PSYCHIATRIC COMORBIDITIES IN PEOPLE WITH EPILEPSY

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ABSTRACT

Psychiatric disorders are relatively frequent in people with epilepsy, with a lifetime history identified in one of every three individuals. Theories of comorbidity are complex, but recurring associations between epilepsy and psychiatric conditions suggest overlap that is more than simple co-occurrence; many have noted that psychiatric disorders are an important prognostic marker of epilepsy. Focusing primarily on the last five years, we review the latest evidence concerning the nature of the association between epilepsy and psychiatric comorbidities. We address the way psychiatric comorbidities affect the long-term management of people with epilepsy and consider how to screen for and diagnose psychiatric comorbidities in routine clinical practice, considering the heterogeneity of clinical scenarios in which psychiatric symptoms can occur. We discuss issues regarding the treatment of psychiatric comorbidities in people with epilepsy, including interactions between antiepileptic drugs and psychotropic medications, common side effects of antidepressants and antipsychotics and seizure risk associated with these drugs.

INTRODUCTION

According to the new International League Against Epilepsy (ILAE) definition, epilepsy is a disorder of the brain characterised by recurrent seizures but also by its "neurobiological, cognitive, psychological and social consequences"[1].

Psychiatric comorbidities in people with epilepsy are due largely to psychosocial and biological factors. Epilepsy is still a stigmatised condition, leading to discrimination and social withdrawal. In addition, significant social limitations (e.g. loss of driving license) and the unpredictability of seizures can lead to poor self-esteem and depression. From a neurobiological perspective, neuroimaging studies in people with primary psychiatric conditions such as depression or schizophrenia, have shown abnormalities in brain networks overlapping with those involved for example in temporal lobe epilepsy, particularly in the amygdala and the hippocampi[2]. People with epilepsy, however, can also present with psychiatric symptoms peri-ictally, either preceding, during or following a seizure, or as a consequence of the treatment, antiseizure medications or epilepsy surgery.

Psychiatric problems could be due to shared neurobiological mechanisms, a consequence of having epilepsy or simply due to the unfortunate occurrence of two conditions in the same individual. Nevertheless, the management of these people can be challenging regardless of the causes. For this reason, physicians must identify comorbid psychiatric disorders and incorporate them into the comprehensive individual management. Accordingly, a multidisciplinary approach is required. This entails the need for health care professionals in other disciplines such as psychiatrists, clinical psychologists, neuropsychologists psychiatric nurses, and social workers, to ensure the individual receive the best management.

We review current evidence about the nature of the association between epilepsy and psychiatric comorbidities and the role of psychiatric comorbidities in the long-term management of people with epilepsy. We assess the evidence on screening and diagnosing in routine clinical practice considering the heterogeneity of clinical scenarios where psychiatric symptoms occur. We also discuss issues regarding the treatment of psychiatric comorbidities in people with epilepsy, including interactions between antiseizure and psychotropic medications and their relevant side effects. Lastly, we review the evidence on whether antidepressants and antipsychotics are associated with seizure risk.

SEARCH STRATEGY AND SELECTION CRITERIA

Articles published between 1st Dec 2013 and 31st July 2019 were identified through searches in PubMed and Embase using the search terms "comorbidity", "comorbid*", "psychiatric disorders", "depression", "anxiety", "psychosis", "seizure, epilepsy and convulsion", "epile*", "seizure*" and "convuls*". No language restrictions were applied. This search generated 638 abstracts which were reviewed by an author (MM). Articles were selected based on originality and relevance to the present topic. Additional articles were identified from the authors' own files and from chosen bibliographies.

EPIDEMIOLOGY

Data from cross-sectional studies show that all psychiatric disorders seem to occur in a higher proportion of adults and children with epilepsy than in those without epilepsy.

