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The Final thesis

Psychosis as an Epilepsy Comorbidity

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1. Introduction

In the present work, scientific publications on symptoms and courses of ictal psychoses were collected and analyzed. The scientific background of the dissertation's topic is based on findings of the last 30 years, demonstrating that neuropsychological disorders represent a serious problem in patients with confirmed epilepsy. It has been shown that psychiatric disorders occur significantly more frequently in patients with epilepsy than in the general population (Baumgartner and Lehner-Baumgartner, 2008). In the following Table 1, the different proportions in the frequency of mental disorders in patients with epilepsy from several studies were compared to their occurrence in the general population.

Table 1: Frequency of psychiatric disorders with or without epilepsy (Baumgartner and Lehner-Baumgartner, 2008); (ADHD= Attention-Deficit-Hyperactivity-Disorder)

Frequency of psychiatric disorders with and without epilepsy	
Depression with epilepsy 11 - 55 %	without epilepsy 2 - 4 %
Anxiety disorders with epilepsy 15 - 25 %	without epilepsy 2,5 - 6,5 %
Suicide with epilepsy 5 - 10 %	without epilepsy 1 - 2 %
Psychosis 2 - 8 % with epilepsy	without epilepsy 0,5 - 0,7 %
ADHD (see above) 10 - 40 % with epilepsy	without epilepsy 2 - 10 %
Dissociative seizures 1 - 10 % with epilepsy	without epilepsy 0,1 - 0,2 %

Compared to Baumgartner and Lehner-Baumgartner's study (2008), an extensive literature search from 1990 to 2011 found higher rates of psychiatric comorbidity among patients with epilepsy (Hamad, 2011). In this study, 17% to 80% of patients with epilepsy had depression, 19% to 66% had anxiety disorders, 13% to 25% had suicides or suicide attempts, 6% to 10% had psychoses,

30% to 40% had attention loss, and 14% to 22% had dissociative disorders. Correlated with these comorbidities, there is a high suicide rate in epilepsy, ranging from 5% to 12% based on mental illnesses (Schmitz, 2005; Jones et al., 2003). Furthermore, the psychiatric comorbidity in epilepsy is significantly higher than in other chronic diseases, such as asthma (Ettinger et al., 2004). This suggests a shared biological basis for psychiatric disorders and epilepsy (Ettinger et al., 2005; Kanner, 2006; Lin et al., 2012). In both studies, it was concluded that the relationship between psychiatric disorders and epilepsy carries significant therapeutic implications. Based on this therapeutic relevance, a comprehensive biopsychosocial approach should be taken to both diseases, focusing on the whole person, not just the disease process per se. Since the 18th century, the phenomenon of the alternating occurrence of epileptic seizures and mental disorders in individual patients has been known (Schmitz and Trimble, 2005). In the 1930s, the observation of an antagonism between psychoses and epileptic seizures in such patients led to the introduction of seizure treatment for psychoses. For the alternating occurrence of epileptic seizures and psychosis or mental disorders, psychiatrist Tellenbach (1965) coined the term "alternative psychosis". He refers to, epileptologist Landolt (1955) who had already emphasized the EEG findings 10 years earlier and formulated the term "forced normalization of the EEG". Tellenbach (1965) "initiated the discussion of the possible relationship between epilepsy and schizophrenia-like psychoses from experiences with epileptic patients who became psychotic during antiepileptic treatment". Landolt (1955) referred to a key observation in an epilepsy patient who showed spike-and-wave complexes, i.e., epilepsy-typical potentials, in a relaxed situation in the EEG. In contrast, however, a normal EEG was present in this patient in a mental state of "tension and anger". For this EEG normalization, which Landolt (1955) interpreted as "an excessive reaction of healthy brain tissue", he chose the term "forced normalization". In choosing the term forced normalization, Landolt (1955) referred to epilepsy patients who had seizures and pathological EEG findings on the one hand, but normal mental findings on the other hand. Additionally, mood disorders and psychotic disorders were observed in epilepsy patients with seizure freedom and normal EEG findings (Fröscher and Steinert, 2019). Regarding the term "forced normalization" chosen by Landolt (1955), Fröscher and Faust (2019) pointed out that the term "alternative psychosis" would more accurately characterize the clinical situation.

The understanding of the parallel occurrence of psychotic and epileptic conditions developed around the turn of the century. In a survey of 67 neurologists who regularly treated epilepsy patients (Gilliam et al., 2004), the following question was asked: "Do you routinely screen epilepsy patients

for depression in your clinics?" The answer from 86% of respondents was "no". Another survey asked: "If a randomized controlled study showed that treating depression improves compliance and health-related quality of life in epilepsy patients, would you systematically screen them for depression in your clinic?" The answer from 85% of respondents was "yes" (Jacoby et al., 1996). These data already showed 20 years ago that there was an urgent need to achieve better evidence for the recommended use of antidepressants in epilepsy (Schmitz, 2005). In this regard, Schmitz (2005) strongly emphasized that there is no satisfactory system of classification of psychiatric disorders in the context of the combination of epilepsy and mental disorders. The coincidence of psychiatric disorders and epilepsy is differentiated according to defined temporal relationships, which were chosen based on the classification of psychoses in relation to epileptic seizures. Based on this, fixed temporal associations between psychoses and epilepsy were established. In addition to ictal psychoses, which are the focus of this work, there are temporal relationships between pre-ictal and post-ictal psychotic disorders. Another differentiation was made for interictal psychotic disorders, which have no temporal relationship to the occurrence of seizures.

1.1 Etiology

Psychiatric disorders affect one in three people with epilepsy and are attributable to psychosocial and biological factors (Mula et al., 2021). In addition to objective impairments, epilepsy still carries stigmata in cases of comorbid neuropsychological disorders, which can lead to discrimination and social isolation. Moreover, significant social limitations, such as loss of a driver's license, as well as the unpredictability of seizures, can lead to decreased self-esteem, probably increasing the risk of depression. From an etiological perspective, neuroimaging studies are of paramount importance, as they have demonstrated that people with depression or schizophrenia exhibit changes in brain networks that resemble those of temporal lobe epilepsy, particularly in the amygdala and hippocampus. However, people with epilepsy can also exhibit psychiatric symptoms that occur before, during, or after a seizure, as well as a result of treatment with antiepileptic drugs or after epilepsy surgery (Mula et al., 2021). There are predominantly three factors that lead to neuro-psychological symptoms or disorders in patients with epilepsy. These include morphological, clinical and demographic, as well as functional factors (Lehner-Baumgartner, 2009).

