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MOOD DISORDERS IN EPILEPSY – DIAGNOSTIC AND METHODOLOGICAL CONSIDERATIONS

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SUMMARY

Background: *Mood disorders are common in people with epilepsy (PWE) with prevalence rates ranging from 11% to 62%. The variation in epidemiological data results probably from the diversity of methodologies employed and selection of the populations across the studies. Moreover, the symptomathology of mood disorders in epilepsy is often atypical, intermittent and pleomorphic and fails to meet DSM-IV-TR categories. Several studies suggested the existence of distinct interictal dysphoric disorder (IDD) in patients with epilepsy. The majority of research studies in mood disorders in epilepsy were based on screening instruments in the diagnosis of mood disorders in PWE. However, the results in validity and reliability in detecting major depression in epilepsy using self-report inventories of mood symptoms is vague. The aim of this study was to review studies on mood disorders in epilepsy with particular focus on diagnostic methods.*

Subjects and methods: *The focus of this Review was on patient studies on mood disorders in epilepsy (2000–2012). We searched PubMed using the following search terms (effective date: 20th May 2012): (epilepsy (Title/Abstract) OR seizure (Title/Abstract)) AND depression (Title/Abstract) OR Dysthymia OR mania OR bipolar disorder OR affective disorder OR Interictal Dysphoric Disorder OR AND (humans (MeSH Terms) AND English (lang) AND (2000/01/01(PDAT): 2012/04/31(PDAT)).*

Results: *Depression is the most frequent comorbid psychiatric disorder in epilepsy. Recent studies pointed out that bipolar disorders are not rare in epilepsy. Most of the research in PWE did not rely on standardized psychiatric measures and only about 18% of studies were based on diagnostic psychiatric interviews (mainly MINI and SCID-I). Mood disorders in epilepsy excluding the ictal or periictal symptoms can be categorized using standardized measures.*

Conclusions: *Common self-report depression measures may be used to screen for depression in clinical settings. The use of screening instruments in epilepsy must be followed by structured psychiatric interviews designed to establish a DSM-IV-TR diagnoses. Standardized psychiatric interview procedures based on DSM criteria like SCID-I or MINI provide a comprehensive way to diagnose mood disorders in patients with epilepsy.*

Key words: *epilepsy – depression – mania - bipolar disorder - interictal dysphoric disorder*

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INTRODUCTION

Mood disorders represent a frequent psychiatric comorbidity in epilepsy which is often unrecognized, under-diagnosed and untreated with adverse conesquences for health-related quality of life, costs and utilization of epilepsy health care, and an increased risk of suicidal ideation and suicide. Depression is the most frequent psychiatric comorbidity in people with epilepsy (PWE). The incidence of depressive disorders in epilepsy ranges from 11% to approximately 62% (Hermann et al. 2000, Barry et al. 2007). It is lower (20-30%) in community-based epilepsy samples and higher (20–55%) in specialist epilepsy clinics. This large variation in epidemiological data results from the diversity of methodologies across the studies, differences in definitions of mood disorder and scientific rigor. Also various factors associated with epilepsy such as type of epilepsy, course of illness, frequency and severity of epilepsy attacks and anti-epileptic drugs (AEDs) side effects could adversely affect the accuracy of diagnosis of mood disorder. Data on frequency of bipolar disorder in epilepsy is still limited although recent studies pointed out that symptoms of bipolar disorder are not rare in epilepsy (Mula et al. 2008). Moreover, the symptomathology of mood disorder in epilepsy is often atypical, intermittent and pleomorphic and fails to meet DSM-IV-TR categories.

In addition, there is also variability in sample size population (many studies were conducted on small sample size), epilepsy diagnosis (mostly temporal lobe epilepsy) sample study population (inpatients, outpatients, surgical patients etc.) and often lack of control groups (Swinkles et al. 2005).

Also, among the studies prevalence was measured in different ways (as point prevalence, life-time prevalence or 1-year prevalence) which could explain some of the variation seen in different reports (Tellez-Zenteno et al. 2008).