In adults, a meta-analysis of 14 population-based studies including over 1,000,000 participants showed an overall prevalence of active (current or last 12 months) depression in

epilepsy of 23.1% (95%CI 20.6% - 28.3%; I^2=97.7%) with increased overall risk of 2.7 (95%CI 2.09 - 3.6; I^2=85.1%) compared with the general population[3]. These estimates, however, varied considerably across studies depending on the ascertainment source (i.e. self-report vs. screening tools vs. structured clinical interviews), countries, regions and settings. A meta-analysis of 27 reports of anxiety disorders in over 3,000 people with epilepsy showed a pooled prevalence of 20.2% (95%CI 15.3-26.0; I^2=92.1) with generalised anxiety disorder being most common (10.2%; 95%CI 7.7%-13.5%)[4]. Another meta-analysis of 57 studies of psychosis and related disorders, including more than 40,000 subjects, showed a pooled prevalence of 5.6% (95%CI 4.8% - 6.4%; I^2>70%) in unselected individuals increasing to 7% (95%CI 4.9% - 9.1%; I^2>70%) in people with mesial temporal lobe epilepsy (TLE), with a pooled odds ratio for risk of psychosis compared to the general population of 7.8 (95%CI 2.8-21.8; I^2>70%)[5]. The pooled prevalence of psychogenic non-epileptic seizures (PNES) in people with epilepsy in a meta-analysis was 12% (95%CI 10% - 14%; I^2=92.7%) while the prevalence of epilepsy in those with PNES was 22% (95%CI 20%-25%; I^2=95.5%)[6].

Data from children with epilepsy are not different despite an obvious emphasis on developmental disorders. A population-based study in 85 children and adolescents (aged 5-15) with active epilepsy in England reported a prevalence of attention deficit hyperactivity disorder (ADHD) of around 33%, autism spectrum disorder (ASD) of 21%, depression of 7% and anxiety of 13%[7]. A nationwide Norwegian registry study in an unselected paediatric population of over 1,000,000 children reported developmental and psychiatric comorbidities in 43% of children with epilepsy, with overall odds ratios (compared with the general child population) of 10.7 (95%CI 9.5 – 12.1) for autism, 5.4 (95%CI 4.8 – 5.9) for ADHD, 2.3 (95%CI 1.8 - 3.0) for anxiety disorders and 1.8 (95%CI 1.4 - 2.5) for depression[8]. The use of

the International Classification of Diseases (ICD) codes to identify psychiatric disorders in many of these studies introduces an important limitation as ICD codes have low sensitivity for psychiatric conditions, leading to possible underestimation of their occurrence[9].

Cross-sectional epidemiological studies provide estimates of the size of the problem but do not help to clarify the nature of the association. Data from prospective observational studies clearly indicate that the relationship between epilepsy and psychiatric disorders is bidirectional. This notion was established over ten years ago and the majority of studies on this subject were published before 2013. More recent studies have further confirmed this observation. A large UK observational cohort study involving over 10,000,000 subjects found that depression was associated with a 2.5-fold (95%CI 2.49 - 2.60) increased risk of developing epilepsy[10]. Suicide risk was increased 2.9 fold (95%CI 2.5-3.4) even before the diagnosis of epilepsy[11]. All these findings suggest the presence of shared pathogenic mechanisms between epilepsy and all major psychiatric disorders. It is also tempting to speculate that psychiatric disorders, in some cases, may represent the premorbid phase of some epileptic syndromes. This specific scenario may have major implications in terms of future treatments and the development of disease modifying agents.

IMPLICATIONS FOR CLINICAL PRACTICE

In epilepsy, treatment and prognosis are dependent on the accurate definition of the epilepsy syndrome. It would then be reasonable to apply the same model for psychiatric comorbidities (for example psychiatric disorders being more common in temporal lobe epilepsy as compared to generalised syndromes). The relative contribution of syndrome-specific variables is still unclear and clinical evidence suggests that psychiatric comorbidities do not

necessarily respect such borders. It is now evident that psychiatric comorbidities have to be considered when informing people about the prospects of long-term prognosis of the epilepsy itself.

Psychiatric comorbidities have been historically associated with poor quality of life in adults[12] and children[13] with epilepsy but there are now data suggesting their role as a prognostic indicator. A population-based cohort study involving 10,595,709 people from the UK showed that depression is associated with high comorbidity rates, as measured by the Charlson Comorbidity Index, and that the severity of the depression itself (based on the type of treatment received) correlates with a lower odds of achieving seizure remission in a Canadian cohort[10]. Psychiatric comorbidities are associated with a high risk of side effects, especially cognitive complaints and psychiatric side effects[14]. Psychiatric comorbidities are associated with a four-fold increased risk of drug resistance in focal[15] and generalised epilepsies[16]. This is further confirmed by a large cohort study from Italy in 1006 people with newly diagnosed epilepsy followed for a median of 16 years, showing that the absence of psychiatric comorbidities predicts early and long-term seizure freedom[17].