1.2 Epidemiology

Around 90% of patients with epilepsy are from developing countries (Kedare and Baliga, 2022). Patients with epilepsy and neuropsychiatric disorders of all diagnoses occur at a higher rate in both adults and children when epilepsy is present. Children with diagnosed epilepsy differ from healthy children in the occurrence of relevant developmental disorders. A nationwide Norwegian registry study found that 43% of children with epilepsy had developmental psychiatric comorbidities (Aaberg et al., 2016). Adults with affective disorders, anxiety disorders, psychotic disorders, and suicidal tendencies have significantly more severe consequences than children with psychiatric disorders such as autism and ADHD. Depression is the most common psychiatric comorbidity with epilepsy, with a synergistic relationship between epilepsy and affective disorders. A meta-analysis of 14 population-based studies found that 23.1% (CI 20,6% - 28,3%) of patients with epilepsy and active depression had depression within 12 months. In contrast, the total risk for active depression in adults without epilepsy was 2.7% (95% CI 2,09% – 3,6%), (Fiest et al., 2013). Conversely, several studies have shown that depression can be a triggering factor for the onset of epilepsy, especially in older people (Hesdorffer et al., 2006; Kanner, 2013). Anxiety disorders are the second most common psychiatric disorders associated with epilepsy (Mensah et al., 2007; Baumgartner and Lehner-Baumgartner, 2008). In addition to the coincidence of epilepsy and psychiatric disorders, the most serious complication is suicidal attempts or suicide. There are different levels of severity in this development, with the suicide rate in epilepsy being five times higher than in the general population and 25 times higher in temporal lobe epilepsy, according to studies by Christensen et al. (2007) and Bell et al. (2009).

1.3 Pathophysiology

Fröscher and Faust (2019) discussed the relationship of psychoses to seizures (table 2, see appendix 1, page 31). They focused in particular on the pathophysiology of the alternation of seizures and psychosis. According to recent statements (Fröscher and Faust, 2019), the pathomechanisms of the alternation and communication of epilepsy and psychosis are not clearly understood despite the existence of many hypotheses (Schmitz and Trimble, 2005; Fröscher and Steinert, 2007). It can be assumed that the bidirectional linkage between epilepsy and depression is based on common pathomechanisms. Changes in serotonergic, noradrenergic, dopaminergic, and GABAergic neurotransmission in conjunction with structural and functional changes in the three regions of the "mesial temporal lobe", "orbitofrontal cortex", and "subcortical structure" are discussed (Kanner et

al., 2012). An increase in glucocorticoid release through a severe activation of the hypothalamic-pituitary-adrenal axis is suspected as a triggering factor for the development of psychosis in connection with epilepsy. Another common pathophysiological factor of epilepsy and psychosis is attributed to the development of inflammatory cortical processes (Kanner et al., 2014). There are the following findings regarding the influence of serotonergic, noradrenergic, dopaminergic, and GABAergic neurotransmission on the bidirectional relationship between epilepsy and depression:

- In an animal model, genetically epileptic rats were bred that could trigger generalized tonic-clonic seizures by acoustic signals. In parallel, the animals had endocrine disorders like depressed patients, such as increased cortisol levels and a decrease in growth and thyroid hormones. An indicative sign of the bidirectional linkage in animal experiments was that a decrease in serotonin or norepinephrine indisputably induced the exacerbation of epileptic seizures, whereas increases in serotonin or norepinephrine did not cause seizures in the experimental animals (Jobe and Browning, 2005).
- Some antiepileptic drugs such as carbamazepine, valproic acid, or lamotrigine have a serotonergic effect with a reduction in seizure propensity. In animal experiments, carbamazepine induced release of serotonin from the hippocampus of rats was detected in vitro. On the other hand, reducing serotonin release resulted in frequent seizures in the experimental animals (Dailey et al., 1998).
- A known anticonvulsant effect via vagus nerve stimulation is likely mediated by the influence of noradrenergic neurons located in the locus coeruleus (Dailey et al., 1998). This mediation is also likely based on vagus nerve stimulation for antidepressant effects (Jobe and Browning, 2005).
- In clinical studies on patients with temporal lobe epilepsy, a decrease in the serotonin receptor could be detected by positron emission tomography (PET), which allowed for reduced serotonin binding in the hippocampus and amygdala ipsilateral to the focus of epilepsy (Savic et al., 2004).
- Another pathophysiological element for the linkage between epilepsy and mental disorders is the occurrence of structural and functional changes with localization in the mesial temporal lobe, orbitofrontal cortex, and subcortical structures. Patients with mesial temporal lobe epilepsy show significantly stronger forms of depression compared to patients with epilepsy with neocortical temporal lesions (Quiske et al., 2000). In a study by Richardson et al. (2007), a significant and positive correlation was demonstrated between

the volume of the amygdala and the severity of parallel depression in patients with temporal lobe epilepsy.

1.4 Diagnostics

Psychiatric illnesses such as depression, anxiety disorders, and psychotic disorders are often underdiagnosed and undertreated in patients with epilepsy due to patient dissimulation and inadequate systematic recording of psychiatric symptoms by healthcare providers (Leyhe, 2016). Psychiatric disorders can manifest before, during, or after the onset of epilepsy (Srinivas und Shah, 2017). To diagnose epilepsy and psychiatric disorders, patient history and questionnaires are used to assess neurological and psychotropic symptoms. Antiepileptic drugs can make diagnosing depression difficult due to side effects like concentration difficulties, fatigue, and memory problems. Special questionnaires like the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E (see appendix 2, page 32) / Gilliam et al. (2006)) and standardized instruments like the Beck Depression Inventory (BDI) and Hospital Anxiety and Depression Scale (HADS) are used to diagnose depression in epilepsy patients.

Ancillary investigations like electroencephalography (EEG), computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), and 18Fluor-Deoxyglucose (FDG)-PET/CT are used to diagnose epilepsy and psychiatric illnesses. The 18Fluorodeoxyglucose (FDG) PET/CT has high accuracy in temporal lobe epilepsy with depression when imaging shows a significant decrease in orbitofrontal glucose metabolism (Salzberg et al., 2006). Similar changes in simultaneous occurrence of psychiatric disorders and epilepsy have been demonstrated in studies using SPECT and PET imaging. These studies have shown that decreased regional cerebral blood flow is associated with reduced glucose metabolism in the prefrontal cortex and anterior cingulate gyrus (Videbech, 2000).