This review aims to examine comorbid mood disorders in adult patients with epilepsy and will focus on the role and importance of contemporary psychiatric classifications (Diagnostic and Statistic Manual (DSM) and International Classification of Diseases (ICD) diagnoses) in the diagnosis of mood disorders in PWE.

DIAGNOSTIC CONSIDERATIONS

Depressive Disorders in Epilepsy

Depressive disorders in epilepsy can be classified according to the Diagnostic and Statistical Manual of

Mental Disorders (DSM). Depressive disorders in the DSM-IV are subdivided into those that meet criteria for a Major Depressive Disorder (MDD), Dysthymic Disorder (DD), Depressive Disorder Not Otherwise Specified (DDNOS) (American Psychiatric Association 1994). Depressive disorder NOS include disorders with depressive features that do not meet the criteria for DSM mood disorders categories and include among others minor depressive disorder and recurrent brief depressive disorder.

Hermann et al. (2000) reviewed the published data using DSM and ICD nosology for rates of mood disorders in epilepsy. In reviewed studies lifetime-to-date MDD diagnosis ranged from 8 to 48% with a mean and median of =30%. Most of the study populations were with chronic refractory seizures. There are only few non-select population based studies that used DSM diagnostic criteria in PWE. In Canadian population the lifetime prevalence of depression among people with epilepsy was estimated at 18.2%, using the Composite International Interview for psychiatric diagnoses, which yields DSM-IV diagnoses (Tellez-Zenteno et al. 2005). From these studies it would appear that depression is common in epilepsy and mood disorders in patients with epilepsy meet criteria as specified by DSM-IV.

Epilepsy-specific mood disorders – a diagnostic dilemma

Unfortunately, mood disorders in epilepsy often have atypical symptomatology and fail to meet DSM-IV criteria. They can also be classified according to the temporal relationship between the onset of psychiatric symptoms and seizure occurrence into ictal (depression as a clinical manifestation of the seizure), periictal (symptoms precede (preictal) and/or follow (postictal) the seizure), and interictal (symptoms occur independently of the seizure occurrence).

Ictal depression can occur as a part of the ictus itself. Ictal depression classically is of sudden onset and is a clinical expression of a simple partial seizure (which often progress into complex partial seizure). It appears to be more common in patients with temporal lobe epilepsy, in whom rates about 15% have been reported (Blanchet et al. 1986, Wiliams et al. 1956). The severity of symptoms can range from mild feelings of sadness to profound helplessness and despair, feelings of guilt, anhedonia. Suicide has been reported during ictal depressive episodes.

Preictal depression could be described as prodromal depressive moods or irritability and can occur hours to days before a seizure, and are often relieved by the ictus (Kanner et al. 2000, Banchet et al. 1986, Wiliams et al. 1956). It has been reported that in a population of children dysphoric moods often take the form of irritability, poor tolerance to frustration, and aggressive behaviour (Kanner et al. 2001).

Although depression lasting hours to days after seizure has been described in some patients it is uncommon to find a patient with postictal depression alone. Postictal symptoms of depression usually last up to 48 hours after ictus with median duration from 6 to 24 hours (Kanner et al. 1999, 2001). Some studies indicate that postictal depression can last up to 2 weeks after ictus and may lead to suicide (Kanner et al. 2000, Daly et al. 1958, Mendez et al. 1992). The most frequent symptoms include anhedonia, irritability, poor frustration tolerance, feelings of hopelessness and helplessness, suicidal ideation, feelings of guilt and self-deprecation, and crying bouts (Kanner et al. 2000)

Interictal depression is the most common form of depressive disorder in epilepsy. Frequently, however it does not meet any of the DSM-IV criteria. Interictal depression in patients with epilepsy commonly presents as a chronic depression or dysthymic disorder but without fulfilling time criteria for these DSM based diagnoses. These episodes of depression have symptomatic periods ranging from hours to days interrupted by symptom-free periods of similar duration.