The impact of psychiatric comorbidities in terms of seizure-outcome and psychiatric-outcome, in epilepsy surgery, is complex and yet to be established. Some studies have found a lower probability of achieving seizure-freedom after temporal lobectomy[18], while others have refuted these findings[19]. The same holds true for psychiatric outcomes, as some studies showed an increased risk of recurrence of depression or anxiety during the first year after surgery[20] while other studies showed long term improvement[21].

Psychiatric comorbidities are associated with premature mortality in epilepsy[22]. This may be due to a variety of reasons, including increased risk of substance or alcohol abuse[23], increased risk of injury[24] and increased suicide rates[11]. Data from a population-based study of over

57,000 people in Sweden showed that females with epilepsy and psychiatric comorbidities had a 5-fold increased risk of sudden unexpected death in epilepsy (SUDEP) compared with those without such comorbidities[25].

Lastly, it is evident that psychiatric comorbidities increase the global burden of epilepsy from a public health perspective with increased health costs[26]. People with epilepsy and psychiatric disorders have high health resource utilization, including increased emergency department admissions and outpatient visits[27]. Data from a US nationwide study assessing almost 400,000 hospital admissions showed that psychiatric comorbidities, depression and psychosis in particular, increase length-of-stay and inpatient costs for people with epilepsy[28].

SCREENING FOR PSYCHIATRIC COMORBIDITIES

Despite robust evidence about the frequency and clinical implications of psychiatric disorders in epilepsy, these problems are still underdiagnosed and undertreated. A recent survey reported that around 50% of epilepsy specialists routinely screen for psychiatric disorders[29]. Barriers to diagnosis and management of psychiatric comorbidities are complex and multi-factorial. These include, amongst other factors, cultural barriers to mental health issues, lack of training of neurologists and psychiatrists about these comorbidities and lack of allocated resources for a multidisciplinary approach[30] (**Table 1**).

In the general population, a few screening tools are available in primary and secondary care settings for almost all major psychiatric conditions. These tools have been shown to be cost-effective because they are short, standardised against DSM criteria and less resource-intensive than a full clinical interview. In the past, the validity of these instruments in people with epilepsy was a major barrier to their use in routine clinical practice. As described in this

section, there are now good data on the validity of clinical instruments for depression and anxiety in adults and for ADHD in children.

A systematic review of studies validating 16 screening tools for depression in adults with epilepsy showed that the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), validated in 13 languages, is the most efficient and practical screening instrument for a major depressive episode in a variety of settings[31]. The NDDI-E has also been validated for suicidality with good sensitivity and specificity[32] and this should allow the development of well-defined clinical pathways for suicide prevention.

Other well-known, self-rating scales, such as the Beck Depression Inventory II (BDI-II) and the Patient Health Questionnaire 9 (PHQ-9) have also been shown to be valid in epilepsy but require use of cut-off scores higher than those adopted in the general population (general population BDI-II = 10, PHQ-9 = 5; epilepsy BDI-II = 15, PHQ-9 = 10)[31]. This can be partially explained by the heterogeneity of clinical presentations of depression in epilepsy, but also highlights the need to adapt these questionnaires to the specific needs of people with epilepsy in order to maximize their sensitivity and specificity.

The Hamilton Depression Rating Scale (HDRS) has been used as an outcome measure in clinical trials of depression outside epilepsy and it has also been validated in epilepsy[33]. This will allow the development of outcome studies of depression in people epilepsy whose results will be comparable with those from the general population.

Two main clinical instruments have been validated for symptoms of anxiety in adults with epilepsy; the Hospital Anxiety and Depression Scale (HADS) and the Generalised Anxiety Disorder 7 (GAD-7). While studies on the validity of the HADS in epilepsy provide conflicting results[34], the validity and cost-effectiveness of the GAD-7 seem to be well

established[35]. Discrepancies among studies are due to the fluctuating nature of anxiety symptoms and the nonconforming phenomenology of psychiatric symptoms in epilepsy.