1.5 Clinic

The International League Against Epilepsy and the International Bureau for Epilepsy defined epileptic seizure as a temporary occurrence of signs and/or symptoms due to abnormal excessive or synchronous neural activity in the brain. This disorder not only induces seizures but also leads to neurological, cognitive, and psychosocial consequences (Fisher et al., 2005).

Patients with newly diagnosed epilepsy and a positive history of depression have a 2.27-fold lower chance of becoming seizure-free under antiepileptic therapy than patients without a history of depression (Hitris et al., 2007). Psychiatric disorders can cause symptoms such as sleep disturbance, poor concentration, lack of confidence, restlessness, and suicidal thoughts. These diagnoses belong into the domain of psychiatry, whereas epileptic disorders belong to neurology. However, there is a predisposition for both seizures and their neurobiological and psychosocial consequences, and overlapping forms between the two disciplines are possible and beneficial for patients (Fisher et al., 2005; Nakken et al., 2021).
In 2014, the ILAE published a definition of epilepsy based on a persistent predisposition to seizures (Fisher et al., 2014).

1.6 Therapy

Regarding the therapy of epilepsy and psychiatric disorders, there are limitations. While seizures in most patients can be successfully controlled by anticonvulsants or epilepsy surgery, at least 25% of patients have treatment-resistant seizures (Elger et al., 2017). Furthermore, achieving remission of all forms of psychiatric comorbidities should always be the goal. The intention of treatment guidelines for psychiatric disorders in epilepsy is therefore to apply standard therapy while considering the individuality of patients with epilepsy. Special attention should be paid to the interaction of drugs with a known risk of epileptic seizures (Mula et al., 2021).
The occurrence of ictal and postictal psychosis is closely related to epileptic seizures. An epileptic seizure is a short-term disturbance in brain function that occurs due to abnormal electrical activity in the brain. Ictal psychoses are psychotic symptoms that may occur during the epileptic seizure, while postictal psychoses refer to psychotic symptoms that may occur after an epileptic seizure.
Control of epileptic seizures is therefore of great importance to avoid the occurrence of ictal and postictal psychoses. Treatment of epilepsy can reduce the frequency and intensity of epileptic seizures. This can help reduce the risk of ictal and postictal psychosis. Regular medical monitoring of patients with epilepsy is also a good preventive measure against ictal and postictal psychosis. With routine examinations, the patient's condition can be monitored and adjustments in therapy can be made if necessary.
However, it is important to note that not all epileptic seizures can be prevented. In such cases, prompt and effective treatment of seizures and appropriate follow-up can help reduce the risk of ictal and postictal psychosis.

For the treatment of general psychiatric impairments, psychological interventions from the group of first-line treatments are the therapy of choice for all forms of anxiety disorders as well as for moderate depression. There are considerations to extend these forms of therapy to epilepsy, but their evidence is still limited. A recent ILAE report supported such psychological interventions, particularly cognitive-behavioral therapy in individuals with mild to moderate depressive symptoms, although the evidence rate is still relatively low (Michaelis et al., 2018). Patient and family education about mental illness, as well as the application of psychological interventions, still represent the first-line treatment for patients with psychogenic, non-epileptic seizures (Gasparini et al., 2019). Patients with psychiatric disorders and epilepsy, antidepressants are used in combination with additional psychological interventions for moderate and severe depression, as well as for all anxiety disorders. Regarding the evidence base for the use of antidepressants, there is still relatively low evidence available. In a Cochrane review by Maguire et al. (2014), only 2 placebo-controlled studies have been conducted to evaluate antidepressants, with numerous open-label studies on the use of the drugs sertraline, citalopram, venlafaxine, and mirtazapine. Based on the analysis of the studies, it has been demonstrated that serotonin reuptake inhibitors such as citalopram and sertraline, as well as the newer antidepressants mirtazapine and venlafaxine, are safe and effective in the treatment of epilepsy. However, the study results are limited by small sample sizes, newly discovered types of epilepsy, and drug resistance. Citalopram and sertraline are generally considered first-line treatments for depression in the context of a chronic health condition. Given the available data, these drugs are a solid option for the treatment of patients with epilepsy and depression (Mula et al., 2021).

1.7 Objective

A literature analysis is conducted over a period from 1990 to 2022 to identify the studies on the comorbidity of epilepsy and neuropsychological disorders. The focus of systematic reviews and meta-analyses is to analyze the frequency of ictal psychosis in relation to the frequency of different forms of psychiatric comorbidities. To answer this question, scientific publications are analyzed in the present systematic literature reviews and meta-analyses, based on which the prevalence of psychiatric comorbidities in patients with epilepsy is examined, based on clinical data from populations.

2. Material and Method

The methodological part of the present work is structured into the necessary and important processes of a systematic literature analysis. These processes include:

- searching for suitable literature (1),
- documenting the search process and the collected literature (2),
- systematically summarizing the search results in the methodological part (3).

Complete statements were therefore possible after obtaining results based on the search for suitable literature (1) and their complete documentation (2). The methodological parts 1 and 2 are also the basic requirement for the systematic summary of the methodology part 3 as well as the basis for the relevant substantive surveys in the final main results section 4.

2.1 Search and documentation of relevant literature

The following are included in the search and documentation:

- Timeframe of the literature search:
  The timeframe for the literature search was from October 20, 2022, to March 31, 2023.
- The temporal limitation of the analyzed publications concerned the period from 1990 to 2022.
- The following search terms and combinations were used for literature sources:
  - Epilepsy + Depression; Ictal depression; ictal depression,
  - Epilepsy + Anxiety; Ictal anxiety; ictal anxiety,
  - Epilepsy + Psychosis; Ictal psychosis; ictal psychosis,
  - Epilepsy + ADHD; Ictal ADHD; ictal ADHD,
  - Epilepsy + Dissociative seizure; Ictal dissociative seizure; ictal dissociative seizure,
  - Epilepsy + Alternative psychosis; Ictal alternative psychosis; ictal alternative psychosis,
  - Epilepsy + Suicide; Ictal suicide; ictal suicide.

After verifying the keywords, it was found that searching for effective keywords is most useful in combinations and in English. Frequently, keywords are already listed in abstracts of reviews.
The most common keywords for the present work included:

- alternative psychosis, metaanalysis
- epilepsy, acute psychiatric disorders, mental health, metaanalysis,
- seizures, acute psychiatry, metaanalysis
- temporal lobe epilepsy, psychiatric comorbidity, metaanalysis
- antiepileptic drugs, antipsychotic drugs, metaanalysis,
- ictal anxiety disorders, ictal depressive disorders.