Blumer et al. (2004) drew attention to these forms of mood disorder commonly seen in patients with epilepsy and coined the term interictal dysphoric disorder. Well before Blumer, analogous clinical observations were made by Kraepelin (1923) who provided the similar clinical description of such a form of mood disturbances in epilepsy. Interictal dysphoric disorder (IDD) is characterized by a constellation of eight symptoms and requires the presence of any of three of the following: depressive mood, fear, paroxysmal irritability, anergy, anxiety, euphoric moods, pain, insomnia. Interictal dysphoric disorder is typically of short duration and symptoms occur at various intervals and tend to last from hours to two or three days. In women, these symptoms become accentuated in the premenstrual period. Blumer considered that almost one-third to one-half of patients with epilepsy suffer from IDD and require pharmacological treatment (Blumer et al. 2004). Unfortunately there are only limited comparative study results in the literature on the issue of evaluation of depression in epilepsy using standardised diagnostic procedures with IDD criteria.

Recently Mula et al. (2007) investigated whether IDD occurs only in patients with epilepsy and validated IDD features against DSM-IV criteria. Consecutive patients with the diagnosis of epilepsy or migraine have been assessed using the BDI, MDQ, and the Interictal Dysphoric Disorder Inventory (IDDI). Diagnosis of current and lifetime DSM-IV Axis I disorders was established using MINI. Validation of IDD against DSM-IV categories showed current major depression being the foremost diagnostic category correlated with IDD in both epilepsy and migraine. They concluded that IDD was not typical only of epilepsy, occurring also in other central nervous system disorders such as migraine.

Other authors suggest that the most common pattern of mood disorder in epilepsy consists of a chronic dysthymic state characterized by symptoms of IDD that sometimes exacerbate and meet the criteria of Major Depressive Disorder. This pattern would be similar to "double depression" seen in nonepileptic patients (Barry et al. 2007).

Kanner et al. (2000) have also noted the presence of atypical symptoms of depression in patients with epilepsy. They evaluated 97 PWE with complaints and found that 28 met DSM-IV criteria for MDD but that 69 could not be categorized according to DSM-IV because of intermittent symptom-free periods. Kanner highlighted the chronic course of this state of moderate depression with symptom-free intervals and used the term dysthymic-like disorder of epilepsy (DLDE). It is important to note that this pattern of mood disorder is similar to minor depression which was not evaluated (Kanner et al. 2001)

To further improve the recognition and treatment of affective disorders in PWE a dedicated subcommission of the ILAE Commission on Neuropsychiatric Aspects has developed a new classification proposal (Krishnamoorthy et al. 2007). The authors attempted to classify psychiatric disorders in PWE into epilepsy-specific disorders, comorbid psychiatric disorders classified according to DSM-IV-TR and ICD-10 and those that reflect ongoing epileptiform activity. This proposed system of classification of epilepsy-specific psychiatric disorders generally follows their relationship to the ictus and was divided into three main categories: psychopathology as a feature of epileptic seizures, interictal psychiatric disorders that are specific to epilepsy and personality disorders. Epilepsy-specific interictal affective disorders were divided into two categories: affective-somatoform (dysphoric) disorders and alternative affective-somatoform syndromes. Affective-somatoform (dysphoric) disorders of epilepsy included interictal dysphoric disorder, prodromal dysphoric disorder, and postictal dysphoric disorder. The second category alternative affective-somatoform syndromes included depression, anxiety, depersonalization, derealisation, and even nonepileptic seizures that have been reported as clinical manifestations of forced normalization.

Bipolar Disorder in Epilepsy

There are two main types of Bipolar Disorder (BD), depending on the occurrence of manic/mixed (type I) or hypomanic (type II) episodes in addition to major depressive episodes, Bipolar Disorder NOS, is the category for so called bipolar spectrum disorders that do not fulfil type I or type II criteria and cyclothimic disorder for more chronic and less severe clinical manifestation.