Data on screening instruments in children with epilepsy are still limited. A systematic review on the management of ADHD in epilepsy reported good evidence for the use of the Strength and Difficulties Questionnaire (SDQ) [36]. Data on clinical instruments for depression and anxiety in the paediatric population are scant but this is due to current clinical practice in general. In fact, two comprehensive documents from the American Academy of Child and Adolescent Psychiatry recommend the use of DSM or ICD-based symptom checklists in the general population [37,38] . A 12-item, self-report screening tool for depression in people with epilepsy aged 12-17 years, called NDDI-E-Youth, has been developed[39] but further studies in this area are needed.

DIAGNOSTIC ISSUES

After a positive screen it is important to confirm the diagnosis, as psychiatric symptoms can be seen in a variety of clinical scenarios including peri-ictal symptoms, side effects of drugs or comorbid psychiatric disorders. The boundaries between these scenarios are often blurred and, as already discussed, people with a psychiatric comorbidity are also more likely to present with psychiatric side effects from antiseizure medications.

Historically, psychiatric symptoms in epilepsy have been categorised according to their temporal relationship with seizures and the practicality of this is well-known as they define different clinical scenarios which are summarised in **Table 2**.

The prevalence and pathophysiology of peri-ictal symptoms are largely unknown and data come from adult samples. Postictal psychoses are probably the most frequently described and

investigated symptom pattern and a meta-analysis reported a point prevalence of 2% (95%CI 1.2% - 2.8%)[5]. Postictal psychoses are typically seen in people with temporal lobe epilepsy and they are characterised by higher rates of violent behaviours and suicide attempts than interictal psychoses[40]. Conversely, non-psychotic postictal psychiatric symptoms are often not recognised, in large part because they are short-lasting and clinicians fail to investigate their presence. In a systematic study of people with drug-resistant focal epilepsy, 43% had postictal symptoms of depression, 45% postictal anxiety and 7% psychotic symptoms. These occurred in more than half of their seizures and lasted for a median of 24 hours[41].

Psychiatric symptoms as side effects of antiseizure medications are frequently reported. A retrospective analysis of medical notes of a large unselected sample from the US including 4085 adults recently started on an antiseizure medications showed that 1 in 6 individuals with epilepsy develops drug-related psychiatric side effects[42]. Sodium channel blockers seem to be less frequently associated with psychiatric side effects[42], but there are no robust head-to-head trials providing strong evidence for that. For this reason, clinicians should bear in mind that psychiatric side effects can happen with any drug in predisposed individuals, such as those with psychiatric comorbidities. Psychiatric side effects of antiseizure medications reported with a prevalence higher than 1% are summarised in **Table 3**.

Lastly, the clinical presentation of psychiatric comorbidities has itself been a matter of debate [43]. In fact, people with epilepsy can develop psychiatric disorders clinically identical to those of individuals without epilepsy but it is also established that some develop psychiatric syndromes characterised by unusual features non adequately captured by classificatory systems such as DSM and ICD[44] (**Table 2**). Psychiatric presentations can be atypical and sometimes challenging in people with intellectual disabilities[45], where also the pattern of psychiatric side effects of antiseizure medications can be different (**Table 3**).

TREATMENT ISSUES

Full remission should always be the ultimate goal of the treatment of any psychiatric comorbidity in epilepsy. As discussed in this section, current evidence on the management of psychiatric comorbidities in epilepsy is limited. There is, however, no reason to consider that guidelines of treatment for psychiatric disorders may not be valid in epilepsy. It seems reasonable, therefore, to follow standard practice bearing in mind the individualities of people with epilepsy, especially drug-interactions and risk of seizures (**Table 4**).

Psychological interventions

In the general population, psychological interventions are the first line treatment for all anxiety disorders and for mild to moderate depression. It is reasonable to apply this guidance also to people with epilepsy but the evidence is still limited and mainly based on quality of life data[46]. A recent ILAE report supported psychological interventions in people with epilepsy and mild to moderate depressive symptoms, although again the evidence level is moderate [47].

Psychoeducation and psychological interventions still represent first line treatments for PNES[48]. No studies have specifically addressed the management of PNES in people with epilepsy, but it is obvious that explaining the diagnosis and educating individuals and caregivers about the differences between epilepsy and PNES are extremely important.