The type of search for literature sources and the number of literature sources in this work focused on the following German and English databases:

- Cochrane Library - is particularly effective for systematic reviews and contains scientific literature with the highest level of evidence;
- Pubmed - offers complete publications with additional inclusion of Medline and Life Science Journals;
- Embase (from Elsevier) - contains some works that are not included in Pubmed;
- Psyclinfo - recommended for the fields of psychiatry and psychology;
- Livivo - provides access not only to its own collections of the Central Library MED, but also connects to certain data sources, allowing for effective literature research to be conducted.

2.2 Literature of relevant magazines

For the literature search, systematic reviews and meta-analyses were collected from reputable journals in psychiatry and neurology. These journals were listed in alphabetical order:
Ann Neurol, BMC Psychiatry, Epilepsy Behav, Epileptologia, Front Neurol, J Neurol Neurochir Psychiatr, Lancet, Lancet Neurol, Nervenarzt, Neurology, Spectrum Psychiatry.
For the systematic reviews, literature searches were conducted that were focused on a single, clearly formulated question, which in the present study was the coincidence of epilepsy and mental disorders. The primary studies collected were critically evaluated and assigned descriptively based on related content. The assignment to specific meta-analyses was based on a systematic analysis of thematically related articles, which were summarized in the meta-analysis to produce an overall result. Since meta-analyses are based on systematic literature searches, the collection of primary data from individual studies enables the gain of all available evidence and thus its importance.

After completing the literature search, the determination of the total number of relevant systematic reviews and meta-analyses found, as well as their literature pre-selection, was only carried out in the results section, considering exclusion criteria. For this step, the results of the present study were differentiated according to:

- The total number of recorded and read systematic reviews and meta-analyses.
- The total number of excluded systematic literature reviews and meta-analyses due to deviations regarding the aim of the studies, the presence of identical sources, and sources with insufficient scientific content.
- The total number of systematic reviews and meta-analyses for the result evaluation in the present study.

2.3 Literature Review and Meta-Analysis

In the present study, the analysis of the relationship between the diagnosis of epilepsy and psychiatric comorbidities was the clear question for the method of conducting a systematic literature review and meta-analysis. Therefore, all available primary studies were systematically and critically reviewed (Deutsches Netzwerk evidenzbasierter Medizin, 2011).

All identified studies were independently considered before analyzing the results. Whether meta-analyses were also included in the analysis besides the literature review depended on the corresponding results.

Depending on the required and available time for literature reviews, it can be differentiated between "Rapid", "Realist", "Scoping", "Umbrella", and "Systematic" reviews, with the time ranging from 1-3 months (Rapid) to 30 months (Systematic). After research in the Cochrane Library, Pubmed (Medline), Web of Science, Psyclinfo, Embase, and PROSPERO (International Prospective Register of Systematic Reviews), there were four systematic reviews on the comorbidity of epilepsy and psychiatric disorders. In addition to searching databases, searches were also conducted in topic-specific journals using the "hand-search" method (see above).

The process of systematic literature research was carried out in the following steps:

- Develop research questions, prepare and formulate topic blocks,
- Select databases and review appropriate reviews and meta-analyses,
- Documentation and literature management,
- Evaluation of the literature.

Table 3 refers to a methodical example of the screening and brief documentation of reviews and meta-analyses.

Table 3: Brief documentation of a review.

Review > J Epil Research 11:21-26 Jan. 25, 2022 pISSN 2233-6249 / eISSN 2233-6757 "Psychiatric Comorbidities in Epilepsy" Rodríguez C.A., Kubis M.M., Arteaga C.B.T., Fustes O.J.H (2022) Abstract: Psychiatric comorbidities (PC) occur more frequently in patients with epilepsy than in the general population. To determine the main PC associated with epilepsy and its association with demographic data and clinical features of epilepsy.

2.4 Screening of the literature

In recent years, applicable "Reporting Guidelines" have been developed for literature screening. These first create a checklist with several "items" that should be present in parts of a study's publication so that analysts have essential information to assess the quality of a study.

For analyses of systematic reviews and meta-analyses of randomized controlled trials, the PRISMA checklist has been particularly recommended in recent years (Page et al., 2021), whose abbreviation stands for "**P**referred **R**eporting **I**tems for **S**ystematic **R**eviews and **M**eta-Analyses". PRISMA is feasible using a flow diagram that graphically depicts the key steps and decisions for analyzing reviews and meta-analyses. In this context, it is important to define and consider appropriate inclusion and exclusion criteria in addition to titles, abstracts, and full texts. Numerous journals already require the inclusion of PRISMA standards for publications.

For the present analysis, the following inclusion (E1 to E5) and exclusion criteria (A1 to A4) were chosen for pain (as an example) based on the PRISMA list (Bayer et al., 2021):

E1: Publication type:	systematic reviews, meta-analyses, randomized-controlled trials
E2: Search period:	Follow-up search from 01/01/2010-31/12/2018
E3: Demographics:	Adult patients >= 18 years of age
E4: Pain type:	Tumor pain or/with neuropathic pain
E5: Therapy:	Regular oral or transdermal use/application of WHO III opioids due to pain
A1 Population:	Studies of patients with chronic non-tumor pain, neuropathic pain without concomitant tumor pain, acute pain, postoperative pain; studies of breakthrough pain therapy only
A2 Population:	Studies on opioid abuse or substitution therapy in opioid-dependent patients
A3 Publication type:	Editorial, commentary, case report, letter, nonsystematic/narrative review, case series n10, retrospective analyses of databases or patient records
A4 Outcome	Observation period < 14 days

Identification of studies based on datasets from databases and registers resulted in the following findings, categorized according to Page et al., 2021:

From databases:	n = 1,788 publications
From registers:	n = 46 publications
Analyses found for retrieval :	n = 5 reviews and meta-analyses
Analyses found suitable for inclusion:	n = 4 reviews and meta-analyses
Publications included in the review:	n = 98 publications.

3. Results

In the present study, systematic reviews and meta-analyses were collected and evaluated, which investigated the relationship between epilepsy and psychiatric disorders. Psychiatric disorders can negatively affect the treatment of epilepsy by disrupting health behavior and increasing seizure frequency. It should be noted that quality of life (QOL) is more strongly influenced by psychiatric comorbidity than by seizure frequency. The results section of this paper includes analyses of 4 systematic reviews on this topic.

Due to the limited number of pages, only 2 systematic reviews are analyzed in more detail in this paper. The other 2 relevant reviews are named and summarized in short form.

3.1 Lu et al. (2021) - Systematic Literature Review of Psychiatric Comorbidities in Adults with Epilepsy

Lu et al, (2021) conducted a systematic literature review of adults in whom psychiatric comorbidities associated with epilepsy were recorded.