The majority of studies of mood disorders in epilepsy focused on major depression with information about bipolar disorder being still limited. In the older literature, it was often stated that BD was rare in epilepsy (Wolf et al. 1982). Recent studies pointed out that manic or hypomanic symptoms are not rare in epilepsy. A large U.S. survey revealed that 12.2% of the epilepsy patients screened positively for bipolar symptoms, of those who, in the screening process, were rated as potential bipolar patients, nearly 50% were rated by a physician as having a bipolar disorder (Ettinger et al. 2005). Mula et al. (2008) examined a group of 143 adult outpatients with epilepsy and revealed that 11.8% had a DSM-based diagnosis of bipolar disorder, only 1.4% of whom could be considered as having ''pure" Bipolar Disorder, because in all other cases BD symptoms were related to symptoms of interictal dysphoric disorder, postictal, manic or hypomanic states, and preictal dysphoria. Perhaps interictal dysphoric disorder with its specific features and labile-angry-irritable states represents the more unstable form of bipolar spectrum disorders. IDD could be a form of cyclothimic disorder that sometimes exacerbates and meets the criteria of Major Depression episode. Authors have speculated that there is enough evidence further suggesting that IDD may be closer to bipolar rather than unipolar mood disorders.

METHODOLOGICAL CONSIDERATIONS

Many different assessment strategies used in epilepsy studies makes interpretation of psychiatric findings associated with epilepsy difficult. Results from different psychometric tests are often quoted as if they were interchangeable. The use of different rating scales may result in variability of results obtained by different authors. In some studies psychometric instruments originally developed to identify symptoms and measure quantitative levels of severity of disorder that had already been diagnosed (e.g. self-administered Beck Depression Inventory BDI or Hamilton Depression Rating Scale) were used to diagnose depression, while in others the same psychometric methods were used according to their purpose. These instruments are not suitable to diagnose psychiatric disorder. Diagnosis of psychiatric disorder requires an examination by a certified psychiatrist or clinical psychologist, based on established diagnostic criteria. Then again in busy clinical settings and in the absence of a psychiatrist the usage of screening tools could improve detection of mood disorders in PWE.

Much of the previous research studies of depression in epilepsy relied on these psychometric instruments in the diagnosis of depression. The validity and reliability to detect major depression in epilepsy using self-administered inventories of mood symptoms (e.g. Beck Depression Inventory BDI, Hospital Anxiety and Depression Scale, HADS, Hamilton Depression Rating Scale HAMD) is to be determined.

Table 1. Systematic studies on Mood Disorders in PWE (SCID-I)

Author	Title	Year	N	Study population	DSM-IV diagnosis methodology
Jeff I. Victoroff	Depression in complex partial seizures. Electroencephalography and cerebral metabolic correlates.	1994	53	PWE with medically intractable complex partial seizures	SCID-P (DSMIIIR) revised for Epilepsy (SCID-E)
Lori Altshuler	Temporal Lobe Epilepsy, Temporal Lobectomy, and Major Depression	1999	62	PWE with medically intractable complex partial seizures	SCID (DSMIIIR)
P. Wiegartz	Co-morbid psychiatric disorder in chronic epilepsy: recognition and etiology of depression.	1999	76	PWE with complex partial seizures from epilepsy teritary centre	mood disorder section from SCID-I
Guillia Glosser	Psychiatric aspects of temporal lobe epilepsy before and after anterior temporal lobectomy	2000	39	Consecutive series of epilepsy patients before and 6 months after anterior temporal loboctomy	interview modelled on SICD for DSMIIIR
Jana E. Jones	Clinical Assessment of Axis I Psychiatric Morbidity in Chronic Epilepsy: A Multicenter Investigation	2005	174	PWE from outpatient epi-centres	mood disorder section from SCID-I, MINI
Vanessa Sanchez-Gistau	Prevalence of interictal psychiatric disorders in patients with refractory temporal and extra-temporal lobe epilepsy in Spain. A comparative study	2010	308	PWE from Epilepsy Inpatient Unit t	SCID-I

