psychiatry. 2000;8:8–17.
25. Mula M, Jauch R, Cavanna A, Collimedaglia L, Barbagli D, Gaus V, Kretz R, Viana M, Tota G, Israel H, Reuter U, Martus P, Cantello R, Monaco F, Schmitz B. Clinical and psychopathological definition of the interictal dysphoric disorder of epilepsy. Epilepsia. 2008;49:650–6.
26. Hellwig S, Mamalis P, Feige B, Schulze-Bonhage A, van Elst LT. Psychiatric comorbidity in patients with pharmacoresistant focal epilepsy and psychiatric outcome after epilepsy surgery. Epilepsy Behav. 2012;23:272–9.
27. Blumer D, Wakhlu S, Davies K, Hermann B. Psychiatric outcome of temporal lobectomy for epilepsy: incidence and treatment of psychiatric complications. Epilepsia. 1998;39:478–86.
28. Trimble MR. The psychoses of epilepsy. New York: Raven Press; 1991.
29. Himmelhoch J. Major mood disorders related to epileptic changes. In: Blumer D, editor. Psychiatric aspects of epilepsy. Washington, DC: American Psychiatric Press; 1984. p. 271–94.
30. Blumer D, Montouris G, Davies K. The interictal dysphoric disorder: recognition, pathogenesis, and treatment of the major psychiatric disorder of epilepsy. Epilepsy Behav. 2004;5:826–40.
31. Blumer D, Herzog AG, Himmelhoch J, Salgueiro CA, Ling FW. To what extent do premenstrual and interictal dysphoric disorder overlap? Significance for therapy. J Affect Disord. 1998;48:215–25.
32. Blumer D, Heilbronn M, Himmelhoch J. Indications for carbamazepine in mental illness: atypical psychiatric disorder or temporal lobe syndrome? Compr Psychiatry. 1988;29:108–22.
33. Post RM, Silberstein SD. Shared mechanisms in affective illness, epilepsy, and migraine. Neurology. 1994;44:S37–47.
34. Mula M, Jauch R, Cavanna A, Gaus V, Kretz R, Collimedaglia L, Barbagli D, Cantello R, Monaco F, Schmitz B. Interictal dysphoric disorder and periictal dysphoric symptoms in patients with epilepsy. Epilepsia. 2010;51:1139–45.

35. Mula M, Schmitz B, Jauch R, Cavanna A, Cantello R, Monaco F, Trimble MR. On the prevalence of bipolar disorder in epilepsy. Epilepsy Behav. 2008;13:658–61.
36. Scaramelli A, Braga P, Avellanal A, Bogacz A, Camejo C, Rega I, Messano T, Arciere B. Prodromal symptoms in epileptic patients: clinical characterization of the pre-ictal phase. Seizure. 2009;18:246–50.
37. Blanchet P, Frommer GP. Mood change preceding epileptic seizures. J Nerv Ment Dis. 1986;174:471–6.
38. Kanner AM, Soto A, Gross-Kanner H. Prevalence and clinical characteristics of postictal psychiatric symptoms in partial epilepsy. Neurology. 2004;62:708–13.
39. Nishida T, Kudo T, Inoue Y, Nakamura F, Yoshimura M, Matsuda K, Yagi K, Fujiwara T. Postictal mania versus postictal psychosis: differences in clinical features, epileptogenic zone, and brain functional changes during postictal period. Epilepsia. 2006;47:2104–14.