Pharmacological treatments

In the general population, antidepressants are used in moderate to severe depression and in all anxiety disorders in combination with psychological interventions. A Cochrane Review on

antidepressants in epilepsy has, however, shown a low level of evidence due to the poor quality of studies[49]. There are only two placebo-controlled trials and several open studies of antidepressants including sertraline, citalopram, fluoxetine, reboxetine and mirtazapine[50]. These studies clearly suggest that selective serotonin reuptake inhibitors (SSRIs) and newer antidepressants are safe and effective in epilepsy but they are limited by the relatively small size and the inclusion of people with different epilepsy types (from newly diagnosed to those with drug-resistant epilepsy). These limitations probably explain the heterogeneous response rates, ranging from 24% to 97% [50]. Citalopram and sertraline are usually considered first-line treatments for depression in the context of a chronic health condition, and given available data, this is a sound option in people with epilepsy and depression.

There seem to be no studies examining the effectiveness of drug treatments for anxiety disorders in epilepsy but SSRIs are usually considered first-line treatment when a pharmacological treatment is needed.

Regarding antipsychotics, the evidence is also scant. A Cochrane Review[51] quotes only a single controlled study investigating olanzapine (10 mg/day) as compared to haloperidol (12 mg/day) in 16 people with epilepsy and psychosis. This was, however, a conference abstract published 15 years ago and the study was never published. Risperidone, olanzapine and quetiapine are usually considered first line treatments in first episode psychosis.

Post-ictal psychoses represent an epilepsy-specific problem and for this reason evidence is less compelling and it is not possible to apply evidence from elsewhere. Historically, a combination of benzodiazepines (i.e. clobazam) and atypical antipsychotics is often used [52]

There are no studies on the use of antipsychotics in people with challenging behaviour, autism and epilepsy. Trials in persons with intellectual disabilities and challenging behaviour

or autism without epilepsy seem to favour risperidone [45]. A post-hoc analysis of a subsample of 35 people from Japan from a large, controlled trial of everolimus suggested some potential beneficial effects on behavioural symptoms in people with autism and epilepsy due to tuberous sclerosis [53].

The level of evidence is higher for treatment of ADHD in epilepsy than for other psychiatric comorbidities, despite the limited number of studies. A systematic review showed response rates for methylphenidate in children with ADHD and epilepsy between 65% and 83%[36]. Data on atomoxetine and amphetamines are available only at the anecdotal level.

Interactions

Old antiseizure medications such as carbamazepine, phenytoin and barbiturates induce drug-metabolizing enzymes such as the CYP and the UGT systems, while valproate is an inhibitor. Among newer drugs, oxcarbazepine is a weak inducer, topiramate is an inducer at daily doses over 200 mg while other newer drugs are less likely to be culprits for drug-interactions [54,55]. Antidepressants are extensively metabolised by multiple systems and this can potentially lead to interactions[54]. Regarding tricyclics, dosage adjustments with inducers should be considered on an individual basis and this is due to a number of pharmacokinetic reasons including the large therapeutic window of this class of antidepressants and the concomitant increase in the free fraction due to a concomitant protein binding displacement interaction [55]. Inducers reduce the levels of SSRIs by around a quarter but again systematic dose adjustments in routine clinical practice are not needed[55]. Fluoxetine, fluvoxamine and, to a lesser extent, sertraline inhibit the CYP2C9 and this can possibly increase the levels of phenytoin and, to a

lesser extent, valproate[54,55]. Inducers like carbamazepine, decrease the blood levels of bupropion by 90% making this interaction clinically relevant[54].

All enzyme-inducing drugs reduce antipsychotic blood levels but this is markedly important for quetiapine; for instance, its use with carbamazepine is associated with undetectable levels of the antipsychotic drug even at a dose of 700 mg[55]. There is no evidence that antipsychotics affect the blood levels of epilepsy medications.

Data on potential interactions of methylphenidate are limited to older compounds but there is no evidence of clinically relevant interactions.