Author	Present MDD (%)	Life-time prevalence MDD (%)	One-year prevalence MDD (%)	Other mood disorder diagnoses (%)
Jeff I. Victoroff		30.00%		Dysthymic Disorder 4% Adjustment disorder with depressed mood 10% Organic mood disorder 17% Depressive Disorder NOS 19%
Lori Altshuler	39.00%			Depressive Disorder NOS 3% Bipolar Disorder 1.6%
Wiegartz P	9.20%	31.60%		Current minor depression 25% Bipolar Disorder 1.3%
Guillia Glosser				Major Depressive Disorder + Dysthymic Disorder 44% (Lifetime prevalence)
Jana E. Jones	17.20%			Dysthymic Disorder 4% Bipolar Disorder 2.8% (mania 17%, hipomania 1.1%)
Vanessa Sanchez-Gistau	11.90%	19.50%	11.90%	Depressive Disorder NOS 4.9% (lifetime prevalence) 2.9% (one-year Prevalence) Dysthymic Disorder 10.5% (lifetime prevalence) 7.3% (one-year prevalence) Bipolar Disorder 1.5% (lifetime prevalence) 0.9% (one-year prevalence)

Jones et al- have examined the validity of the BDI and Centre for Epidemiological Study of Depression (CES-D) and compared results with the Mini International Neuropsychiatric Interview (MINI). Both psychometric tools had good correlation and can be used in patients with epilepsy (Jones et al. 2005).

When assessing depression in patients with epilepsy with screening tools, it is also crucial to define proper cut off scores to prevent over-diagnosing depression. Studies conducted in PWE used different cut off values for diagnosis of depression with HAMD and BDI scales. It should be noted that results from some studies suggest different from recommended clinical scores as optimal cut-off scores for screening depression in PWE. For example based on analyses optimal trade-off between sensitivity and specificity cut-off scores for BDI-II >11 and CES-D >14 for depression in PWE were different those generally recommended (CES>= 15, BDI-II>=10) (Jones et al. 2005).

It is also important to remember that the scales dedicated for the depressive symptoms assessment may over-diagnose mood disorder in PWE, since they do not

distinguish the physical symptoms and cognitive impairment related to epilepsy or adverse AEDs side effects from depression with its somatic symptoms. Screening instruments aimed at detection of major depression in people with epilepsy have been developed. The neurological disorders depression inventory for epilepsy (NDDI-E) was created for this purpose (Gilliam et al. 2006). NDDI-E was constructed in a way that it could help to differentiate symptoms of depression from symptoms of cognitive impairment associated with epilepsy or adverse AEDs side effects (Gilliam et al. 2006).

The same problem is also related to DSM-IV-defined mood disorders criteria. Applying DSM-IV diagnostic criteria to patients with epilepsy poses the problem of whether to attribute certain symptoms to epilepsy, or, instead, to a diagnosis of depression (Robertson 1998, Lambert et al. 1999, Hermann et al. 2000). The use of screening instruments must be followed by structured psychiatric interviews designed to establish a DSM or ICD diagnoses. The Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Disease (ICD) proposed criteria that became diagnostic 'gold standards' in psychiatry. These criteria are not perfect and were developed for the general population and that is why sometimes they do not satisfy the descriptive needs of mood disorders in epilepsy. Nevertheless, in order to determine the diagnosis of mood disorders in patients with epilepsy DSM criteria can be used. Standardized psychiatric interview procedures based on DSM criteria provide a comprehensive way to characterize the presence and nature of current Axis I DSM–IV disorders. However, these procedures, such as the Structured Clinical Interview for DSM–IV Axis I Disorders-Research Version (SCID-I, First et al., 2002) or Composite International Diagnostic Interview for ICD-10 (CIDI) classification can be too time consuming for routine clinical use. There are only a few studies based on diagnostic psychiatric interviews. An example of a standardized psychiatric interview procedures that is more time efficient yet reliable, valid, and comprehensive, focusing predominantly on current Axis I DSM–IV disorders is The Mini International Neuropsychiatric Interview (MINI) (Sheehan et al. 1998). MINI has been recently used more often in the investigation of psychiatric morbidity in epilepsy.