The systematic literature search included original publications in which both epilepsy and psychiatric comorbidities were clinically assessed. The electronic databases PubMed, PsycINFO, Ovid, and Cochrane were examined for articles on the prevalence of psychiatric comorbidities in patients with epilepsy. All included articles were in English and published between 2008 and 2018. Search terms were selected with the assistance of an institutional librarian from the Academic Medical Center at University Hospital of Cleveland, Ohio, USA. The authors recorded a total of 3,138 publications for this literature search, omitting basic source data. 2 Authors screened all publications for inclusion and exclusion criteria based on software from Rayyan Qatar Computing Research Institute (Cambridge, USA/Doha, Qatar), with an a priori list regarding inclusion and exclusion criteria. Publications were included if clinically confirmed diagnoses of epilepsy and psychiatric diagnoses were documented in medical records and if patients had an age of ≥ 18 years. After completion of a screening process, 23 publications (21 observational studies and 2 case-control studies) were included in the present literature search. Eighteen publications (78.3%) included a prevalence of psychiatric comorbidities within a sample of epilepsy without comparison groups. Fifteen publications were cross-sectional studies (65.2%) and three publications were database/epidemiological studies (13.0%). Three other studies (13.0%) compared psychiatric comorbidities in different epilepsy subtypes based on matched-cohort studies. Only 2 studies

(8.7%) compared patients with epilepsy and a control group, which had not been done in 21 (91.3%) of the 23 studies. Regarding bibliometric data, all 23 publications had been published in 12 different peer-reviewed journals. To evaluate the 23 publications, the modified Newcastle-Ottawa Scale (NOS) was used in 3 categories, and 2 authors reviewed the determined NOS. These 3 categories were study group selection (1), study group comparability (2), and outcome ascertainment (3). The overall score for the 23 publications was a very good score of 9.0 and ranged in scoring from a minimum of 6.0 to a maximum of 11 (Table 4).

Table 4: Evaluation of 23 publications on the comorbidity of epilepsy and psychiatric disorders.

NOS rating	Publications number
6,0	n = 1
7,0	n = 1
8,0	n= 4
9,0	n = 10
10,0	n = 4
11,0	n = 3

Regarding outcomes, four different psychiatric comorbidities were detectable in all 23 studies in addition to epilepsy.

These included the four main categories:

- Mood disorders with 46.0%,
- Anxiety disorders with 36.1%,
- Drug related disorders with 10.5%, and
- Psychotic disorders with 7.4%.

Mood disorders most frequently included as major depression "major depressive disorder" (MDD) in 17 of 23 publications, "dysthymia" in 9 publications, and "bipolar disorder" with manic-depressive fluctuations in 6 of 23 publications.

Anxiety disorders most frequently included "generalized anxiety disorder" (GAD) in 10 publications, obsessive compulsive disorder (OCD) in 7 publications, "panic disorders" with

unexpected panic attacks in 6 publications, and "post-traumatic stress disorder" (PTSD) or stress disorder (PTSD) in 4 publications.

Drug-related disorders included alcohol abuse in 4 of the 23 publications and abuse with drugs such as cannabis, amphetamine, ecstasy, LSD, heroin, and opiates in 2 of the publications.

Psychotic disorders in the present literature review included both schizophrenia in 4 publications and psychosis or psychotic episodes in 3 of 23 publications.

Although the diagnosis of "psychosis" can be used clinically as an umbrella term, it was differentiated in the present review of the 23 publications to include diagnoses such as schizophrenia and bipolar disorder as separate diagnoses.

In the results section of the present study (Fig. 3, see appendix 3, page 32), the pooled prevalence rates were compared with those of the NCS-R (Harvard Medical School). This was a survey-based study conducted between 2001 and 2003 using DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) criteria to collect prevalence data from 9,282 randomly selected participants. This comparison revealed that individuals with epilepsy were more likely to have anxiety, mood, and psychotic disorders. Although rates of psychiatric comorbidities were generally higher in PWE than in the general population, this trend was not observed for the combined addictive disorders. However, separate prevalence rates for substance abuse and alcohol abuse were higher in persons with epilepsy. The present study also differentiated whether differences were detectable between outpatients and inpatients because psychiatric comorbidity varied depending on inpatient or outpatient control. Two studies (8.6%) were excluded for this analysis because no conclusions were available for these two studies.

The overall prevalence of psychiatric comorbidity was higher in the inpatient group (n=5, 21.7%) than in the outpatient group (n=16, 69.6%). This difference was attributed to the fact that inpatients tended to have more severe symptoms than patients in outpatient/communal settings.

Regarding the prevalence rates of psychiatric diagnoses collected in the present review, these differed depending on the diagnostic methods used, so that, based on the method of diagnosis used, a division into 3 groups was made:

- 16 of the 23 publications (69.6%) used clinical interviews such as MINI (Neuropsychiatric Interview) or SCID (Structured Clinical Interview) for diagnosis,
- 4 publications (17.4%) used information from medical records and population-based registries, and
- 3 publications (13.0%) used questionnaires such as PHQ-9 (Patient Health Questionnaire).

Regarding suicide risk, one of the case-control studies found that suicides were significantly more frequent in patients with epilepsy and with an increase in the severity of epileptic seizures. The pooled prevalence for suicide in 2 studies was 9.3%, whereas the suicide rate in the US adult population without epilepsy was only 0.6%.

Treatment outcomes in the 23 studies by Lu et al, (2021) demonstrated that a positive response to treatment for epilepsy was consistent with a decrease in psychiatric comorbidities. Four of the 23 studies compared the rate of psychiatric comorbidities between successful and unsuccessful epilepsy therapy. This demonstrated that MDD was present in 54% of patients with uncontrolled epilepsy, whereas MDD was detectable in only 12.5% of patients with controlled epilepsy.

The results of the literature review by Lu et al, (2021) showed that treatment-resistant epilepsy is associated with an increased risk of MDD and anxiety disorders. This statement is consistent with previous literature (Clancy et al., 2014).

As a caveat, however, these findings do not explain whether uncontrolled seizures cause psychiatric symptoms or whether there is a common underlying neurophysiology that causes both intractable epilepsy and psychiatric disorders.

Some studies have demonstrated that patients with a psychiatric diagnosis are more likely to develop epilepsy, which would support the case for a common pathology (Mula et al., 2019).

Finally, the authors of the study concluded that there continues to be a lack of research regarding the associations and causes between treatment-resistant epilepsy and psychiatric disorders.