Pharmacodynamic interactions are rarely systematically investigated but they can affect adherence and successful response to treatment. They are usually classified into positive and negative interactions. Positive interactions include synergistic or additive treatment effects such as the combination of SSRIs and pregabalin in some anxiety disorders[56]. Negative interactions include, for example, the amplification of potential side effects by the combination of two medications and these can be sedation, weight gain, sexual dysfunction, hyponatraemia, osteopenia and heart problems. For these reasons, neurologists need to familiarise themselves with the spectrum of side effects of psychotropic medications, in particular antidepressants[54].

Seizure risk

Historically, psychotropic drugs were thought to be associated with an increased risk of seizures and this is reported in the information leaflet of many psychotropic medications, from antidepressants to antipsychotics. This, however, has never been based on any robust

clinical evidence. Conversely, the analysis of seizure incidence in Phase II–III studies of psychotropic drugs approved by the Food and Drug Administration between 1985 and 2004 involving over 75,000 individuals showed that seizure incidence was not different from that of placebo. The only exception was for high-dose clomipramine (>150 mg) which showed a standardised incidence ratio of 4 (95%CI 2.6-6.0) [57].

Regarding psychostimulants, a Swedish study involving more than 21,000 children with seizures, showed no increased risk of seizures from ADHD medications[58] and this has been also endorsed by a recent ILAE consensus report[36].

Regarding antipsychotic drugs, clozapine has the highest risk of seizures when compared to placebo with a standardised incident ratio of 9.5 (95%CI 7.2-12.2)[57]. Olanzapine and quetiapine carry also some risk but to a lesser extent, while all other antipsychotics are no different from placebo[57]. A large community-based Taiwanese study involving 288,397 people showed that second generation antipsychotics like risperidone and aripiprazole have an even lower risk of seizures than first generation drugs like chlorprothixene, thioridazine and haloperidol[59].

The risk of seizures with clozapine is dose- and titration-dependent[60] although, in people with epilepsy, seizure aggravation has been reported even at low doses.

Nonetheless, it is still unknown whether all these data coming from the psychiatric realm can be directly transferred to people with epilepsy and psychiatric comorbidities. The few available open studies in epilepsy previously mentioned do not suggest deterioration in seizure frequency on a stable epilepsy drug regime.

Drug-related seizures are a complex problem and it is not just restricted to psychotropic medications. There is no doubt, however, that the incorrect over-estimation of the risk of

seizures with psychotropic medications has had a deleterious impact on access to proper treatment in people with epilepsy and psychiatric comorbidities.

CONCLUSIONS AND FUTURE DIRECTION

Psychiatric disorders are a relatively frequent comorbidity in people with epilepsy and they need to be an integral part of the management. For this reason, epilepsy clinics should have a clear pathway for access to mental health care. There are now several screening instruments which can be adopted in routine clinical practice even in resource poor settings. In the absence of epilepsy-specific guidelines, internationally adopted guidelines concerning the treatment and management of primary psychiatric disorders should be adopted, taking into account the peculiarities of people with epilepsy.

Future studies need to clarify whether these disorders are mediators or moderators of seizure outcome; that is, are psychiatric disorders merely indicators of poor prognosis or can their early identification and prompt treatment have an impact on the prognosis of the epilepsy itself?

High quality outcome studies for major psychiatric comorbidities such as mood, anxiety disorders and psychoses in people with epilepsy are needed to develop evidence-based treatment strategies.

Appendix 1. Authors contribution

Name	Location	Role	Contribution
Marco Mula MD	St George's University of London, United Kingdom	Author	Conceptualized the paper; literature search and abstract review; drafted the manuscript
Andres Kanner MD	Miller School of Medicine, University of Miami	Author	Revised the manuscript for intellectual content
Nathalie Jette MD	Icahn School of Medicine at Mount Sinai, New York	Author	Revised the manuscript for intellectual content
Ley Sander MD	UCL Queen Square Institute of Neurology, Queen Square, London, United Kingdom	Author	Conceptualized the paper; Revised the manuscript for intellectual content

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Table 1. Barriers to access to mental health care in people with epilepsy [44].