According to a recent clinical review of depression in epilepsy DSM-IV classification was used in 70 (39.3%) studies in PWE (Hoppe et al. 2011) of which structured interviews were used in about 18%. Structured Clinical Interview for DSM-IV Axis I Disorders was used in 18 (10.5%) and Mini-International Neuropsychiatric Interview in 13 (7.6%) studies. Examining carefully studies based on SCID-I there are still important methodology differences. Some of the studies used MINI to diagnose psychiatric disorder and in the same study mood disorder section of SCID-I to specifically diagnose depression (Jones et al. 2005) or used only the mood disorder section of SCID-I (Wiegartz et al. 1999). Other studies used different versions of SCID like Patient Version (SCID-I/P) (Ertekin et al. 2009) or “revised for epilepsy” version of SCID (Victoroff et al. 1994) or interview “modelled on SCID” (Glosser et al. 2000) (Table 1). These procedures may make worse the validity and sensibility of the applied methodologies to diagnose mood disorder according to DSM-IV classification.

Wiegartz et al. (1999) found that 9.2% of PWE had a current major depressive disorder and 25% a minor depression using Mood Disorder section of SCID-I for DSM-IV However in this study included the diagnosis of minor depression adjustment disorder with depressed mood, dysthymic disorder and depressive disorder NOS (DDNOS). Also the clinical description of DDNOS in this study - symptoms lasting from 2 to 7 days and typically recurring on a monthly to biweekly basis - was similar to the diagnosis of recurrent brief depression. The categories of minor depression and recurrent brief depression are still in the investigation part of DSM. Nonetheless, it seems that these atypical forms of Depressive Disorders if taken into account could be more often recognized as comorbidity in PWE and perhaps be used instead of the still disputable diagnoses of epilepsy-specific mood disorders. Jones et al. (2005) examined 174 PWE from outpatient epilepsy centres using MINI and Mood Disorder section of SCID-I. Point Prevalence of MDD was 17.2% and for dysthymia 4%. Sanchez-Gistau et al. (2010) studied 308 patients that were carefully classified as having epileptiform foci that were temporal or extratemporal in localization. These patients were then administered the Structured Interview for DSM-IV Axis I Psychiatric Disorders (SCID-I). Of the study group, 22% had a lifetime prevalence of Major Depressive Disorder, and 14.6% had previous one-year prevalence of this disorder, 4.9% had a lifetime prevalence of Depressive Disorder NOS and 2.9% one-year prevalence. Dysthymic Disorder was diagnosed in 10.5% for lifetime prevalence and 7.3% for one-year prevalence.

CONCLUSION

The problem of adequate diagnosis of mood disorders is not only common in PWE but also in other populations of patients with a medical condition. Discrepancies in the reported frequencies reflect the use of different definitions of depression, thresholds for identification of a mood disorder, and assessment strategies which is also very true not only in PWE but also in other neurological conditions such as Parkinson’s disease (Cummings 1992).

Depression is the most frequent comorbid psychiatric disorder in epilepsy. In summary, mood disorders 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 a comprehensive way to diagnose mood disorders in patients with epilepsy. However, these procedures, can be too time consuming for routine clinical use. It appears that common self-report depression measures can be used to screen for major depression in clinical settings. Use of these measures could assist in the clinical identification of patients with depression. The use of these screening instruments in epilepsy must be followed by structured psychiatric interviews designed to establish a DSM-IV-TR diagnoses. Also side-effects of antiepileptic drugs that mimic somatic symptoms of depression have to be taken into account while diagnosing mood disorders in epilepsy.

There may be unique features to the mood disorder in epilepsy, but these observations remain speculative at present. Different authors suggested the occurrence of a pleomorphic affective syndrome in patients with epilepsy named interictal dysphoric disorder (IDD). There are only limited data on comparisons in the literature evaluating depression in epilepsy using standard diagnostic techniques with IDD criteria. Standardized measures that include these unique aspects of depression in epilepsy need to be developed and more direct comparison evaluations with other populations should be completed (Kanner et al. 2001).

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