3.1.1 Conclusions

The systematic literature review by Lu et al. (2021) demonstrated that the prevalence of concomitant mental disorders is relatively high in patients with epilepsy, also in Germany. Mood and anxiety disorders are the most common comorbidities, while psychotic conditions such as schizophrenia and bipolar disorders are much less common. The prevalence of psychiatric diagnoses in individuals with epilepsy may vary depending on the type of epilepsy and its treatment outcomes. These findings suggest that screening methods regarding depression and anxiety should be part of the knowledge transfer in the continuing education of therapy for epilepsy, as posttraumatic stress disorder (PTSD) or stress disorder (PTSD) and abuse states should be a responsibility of treatment by neurologists.

3.2 Gurgu et al. (2021) - Systematic Literature Review of Psychiatric Comorbidities in Adults with Epilepsy

The comorbidity of epilepsy and mental disorders has been known for some time, and the intention for the present systematic review was to analyze specific interictal disorders in patients with epilepsy. The focus was to assess associations between psychiatric disorders and other sociodemographic or clinical characteristics of patients with epilepsy. The study aimed to assess the prevalence of specific interictal psychiatric disorders such as depressive disorders, anxiety disorders, psychotic disorders, and personality disorders in patients with epilepsy, and to compare these with the prevalence of psychiatric disorders in the general population. MEDLINE and ScienceDirect were searched for original articles published between January 2015 and February 2021 that included patients with psychiatric comorbidities and epilepsy. 13 studies with different methods and outcomes were analyzed. Databases were searched by combinations of the following keywords: Depression, anxiety, affective disorder, psychotic disorder, psychose, personality, epilepsy, and seizures. Individuals aged ≥ 18 years were included.

Inclusion Criteria:

Only controlled studies such as randomized cohort, cross-sectional, and case-control studies were included in the analysis. Studies were accepted if they included patients diagnosed with unprovoked single epileptic seizures (1), if the diagnostic methods for epilepsy and psychiatric disorders were listed (2), if the characterization of epilepsy and psychiatric disorders was considered adequate (3), and if the methodology, including statistical analysis was deemed appropriate and adequately described (4).

Exclusion Criteria:

Studies were excluded if the primary inclusion criteria were not met and included only ictal, peri ictal mental manifestations, outcomes of treatments, or adverse events.

Data extraction:

Data extraction of studies included in the review included study characteristics such as publication details, research institution, study type and objectives, inclusion and exclusion criteria, number and age of subject group, details of comparison groups, epilepsy details (diagnostic criteria, epilepsy syndrome, seizure frequency, antiepileptic drugs).

Assessment of study quality:

Bias risk for the included 13 studies was removed using the quality assessment tools RoB 2.0 tool for randomized trials, Newcastle-Ottawa Scale (NOS) for cohort or case-control studies, Joanna Briggs Institute (JBI) Critical Appraisal Checklist for cross-sectional analytic studies, and Crombie's items for cross-sectional purely descriptive studies.

Publication Search Results:

Considering the above search criteria, a total of 3,986 publications were identified. Of these, 1,550 publications were in the MEDLINE database and 2,436 publications were in the ScienceDirect database. Initially, 258 publications were screened for eligibility and finally 13 publications were included in the present review. Patient data from 13 studies with a total of 1,377 patients from 7 countries were analyzed from several study types.

- In a randomized controlled trial (RCT) of 97 patients, multidisciplinary therapy was used to assess the decrease in depression and anxiety in epilepsy patients, and the severity of psychiatric disorders after 12 months in the therapy group was compared with the control group (Zheng et al., 2019).

  A total of 13 publications were analyzed in detail in 7 countries (Table 5).

Table 5: Analysis of 13 studies on 1,377 patients with epilepsy and psychiatric disorders.

Lead author, Year, Country	Study-type	Patients (n)
Alonso et, 2019, Brasil	cross-sectional	200
Baldin et, 2015, USA	cohort	257
Filho et, 2017, Brasil	cross-sectional	95
Galioto et, 2017, USA	cross-sectional	51
Kavanaugh et, 2017, USA	cross-sectional	20
Konishi et, 2020, Japan	cohort	98
Labudda et, 2017, German	unspecified	120

Labudda et, 2018, German	unspecified	120
Pavia et, 2020, Brasil	unspecified	112
Ramos-Perd., 2016, Spain	prospective case control	85
Rayner et, 2016, Australia	unspecified	77
Shen et, 2020, China	unspecified	45
Zheng et, 2019, China	random. control.trial	97

- In 2 cohort studies, one study was conducted to detect depression and anxiety disorders in adult patients with childhood epilepsy (Baldin et al., 2015) and another to analyze psychotic disorders in idiopathic focal epilepsy (Konishi and Kanemoto, 2020).
- In a case-control study, psychiatric outcome was specifically assessed in drug-resistant epilepsy patients who had undergone surgical epilepsy treatment. These patients were compared with controls who did not undergo surgery. Both groups of patients were reassessed by a psychiatrist after 6 months and compared psychiatrically (Ramos-Perdigues et al., 2016).
- 4 studies were included with cross-sectional study designs in the study review presented here. These included:
    1. an assessment of interictal personality in patients with juvenile myoclonic epilepsy (JME) and in patients with mesial temporal lobe epilepsy (TLE) in the presence of hippocampal sclerosis (Alonso et al., 2019),
    2. an analysis of interictal dysphoric disorder and interictal per-sonality in drug-resistant TLE (de Araújo Filho et al., 2017),
    3. an assessment of depressive symptoms and executive functions in terms of mental abilities in patients with TLE (Galioto et al., 2017), and
    4. an examination of brain white matter changes in patients with TLE and depression (Kavanaugh et al., 2017).

Included in the present study were 5 other publications that examined a relationship between interictal dysphoric disorder and other psychiatric disorders in patients with epilepsy:

- A relationship between childhood trauma and psychiatric comorbidities and epilepsy (Labudda et al., 2017; Labudda et al., 2018).
- Social adjustment determinants in the presence of JME (Paiva et al., 2020),
- Possible phenotypes of depression in concurrent epilepsy (Rayner et al., 2016); and
- Sonographic evidence of brainstem changes in patients with idiopathic generalized epilepsy (IGE) (Shen et al., 2020).

3.2.1 Conclusions

The 13 studies included in the study were heterogeneous in terms of aims, methods, and results. Psychiatric disorders were detectable in a large proportion of patients with epilepsy. The prevalence of all observed psychiatric disorders was up to 51% in IGE, up to 43.1% in TLE, and up to 43.3% in patients with general epilepsy.