HEALTH-CARE PROVIDER RELATED		**POTENTIAL SOLUTIONS**
Neurologist related	Lack of training about the psychiatric aspects of neurological disorders Lack of knowledge about the management of psychiatric disorders and the use of psychotropic drugs Lack of time in the outpatient setting Misconceptions about seizure risk with psychotropic medications Failure to educate people with epilepsy and their family members about psychiatric comorbidities Lack of communication with psychiatrists	Neurology and psychiatry residency programs with expanded curricula covering psychiatric aspects of neurological disorders and vice versa To implement routine use of screening instruments in clinical practice Well-defined clinical pathway to access mental health care for people with epilepsy Tertiary Epilepsy Centres should have a psychiatrist as part of the team Information leaflets about psychiatric disorders available for individuals and to be given in clinic routinely
Psychiatrist related	Lack of training about the psychiatric aspects of neurological disorders Failure to recognise all the aspects of the clinical manifestations of psychiatric comorbidities in epilepsy Misconception about the association between psychiatric comorbidities and the underlying epilepsy leading to refusal to treat people with epilepsy Misconceptions about seizure risk with psychotropic medications Lack of communication with neurologists	Neurology and psychiatry residency programs with expanded curricula covering psychiatric aspects of neurological disorders and vice versa Well-defined clinical pathway to access mental health care for people with epilepsy Tertiary Epilepsy Centre should have a psychiatrist as part of the team
PATIENT AND FAMILY RELATED		

Cultural barriers	Individual and family members' refusal to accept the existence of psychiatric comorbidities Stigma towards mental health problems (Double-stigma)	Information leaflets about psychiatric disorders available for people and to be given in clinic routinely To routinely discuss about psychiatric problems during the clinical consultation
Barriers in the individual with epilepsy	Misconception that it is "normal" to feel anxious and /or depressed if you have epilepsy Misconceptions about the chronic nature of epilepsy Refusal to take "more" medications	Information leaflets about psychiatric disorders available for people and to be given in clinic routinely To routinely discuss about psychiatric problems during the clinical consultation
<u>ECONOMIC BARRIERS</u>		
Lack of resources	Limited and/or no allocated resources to mental health care.	To implement routine use of screening instruments in clinical practice Well-defined clinical pathway to access mental health care depending on resources

Table 2. Classification of psychiatric symptoms according to their temporal relation with seizures [61-66].

PERI-ICTAL	**PRE-ICTAL**	Symptoms preceding a seizure, mostly bilateral tonic-clonic seizures; prevalence unknown; mostly described in the context of temporal lobe epilepsy and include irritability, insomnia, dysphoria; duration from a few hours to 2 days
	ICTAL	These symptoms are the main manifestations of a seizure and may present as: 1) Focal aware seizures, non-motor, emotional (e.g. ictal fear, ictal depression); 2) Non-convulsive status epilepticus (e.g. ictal psychosis)
	POST-ICTAL	Symptoms following a seizure, mostly bilateral tonic-clonic seizures; Post-ictal psychoses: prevalence around 2%; florid brief-psychotic episodes lasting from hours to weeks; subtle onset after 48 hours of lucid interval from the seizure; high mortality risk due to high suicidal ideation and violent behaviour Post-ictal mood and anxiety symptoms: prevalence unknown (case series suggest up to 40% in people with drug-resistant temporal lobe epilepsy); duration a few hours up to 1 day; often described as post-ictal worsening of comorbid mood and anxiety disorder
PARA-ICTAL	**FORCED NORMALISATION**	Behavioural disturbance of acute/subacute onset including psychosis, significant mood change, anxiety with depersonalisation/derealisation or psychogenic non-epileptic attacks AND Reduction in the total number of spikes by over 50% in a routine EEG compared to a previous recording performed during a normal mental state
	ALTERNATIVE PSYCHOPATHOLOGY	Behavioural disturbance of acute/subacute onset including psychosis, significant mood change, anxiety with depersonalisation/derealisation or psychogenic non-epileptic attacks AND Complete cessation of seizures for at least 1 week, corroborated by a relative or carer

INTER-ICTAL	**EPILEPSY-SPECIFIC**	Schizophrenia-like psychosis: chronic psychosis with preserved affect and without progressive cognitive deterioration; historically described in the context of active temporal lobe epilepsy Interictal dysphoric disorder: chronic affective-somatoform syndrome characterised by mood swings with irritability with multiple somatic symptoms; historically described in temporal lobe epilepsy - probably not specific to epilepsy Interictal personality changes: e.g. Geschwind syndrome characterised by dysthymic mood with obsessionality, increased philosophical/religious interests, hyposexuality and hypergraphia; historically described in the context of temporal lobe epilepsy
	COMORBID DISORDERS	Any DSM-based diagnosis

Para-ictal=related to significant improvement in seizure frequency/seizure freedom or neurophysiological (EEG) parameters; EEG=electroencephalogram; DSM=Diagnostic and statistical manual of mental disorders

Table 3. Common psychiatric side effects of antiseizure medications [26,58,64].