The most common psychiatric comorbidities of epilepsy were:

- affective disorders with up to 40% in lifetime onset and up to 23% in current onset,
- anxiety disorders with up to 30.8% at lifetime onset and up to 15.6% at current onset,
- personality disorders with up to 11% in juvenile myoclonic epilepsy (JME), and
- psychotic disorders with up to 4% of patients with epilepsy.

Personality disorders and anxiety disorders are more frequently described, -and studied- in IGE patients, while depressive disorders and psychotic disorders are more frequently detected in focal epilepsy (mainly TLE) and pharmaco-resistant epilepsy.

Experiences of maltreatment in childhood are a powerful predictor of the presence of psychiatric comorbidities in patients with epilepsy, whereas data on the association of other epilepsy characteristics (age at onset, epilepsy duration, seizure type, seizure localization and lateralization, seizure frequency) with the presence of a psychiatric disorder are conflicting. Anxiety disorders are associated with higher frequency of generalized tonic-clonic seizures and poorer social functioning. Psychotic disorders are associated with longer duration of epilepsy.

Future research should assess the presence of psychiatric disorders in newly diagnosed epilepsy and after a single unprovoked seizure. In addition, a detailed sociodemographic description should be performed for all patients. Standardized assessment tools should be used, including standardized

epilepsy and seizure classification, standardized seizure frequency reporting as recommended by the International League Against Epilepsy (ILAE) for clinical practice. This should include standardized structured clinical interviews for the diagnosis of psychiatric disorders and stratified data should be collected according to the specific epilepsy and psychiatric diagnosis.

3.3 Tsigebrhan et al. (2021) - Association with quality of life in low- and middle-income-countries: Comorbid mental health conditions in people with epilepsy and a systematic review and meta-analysis.

Regarding the intention for the present study, the authors of the systematic review and meta-analysis published here also pointed out that comorbid mental disorders are a common entity in people with epilepsy. In many cases, this results in serious effects on the course of epilepsy, whereby these findings were predominantly acquired from countries and regions with a higher financial standard (high income countries (HICs)).

The systematic review aimed to analyze dependencies of comorbid mental disorders on “Health Quol Life-Outcome” in people with epilepsy in low- and middle-income countries (LMICs).

3.3.1 Conclusions

The present systematic review and meta-analysis have demonstrated that effects of depression on quality of life can be severe. The literature in countries with HIC has responded that the need for early detection and for strategies to influence depression and anxiety in people with epilepsy are eminent (Lopez et al., 2019). Early detection and treatment of comorbid mental illness in people with epilepsy is of high priority, regardless of low-income or high-income countries. The WHO “Mental Health Gap Action” program could achieve better results by including people with epilepsy and depressions or even anxiety. It could draw on existing intervention studies that recommend pharmacological treatment for people with epilepsy and mental illness. Future research should focus on prospective studies that can measure changes in quality of life and identify a temporal relationship between depression and dysfunction. In conclusion, the negative impact of comorbid depression and anxiety on quality of life in people with epilepsy living in LMIC requires high and intensive care, combined with early identification and treatment of these comorbidities including epilepsy control.

3.4 Brizard et al. (2021) - Association between epilepsy and psychiatric disorders in adults with intellectual disabilities: systematic review and meta-analysis.

Epilepsy and psychiatric disorders in adults with intellectual disabilities can be conspicuous by problematic behavior as well as autism spectrum disorders (ASD). In this regard, the overall rate of psychiatric disorders with intellectual disability appears to be higher at 40.9% (Cooper et al., 2007)) than in the general population at 16% (Meltzer et al., 1995). The point prevalence of psychosis assessed at specific cut-off dates is also significantly higher in adults with intellectual disability at 3.4% to 4.4% and without intellectual disability at 1% (Cooper et al., 2007). Rates of major depression are comparable with and without intellectual disability, while rates of anxiety disorders are higher in adults with intellectual disability at 14% vs. 10% without disability. However, diagnosis of psychiatric disorders can be difficult in many adults with intellectual disability, (BJPsych Open (2021) 7, e95, 1-21. doi: 10.1192/bjo.2021.551), especially for those who have severe and profound intellectual disability and cannot communicate their thoughts and feelings to others (Bizard et al., 2021). Therefore, both false positive and false negative diagnoses may occur. It also remains an open question whether there is a correlation between epilepsy and psychiatric disorders in adults with intellectual disabilities.

3.4.1 Conclusions

In summary, diagnostic classification systems have changed over time and different studies have used different criteria for diagnosing mental retardation and psychiatric disorders. Furthermore, appropriate and adequate control groups are often missing in many included studies.

To make a definitive statement about the association between psychiatric disorders and epilepsy in adults with intellectual disability, more methodologically sound studies with appropriately matched control groups and standardized instruments for detecting and defining psychiatric disorders are needed for analyses of these populations in the future.

4. Discussion and Conclusion

The results of these reviews highlight the importance of attention to psychiatric comorbidities in patients with epilepsy and the need for integrated treatment for these patients. The four reviews have many similarities in their findings because they all examine the same topic: psychiatric comorbidities in patients with epilepsy.

Some important similarities are:

- Frequency of psychiatric comorbidities: All reviews indicate that psychiatric comorbidities are common in patients with epilepsy. Depression and anxiety disorders were identified as the most common psychiatric comorbidities.
- Increased risk for psychiatric comorbidities: All reviews emphasize that people with epilepsy are at higher risk for psychiatric comorbidities than people without epilepsy.
- Importance of comprehensive treatment: All reviews emphasize the importance of comprehensive treatment of psychiatric comorbidities in people with epilepsy. Appropriate treatment of psychiatric comorbidities can not only improve the mental health of people with epilepsy, but also improve their seizure control and quality of life.
- Methods: All reviews conducted a systematic literature search and assessed the quality of the included studies. This allowed for a comprehensive analysis of the available evidence on this topic.

Lu et al, Gurgu et al, Tsigebrhan et al, and Brizard et al all studied the same topic, but there are some differences between the reviews. These may be due to differences in the selection of included studies, populations, or methods of analysis used. Therefore, it is important to consider the results of each review in the context of its specific methodology and population.

Some important differences are:

- Objective: Lu et al. and Gurgu et al. focused on psychiatric comorbidities in adult epilepsy patients, whereas Tsigebrhan et al. examined the impact of psychiatric comorbidities on quality of life in epilepsy patients in low- and middle-income countries. Brizard et al. have focused on the association between epilepsy and psychiatric disorders in adults with intellectual impairment.
- Methods: Lu et al. and Gurgu et al. both conducted a systematic literature search, but they used different inclusion criteria and assessment methods. In doing so, Lu et al. included a larger number of studies and examined a broader range of psychiatric disorders, whereas

Gurgu et al. included only high-quality studies. Tsigebrhan et al. conducted a systematic literature search and meta-analysis. This means that they pooled data from multiple studies to make a statement about how psychiatric comorbidities affect the quality of life of epilepsy patients in low- and middle-income countries. Brizard et al. also conducted a systematic literature search, but they included only studies of adult patients with intellectual impairment.

- Population: The included populations differ in the reviews. Lu et al. and Gurgu et al. focused on adult epilepsy patients, whereas Tsigebrhan et al. limited the population to epilepsy patients in low- and middle-income countries. Brizard et al. focused on adults with epilepsy and intellectual impairment.
- Results: The reviews have produced mixed results. For example, Lu et al. and Gurgu et al. have found similar results regarding the prevalence of depression and anxiety disorders, whereas Tsigebrhan et al. have found that psychiatric comorbidities can significantly affect the quality of life of patients with epilepsy in low- and middle-income countries. Brizard et al. have shown that the prevalence of psychiatric disorders is higher in epilepsy patients with intellectual impairments than in those without impairments.

Overall, the four reviews show that psychiatric comorbidities are an important issue in patients with epilepsy and that comprehensive treatment of these disorders is necessary in these patients.
It is important to note that differences between reviews do not necessarily mean that one study is better or worse than another. However, differences in the focus and methods of each review may mean that they produce different results and illuminate different aspects of the relationship between epilepsy and mental disorders.

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6. Appendix

Appendix 1: Table 2

Psychotic disorders in epilepsy

	Interictal psychosis	Periictal confusion	Postictal psychosis	Alternative psychosis	Ictal psychosis
Risk factors	Focal complex seizures Temporal lobe epilepsy GABAergic anticonvulsants (VGB, TPM)	Focal complex seizures Temporal lobe epilepsy Seizure cluster	Focal complex seizures Temporal lobe epilepsy Seizure cluster occurred status epilepticus	Focal complex seizures Temporal lobe epilepsy Seizure reduction or absence	Single-focal seizures, absences Seizure origin often frontal or extra-temporal Seizure cluster in status epilepticus
Symptomatic	Duration weeks to months Consciousness clear Development independent of the seizure event Paranoid-hallucinatory symptoms Preserved affect Rarely negative symptoms	Duration days to weeks Consciousness often clouded Symptoms develop slowly, proportional to seizure frequency Productive symptoms Affective disorder in the background	Duration Days to weeks Consciousness cloudy or clear Symptom-free interval from 1 day to 1 week after seizure onset Productive symptoms Mood swings	Duration Days to weeks Consciousness clear Improvement of symptoms after seizure Polymorphic psy-chopathological picture, psychotic symptoms not obligatory Mood swings Agitation, Anxiety	Duration hours to days Consciousness often clouded Symptoms self-limiting Paranoid-hallucinatory symptoms Mood swings
EEG	Unchanged	Increase in interictal Spike activity Increase in decelerations	Increase in interictal Spike activity Increase in decelerations	Normalization	Status epilepticus
Treatment	Neuroleptics, ev. combination with AD Further Therapy with AD	Optimization of antiepileptic therapy, ev. neuroleptics or benzodiazepines	Optimization of antiepileptic therapy, ev. neuroleptics or benzodiazepines, frequently spontaneous remission	Reduction of antiepileptic therapy	Antiepileptic i.v.

https://www.kup.at/kup/pdf/748.pdf - Translated from German

Appendix 2:

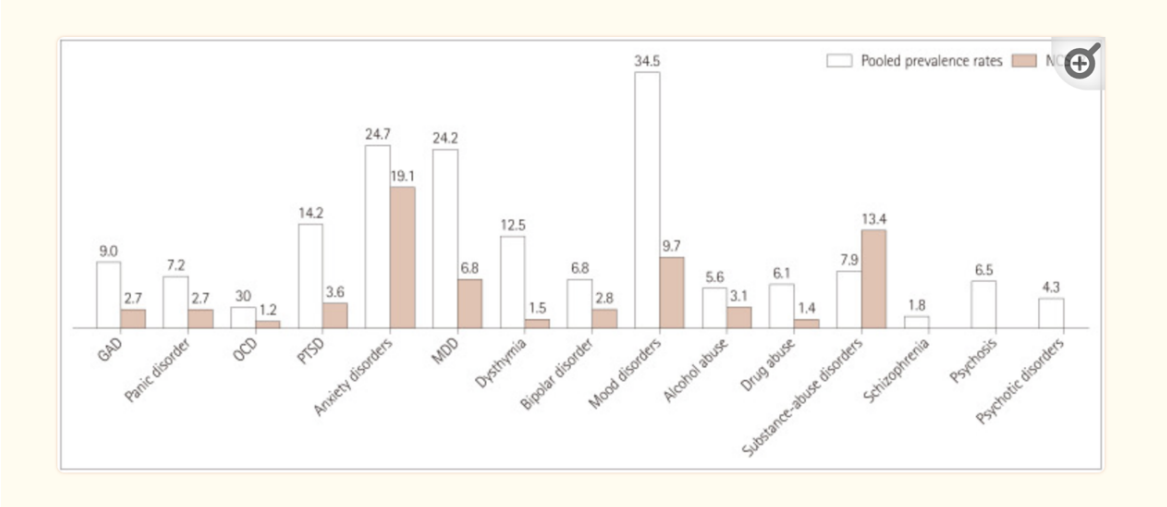
Neurological Disorders Depression Inventory for Epilepsy (NDDI-E)

TABLE. THE NEUROLOGIC DISORDER DEPRESSION INVENTORY EPILEPSY (NDDIE)				
In the past 2 weeks how often have you felt:	Always or often	Some of the time	Rarely	Never
Everything is a struggle	4	3	2	1
Nothing I do is right	4	3	2	1
Feel guilty	4	3	2	1
I'd be better off dead	4	3	2	1
Frustrated	4	3	2	1
Difficulty finding pleasure	4	3	2	1

https://practicalneurology.com/articles/2020-oct/epilepsy-and-depression

Appendix 3: Fig. 3

Comparisons of pooled prevalence rates with those from the NCS-R. GAD: generalized anxiety disorder, MDD: major depressive disorder, NCS-R: National Comorbidity Survey Replication, OCD: obsessive-compulsive disorder, PTSD:post-traumatic stress disorder.



https://thejcn.com/DOIx.php?id=10.3988/jcn.2021.17.2.176