Drug	Psychiatric side effects
Barbiturates	Depression Children and individuals with intellectual disabilities: hyperactivity, irritability, aggression
Benzodiazepines	Children, elderly and individuals with intellectual disabilities: hyperactivity, irritability, aggression
Brivaracetam	Aggressive behaviour, depression, psychosis but better tolerated than Levetiracetam
Carbamazepine	-
Eslicarbazepine	-
Ethosuximide	Psychosis
Felbamate	Anxiety, psychosis
Gabapentin	Children and individuals with intellectual disabilities: hyperactivity, aggression, irritability
Lacosamide	-
Lamotrigine	Individuals with intellectual disabilities: hyperactivity, irritability, aggression
Levetiracetam	Irritability, aggression, anxiety, depression, psychosis
Oxcarbazepine	-
Phenytoin	Psychosis (particularly at high serum levels)
Pregabalin	Depression
Rufinamide	-
Stiripentol	Hyperactivity, irritability, aggression
Tiagabine	Irritability
Topiramate	Depression, psychosis, irritability
Valproate	-
Vigabatrin	Psychosis, depression Children and individuals with intellectual disabilities: hyperactivity, aggression, agitation
Zonisamide	Psychosis, depression, irritability

Table 4. Recommendations for the management of psychiatric comorbidities in epilepsy.

	Management	Comments

Peri-ictal symptoms	✓ Improve seizure control ✓ Consider surgery as for any case ✓ Treat psychiatric comorbidity if present	✓ Psychiatric opinion in multidisciplinary approach to clarify diagnosis and management plan
Para-ictal symptoms	✓ Consider reducing the dose of antiepileptic drug or eventually to switch to alternative medication	✓ Psychiatric opinion in multidisciplinary approach to clarify diagnosis and management plan
Major depression	✓ Mild to moderate: psychological treatment ✓ Severe: SSRIs (either sertraline 50 mg or citalopram 20 mg) +/- psychological treatment ✓ If individual fails two antidepressant refer to psychiatry ✓ If suicidal ideation or psychotic symptoms urgent referral to psychiatry	✓ Consider interaction with inducers ✓ Consider side effects of SSRIs (i.e. hyponatraemia, sexual dysfunction, osteoporosis, bleeding, weight gain)
Anxiety disorders	✓ Mild to moderate: psychological treatment ✓ Severe: SSRIs (either sertraline 50 mg or citalopram 20 mg) +/- psychological treatment ✓ If fails two interventions refer to psychiatry	✓ Consider interaction with inducers ✓ Consider side effects of SSRIs (i.e. hyponatraemia, sexual dysfunction, osteoporosis, bleeding, weight gain)

First episode psychoses	✓ Urgent referral to psychiatry ✓ First choice: Risperidone ✓ Second choice: Olanzapine or quetiapine	✓ Consider interaction between quetiapine and inducers (.ie. undetectable levels of quetiapine up to 700 mg when in combination with carbamazepine) ✓ Consider side effects of antipsychotics (.ie. sedation, weight gain with olanzapine)
Attention deficit hyperactivity disorder	✓ Methylphenidate ✓ Psychological interventions	✓ Review at transition to discuss opportunity of continuing treatment during adulthood
Psychogenic Non-Epileptic Seizures (PNES)	✓ Explain diagnosis ✓ Educate patients and caregivers about differences between PNES and epileptic seizures ✓ Psychoeducational and psychotherapeutic interventions as in people with PNES only ✓ Always refer to psychiatry to identify other psychiatric disorders in comorbidity ✓ To treat other psychiatric comorbidities (e.g. depression, anxiety etc.)	✓ Individualised multidisciplinary approach is always recommended

SSRIs=Selective serotonin reuptake inhibitors